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TITLE

Diseases prevalent before major depressive disorder diagnosis: a nested case-control study using health insurance–based claims data

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ABSTRACT

Objectives Major depressive disorder (MDD) is often comorbid with other chronic and/or serious diseases. However, little is known about the prevalence of various diseases that are present before MDD onset. We examined the prevalence of all pre-existing diseases in the 12 months before an MDD diagnosis.

Design Nested case-control study.

Setting Data, including diagnoses based on ICD-10 codes, were from a Japanese health insurance database (JMDC).

Participants Adults newly diagnosed with MDD during 2015, 2016, or 2017 (but not the preceding year) (cases) were matched 1:10 to controls by age, sex, index date, and working status.

Primary and secondary outcome measures The primary outcome was the proportion of patients in each group with each pre-existing disease during the 12 months before the index date (ie, before MDD diagnosis in cases). Odds ratios (ORs) for onset of MDD were calculated for each pre-existing disease. A post hoc multivariate analysis examined interactions of lifestyle diseases (diabetes, hypertension, dyslipidaemia), psychiatric disorders (sleep disorders, psychiatric disorders other than depression), and MDD-related symptoms (headache, pain, autonomic nerve imbalance) on MDD diagnosis.

Results There were 13,420 cases and 134,200 controls (mean age 41.9 years; 66.5% male). The prevalence of almost all pre-existing diseases was higher in cases than in controls. The highest ORs (5.8–21.0) were for psychiatric diseases and sleep disorders. Insomnia (21.1% of patients; OR 8.7) and neurosis (9.7%; OR 10.6) were particularly prevalent in the case group. The odds of MDD increased in the presence of lifestyle diseases, psychiatric disorders, and/or MDD-related symptoms.

Conclusions The high ORs of pre-existing diseases and/or prodromal symptoms in patients who develop MDD indicate a high medical burden for these patients. Patients with chronic and/or serious diseases should be monitored for depressive symptoms, and pre-existing diseases should be considered when prescribing MDD treatment.

ARTICLE SUMMARY

Strengths and limitations of this study

- This is the first nested case-control study to examine a broad range of pre-existing diseases in people who develop major depressive disorder (MDD) compared with people who do not.
- The use of a national health insurance database resulted in a sample size large enough to allow examination of less common pre-existing diseases.
- The nested case-control design and the use of a database minimised selection and recall biases that may occur in other case-control studies.
- Because of the nature of the database, the study did not include people aged ≥75 years, and information on the physician making the MDD diagnosis was not available.

Keywords: Administrative claims, healthcare; Comorbidity; Depressive disorder; Epidemiology; Risk factors

INTRODUCTION

Depression is frequently comorbid with other diseases, particularly chronic and/or serious diseases such as diabetes, cardiovascular/cerebrovascular disease, cancer, asthma, and arthritis.[1-3] The relationship between depression and most comorbidities is complex. For example, the temporal relationship appears to be bi-directional, in that depression can increase the risk of developing a chronic disease and vice versa.[3] Further, some symptoms of depression (eg, fatigue, loss of appetite) overlap with those of chronic illnesses.[4] If a physical disease is diagnosed first, depression may go unrecognised if the focus of both the patient and physician is on the physical condition. In addition, patients may think that their mood is 'normal' for someone with a chronic illness and may not realise or admit that they are experiencing depressive symptoms. Thus, major depressive disorder (MDD) may be underdiagnosed in patients with pre-existing chronic or serious diseases. Moreover, the presence of MDD in patients with pre-existing diseases is associated with worse outcomes and quality of life, and possibly decreased survival.[2]

An epidemiological study conducted in Japan between 2013 and 2015 reported the lifetime and 12-month prevalence rates of MDD to be 5.7% and 2.7%, respectively.[5] However, fewer than half of Japanese people with a mood disorder seek medical treatment.[5] This reluctance to seek medical treatment may be related to a perceived 'stigma' associated with psychiatric disease.[6] These factors may further reduce the detection and diagnosis of MDD in patients with a chronic disease, despite the potentially increased risk of MDD in these patients. However, little is known about the prevalence of underlying diseases that are comorbid with MDD. Given that around 20,000 people in Japan commit suicide every year,[7] with the highest rate of about 50 per 100,000 persons in men aged 50–59 years,[8] most of which are probably related to mental disorders, additional information on factors associated with MDD that could assist with early detection and treatment may help reduce the number of suicides.

The aim of this nested case-control study of patients enrolled in a Japanese health insurance database was to comprehensively examine the prevalence of pre-existing diseases in the 12 months before an MDD diagnosis. In this context, a pre-existing disease was defined as any diagnosis other than MDD and related mental disorders (bipolar affective disorders; organic mental disorders; schizophrenia, schizotypal, and delusional disorders), which could include conditions that are prodromal symptoms of MDD (eg, sleep disorders). In addition, we determined an odds ratio (OR) for the onset of MDD for each pre-existing disease to identify those that are most commonly associated with development of MDD and to evaluate the association of MDD with common lifestyle diseases.

METHODS

Study design

This was a nested case-control study. Data on patient demographics and diagnoses based on International Statistical Classification of Diseases and Related Health Problems, 10th revision[9] (ICD-10) were derived from the JMDC Inc. (Tokyo, Japan) database of medical expense claims for company employees in Japan.[10]

The study was approved by the Ethics Review Committee of the Research Institute of Healthcare Data Science (Tokyo, Japan) on 6 August 2019. Only anonymised information was accessible from the database; therefore, in accordance with the Ethical Guidelines for Medical and Health Research Involving Human Subjects in Japan,[11] informed consent was not required.

Study population

The study analysed data collected for the population registered in the JMDC database between January 2014 and December 2018 who were aged ≥18 years on 1 January of the inclusion year (2015, 2016, or 2017) and had continuous registration for the inclusion year, the previous year, and the subsequent year (study period). Individuals were excluded if they

had a diagnosis of any bipolar affective disorder (ICD-10 codes F30 [manic episode], F31), organic mental disorder including symptomatic mental disorders (F00–F09), or schizophrenia, schizotypal, and delusional disorder (F20–F29) in the study period, or a diagnosis of MDD (ICD-10 codes F32 ['Depressive episode'] or F33 ['Recurrent depressive disorder']) in the year before the inclusion year, or no medical history for the year before the inclusion year.

Within the study population, case patients had a diagnosis of MDD in the inclusion year (the date of the first MDD treatment after ≥1 year with no MDD diagnosis was designated as the index date) and ≥2 months of treatment for depression within 90 days of the index date. Control patients had no diagnosis of MDD in the study period and were matched 10:1 (random sampling) to case patients according to age at index date, sex, and working status.

Outcomes

The primary end point was the proportion of patients with documented diagnosis of each pre-existing disease during the 12 months before the index date (ie, before MDD diagnosis in case patients). An OR for the onset of MDD was calculated for each underlying disease, which was based on presence or absence of ICD-10 codes, Charlson comorbidity index (CCI)–related diseases, or other chronic diseases (online supplemental table 1). Demographic and patient characteristics were collected, including age, sex, working status, and inclusion year (2015/2016/2017).

Statistical analysis

As noted above, the proportion of patients with each pre-existing disease was determined for each group and an OR for the onset of MDD was calculated. Prevalence data and ORs are reported for pre-existing diseases that were present in ≥1% of the case group and ≥0.1% of the control group. No inferential statistics were conducted. A post hoc analysis examined the possible interaction of the presence of three pre-existing disease categories that exhibited

high ORs in the primary analysis or are common diseases: lifestyle diseases (diabetes, hypertension, dyslipidaemia), MDD-related symptoms (headache, pain, autonomic nerve imbalance), and psychiatric disorders (sleep disorders, psychiatric disorders other than depression) (online supplemental table 1). A multivariate logistic regression model was used to determine ORs in the eight subgroups (ie, with/without lifestyle disease, MDD-related symptoms, and/or psychiatric disease) for the onset of MDD using the following covariates: sex, age (<40 years versus ≥40 years), and working status. Netezza N2002-010 7.1.0.4.P2 (IBM, Armonk, NY, USA) was used as the data warehouse platform. SAS version 9.4 (SAS Institute, Cary, NC, USA) was used for statistical analysis.

Patient and public involvement

Patients and members of the public were not involved in the study.

RESULTS

Demographic characteristics

From more than 6.5 million people enrolled in the JMDC database between 2014 and 2018, we identified 13,420 case patients who met the inclusion criteria and had MDD diagnosed in 2015, 2016, or 2017 (case group; online supplemental figure). From 4,212,652 control patients who met the inclusion criteria and did not have an MDD diagnosis in either the inclusion year or the subsequent year, 134,200 were matched to case patients (control group; online supplemental figure). More than half (66.5%) of patients in both groups were male, with a mean age of 41.9 years (**table 1**). About 40% of patients were <40 years. Most (77.8%) patients were workers.

Table 1 Background and characteristics of case group and matched control group

Variable	Case group N=13,420	Matched control group N=134,200
Male sex	8924 (66.5)	89,240 (66.5)
Age		
Mean (SD), years	41.9 (10.4)	41.9 (10.4)
Median (range), years	42.0 (18–73)	42.0 (18–73)
<40 years	5390 (40.2)	53,900 (40.2)
≥40 years	8030 (59.8)	80,300 (59.8)
Working status		
Working	10,447 (77.8)	104,470 (77.8)
Non-working	2973 (22.2)	29,730 (22.2)
Inclusion year		
2015	3853 (28.7)	38,530 (28.7)
2016	4076 (30.4)	40,760 (30.4)
2017	5491 (40.9)	54,910 (40.9)
Number of beds in hospital where MDD was diagnosed		
<20	10,851 (80.9)	NA
≥20	2569 (19.1)	NA
Psychiatric facilities in hospital where MDD was diagnosed		
Yes	7026 (52.4)	NA
No	6394 (47.6)	NA

Data are n (%), unless otherwise noted.
MDD, major depressive disorder; NA, not applicable; SD, standard deviation.

Prevalence of pre-existing diseases in the year before MDD diagnosis

CCI-related diseases and other chronic diseases

The prevalence of almost all chronic diseases was higher in the case group than in the control group, with most ORs between 1.3 and 2.0 (**table 2**). The highest ORs were seen for attention deficit hyperkinetic disorders (OR 12.2), psychiatric diseases except depression (OR 9.9), dementia (OR 8.7, although prevalence was ≤0.1% in both groups), sleep disorders (OR 7.2), and autonomic nerve imbalance (OR 6.5). Of these, psychiatric diseases except depression and sleep disorders were highly prevalent in the case group (30.4% and 23.3%, respectively). ORs ≥2.0 were also observed (in descending order of prevalence in the case group) for pain (2.0), chronic gastritis (2.1), headache (2.7), peptic ulcer disease (2.0), dizziness (3.2), irritable bowel syndrome (3.2), angina pectoris (2.0), epilepsy (2.4), chronic enteritis (2.7), diabetes without chronic complication (2.1), metastatic solid tumour (2.2), hemiplegia or paraplegia (2.8), and Parkinson's disease (3.2).

Table 2 Prevalence of pre-existing diseases, ranked by prevalence in the case group

Disease	Case group N=13,420	Matched control group N=134,200	Odds ratio (95% CI)
CCI-related diseases			
Peptic ulcer disease	1431 (10.7)	7659 (5.7)	2.0 (1.9–2.1)
Mild liver disease	1392 (10.4)	9336 (7.0)	1.5 (1.5–1.6)
Chronic pulmonary disease (ex. asthma)	973 (7.3)	7381 (5.5)	1.3 (1.3–1.4)
Cerebrovascular disease	448 (3.3)	2378 (1.8)	1.9 (1.7–2.1)
Peripheral vascular disease	359 (2.7)	2237 (1.7)	1.6 (1.4–1.8)
Congestive heart failure	347 (2.6)	1885 (1.4)	1.9 (1.7–2.1)
Second solid tumour (non-metastatic)	327 (2.4)	2357 (1.8)	1.4 (1.2–1.6)
Diabetes with chronic complication	239 (1.8)	1758 (1.3)	1.4 (1.2–1.6)
Rheumatic disease	192 (1.4)	1066 (0.8)	1.8 (1.6–2.1)
Diabetes without chronic complication	107 (0.8)	502 (0.4)	2.1 (1.7–2.6)
Renal disease	77 (0.6)	708 (0.5)	1.1 (0.9–1.4)
Metastatic solid tumour	52 (0.4)	241 (0.2)	2.2 (1.6–2.9)
Myocardial infarction	46 (0.3)	338 (0.3)	1.4 (1.0–1.9)
Hemiplegia or paraplegia	39 (0.3)	138 (0.1)	2.8 (2.0–4.0)
Lymphoma/multiple myeloma	25 (0.2)	174 (0.1)	1.4 (0.9–2.2)
Dementia	13 (0.1)	15 (<0.1)	8.7 (4.1–18.2)
Leukaemia	9 (0.1)	97 (0.1)	0.9 (0.5–1.8)
Moderate or severe liver disease	7 (0.1)	54 (<0.1)	1.3 (0.6–2.8)
Other chronic diseases			
Pain	4598 (34.3)	27,452 (20.5)	2.0 (2.0–2.1)
Psychiatric diseases except depression	4084 (30.4)	5691 (4.2)	9.9 (9.4–10.3)
Sleep disorders	3128 (23.3)	5462 (4.1)	7.2 (6.8–7.5)
Chronic gastritis	2349 (17.5)	12,568 (9.4)	2.1 (2.0–2.2)
Dyslipidaemia	2286 (17.0)	17,438 (13.0)	1.4 (1.3–1.4)
Headache	2129 (15.9)	8634 (6.4)	2.7 (2.6–2.9)
Hypertensive disease	1987 (14.8)	15,052 (11.2)	1.4 (1.3–1.4)
Asthma	1861 (13.9)	12,923 (9.6)	1.5 (1.4–1.6)
Dizziness	1309 (9.8)	4345 (3.2)	3.2 (3.0–3.4)
Arthritis	729 (5.4)	5217 (3.9)	1.4 (1.3–1.5)
Osteoarthritis	654 (4.9)	4290 (3.2)	1.6 (1.4–1.7)
Atopic dermatitis	608 (4.5)	5984 (4.5)	1.0 (0.9–1.1)
Irritable bowel syndrome	588 (4.4)	1900 (1.4)	3.2 (2.9–3.5)
Thyroid disease	551 (4.1)	3394 (2.5)	1.7 (1.5–1.8)
Autonomic nerve imbalance	409 (3.0)	647 (0.5)	6.5 (5.7–7.4)

Disease	Case group N=13,420	Matched control group N=134,200	Odds ratio (95% CI)
Angina pectoris	405 (3.0)	2058 (1.5)	2.0 (1.8–2.2)
Osteoporosis	226 (1.7)	1611 (1.2)	1.4 (1.2–1.6)
Epilepsy	177 (1.3)	729 (0.5)	2.4 (2.1–2.9)
Chronic enteritis	153 (1.1)	561 (0.4)	2.7 (2.3–3.3)
Obesity	74 (0.6)	513 (0.4)	1.4 (1.1–1.8)
Attention deficit hyperkinetic disorders	56 (0.4)	46 (<0.1)	12.2 (8.3–18.1)
Parkinson's disease	24 (0.2)	76 (0.1)	3.2 (2.0–5.0)

The prevalence of CCI-related diseases and other chronic diseases in the 12 months before the index date in the case group and matched control group is shown ranked by prevalence in the case group. Data are n (%), unless otherwise noted.
CCI, Charlson comorbidity index; CI, confidence interval.

Table 3 Prevalence of pre-existing diseases in the case group and matched control group by ICD-10 block

ICD-10 block	ICD-10 block name	Case group N=13,420	Matched control group N=134,200	Odds ratio (95% CI)
A00–B99	Certain infectious and parasitic diseases	4583 (34.2)	33,852 (25.2)	1.5 (1.5–1.6)
C00–D48	Neoplasms	1575 (11.7)	12,007 (8.9)	1.4 (1.3–1.4)
D50–D89	Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	1041 (7.8)	7612 (5.7)	1.4 (1.3–1.5)
E00–E90	Endocrine, nutritional, and metabolic diseases	4477 (33.4)	32,630 (24.3)	1.6 (1.5–1.6)
F00–F99	Mental and behavioural disorders	4084 (30.4)	5691 (4.2)	9.9 (9.4–10.3)
G00–G99	Diseases of the nervous system	4965 (37.0)	14,847 (11.1)	4.7 (4.5–4.9)
H00–H59	Diseases of the eye and adnexa	5035 (37.5)	46,365 (34.5)	1.1 (1.1–1.2)
H60–H95	Diseases of the ear and mastoid process	1735 (12.9)	10,245 (7.6)	1.8 (1.7–1.9)
I00–I99	Diseases of the circulatory system	3038 (22.6)	20,545 (15.3)	1.6 (1.6–1.7)
J00–J99	Diseases of the respiratory system	9232 (68.8)	77,686 (57.9)	1.6 (1.5–1.7)
K00–K93	Diseases of the digestive system	7015 (52.3)	47,838 (35.6)	2.0 (1.9–2.0)
L00–L99	Diseases of the skin and subcutaneous tissue	4428 (33.0)	37,648 (28.1)	1.3 (1.2–1.3)
M00–M99	Diseases of the musculoskeletal system and connective tissue	5322 (39.7)	35,387 (26.4)	1.8 (1.8–1.9)
N00–N99	Diseases of the genitourinary system	2880 (21.5)	20,016 (14.9)	1.6 (1.5–1.6)
O00–O99	Pregnancy, childbirth, and the puerperium	178 (1.3)	2944 (2.2)	0.6 (0.5–0.7)
P00–P96	Certain conditions originating in the perinatal period	19 (0.1)	212 (0.2)	0.9 (0.6–1.4)
Q00–Q99	Congenital malformations, deformations, and chromosomal abnormalities	199 (1.5)	1496 (1.1)	1.3 (1.2–1.5)
R00–R99	Symptoms, signs, and abnormal clinical and laboratory findings, not elsewhere classified	5241 (39.1)	28,989 (21.6)	2.3 (2.2–2.4)
S00–T98	Injury, poisoning, and certain other consequences of external causes	2209 (16.5)	17,661 (13.2)	1.3 (1.2–1.4)
Z00–Z99	Factors influencing health status and contact with health services	252 (1.9)	1878 (1.4)	1.3 (1.2–1.5)
U00–U99	Codes for special purposes	0 (0)	1 (<0.1)	NE

Data are n (%), unless otherwise noted.

CI, confidence interval; ICD-10, International Statistical Classification of Diseases and Related Health Problems, 10th revision; NE, not estimable.

ICD-10 blocks

At the level of ICD-10 blocks, the prevalence of most pre-existing diseases in the year before MDD diagnosis was slightly higher (OR 1.1–2.0) in the case group than in the control group (**table 3**). Exceptions were blocks O00–O99 and P00–P96, which are associated with pregnancy and/or childbirth. However, the prevalence rates of mental and behavioural disorders (F00–F99) and diseases of the nervous system (G00–G99) were markedly higher in the case group, with ORs of 9.9 and 4.7, respectively. Among diseases of the circulatory system (I00–I99), respiratory system (J00–J99), and digestive system (K00–K93), the OR for digestive diseases was the highest (2.0 for digestive versus 1.6 for circulatory and respiratory). The OR for diseases of the eye and adnexa (H00–H59) was low (1.1), whereas the OR for diseases of the ear and mastoid process (H60–H95) was relatively high (1.8).

ICD-10 codes

As with the ICD-10 blocks, the prevalence of almost all pre-existing diseases based on three- or four-character ICD-10 codes in the year before MDD diagnosis was slightly higher in the case group than in the control group (**figure**; online supplemental table 2). The highest ORs for the onset of MDD were observed for psychiatric diseases and sleep disorders (**figure**). ORs >5 were seen for adjustment disorders, panic disorder, anxiety disorder, depressive neurosis, neurosis, insomnia, psychosomatic disorder, anxiety, sleeping disorder, autonomic ataxia, and palpitations. Of these comorbidities, insomnia and neurosis were particularly prevalent in the case group (21.1% and 9.7% of patients, respectively).

Multivariate analysis

A post hoc multivariate analysis indicated that the odds of developing MDD were lower in women than in men, in patients ≥40 years than in younger patients, and in non-workers than in workers (**table 4**). The odds of MDD also increased in subgroups with lifestyle diseases, psychiatric disorders, and/or MDD-related symptoms, relative to 84,763 individuals without any of these diseases (online supplemental table 3). The highest ORs (>10) were seen in

subgroups with psychiatric disorders. The odds of MDD increased significantly in subgroups with both MDD-related symptoms and lifestyle disease and/or psychiatric disorder. However, the odds of MDD decreased significantly in subgroups with both lifestyle diseases and psychiatric disorders (with or without MDD-related symptoms).

Table 4 Multivariate logistic regression analysis for the onset of MDD

Dependent variable	Explanatory variable	Reference	Category			Odds ratio (95% CI)
Group (reference = control group)	Sex	Male	Female			0.93 (0.89–0.98)
	Age	<40 years	≥40 years			0.80 (0.77–0.83)
	Working status	Worker	Non-worker			0.92 (0.86–0.97)
	Presence of lifestyle disease, psychiatric disorder, and/or MDD-related symptoms during the 12 months before index date	None	Lifestyle disease	Psychiatric disorder	MDD-related symptoms	
			No	No	Yes	1.81 (1.71–1.91)
			No	Yes	No	10.22 (9.58–10.91)
			No	Yes	Yes	13.47 (12.54–14.47)
			Yes	No	No	1.14 (1.06–1.23)
			Yes	No	Yes	2.27 (2.10–2.46)
			Yes	Yes	No	7.27 (6.61–7.99)
			Yes	Yes	Yes	11.49 (10.63–12.41)

'Lifestyle diseases' included diabetes, hypertension, and dyslipidaemia; 'psychiatric disorders' included sleep disorders and psychiatric diseases other than depression; 'MDD-related symptoms' included headache, pain, and autonomic nerve imbalance (online supplemental table 1).
CI, confidence interval; MDD, major depressive disorder.

DISCUSSION

This is the first nested case-control study to demonstrate that a broad range of pre-existing diseases are more prevalent in people who develop MDD than in those who do not. These results indicate that most patients have complex health conditions before starting treatment for MDD. The highest ORs were seen for sleep disorders and psychiatric diseases other than depression, which were also among the most prevalent pre-existing diseases in the case group. Other common diseases that were more prevalent in the case group included pain, headache, autonomic disturbances, gastrointestinal diseases, and lifestyle diseases, such as dyslipidaemia, hypertension, and diabetes.

Our results support and extend the results of previous studies reporting a high prevalence of pre-existing or comorbid diseases in patients with depression. Most previous studies have been cross-sectional or small case-control studies focused on specific comorbid diseases.[2 3 12-15] Two large case-control studies conducted in the United States, using electronic health records at the Mayo Clinic,[16] and South Korea, using the National Health Insurance Service,[17] identified pre-existing chronic physical conditions that were risk factors for the development of MDD. However, these studies focused on a smaller number (24 and 19) of specific chronic conditions compared with our study, which examined a broad range of both chronic and acute conditions.

Stress, such as diagnosis with a chronic or serious disease, can contribute to the development of MDD in vulnerable individuals.[18] Further, stress can lead to psychological and physiological changes that affect both mental and physical health, and may contribute directly to depression.[19] Psychiatric disorders can be particularly stressful and may increase the chances of MDD. Depression is often comorbid with other mental disorders, particularly anxiety, and may share symptoms and underlying aetiologies.[20-23] Stress is also associated with many gastrointestinal disorders,[24] such as irritable bowel syndrome, which were twice as prevalent in the case group than in the control group.

Depression-related symptoms (sleep disorders, pain, autonomic imbalance) may be diagnosed in advance of MDD and therefore may be prodromal symptoms of MDD.[25] Somatic symptoms of MDD, such as fatigue, appetite loss, pain (especially headache), dizziness, and sleep disturbance, can be non-specific and may be attributed to physical illness.[4] Doctors may first diagnose another disorder instead of MDD to avoid the stigma sometimes associated with depression in Japan.[6] In addition, diagnoses based on relatively vague symptoms may be made for insurance purposes, eg, to permit subsidised prescriptions. MDD may only be diagnosed later, when symptoms worsen or other depression-related symptoms occur. Indeed, a significant proportion of patients with MDD present with only somatic symptoms.[26] One reason is denial of psychological symptoms, which is particularly prevalent in Japan.[26] These results support the idea that depression is under-recognised when patients first seek medical help in Japan, and also support our findings that digestive diseases, sleep disorders, and other somatic symptoms, including in the otological area (eg, dizziness), were highly prevalent in patients who later developed MDD. Interestingly, we observed that the OR for diseases of the ear and mastoid process was higher than for diseases of the eye and adnexa (1.8 versus 1.1). We suggest that physicians in otolaryngology departments may be aware of the link between somatic symptoms and MDD and consider psychological evaluation for patients with such symptoms. In contrast, physicians in ophthalmology departments may need to pay more attention to the risk of MDD in patients with severe visual dysfunction because both hearing loss and vision loss are associated with the development of depression.[27]

Our multivariate analysis indicated that the odds of an MDD diagnosis were significantly increased in patients who had depression-related symptoms (headache, pain, autonomic imbalance), particularly if the patient also had a sleep/psychiatric disorder or lifestyle disease. Interestingly, the odds of MDD decreased significantly in subgroups with lifestyle diseases in addition to psychiatric disorders. Although the reason for this finding is unclear, it

may be that these patients are managed by multiple physicians who focus on treating each disease separately (eg, psychiatrist treating psychiatric diseases; general practitioner treating lifestyle diseases), with the result that MDD is not sufficiently recognised. Indeed, some general practitioners and other non-psychiatrist doctors in Japan fail to recognise or are reluctant to treat MDD,[28 29] which may contribute to underdiagnosis of MDD in patients with lifestyle diseases. Psychiatrists, on the other hand, may underestimate somatic depressive symptoms in patients they are treating for another mental illness who also have a lifestyle-related illness treated by another doctor, considering fatigue and autonomic dysfunction as caused by the physical illness. However, depression is known to lead to treatment non-adherence in patients with diabetes,[30] which increases the risk of severe complications.[31] In addition, treating lifestyle-related diseases and depression simultaneously may provide patients with better clinical outcomes.[32] Further research is needed on the unmet needs for the diagnosis and treatment of depression in patients with presymptomatic depression in addition to lifestyle-related diseases, and on the effects of coordinated care management of multiple conditions.

Many comorbidities may share underlying biological mechanisms with MDD. For example, inflammatory mechanisms play a role in the aetiology of many diseases, including diabetes, cardiovascular disease, arthritis, and asthma, as well as depression.[33-35] Neural pathways and neurotransmitters that are altered in chronic pain may also affect mood, including depression.[36] Migraine and depression can both be related to specific genetic variants and/or neuroanatomic features.[37] Most of these biological mechanisms are exacerbated by stress.[3 34 37] Thus, MDD may develop in parallel with certain diseases, but its diagnosis may be delayed compared with physical disease.

Strengths and limitations

Our study is strengthened by the use of a health insurance database consisting of mostly working-age people, which resulted in a sample size large enough to allow examination of a

broad range of pre-existing diseases. The nested case-control design and the use of a database minimised selection and recall biases that may occur in other case-control studies. We used a strict definition of MDD onset, which required a 1-year depression-free period and the diagnosis for inclusion to be recorded on at least three doctor visits within 90 days; this definition increased our certainty that case patients had true, newly diagnosed MDD.

Despite these strengths, some caveats do apply when interpreting our results. For example, our data set did not include an older population aged ≥75 years. Patients with chronic diseases are likely to visit their physicians frequently, increasing the opportunity for detection and diagnosis of MDD. Further, patients with pre-existing psychiatric disorders are likely to be treated by psychiatrists, who may be better at diagnosing MDD than other physicians, which might lead to higher ORs for psychiatric diseases than for physical diseases; however, MDD diagnosis by general practitioners is also higher in patients with psychiatric comorbidity than in those with physical comorbidity.[38] Nevertheless, MDD is often under-recognised and underdiagnosed, and this is probably even more true in patients with chronic disease as physicians focus on the disease and may attribute non-specific symptoms to the physical illness.[39] We only assessed disease prevalence, and not incidence, during the year before the inclusion year; therefore, we do not know if the disease was diagnosed during that year or in a previous year. This limitation could potentially result in a disproportionate number of people in the control group who had longer-term diseases and were not vulnerable to MDD. For some high-stress diseases such as cancer or stroke, MDD often occurs soon after diagnosis[40 41]; hence, less vulnerable patients who did not develop MDD would have remained within the control group, leading to lower ORs for those diseases than might be expected. Although comparing ORs for the onset of MDD across a broad range of pre-existing diseases can help develop hypotheses regarding possible underlying mechanisms, the risk of MDD occurring in specific diseases should be investigated on an individual basis.

CONCLUSIONS

This large, nested case-control study has documented the high prevalence of pre-existing diseases in Japanese patients with MDD compared with matched controls without MDD. The high prevalence of pre-existing diseases in patients who develop MDD reflects the complex relationship between physical and mental disorders and indicates a high medical burden for these patients. These results confirm that patients with chronic and/or serious diseases should be monitored for depressive symptoms, and pre-existing diseases should be taken into consideration when prescribing treatment for MDD.

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Author contributions

All authors participated in the study design and interpretation of the study results, and in the drafting, critical revision, and approval of the final version of the manuscript. Dr Mishiro conducted the statistical analysis.

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Data availability statement

The data that support the findings of this study are available from JMDC Inc. but were used under licence for the current study; therefore, restrictions apply and the data are not publicly available. For inquiries about access to the data set used in this study, please contact JMDC (https://www.jmdc.co.jp).

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

Dr Cho reports grants from Shionogi & Co., Ltd. and Otsuka Pharmaceutical Co., Ltd., and personal fees from Shionogi & Co., Ltd., Otsuka Pharmaceutical Co., Ltd., Eli Lilly Japan K.K., Kyowa Kirin Co. Ltd., Pfizer Japan Inc., Meiji Seika Pharma Co., Ltd., Mitsubishi Tanabe Pharma Corporation, Sumitomo Dainippon Pharma Co., Ltd., Astellas Pharma Inc., MSD K.K., Takeda Pharmaceutical Company Limited, and Lundbeck Japan K.K., outside the submitted work. Drs Mishiro, Akaki, Akimoto, and Fujikawa report personal fees from Takeda Pharmaceutical Company Limited, outside the submitted work.

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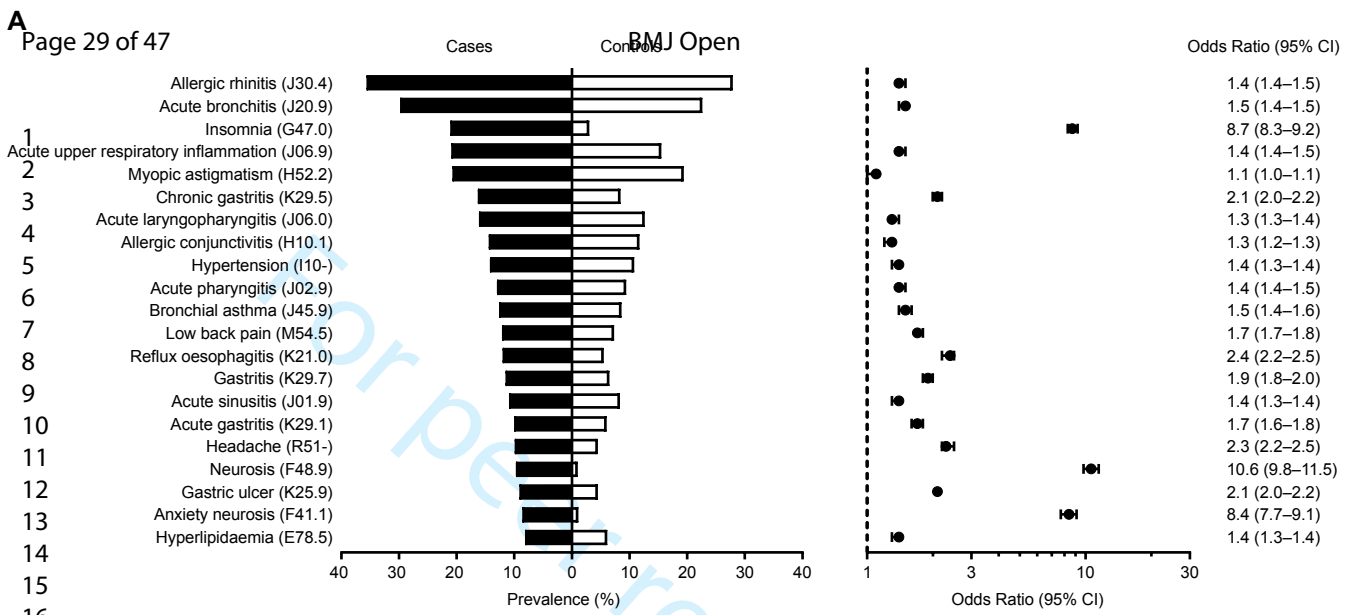
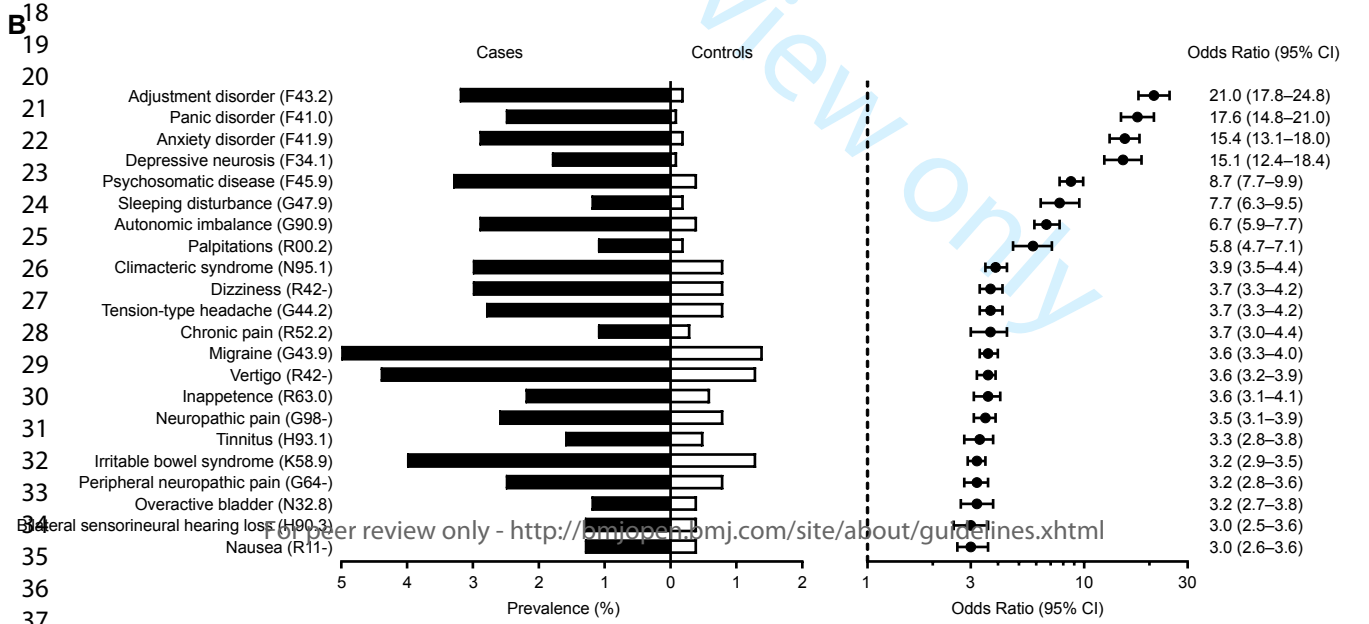
FIGURE LEGEND

Figure A, Diseases with prevalence >8% in the case group in the 12 months before MDD diagnosis. B, Diseases with odds ratio >3.0. Shown are the prevalence rates in the case group and in the matched control group, as well as the odds ratio (95% CI). CI, confidence interval; MDD, major depressive disorder.





Supplemental Material

TITLE

Diseases prevalent before major depressive disorder diagnosis: a nested case-control study using health insurance–based claims data

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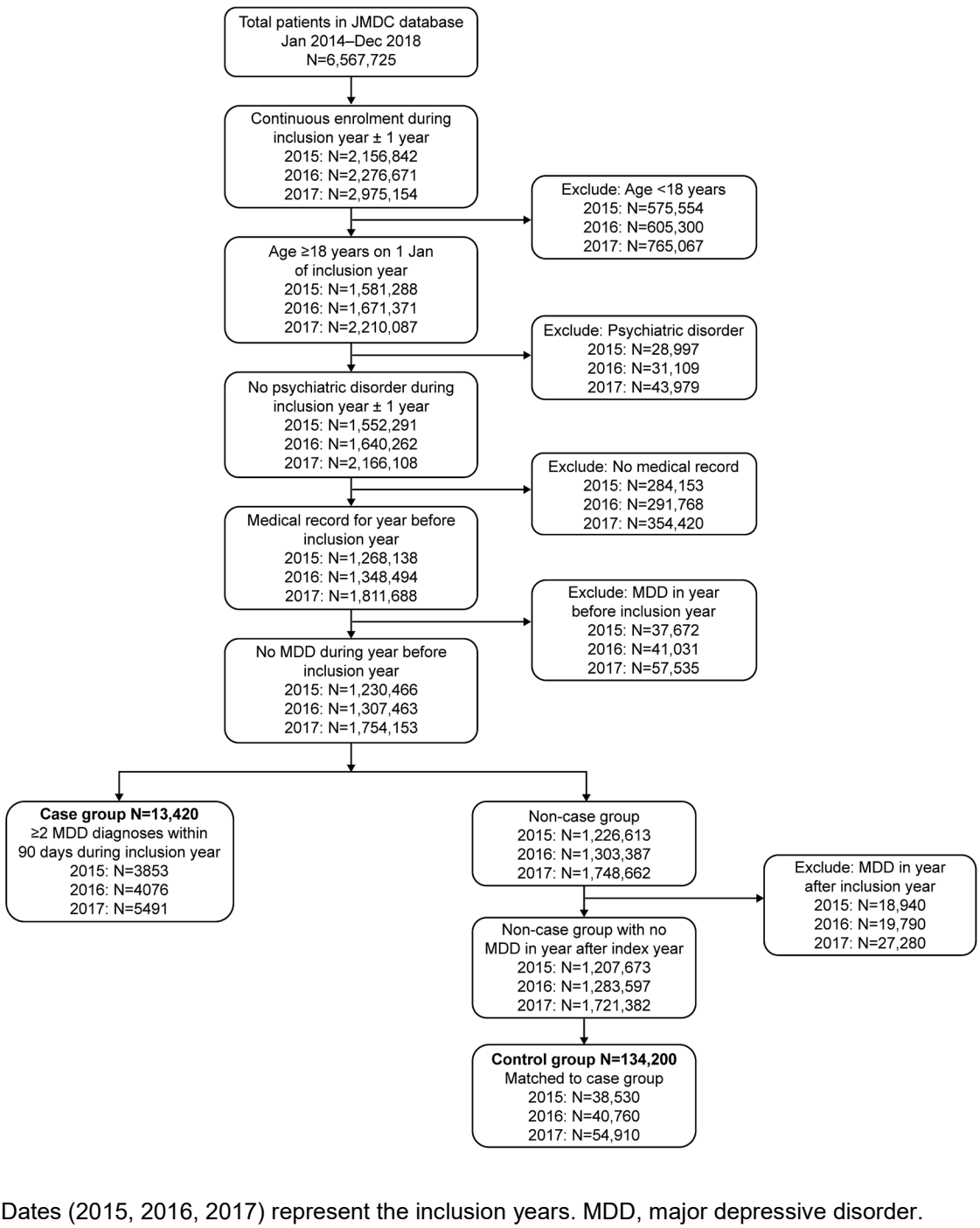
Supplemental figure Flow diagram of patients included in the case group and matched control group. Dates (2015, 2016, 2017) represent the inclusion years. MDD, major depressive disorder.

Supplemental table 1 ICD-10 codes and other terms used to identify pre-existing diseases

Supplemental table 2 Prevalence of diseases in the 12 months before the index date by ICD-10 code, ICD-10 name, and standard disease name in the case group and matched control group, ranked by prevalence in the case group

Supplemental table 3 Number of patients in post hoc multivariate analysis subgroups

Supplemental figure Flow diagram of patients included in the case group and matched control group.



Dates (2015, 2016, 2017) represent the inclusion years. MDD, major depressive disorder.

Supplemental table 1 ICD-10 codes and other terms used to identify pre-existing diseases

Disease	ICD-10 codes and other terms
CCI-related diseases	
Myocardial infarction	I21, I22, I25.2
Cardiac failure, congestive	I43, I50, I09.9, I11.0, I25.5, I42.0, I42.5, I42.6, I42.7, I42.8, I42.9, I13.0, I13.2, P29.0
Peripheral vascular disease	I70, I71, I73.1, I73.8, I73.9, I77.1, K55.1, K55.9, Z95.8, I79.0, I79.2, K55.8, Z95.9
Cerebrovascular disease	G45, G46, I60–I69, H34.0, I72.0, I72.5, I72.6
Dementia	F00, F01, F02, F03, G30, F05.1, G31.1
Chronic lung disease (excluding asthma)	J40–J47, J60–J67, I27.8, I27.9, J68.4, J70.1, J70.3
Rheumatic disease	M05–M06, M32–M34, M31.5, M35.1, M35.3, M36.0
Peptic ulcer disease	K25–K28
Mild liver disease	B18, K73–K74, K70.0–K70.3, K70.9, K71.3, K71.4, K71.5, K71.7, K76.0, K76.2, K76.3, K76.4, K76.8, K76.9, Z94.4, K75.8
Diabetes mellitus without complications	E10.0, E10.1, E10.9, E11.0, E11.1, E11.9, E12.0, E12.1, E12.9, E13.0, E13.1, E13.9, E14.0, E14.1, E14.9
Diabetes mellitus with complications	E10.2–E10.8, E11.2, E11.3–E11.8, E12.2–E12.8, E13.2–E13.8, E14.2–E14.8
Hemiplegia or paraplegia	G81, G82, G041, G11.4, G80.1, G80.2, G83.9, G83.0–G83.4
Renal disease	N18, N19, I12.0, I13.1, N03.2–N03.7, N05.2–N05.7, N25.0, Z49.0–Z49.2, Z94.0, Z99.2
Solid tumours without metastasis	C00–C76, C80, C97
Leukaemia	C91–C96, D47.1, D47.5
Malignant lymphoma and multiple myeloma	C81–C90
Moderate or severe liver disease	I85.0, I85.9, I86.4, I98.2, K70.4, K71.1, K72.1, K72.9, K76.5–K76.7
Metastatic cancer	C77–C79
Other chronic diseases	
Angina pectoris	I20, Post-infarction angina pectoris
Dyslipidaemia (hyperlipidaemia)	E78.0–E78.2, E78.4, E78.5
Hypertensive disease	I10
Obesity	E65, E66
Atopic dermatitis	L20
Asthma	J45, J46
Thyroid disease	E01–E06, E07.0, E07.8, E07.9
Osteoarthritis	M05, M06 Other disease name with ‘osteoarthritis’
Arthritis	M00–M03, M05–M14 Other disease name with ‘arthritis’
Epilepsy	G40, G41
Headache	G43, G44, R51
Osteoporosis	M80, M81

Disease	ICD-10 codes and other terms
Parkinsonism	G20, G21
Pain	B02, F45.4, G50–G59, G64, G98, M25, M43, M45–M49, M50–M54, M79.1, M79.2, M79.6, M79.7, M89.0, R52 Diabetic neuropathic pain
Irritable bowel syndrome	K58
Chronic gastritis	K29.3, K29.4, K29.5
Chronic enteritis	K52.9
Dizziness	R42, H81, I95.1 Epidemic dizziness, psychogenic dizziness, low-tone dizziness
Autonomic nerve imbalance	G90
Attention deficit hyperactivity disorder	F90
Psychiatric disorders other than depression	F00–F99* *Except F00–F09, F20–F29, F30–F33
Sleep disorders	G47
Lifestyle diseases	
Diabetes mellitus without complications	E10.0, E10.1, E10.9, E11.0, E11.1, E11.9, E12.0, E12.1, E12.9, E13.0, E13.1, E13.9, E14.0, E14.1, E14.9
Diabetes mellitus with complications	E10.2–E10.8, E11.2–E11.8, E12.2–E12.8, E13.2–E13.8, E14.2–E14.8
Dyslipidaemia (hyperlipidaemia)	E78.0–E78.2, E78.4, E78.5
Hypertensive disease	I10
Psychiatric disorders	
Psychiatric disorders other than depression	F00–F99* *Except F00–F09, F20–F29, F30–F33
Sleep disorders	G47
MDD-related symptoms	
Headache	G43, G44, R51
Pain	B02, F45.4, G50–G59, G64, G98, M25, M43, M45–M49, M50–M54, M79.1, M79.2, M79.6, M79.7, M89.0, R52 Diabetic neuropathic pain
Autonomic nerve imbalance	G90

CCI, Charlson comorbidity index; ICD-10, International Statistical Classification of Diseases and Related Health Problems, 10th revision; MDD, major depressive disorder.

Supplemental table 2 Prevalence of diseases in the 12 months before the index date by ICD-10 code, ICD-10 name, and standard disease name in the case group and matched control group, ranked by prevalence in the case group

ICD-10 level 4 code	ICD-10 level 4 name	Standard disease name	Case group N=134,420	Control group N=134,200	Odds ratio (95% CI)
J30.4	Allergic rhinitis, unspecified	Allergic rhinitis	4782 (35.6)	37,507 (27.9)	1.4 (1.4–1.5)
J20.9	Acute bronchitis, unspecified	Acute bronchitis	4005 (29.8)	30,359 (22.6)	1.5 (1.4–1.5)
G47.0	Disorders of initiating and maintaining sleep [insomnias]	Insomnia	2836 (21.1)	4010 (3.0)	8.7 (8.3–9.2)
J06.9	Acute upper respiratory infection, unspecified	Acute infection of upper respiratory tract	2807 (20.9)	20,738 (15.5)	1.4 (1.4–1.5)
H52.2	Astigmatism	Myopic astigmatism	2784 (20.7)	26,090 (19.4)	1.1 (1.0–1.1)
K29.5	Chronic gastritis, unspecified	Chronic gastritis	2189 (16.3)	11,246 (8.4)	2.1 (2.0–2.2)
J06.0	Acute laryngopharyngitis	Acute laryngopharyngitis	2156 (16.1)	16,963 (12.6)	1.3 (1.3–1.4)
H10.1	Acute atopic conjunctivitis	Allergic conjunctivitis	1928 (14.4)	15,748 (11.7)	1.3 (1.2–1.3)
I10-	Essential (primary) hypertension	Hypertension	1903 (14.2)	14,477 (10.8)	1.4 (1.3–1.4)
J02.9	Acute pharyngitis, unspecified	Acute pharyngitis	1740 (13.0)	12,573 (9.4)	1.4 (1.4–1.5)
J45.9	Asthma, unspecified	Bronchial asthma	1689 (12.6)	11,547 (8.6)	1.5 (1.4–1.6)
M54.5	Low back pain	Low back pain	1628 (12.1)	9821 (7.3)	1.7 (1.7–1.8)
K21.0	Gastro-oesophageal reflux disease with oesophagitis	Reflux oesophagitis	1607 (12.0)	7322 (5.5)	2.4 (2.2–2.5)
K29.7	Gastritis, unspecified	Gastritis	1547 (11.5)	8762 (6.5)	1.9 (1.8–2.0)
J01.9	Acute sinusitis, unspecified	Acute sinusitis	1468 (10.9)	11,115 (8.3)	1.4 (1.3–1.4)
K29.1	Other acute gastritis	Acute gastritis	1342	8075	1.7

ICD-10 level 4 code	ICD-10 level 4 name	Standard disease name	Case group N=13,420	Control group N=134,200	Odds ratio (95% CI)
			(10.0)	(6.0)	(1.6–1.8)
R51-	Headache	Headache	1332 (9.9)	6046 (4.5)	2.3 (2.2–2.5)
F48.9	Neurotic disorder, unspecified	Neurosis	1306 (9.7)	1350 (1.0)	10.6 (9.8–11.5)
K25.9	Gastric ulcer/Unspecified as acute or chronic, without haemorrhage or perforation	Gastric ulcer	1216 (9.1)	6086 (4.5)	2.1 (2.0–2.2)
F41.1	Generalised anxiety disorder	Anxiety neurosis	1155 (8.6)	1492 (1.1)	8.4 (7.7–9.1)
E78.5	Hyperlipidaemia, unspecified	Hyperlipidaemia	1091 (8.1)	8244 (6.1)	1.4 (1.3–1.4)
J02.9	Acute pharyngitis, unspecified	Pharyngitis	1061 (7.9)	7940 (5.9)	1.4 (1.3–1.5)
L30.9	Dermatitis, unspecified	Eczema	1032 (7.7)	7799 (5.8)	1.4 (1.3–1.4)
K59.0	Constipation	Constipation	1030 (7.7)	6014 (4.5)	1.8 (1.7–1.9)
E86-	Volume depletion	Dehydration	1003 (7.5)	4825 (3.6)	2.2 (2.0–2.3)
E78.0	Pure hypercholesterolaemia	Hypercholesterolaemia	940 (7.0)	7031 (5.2)	1.4 (1.3–1.5)
R11-	Nausea and vomiting	Vomition	933 (7.0)	4031 (3.0)	2.4 (2.2–2.6)
M53.1	Cervicobrachial syndrome	Cervico-omo-brachial syndrome	905 (6.7)	3380 (2.5)	2.8 (2.6–3.0)
J00-	Acute nasopharyngitis [common cold]	Common cold	894 (6.7)	5998 (4.5)	1.5 (1.4–1.6)
A09.9	Gastroenteritis and colitis of unspecified origin	Acute gastroenteritis	873 (6.5)	5140 (3.8)	1.7 (1.6–1.9)
E14-	Unspecified diabetes mellitus	Diabetes mellitus	870 (6.5)	6285 (4.7)	1.4 (1.3–1.5)
J32.9	Chronic sinusitis, unspecified	Chronic sinusitis	818 (6.1)	5551 (4.1)	1.5 (1.4–1.6)
A09.9	Gastroenteritis and colitis of unspecified origin	Diarrhoea	781 (5.8)	4311 (3.2)	1.9 (1.7–2.0)

ICD-10 level 4 code	ICD-10 level 4 name	Standard disease name	Case group N=13,420	Control group N=134,200	Odds ratio (95% CI)
G62.9	Polyneuropathy, unspecified	Peripheral neuropathy	775 (5.8)	3374 (2.5)	2.4 (2.2–2.6)
J40-	Bronchitis, not specified as acute or chronic	Bronchitis	716 (5.3)	5644 (4.2)	1.3 (1.2–1.4)
E79.0	Hyperuricaemia without signs of inflammatory arthritis and tophaceous disease	Hyperuricaemia	700 (5.2)	5880 (4.4)	1.2 (1.1–1.3)
G43.9	Migraine, unspecified	Migraine	669 (5.0)	1917 (1.4)	3.6 (3.3–4.0)
H04.1	Other disorders of lacrimal gland	Dry eye	663 (4.9)	4312 (3.2)	1.6 (1.4–1.7)
D50.9	Iron deficiency anaemia, unspecified	Iron deficiency anaemia	650 (4.8)	4957 (3.7)	1.3 (1.2–1.4)
E78.5	Hyperlipidaemia, unspecified	Dyslipidaemia	646 (4.8)	4684 (3.5)	1.4 (1.3–1.5)
H10.9	Conjunctivitis, unspecified	Conjunctivitis	644 (4.8)	5118 (3.8)	1.3 (1.2–1.4)
H52.1	Myopia	Myopia	636 (4.7)	6292 (4.7)	1.0 (0.9–1.1)
J10.1	Influenza with other respiratory manifestations, seasonal influenza virus identified	Human influenza A	613 (4.6)	5585 (4.2)	1.1 (1.0–1.2)
M75.0	Adhesive capsulitis of shoulder	Periarthritis scapulohumeralis	605 (4.5)	3523 (2.6)	1.8 (1.6–1.9)
L20.9	Atopic dermatitis, unspecified	Atopic dermatitis	601 (4.5)	5924 (4.4)	1.0 (0.9–1.1)
L85.3	Xerosis cutis	Xerosis	596 (4.4)	4954 (3.7)	1.2 (1.1–1.3)
R42-	Dizziness and giddiness	Vertigo	585 (4.4)	1701 (1.3)	3.6 (3.2–3.9)
K76.9	Liver disease, unspecified	Hepatic dysfunction	571 (4.3)	3458 (2.6)	1.7 (1.5–1.8)
K58.9	Irritable bowel syndrome without diarrhoea	Irritable bowel syndrome	539 (4.0)	1756 (1.3)	3.2 (2.9–3.5)

ICD-10 level 4 code	ICD-10 level 4 name	Standard disease name	Case group N=13,420	Control group N=134,200	Odds ratio (95% CI)
K76.0	Fatty (change of) liver, not elsewhere classified	Hepatic steatosis	537 (4.0)	3564 (2.7)	1.5 (1.4–1.7)
J11.1	Influenza with other respiratory manifestations, virus not identified	Influenza	529 (3.9)	4256 (3.2)	1.3 (1.1–1.4)
L50.9	Urticaria, unspecified	Urticaria	524 (3.9)	3755 (2.8)	1.4 (1.3–1.5)
L85.3	Xerosis cutis	Asteatotic eczema	511 (3.8)	4328 (3.2)	1.2 (1.1–1.3)
M47.8	Other spondylosis	Cervical spondylosis	505 (3.8)	2012 (1.5)	2.6 (2.3–2.8)
J03.9	Acute tonsillitis, unspecified	Acute tonsillitis	495 (3.7)	3922 (2.9)	1.3 (1.2–1.4)
A09.9	Gastroenteritis and colitis of unspecified origin	Acute enteritis	481 (3.6)	2707 (2.0)	1.8 (1.6–2.0)
K21.0	Gastro-oesophageal reflux disease with oesophagitis	Refractory reflux oesophagitis requiring maintenance therapy	477 (3.6)	1989 (1.5)	2.4 (2.2–2.7)
E28.3	Primary ovarian failure	Ovarian insufficiency	470 (3.5)	3125 (2.3)	1.5 (1.4–1.7)
N86-	Erosion and ectropion of cervix uteri	Uterovaginal erosion	452 (3.4)	3170 (2.4)	1.4 (1.3–1.6)
A09.0	Other and unspecified gastroenteritis and colitis of infectious origin	Infectious gastroenteritis	449 (3.3)	2964 (2.2)	1.5 (1.4–1.7)
J06.0	Acute laryngopharyngitis	Laryngopharyngitis	447 (3.3)	3059 (2.3)	1.5 (1.3–1.6)
M51.9	Intervertebral disc disorder, unspecified	Lumbar vertebral discopathy	440 (3.3)	2565 (1.9)	1.7 (1.6–1.9)
F45.9	Somatoform disorder, unspecified	Psychosomatic disease	437 (3.3)	515 (0.4)	8.7 (7.7–9.9)
F43.2	Adjustment disorders	Adjustment disorder	427 (3.2)	210 (0.2)	21.0 (17.8–24.8)
J03.9	Acute tonsillitis, unspecified	Tonsillitis	413 (3.1)	2958 (2.2)	1.4 (1.3–1.6)
H52.4	Presbyopia	Presbyopia	408 (3.0)	2977 (2.2)	1.4 (1.2–1.5)

ICD-10 level 4 code	ICD-10 level 4 name	Standard disease name	Case group N=13,420	Control group N=134,200	Odds ratio (95% CI)
R42-	Dizziness and giddiness	Dizziness	407 (3.0)	1113 (0.8)	3.7 (3.3–4.2)
N95.1	Menopausal and female climacteric states	Climacteric syndrome	399 (3.0)	1050 (0.8)	3.9 (3.5–4.4)
F41.9	Anxiety disorder, unspecified	Anxiety disorder	387 (2.9)	259 (0.2)	15.4 (13.1–18.0)
G90.9	Disorder of autonomic nervous system, unspecified	Autonomic imbalance	385 (2.9)	585 (0.4)	6.7 (5.9–7.7)
L25.9	Unspecified contact dermatitis, unspecified cause	Contact dermatitis	376 (2.8)	3018 (2.2)	1.3 (1.1–1.4)
B35.3	Tinea pedis	Foot tinea	375 (2.8)	3393 (2.5)	1.1 (1.0–1.2)
M51.2	Other specified intervertebral disc displacement	Lumbar disc herniation	375 (2.8)	2106 (1.6)	1.8 (1.6–2.0)
G44.2	Tension-type headache	Tension-type headache	372 (2.8)	1014 (0.8)	3.7 (3.3–4.2)
D25.9	Leiomyoma of uterus, unspecified	Uterus myoma	368 (2.7)	2690 (2.0)	1.4 (1.2–1.5)
H53.1	Subjective visual disturbances	Asthenopia	366 (2.7)	2355 (1.8)	1.6 (1.4–1.8)
E11-	Type 2 diabetes mellitus	Type 2 diabetes mellitus	365 (2.7)	2654 (2.0)	1.4 (1.2–1.5)
M17.9	Gonarthrosis, unspecified	Knee osteoarthritis	355 (2.6)	2589 (1.9)	1.4 (1.2–1.5)
G98-	Other disorders of nervous system, not elsewhere classified	Neuropathic pain	345 (2.6)	1011 (0.8)	3.5 (3.1–3.9)
F41.0	Panic disorder [episodic paroxysmal anxiety]	Panic disorder	341 (2.5)	198 (0.1)	17.6 (14.8–21.0)
A09.0	Other and unspecified gastroenteritis and colitis of infectious origin	Infectious enteritis	340 (2.5)	2222 (1.7)	1.5 (1.4–1.7)
H16.8	Other keratitis	Keratoconjunctivitis sicca	336 (2.5)	2509 (1.9)	1.3 (1.2–1.5)

ICD-10 level 4 code	ICD-10 level 4 name	Standard disease name	Case group N=13,420	Control group N=134,200	Odds ratio (95% CI)
R50.9	Fever, unspecified	Pyrexia	335 (2.5)	2385 (1.8)	1.4 (1.3–1.6)
G64-	Other disorders of peripheral nervous system	Peripheral neuropathic pain	334 (2.5)	1061 (0.8)	3.2 (2.8–3.6)
I20.9	Angina pectoris, unspecified	Angina pectoris	334 (2.5)	1759 (1.3)	1.9 (1.7–2.2)
J04.0	Acute laryngitis	Acute laryngitis	313 (2.3)	2428 (1.8)	1.3 (1.2–1.5)
I49.9	Cardiac arrhythmia, unspecified	Arrhythmia	307 (2.3)	1184 (0.9)	2.6 (2.3–3.0)
H81.0	Ménière disease	Ménière's disease	302 (2.3)	1066 (0.8)	2.9 (2.5–3.3)
K64.9	Haemorrhoids, unspecified	Internal haemorrhoids	300 (2.2)	1856 (1.4)	1.6 (1.4–1.8)
L21.9	Seborrheic dermatitis, unspecified	Seborrheic dermatitis	299 (2.2)	2434 (1.8)	1.2 (1.1–1.4)
J00-	Acute nasopharyngitis [common cold]	Acute rhinitis	295 (2.2)	2089 (1.6)	1.4 (1.3–1.6)
B07-	Viral warts	Verruca vulgaris	294 (2.2)	2660 (2.0)	1.1 (1.0–1.3)
L08.9	Local infection of skin and subcutaneous tissue, unspecified	Cutaneous infection	291 (2.2)	2252 (1.7)	1.3 (1.1–1.5)
N94.6	Dysmenorrhoea, unspecified	Dysmenorrhoea	290 (2.2)	1105 (0.8)	2.7 (2.3–3.0)
R63.0	Anorexia	Inappetence	290 (2.2)	826 (0.6)	3.6 (3.1–4.1)
H61.2	Impacted cerumen	Impacted cerumen	286 (2.1)	2199 (1.6)	1.3 (1.2–1.5)
H60.5	Acute otitis externa, non-infective	External ear eczema	281 (2.1)	2098 (1.6)	1.3 (1.2–1.5)
A49.8	Other bacterial infections of unspecified site	*Helicobacter pylori* infection	277 (2.1)	2222 (1.7)	1.3 (1.1–1.4)
R10.4	Other and unspecified abdominal pain	Abdominal pain	269 (2.0)	1301 (1.0)	2.1 (1.8–2.4)
G47.3	Sleep apnoea	Sleep apnoea syndrome	268 (2.0)	1335 (1.0)	2.0 (1.8–2.3)

ICD-10 level 4 code	ICD-10 level 4 name	Standard disease name	Case group N=13,420	Control group N=134,200	Odds ratio (95% CI)
N30.9	Cystitis, unspecified	Cystitis	264 (2.0)	1564 (1.2)	1.7 (1.5–1.9)
K12.1	Other forms of stomatitis	Stomatitis	262 (2.0)	1669 (1.2)	1.6 (1.4–1.8)
H52.2	Astigmatism	Hyperopic astigmatism	260 (1.9)	1851 (1.4)	1.4 (1.2–1.6)
M79.1	Myalgia	Myalgia	248 (1.8)	1226 (0.9)	2.0 (1.8–2.3)
F34.1	Dysthymia	Depressive neurosis	239 (1.8)	161 (0.1)	15.1 (12.4–18.4)
H40.9	Glaucoma, unspecified	Glaucoma	239 (1.8)	2136 (1.6)	1.1 (1.0–1.3)
H60.9	Otitis externa, unspecified	Otitis externa	239 (1.8)	1932 (1.4)	1.2 (1.1–1.4)
K63.5	Polyp of colon	Colorectal polyp	239 (1.8)	1947 (1.5)	1.2 (1.1–1.4)
A09.9	Gastroenteritis and colitis of unspecified origin	Gastroenteritis	238 (1.8)	1351 (1.0)	1.8 (1.5–2.0)
K21.0	Gastro-oesophageal reflux disease with oesophagitis	Intractable regurgitant oesophagitis	238 (1.8)	1123 (0.8)	2.1 (1.9–2.5)
N76.0	Acute vaginitis	Bacterial vaginitis	232 (1.7)	1569 (1.2)	1.5 (1.3–1.7)
M10.9	Gout, unspecified	Gout	230 (1.7)	1763 (1.3)	1.3 (1.1–1.5)
L30.9	Dermatitis, unspecified	Acute eczema	229 (1.7)	1856 (1.4)	1.2 (1.1–1.4)
H16.0	Corneal ulcer	Corneal erosion	222 (1.7)	1935 (1.4)	1.1 (1.0–1.3)
H93.1	Tinnitus	Tinnitus	217 (1.6)	672 (0.5)	3.3 (2.8–3.8)
D64.9	Anaemia, unspecified	Anaemia	216 (1.6)	1337 (1.0)	1.6 (1.4–1.9)
M47.8	Other spondylosis	Lumbar osteoarthritis	216 (1.6)	1105 (0.8)	2.0 (1.7–2.3)
H01.0	Blepharitis	Blepharitis	215 (1.6)	1665 (1.2)	1.3 (1.1–1.5)

ICD-10 level 4 code	ICD-10 level 4 name	Standard disease name	Case group N=13,420	Control group N=134,200	Odds ratio (95% CI)
H26.9	Cataract, unspecified	Cataract	214 (1.6)	1653 (1.2)	1.3 (1.1–1.5)
H52.1	Myopia	High myopia	213 (1.6)	2000 (1.5)	1.1 (0.9–1.2)
J30.1	Allergic rhinitis due to pollen	Pollinosis	210 (1.6)	1670 (1.2)	1.3 (1.1–1.5)
L30.9	Dermatitis, unspecified	Chronic eczema	210 (1.6)	1693 (1.3)	1.2 (1.1–1.4)
M81.9	Osteoporosis, unspecified	Osteoporosis	207 (1.5)	1455 (1.1)	1.4 (1.2–1.7)
R07.4	Chest pain, unspecified	Chest pain	206 (1.5)	789 (0.6)	2.6 (2.3–3.1)
J37.0	Chronic laryngitis	Chronic pharyngopharyngitis	205 (1.5)	1259 (0.9)	1.6 (1.4–1.9)
K64.9	Haemorrhoids, unspecified	Haemorrhoid	203 (1.5)	1281 (1.0)	1.6 (1.4–1.8)
J42-	Unspecified chronic bronchitis	Chronic bronchitis	201 (1.5)	1422 (1.1)	1.4 (1.2–1.6)
K29.4	Chronic atrophic gastritis	Atrophic gastritis	201 (1.5)	1503 (1.1)	1.3 (1.2–1.6)
M48.0	Spinal stenosis	Lumbar spinal canal stenosis	201 (1.5)	880 (0.7)	2.3 (2.0–2.7)
H40.0	Glaucoma suspect	Enlargement of optic disc cupping	200 (1.5)	1628 (1.2)	1.2 (1.1–1.4)
H90.5	Sensorineural hearing loss, unspecified	Sensorineural hearing loss	199 (1.5)	917 (0.7)	2.2 (1.9–2.6)
E03.9	Hypothyroidism, unspecified	Hypothyroidism	197 (1.5)	938 (0.7)	2.1 (1.8–2.5)
N40-	Hyperplasia of prostate	Prostatic hyperplasia	197 (1.5)	1098 (0.8)	1.8 (1.6–2.1)
L70.0	Acne vulgaris	Acne vulgaris	195 (1.5)	1555 (1.2)	1.3 (1.1–1.5)
L30.9	Dermatitis, unspecified	Hand eczema	193 (1.4)	1665 (1.2)	1.2 (1.0–1.3)

ICD-10 level 4 code	ICD-10 level 4 name	Standard disease name	Case group N=13,420	Control group N=134,200	Odds ratio (95% CI)
H00.0	Hordeolum and other deep inflammation of eyelid	Hordeolum	190 (1.4)	1560 (1.2)	1.2 (1.0–1.4)
M47.8	Other spondylosis	Cervical spondylosis	190 (1.4)	830 (0.6)	2.3 (2.0–2.7)
A09.9	Gastroenteritis and colitis of unspecified origin	Enterocolitis	185 (1.4)	1046 (0.8)	1.8 (1.5–2.1)
J45.9	Asthma, unspecified	Asthmatic bronchitis	185 (1.4)	1373 (1.0)	1.4 (1.2–1.6)
H16.1	Other superficial keratitis without conjunctivitis	Superficial punctate keratitis	183 (1.4)	1451 (1.1)	1.3 (1.1–1.5)
M62.8	Other specified disorders of muscle	Shoulder stiffness	181 (1.3)	755 (0.6)	2.4 (2.1–2.8)
H90.3	Sensorineural hearing loss, bilateral	Bilateral sensorineural hearing loss	176 (1.3)	590 (0.4)	3.0 (2.5–3.6)
J00-	Acute nasopharyngitis [common cold]	Acute nasopharyngitis	176 (1.3)	1291 (1.0)	1.4 (1.2–1.6)
R11-	Nausea and vomiting	Nausea	176 (1.3)	585 (0.4)	3.0 (2.6–3.6)
K31.7	Polyp of stomach and duodenum	Stomach polyp	175 (1.3)	1108 (0.8)	1.6 (1.4–1.9)
M50.2	Other cervical disc displacement	Cervical disc herniation	175 (1.3)	865 (0.6)	2.0 (1.7–2.4)
K73.9	Chronic hepatitis, unspecified	Chronic hepatitis	174 (1.3)	1179 (0.9)	1.5 (1.3–1.7)
L29.9	Pruritus, unspecified	Pruritus cutaneous	173 (1.3)	1176 (0.9)	1.5 (1.3–1.7)
N64.9	Disorder of breast, unspecified	Mastopathy	173 (1.3)	1176 (0.9)	1.5 (1.3–1.7)
H68.1	Obstruction of Eustachian tube	Stenosis of Eustachian tube	172 (1.3)	929 (0.7)	1.9 (1.6–2.2)
L81.0	Post-inflammatory hyperpigmentation	Post-inflammatory pigmentation	171 (1.3)	1272 (0.9)	1.3 (1.1–1.6)
R52.9	Pain, unspecified	Pain	169 (1.3)	904 (0.7)	1.9 (1.6–2.2)
N80.9	Endometriosis, unspecified	Endometriosis	165	872	1.9

ICD-10 level 4 code	ICD-10 level 4 name	Standard disease name	Case group N=13,420	Control group N=134,200	Odds ratio (95% CI)
			(1.2)	(0.6)	(1.6–2.3)
H65.9	Nonsuppurative otitis media, unspecified	Otitis media with effusion	164 (1.2)	1191 (0.9)	1.4 (1.2–1.6)
J32.9	Chronic sinusitis, unspecified	Sinusitis	164 (1.2)	1146 (0.9)	1.4 (1.2–1.7)
N32.8	Other specified disorders of bladder	Overactive bladder	164 (1.2)	519 (0.4)	3.2 (2.7–3.8)
G62.9	Polyneuropathy, unspecified	Peripheral neuritis	163 (1.2)	662 (0.5)	2.5 (2.1–2.9)
L30.9	Dermatitis, unspecified	Dermatitis	163 (1.2)	1336 (1.0)	1.2 (1.0–1.4)
L70.0	Acne vulgaris	Facial common acne	162 (1.2)	1446 (1.1)	1.1 (1.0–1.3)
I50.9	Heart failure, unspecified	Chronic cardiac failure	159 (1.2)	815 (0.6)	2.0 (1.7–2.3)
G47.9	Sleep disorder, unspecified	Sleeping disturbance	157 (1.2)	205 (0.2)	7.7 (6.3–9.5)
M06.9	Rheumatoid arthritis, unspecified	Rheumatoid arthritis	155 (1.2)	830 (0.6)	1.9 (1.6–2.2)
J32.9	Chronic sinusitis, unspecified	Acute exacerbation of chronic sinusitis	153 (1.1)	1272 (0.9)	1.2 (1.0–1.4)
N20.1	Calculus of ureter	Ureterolithiasis	151 (1.1)	1139 (0.8)	1.3 (1.1–1.6)
R52.2	Other chronic pain	Chronic pain	151 (1.1)	417 (0.3)	3.7 (3.0–4.4)
R31-	Unspecified haematuria	Haematuria	149 (1.1)	1024 (0.8)	1.5 (1.2–1.7)
K76.9	Liver disease, unspecified	Liver disorder	148 (1.1)	955 (0.7)	1.6 (1.3–1.9)
R00.2	Palpitations	Palpitations	148 (1.1)	257 (0.2)	5.8 (4.7–7.1)
H10.3	Acute conjunctivitis, unspecified	Acute conjunctivitis	147 (1.1)	1212 (0.9)	1.2 (1.0–1.4)

ICD-10 level 4 code	ICD-10 level 4 name	Standard disease name	Case group N=13,420	Control group N=134,200	Odds ratio (95% CI)
J10.1	Influenza with other respiratory manifestations, seasonal influenza virus identified	Influenza B	147 (1.1)	1427 (1.1)	1.0 (0.9–1.2)
D27-	Benign neoplasm of ovary	Ovarian cystoma	141 (1.1)	967 (0.7)	1.5 (1.2–1.7)
B37.3	Candidiasis of vulva and vagina	Vulvovaginal candidiasis	140 (1.0)	930 (0.7)	1.5 (1.3–1.8)
B02.9	Zoster without complication	Herpes zoster	137 (1.0)	884 (0.7)	1.6 (1.3–1.9)
L73.9	Follicular disorder, unspecified	Folliculitis	136 (1.0)	1024 (0.8)	1.3 (1.1–1.6)
N20.0	Calculus of kidney	Nephrolithiasis	136 (1.0)	912 (0.7)	1.5 (1.2–1.8)
M47.2	Other spondylosis with radiculopathy	Cervical spondylotic radiculopathy	135 (1.0)	725 (0.5)	1.9 (1.6–2.3)

Shown are diseases with prevalence ≥1.0% in the case group and ≥0.1% in the control group. Data are n (%), unless otherwise noted.
CI, confidence interval; ICD-10, International Statistical Classification of Diseases and Related Health Problems, 10th revision.

Supplemental table 3 Number of patients in post hoc multivariate analysis subgroups

Explanatory variable	Category			Number of cases	Number of controls	Total number
Sex	Male			8924	89,240	98,164
	Female			4496	44,960	49,456
Age	<40 years			5390	53,900	59,290
	≥40 years			8030	80,300	88,330
Working status	Worker			10,447	104,470	114,917
	Non-worker			2973	29,730	32,703
Presence of lifestyle disease, psychiatric disorder, and/or MDD-related symptoms during the 12 months before index date	Lifestyle disease	Psychiatric disorder	MDD-related symptoms			
	No	No	No	4329	80,434	84,763
	No	No	Yes	1998	20,752	22,750
	No	Yes	No	1794	3314	5108
	No	Yes	Yes	1595	2301	3896
	Yes	No	No	901	15,660	16,561
	Yes	No	Yes	854	7588	8442
	Yes	Yes	No	675	1866	2541
	Yes	Yes	Yes	1274	2285	3559
Total				13,420	134,200	147,620

MDD, major depressive disorder.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *case-control studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5-6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	6-7
		(*b*) For matched studies, give matching criteria and the number of controls per case	7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-8
Bias	9	Describe any efforts to address potential sources of bias	NA
Study size	10	Explain how the study size was arrived at	NA
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7-8
		(*b*) Describe any methods used to examine subgroups and interactions	7-8
		(*c*) Explain how missing data were addressed	NA
		(*d*) If applicable, explain how matching of cases and controls was addressed	7
		(*e*) Describe any sensitivity analyses	NA
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8, Supplementary Figure
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	Supplementary Figure
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8, Table 1
		(b) Indicate number of participants with missing data for each variable of interest	NA
Outcome data	15*	Report numbers in each exposure category, or summary measures of exposure	8-10, Tables 2 and 3, Figure 1, Supplementary Tables
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8-10, Tables 2 and 3, Figure 1, Supplementary Tables
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8-10, Tables 2 and 3, Figure 1, Supplementary Tables
Discussion			
Key results	18	Summarise key results with reference to study objectives	10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13-14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	13-14
Other information			

Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Funding statement

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Diseases prevalent before major depressive disorder diagnosis: an exploratory nested case-control study using health insurance–based claims data

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TITLE

Diseases prevalent before major depressive disorder diagnosis: an exploratory nested case-control study using health insurance–based claims data

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ABSTRACT

Objectives Major depressive disorder (MDD) is often comorbid with other chronic and/or serious diseases. However, little is known about the prevalence of various diseases that are present before MDD onset. We examined the prevalence of all pre-existing diseases in the 12 months before an MDD diagnosis.

Design Exploratory nested case-control study.

Setting Data, including diagnoses based on ICD-10 codes, were from a Japanese health insurance database (JMDC).

Participants Adults newly diagnosed with MDD during 2015, 2016, or 2017 (but not the preceding year) (cases) were matched (exact) 1:10 to controls by age, sex, index date, and working status.

Primary and secondary outcome measures The primary outcome was the proportion of patients in each group with each pre-existing disease during the 12 months before the index date (ie, before MDD diagnosis in cases). Odds ratios (ORs) for onset of MDD were calculated for each pre-existing disease. A post hoc multivariate analysis examined interactions of metabolic risk factors (diabetes, hypertension, dyslipidaemia), psychiatric disorders (sleep disorders, psychiatric disorders other than depression), and MDD-related symptoms (headache, pain, autonomic nerve imbalance) on MDD diagnosis.

Results There were 13,420 cases and 134,200 controls (mean age 41.9 years; 66.5% male). The prevalence of almost all pre-existing diseases was higher in cases than in controls. The highest ORs (5.8–21.0) were for psychiatric diseases and sleep disorders. Insomnia (21.1% of patients; OR 8.7) and neurosis (9.7%; OR 10.6) were particularly prevalent in the case group. The odds of MDD increased in the presence of metabolic risk factors , psychiatric disorders, and/or MDD-related symptoms.

Conclusions The high ORs of pre-existing diseases and/or prodromal symptoms in patients who develop MDD indicate a high medical burden for these patients. Patients with chronic and/or serious diseases should be monitored for depressive symptoms, and pre-existing diseases should be considered when prescribing MDD treatment.

Strengths and limitations of this study

- This is the first nested case-control study to examine a broad range of pre-existing diseases in people who develop major depressive disorder (MDD) compared with people who do not.
- The use of a national health insurance database resulted in a sample size large enough to allow examination of less common pre-existing diseases.
- The nested case-control design and the use of a database minimised selection and recall biases that may occur in other case-control studies.
- Because of the nature of the database, the study did not include people aged ≥75 years, and information on the physician making the MDD diagnosis was not available.

Keywords: Administrative claims, healthcare; Comorbidity; Depressive disorder; Epidemiology; Risk factors

INTRODUCTION

Depression is frequently comorbid with other diseases, particularly chronic and/or serious diseases such as diabetes, cardiovascular/cerebrovascular disease, cancer, asthma, and arthritis.[1-3] The relationship between depression and most comorbidities is complex. For example, the temporal relationship appears to be bi-directional, in that depression can increase the risk of developing a chronic disease and vice versa.[3] In addition, the relationship with depression varies with the type, duration, and severity of disease, among other factors.[1-3] Moreover, the presence of depression in patients with pre-existing diseases is associated with worse outcomes and quality of life, and possibly decreased survival.[2] However, despite the accumulation of evidence for a link between depression and chronic illness, few studies have comprehensively compared the risk of depression in people with a broad range of pre-existing diseases.

An epidemiological study conducted in Japan between 2013 and 2015 reported the lifetime and 12-month prevalence rates of major depressive disorder (MDD) to be relatively low, at 5.7% and 2.7%, respectively.[4] Other studies have confirmed that major depressive episodes are less prevalent in Japan than in other countries.[5 6] However, fewer than half of Japanese people with a mood disorder seek medical treatment.[4] This reluctance to seek medical treatment may be related to a perceived 'stigma' associated with psychiatric disease.[7] These factors may further reduce the detection and diagnosis of MDD in patients with a chronic disease, despite the potentially increased risk of MDD in these patients. However, little is known about the prevalence of underlying diseases that are comorbid with MDD. Given that around 20,000 people in Japan commit suicide every year,[8] with the highest rate of about 50 per 100,000 persons in men aged 50–59 years,[9] most of which are probably related to mental disorders, additional information on factors associated with MDD that could assist with early detection and treatment may help reduce the number of suicides.

The aim of this exploratory nested case-control study of patients enrolled in a Japanese health insurance database was to comprehensively examine the prevalence of pre-existing diseases in the 12 months before an MDD diagnosis (defined using the International Statistical Classification of Diseases and Related Health Problems, 10th revision [ICD-10][10] codes F32 ['Depressive episode'] or F33 ['Recurrent depressive disorder']). In this context, a pre-existing disease was defined as any diagnosis other than MDD and related mental disorders (bipolar affective disorders; organic mental disorders; schizophrenia, schizotypal, and delusional disorders); the latter were excluded to avoid including patients with secondary diagnoses of MDD as cases. However, our definition of pre-existing conditions did include those that are prodromal symptoms of MDD (eg, sleep disorders). In addition, we determined an odds ratio (OR) for the onset of MDD for each pre-existing disease to identify those that are most commonly associated with development of MDD and to evaluate the association of MDD with common metabolic risk factors.

METHODS

Study design

This was a nested case-control study. Data on patient demographics and diagnoses based on ICD-10 were derived from the JMDC Inc. (Tokyo, Japan) database of medical expense claims for company employees in Japan.[11]

The study was approved by the Ethics Review Committee of the Research Institute of Healthcare Data Science (Tokyo, Japan) on 6 August 2019. Only anonymised information was accessible from the database; therefore, in accordance with the Ethical Guidelines for Medical and Health Research Involving Human Subjects in Japan,[12] informed consent was not required.

Study population

The study analysed data collected for the population registered in the JMDC database between January 2014 and December 2018 who were aged ≥18 years on 1 January of the inclusion year (2015, 2016, or 2017) and had continuous registration for the inclusion year, the previous year, and the subsequent year (study period). Individuals were excluded if they had a diagnosis of any bipolar affective disorder (ICD-10 codes F30 [manic episode], F31), organic mental disorder including symptomatic mental disorders (F00–F09), or schizophrenia, schizotypal, and delusional disorder (F20–F29) in the study period, or a diagnosis of MDD (ICD-10 codes F32 ['Depressive episode'] or F33 ['Recurrent depressive disorder']) in the year before the inclusion year, or no medical history for the year before the inclusion year.

Within the study population, case patients had a diagnosis of MDD in the inclusion year (the date of the first MDD treatment after ≥1 year with no MDD diagnosis was designated as the index date) and ≥2 months of treatment for depression within 90 days of the index date. Control patients had no diagnosis of MDD in the study period and were matched 10:1 (exact matching using random sampling) to case patients according to age at index date, sex, and working status.

Outcomes

The primary end point was the proportion of patients with documented diagnosis of each pre-existing disease during the 12 months before the index date (ie, before MDD diagnosis in case patients). An OR for the onset of MDD was calculated for each underlying disease, which was based on presence or absence of ICD-10 codes, Charlson comorbidity index (CCI)–related diseases, or other chronic diseases (online supplemental table 1). Demographic and patient characteristics were collected, including age, sex, working status, and inclusion year (2015/2016/2017).

Statistical analysis

As noted above, the proportion of patients with each pre-existing disease was determined for each group and an OR for the onset of MDD was calculated. Prevalence data and ORs are reported for pre-existing diseases that were present in ≥1% of the case group and ≥0.1% of the control group. No inferential statistics were conducted. A post hoc analysis examined the possible interaction of the presence of three pre-existing disease categories that exhibited high ORs in the primary analysis or are common diseases: metabolic risk factors (diabetes, hypertension, dyslipidaemia), MDD-related symptoms (headache, pain, autonomic nerve imbalance), and psychiatric disorders (sleep disorders, psychiatric disorders other than depression) (online supplemental table 1). A multivariate logistic regression model was used to determine ORs in the eight subgroups (ie, with/without metabolic risk factors, MDD-related symptoms, and/or psychiatric disease) for the onset of MDD using the following covariates: sex, age (<40 years versus ≥40 years), and working status. A similar post hoc analysis was conducted to estimate ORs for the onset of MDD according to the number of low-risk (1≤OR ≤2 in the primary analysis) CCI-related and other chronic diseases that were present during the preceding year. As above, sex, age, and working status were adjusted for in the multivariate logistic regression model. Netezza N2002-010 7.1.0.4.P2 (IBM, Armonk, NY, USA) was used as the data warehouse platform. SAS version 9.4 (SAS Institute, Cary, NC, USA) was used for statistical analysis.

Patient and public involvement

Patients and members of the public were not involved in the study.

RESULTS

Demographic characteristics

From more than 6.5 million people enrolled in the JMDC database between 2014 and 2018, we identified 13,420 case patients who met the inclusion criteria and had MDD diagnosed in

2015, 2016, or 2017 (case group; online supplemental figure). From 4,212,652 control patients who met the inclusion criteria and did not have an MDD diagnosis in either the inclusion year or the subsequent year, 134,200 were matched to case patients (control group; online supplemental figure). More than half (66.5%) of patients in both groups were male, with a mean age of 41.9 years (**table 1**). About 40% of patients were <40 years. Most (77.8%) patients were workers.

Table 1 Background and characteristics of case group

Variable	Case group N=13,420
Male sex	8924 (66.5)
Age	
Mean (SD), years	41.9 (10.4)
Median (range), years	42.0 (18–73)
<40 years	5390 (40.2)
≥40 years	8030 (59.8)
Working status	
Working	10,447 (77.8)
Non-working	2973 (22.2)
Inclusion year	
2015	3853 (28.7)
2016	4076 (30.4)
2017	5491 (40.9)
Number of beds in hospital where MDD was diagnosed	
<20	10,851 (80.9)
≥20	2569 (19.1)
Psychiatric facilities in hospital where MDD was diagnosed	
Yes	7026 (52.4)
No	6394 (47.6)

Data are n (%), unless otherwise noted.
MDD, major depressive disorder; SD, standard deviation.

Prevalence of pre-existing diseases in the year before MDD diagnosis

CCI-related diseases and other chronic diseases

The prevalence of almost all chronic diseases was higher in the case group than in the control group, with most ORs between 1.3 and 2.0 (**table 2**). The highest ORs were seen for attention deficit hyperkinetic disorders (OR 12.2), psychiatric diseases except depression (OR 9.9), dementia (OR 8.7, although prevalence was ≤0.1% in both groups), sleep disorders (OR 7.2), and autonomic nerve imbalance (OR 6.5). Of these, psychiatric diseases except depression and sleep disorders were highly prevalent in the case group (30.4% and

23.3%, respectively). ORs ≥2.0 were also observed (in descending order of prevalence in the case group) for pain (2.0), chronic gastritis (2.1), headache (2.7), peptic ulcer disease (2.0), dizziness (3.2), irritable bowel syndrome (3.2), angina pectoris (2.0), epilepsy (2.4), chronic enteritis (2.7), diabetes without chronic complication (2.1), metastatic solid tumour (2.2), hemiplegia or paraplegia (2.8), and Parkinson's disease (3.2).

Table 2 Prevalence of pre-existing diseases, ranked by prevalence in the case group

Disease	Case group N=13,420	Matched control group N=134,200	Odds ratio (95% CI)
CCI-related diseases			
Peptic ulcer disease	1431 (10.7)	7659 (5.7)	2.0 (1.9–2.1)
Mild liver disease	1392 (10.4)	9336 (7.0)	1.5 (1.5–1.6)
Chronic pulmonary disease (ex. asthma)	973 (7.3)	7381 (5.5)	1.3 (1.3–1.4)
Cerebrovascular disease	448 (3.3)	2378 (1.8)	1.9 (1.7–2.1)
Peripheral vascular disease	359 (2.7)	2237 (1.7)	1.6 (1.4–1.8)
Congestive heart failure	347 (2.6)	1885 (1.4)	1.9 (1.7–2.1)
Second solid tumour (non-metastatic)	327 (2.4)	2357 (1.8)	1.4 (1.2–1.6)
Diabetes with chronic complication	239 (1.8)	1758 (1.3)	1.4 (1.2–1.6)
Rheumatic disease	192 (1.4)	1066 (0.8)	1.8 (1.6–2.1)
Diabetes without chronic complication	107 (0.8)	502 (0.4)	2.1 (1.7–2.6)
Renal disease	77 (0.6)	708 (0.5)	1.1 (0.9–1.4)
Metastatic solid tumour	52 (0.4)	241 (0.2)	2.2 (1.6–2.9)
Myocardial infarction	46 (0.3)	338 (0.3)	1.4 (1.0–1.9)
Hemiplegia or paraplegia	39 (0.3)	138 (0.1)	2.8 (2.0–4.0)
Lymphoma/multiple myeloma	25 (0.2)	174 (0.1)	1.4 (0.9–2.2)
Dementia	13 (0.1)	15 (<0.1)	8.7 (4.1–18.2)
Leukaemia	9 (0.1)	97 (0.1)	0.9 (0.5–1.8)
Moderate or severe liver disease	7 (0.1)	54 (<0.1)	1.3 (0.6–2.8)
Other chronic diseases			
Pain	4598 (34.3)	27,452 (20.5)	2.0 (2.0–2.1)
Psychiatric diseases except depression	4084 (30.4)	5691 (4.2)	9.9 (9.4–10.3)
Sleep disorders	3128 (23.3)	5462 (4.1)	7.2 (6.8–7.5)
Chronic gastritis	2349 (17.5)	12,568 (9.4)	2.1 (2.0–2.2)
Dyslipidaemia	2286 (17.0)	17,438 (13.0)	1.4 (1.3–1.4)
Headache	2129 (15.9)	8634 (6.4)	2.7 (2.6–2.9)
Hypertensive disease	1987 (14.8)	15,052 (11.2)	1.4 (1.3–1.4)
Asthma	1861 (13.9)	12,923 (9.6)	1.5 (1.4–1.6)
Dizziness	1309 (9.8)	4345 (3.2)	3.2 (3.0–3.4)
Arthritis	729 (5.4)	5217 (3.9)	1.4 (1.3–1.5)
Osteoarthritis	654 (4.9)	4290 (3.2)	1.6 (1.4–1.7)
Atopic dermatitis	608 (4.5)	5984 (4.5)	1.0 (0.9–1.1)
Irritable bowel syndrome	588 (4.4)	1900 (1.4)	3.2 (2.9–3.5)
Thyroid disease	551 (4.1)	3394 (2.5)	1.7 (1.5–1.8)
Autonomic nerve imbalance	409 (3.0)	647 (0.5)	6.5 (5.7–7.4)

Disease	Case group N=13,420	Matched control group N=134,200	Odds ratio (95% CI)
Angina pectoris	405 (3.0)	2058 (1.5)	2.0 (1.8–2.2)
Osteoporosis	226 (1.7)	1611 (1.2)	1.4 (1.2–1.6)
Epilepsy	177 (1.3)	729 (0.5)	2.4 (2.1–2.9)
Chronic enteritis	153 (1.1)	561 (0.4)	2.7 (2.3–3.3)
Obesity	74 (0.6)	513 (0.4)	1.4 (1.1–1.8)
Attention deficit hyperkinetic disorders	56 (0.4)	46 (<0.1)	12.2 (8.3–18.1)
Parkinson's disease	24 (0.2)	76 (0.1)	3.2 (2.0–5.0)

The prevalence of CCI-related diseases and other chronic diseases in the 12 months before the index date in the case group and matched control group is shown ranked by prevalence in the case group. Data are n (%), unless otherwise noted.
CCI, Charlson comorbidity index; CI, confidence interval.

Table 3 Prevalence of pre-existing diseases in the case group and matched control group by ICD-10 block

ICD-10 block	ICD-10 block name	Case group N=13,420	Matched control group N=134,200	Odds ratio (95% CI)
A00–B99	Certain infectious and parasitic diseases	4583 (34.2)	33,852 (25.2)	1.5 (1.5–1.6)
C00–D48	Neoplasms	1575 (11.7)	12,007 (8.9)	1.4 (1.3–1.4)
D50–D89	Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	1041 (7.8)	7612 (5.7)	1.4 (1.3–1.5)
E00–E90	Endocrine, nutritional, and metabolic diseases	4477 (33.4)	32,630 (24.3)	1.6 (1.5–1.6)
F00–F99	Mental and behavioural disorders	4084 (30.4)	5691 (4.2)	9.9 (9.4–10.3)
G00–G99	Diseases of the nervous system	4965 (37.0)	14,847 (11.1)	4.7 (4.5–4.9)
H00–H59	Diseases of the eye and adnexa	5035 (37.5)	46,365 (34.5)	1.1 (1.1–1.2)
H60–H95	Diseases of the ear and mastoid process	1735 (12.9)	10,245 (7.6)	1.8 (1.7–1.9)
I00–I99	Diseases of the circulatory system	3038 (22.6)	20,545 (15.3)	1.6 (1.6–1.7)
J00–J99	Diseases of the respiratory system	9232 (68.8)	77,686 (57.9)	1.6 (1.5–1.7)
K00–K93	Diseases of the digestive system	7015 (52.3)	47,838 (35.6)	2.0 (1.9–2.0)
L00–L99	Diseases of the skin and subcutaneous tissue	4428 (33.0)	37,648 (28.1)	1.3 (1.2–1.3)
M00–M99	Diseases of the musculoskeletal system and connective tissue	5322 (39.7)	35,387 (26.4)	1.8 (1.8–1.9)
N00–N99	Diseases of the genitourinary system	2880 (21.5)	20,016 (14.9)	1.6 (1.5–1.6)
O00–O99	Pregnancy, childbirth, and the puerperium	178 (1.3)	2944 (2.2)	0.6 (0.5–0.7)
P00–P96	Certain conditions originating in the perinatal period	19 (0.1)	212 (0.2)	0.9 (0.6–1.4)
Q00–Q99	Congenital malformations, deformations, and chromosomal abnormalities	199 (1.5)	1496 (1.1)	1.3 (1.2–1.5)
R00–R99	Symptoms, signs, and abnormal clinical and laboratory findings, not elsewhere classified	5241 (39.1)	28,989 (21.6)	2.3 (2.2–2.4)
S00–T98	Injury, poisoning, and certain other consequences of external causes	2209 (16.5)	17,661 (13.2)	1.3 (1.2–1.4)
Z00–Z99	Factors influencing health status and contact with health services	252 (1.9)	1878 (1.4)	1.3 (1.2–1.5)
U00–U99	Codes for special purposes	0 (0)	1 (<0.1)	NE

Data are n (%), unless otherwise noted.

CI, confidence interval; ICD-10, International Statistical Classification of Diseases and Related Health Problems, 10th revision; NE, not estimable.

ICD-10 blocks

At the level of ICD-10 blocks, the prevalence of most pre-existing diseases in the year before MDD diagnosis was slightly higher (OR 1.1–2.0) in the case group than in the control group (**table 3**). Exceptions were blocks O00–O99 and P00–P96, which are associated with pregnancy and/or childbirth. However, the prevalence rates of mental and behavioural disorders (F00–F99) and diseases of the nervous system (G00–G99) were markedly higher in the case group, with ORs of 9.9 and 4.7, respectively. Among diseases of the circulatory system (I00–I99), respiratory system (J00–J99), and digestive system (K00–K93), the OR for digestive diseases was the highest (2.0 for digestive versus 1.6 for circulatory and respiratory). The OR for diseases of the eye and adnexa (H00–H59) was low (1.1), whereas the OR for diseases of the ear and mastoid process (H60–H95) was relatively high (1.8).

ICD-10 codes

As with the ICD-10 blocks, the prevalence of almost all pre-existing diseases based on three- or four-character ICD-10 codes in the year before MDD diagnosis was slightly higher in the case group than in the control group (**figure**; online supplemental table 2). The highest ORs for the onset of MDD were observed for psychiatric diseases and sleep disorders (**figure**). ORs >5 were seen for adjustment disorders, panic disorder, anxiety disorder, depressive neurosis, neurosis, insomnia, psychosomatic disorder, anxiety, sleeping disorder, autonomic ataxia, and palpitations. Of these comorbidities, insomnia and neurosis were particularly prevalent in the case group (21.1% and 9.7% of patients, respectively).

Multivariate analysis

A post hoc multivariate analysis indicated that the odds of developing MDD were lower in women than in men, in patients ≥40 years than in younger patients, and in non-workers than in workers (**table 4**). The odds of MDD also increased in subgroups with metabolic risk factors, psychiatric disorders, and/or MDD-related symptoms, relative to 84,763 individuals without any of these diseases (online supplemental table 3). The highest ORs (>10) were

seen in subgroups with psychiatric disorders. Compared with subgroups with MDD-related symptoms only, the odds of MDD were increased in subgroups who also had metabolic risk factors or psychiatric disorders. However, the odds of MDD decreased in subgroups who had both metabolic risk factors and psychiatric disorders relative to subgroups with only one of these factors (with or without MDD-related symptoms). Finally, we identified 72,923 people (8329 cases with MDD and 64,594 controls) who had at least one low-risk (1≤OR≤2) pre-existing CCI-related or other chronic disease (**table 2**) and categorised them based on the number of diseases from one (N=36,993) to 11–13 (N=46). Relative to people with only one pre-existing disease, the OR for MDD increased with the number of pre-existing chronic diseases, from 1.34 in people with two pre-existing diseases to more than three in people with nine or more comorbidities (online supplemental table 4).

Table 4 Multivariate logistic regression analysis for the onset of MDD

Dependent variable	Explanatory variable	Reference	Category			Odds ratio (95% CI)
Group (reference = control group)	Sex	Male	Female			0.93 (0.89–0.98)
	Age	<40 years	≥40 years			0.80 (0.77–0.83)
	Working status	Worker	Non-worker			0.92 (0.86–0.97)
	Presence of metabolic risk factor, psychiatric disorder, and/or MDD-related symptoms during the 12 months before index date	None	Metabolic risk factor	Psychiatric disorder	MDD-related symptoms	
			No	No	Yes	1.81 (1.71–1.91)
			No	Yes	No	10.22 (9.58–10.91)
			No	Yes	Yes	13.47 (12.54–14.47)
			Yes	No	No	1.14 (1.06–1.23)
			Yes	No	Yes	2.27 (2.10–2.46)
			Yes	Yes	No	7.27 (6.61–7.99)
			Yes	Yes	Yes	11.49 (10.63–12.41)

'Metabolic risk factors' included diabetes, hypertension, and dyslipidaemia; 'psychiatric disorders' included sleep disorders and psychiatric diseases other than depression; 'MDD-related symptoms' included headache, pain, and autonomic nerve imbalance (online supplemental table 1).
CI, confidence interval; MDD, major depressive disorder.

DISCUSSION

This is the first nested case-control study to demonstrate that a broad range of pre-existing diseases are more prevalent in people who develop MDD than in those who do not. These results indicate that most patients have complex health conditions before starting treatment for MDD. The highest ORs were seen for sleep disorders and psychiatric diseases other than depression, which were also among the most prevalent pre-existing diseases in the case group. Other common diseases that were more prevalent in the case group included pain, headache, autonomic disturbances, gastrointestinal diseases, and metabolic risk factors, such as dyslipidaemia, hypertension, and diabetes.

Our results support and extend the results of previous studies reporting a high prevalence of pre-existing or comorbid diseases in patients with depression. Most previous studies have been cross-sectional or small case-control studies focused on specific comorbid diseases.[2 3 13-16] Two large case-control studies conducted in the United States, using electronic health records at the Mayo Clinic,[17] and South Korea, using the National Health Insurance Service,[18] identified pre-existing chronic physical conditions that were risk factors for the development of MDD. However, these studies focused on a smaller number (24 and 19) of specific chronic conditions compared with our study, which examined a broad range of both chronic and acute conditions.

Stress, such as diagnosis with a chronic or serious disease, can contribute to the development of MDD in vulnerable individuals.[19] Further, stress can lead to psychological and physiological changes that affect both mental and physical health, and may contribute directly to depression.[20] Psychiatric disorders can be particularly stressful and may increase the chances of MDD. Depression is often comorbid with other mental disorders, particularly anxiety, and may share symptoms and underlying aetiologies.[21-24] Stress is also associated with many gastrointestinal disorders,[25] such as irritable bowel syndrome, which were twice as prevalent in the case group than in the control group.

Depression-related symptoms (sleep disorders, pain, autonomic imbalance) may be diagnosed in advance of MDD and therefore may be prodromal symptoms of MDD.[26] Somatic symptoms of MDD, such as fatigue, appetite loss, pain (especially headache), dizziness, and sleep disturbance, can be non-specific and may be attributed to physical illness.[27] Indeed, a significant proportion of patients with MDD present with only somatic symptoms.[28] One reason is denial of psychological symptoms, which is particularly prevalent in Japan.[28] These results support the idea that depression is under-recognised when patients first seek medical help in Japan, and also support our findings that digestive diseases, sleep disorders, and other somatic symptoms, including in the otological area (eg, dizziness), were highly prevalent in patients who later developed MDD. Interestingly, we observed that the OR for diseases of the ear and mastoid process was higher than for diseases of the eye and adnexa (1.8 versus 1.1). We suggest that physicians in otolaryngology departments may be aware of the link between somatic symptoms and MDD and consider psychological evaluation for patients with such symptoms. In contrast, physicians in ophthalmology departments may need to pay more attention to the risk of MDD in patients with severe visual dysfunction because both hearing loss and vision loss are associated with the development of depression.[29]

Our multivariate analysis indicated that the odds of an MDD diagnosis were increased in patients who had depression-related symptoms (headache, pain, autonomic imbalance), particularly if the patient also had a sleep/psychiatric disorder or metabolic risk factor. Interestingly, the odds of MDD decreased in subgroups with metabolic risk factors in addition to psychiatric disorders. Although the reason for this finding is unclear, it may be that these patients are managed by multiple physicians who focus on treating each disease separately (eg, psychiatrist treating psychiatric diseases; general practitioner treating metabolic risk factors), with the result that MDD is not sufficiently recognised. Indeed, some general practitioners and other non-psychiatrist doctors in Japan fail to recognise or are reluctant to

treat MDD,[30 31] which may contribute to underdiagnosis of MDD in patients with metabolic risk factors. Psychiatrists, on the other hand, may underestimate somatic depressive symptoms in patients they are treating for another mental illness who also have a metabolic-related illness treated by another doctor, considering fatigue and autonomic dysfunction as caused by the physical illness. However, depression is known to lead to treatment non-adherence in patients with diabetes,[32] which increases the risk of severe complications.[33] In addition, treating metabolic-related diseases and depression simultaneously may provide patients with better clinical outcomes.[34] Further research is needed on the unmet needs for the diagnosis and treatment of depression in patients with presymptomatic depression in addition to metabolic-related diseases, and on the effects of coordinated care management of multiple conditions.

We also found that the risk of MDD increased with increasing number of relatively low-risk (OR≤2) CCI-related and other chronic diseases. Thus, increased medical burden appears to be associated with greater risk of depression among working-age people, consistent with a recent study conducted in Denmark.[35]

Many comorbidities may share underlying biological mechanisms with MDD. For example, inflammatory mechanisms play a role in the aetiology of many diseases, including diabetes, cardiovascular disease, arthritis, and asthma, as well as depression.[36-38] Neural pathways and neurotransmitters that are altered in chronic pain may also affect mood, including depression.[39] Migraine and depression can both be related to specific genetic variants and/or neuroanatomic features.[40] Most of these biological mechanisms are exacerbated by stress.[3 37 40] Thus, MDD may develop in parallel with certain diseases, but its diagnosis may be delayed compared with physical disease.

Our study is strengthened by the use of a health insurance database consisting of mostly working-age people, which resulted in a sample size large enough to allow examination of a

broad range of pre-existing diseases. The nested case-control design and the use of a database minimised selection and recall biases that may occur in other case-control studies. We used a strict definition of MDD onset, which required a 1-year depression-free period and the diagnosis for inclusion to be recorded on at least three doctor visits within 90 days; this definition increased our certainty that case patients had true, newly diagnosed MDD. In addition, our inclusion criteria meant that people in both the control and case groups needed to have visited a doctor at least once to have a medical record within the observation period. Because of the comprehensive insurance available in Japan, medical care is readily accessible, and consultations for relatively minor concerns are common. Therefore, the controls in our study can essentially be considered as representative of the general population, except for the absence of people aged 75 years or older, who are covered by government-administered insurance, and the relatively low proportion of people aged 65–74 years, many of whom would be retired from work.

Despite these strengths, some caveats do apply when interpreting our results. As with any claims database study, the data were not collected specifically for the purpose of the study. As such, we could not evaluate variables like socioeconomic factors or severity/history of MDD. Further, errors in ICD-10 coding may have occurred, although equally in cases and controls. Patients with chronic diseases are likely to visit their physicians frequently, increasing the opportunity for detection and diagnosis of MDD. Further, patients with pre-existing psychiatric disorders are likely to be treated by psychiatrists, who may be better at diagnosing MDD than other physicians, which might lead to higher ORs for psychiatric diseases than for physical diseases; however, MDD diagnosis by general practitioners is also higher in patients with psychiatric comorbidity than in those with physical comorbidity.[41] Nevertheless, MDD is often under-recognised and underdiagnosed, which may mean that the control group included patients who actually had depression or depressive symptoms. We only assessed disease prevalence, and not incidence, during the year before the inclusion year; therefore, we do not know if the disease was diagnosed during that year or in

a previous year. This limitation could potentially result in a disproportionate number of people in the control group who had longer-term diseases and were not vulnerable to MDD. For some high-stress diseases such as cancer or stroke, MDD often occurs soon after diagnosis[42 43]; hence, less vulnerable patients who did not develop MDD would have remained within the control group, leading to lower ORs for those diseases than might be expected. Finally, the relatively short observation period limits our ability to look at the long-term relationship between MDD, which can re-occur multiple times in a patient's life, and other chronic conditions. Although comparing ORs for the onset of MDD across a broad range of pre-existing diseases can help develop hypotheses regarding possible underlying mechanisms, the risk of MDD occurring in specific diseases should be investigated on an individual basis.

CONCLUSIONS

This large, preliminary, nested case-control study has documented the high prevalence of pre-existing diseases in Japanese patients with MDD compared with matched controls without MDD. The high prevalence of pre-existing diseases in patients who develop MDD reflects the complex relationship between physical and mental disorders and indicates a high medical burden for these patients. These results confirm that patients with chronic and/or serious diseases, including prodromal symptoms that are not always recognised as related to MDD, should be monitored for depressive symptoms, and pre-existing diseases should be taken into consideration when prescribing treatment for MDD.

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Contributors

Yoshinori Cho designed the study and data collection, interpreted the study results, and participated in the drafting, critical revision, and approval of the final version of the manuscript. Izumi Mishiro designed the study and data collection, wrote the statistical analysis plan, interpreted the study results, and participated in the drafting, critical revision, and approval of the final version of the manuscript. Tsuyoshi Akaki designed the study and data collection, interpreted the study results, and participated in the drafting, critical revision, and approval of the final version of the manuscript. Takafumi Akimoto designed the study and data collection, interpreted the study results, and participated in the drafting, critical revision, and approval of the final version of the manuscript. Keita Fujiwara designed the study and data collection, interpreted the study results, and participated in the drafting, critical revision, and approval of the final version of the manuscript.

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Data availability statement

The data that support the findings of this study are available from JMDC Inc. but were used under licence for the current study; therefore, restrictions apply and the data are not publicly available. For inquiries about access to the data set used in this study, please contact JMDC (https://www.jmdc.co.jp).

Competing interests

Dr Cho reports grants from Shionogi & Co., Ltd. and Otsuka Pharmaceutical Co., Ltd., and personal fees from Shionogi & Co., Ltd., Otsuka Pharmaceutical Co., Ltd., Eli Lilly Japan K.K., Kyowa Kirin Co. Ltd., Pfizer Japan Inc., Meiji Seika Pharma Co., Ltd., Mitsubishi Tanabe Pharma Corporation, Sumitomo Dainippon Pharma Co., Ltd., Astellas Pharma Inc., MSD K.K., Takeda Pharmaceutical Company Limited, and Lundbeck Japan K.K., outside the submitted work. Drs Mishiro, Akaki, Akimoto, and Fujikawa report personal fees from Takeda Pharmaceutical Company Limited, outside the submitted work.

Ethics statements

Ethics approval

The study was approved by the Ethics Review Committee of the Research Institute of Healthcare Data Science (Tokyo, Japan) on 6 August 2019 (approval number RI2019004). Only anonymised information was accessible from the database; therefore, in accordance with the Ethical Guidelines for Medical and Health Research Involving Human Subjects in Japan, informed consent was not required.

Patient consent for publication

Not applicable.

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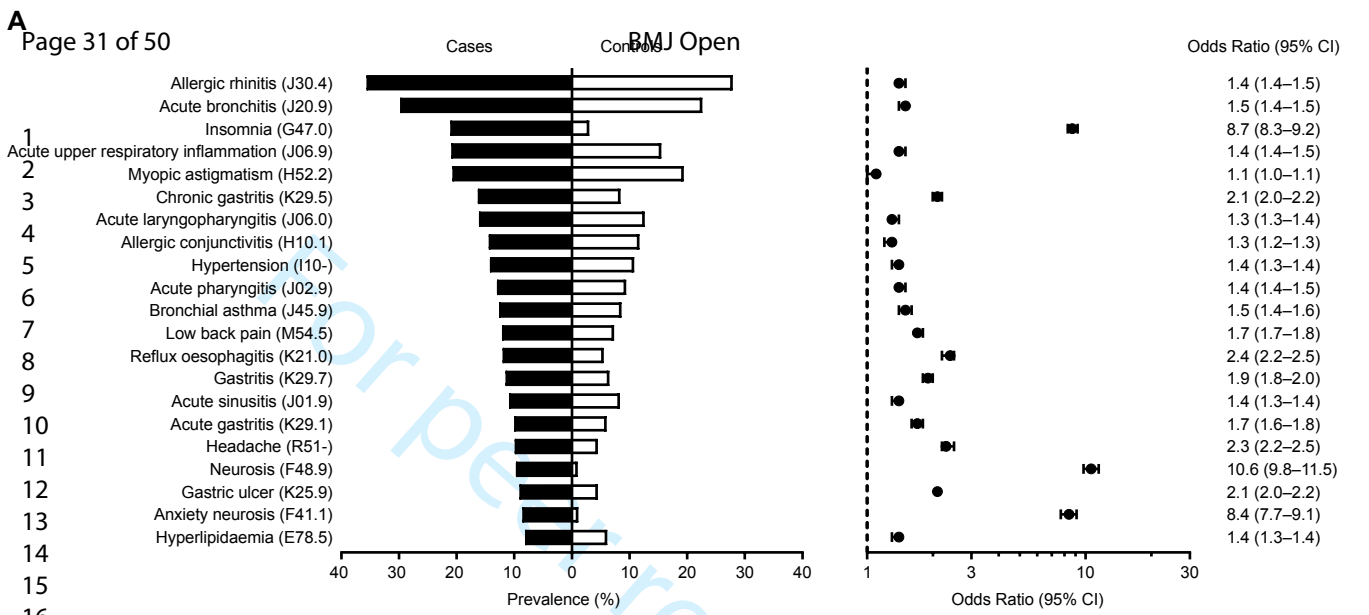
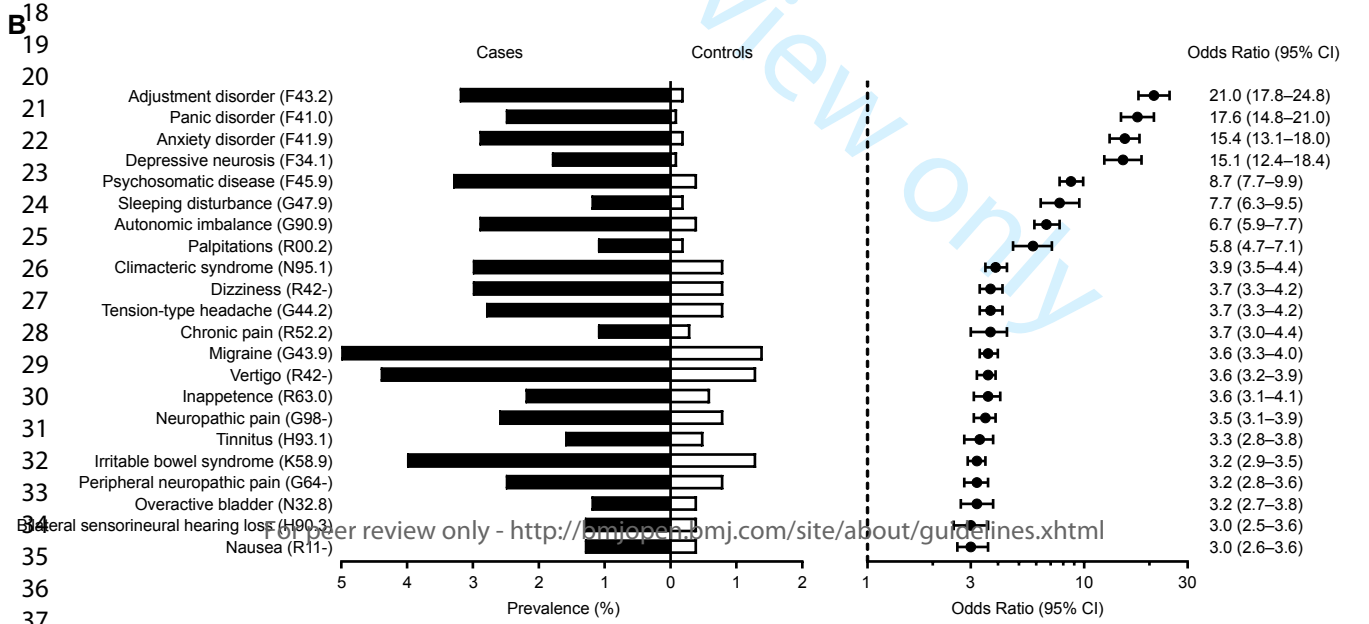
FIGURE LEGEND

Figure A, Diseases with prevalence >8% in the case group in the 12 months before MDD diagnosis. B, Diseases with odds ratio >3.0. Shown are the prevalence rates in the case group and in the matched control group, as well as the odds ratio (95% CI). CI, confidence interval; MDD, major depressive disorder.





Supplemental Material

TITLE

Diseases prevalent before major depressive disorder diagnosis: an exploratory nested case-control study using health insurance–based claims data

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Supplemental figure Flow diagram of patients included in the case group and matched control group. Dates (2015, 2016, 2017) represent the inclusion years. MDD, major depressive disorder.

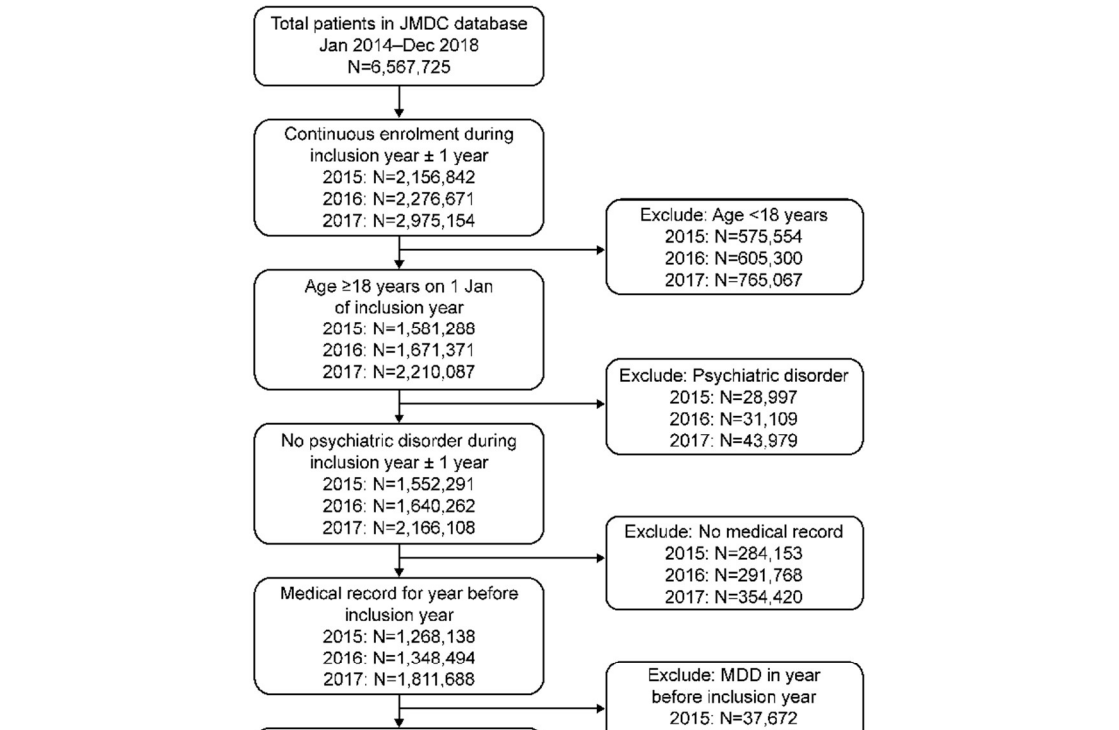
Supplemental table 1 ICD-10 codes and other terms used to identify pre-existing diseases

Supplemental table 2 Prevalence of diseases in the 12 months before the index date by ICD-10 code, ICD-10 name, and standard disease name in the case group and matched control group, ranked by prevalence in the case group

Supplemental table 3 Number of patients in post hoc multivariate analysis subgroups

Supplemental table 4 Multivariate logistic regression analysis for the relationship between the number of CCI-related and other chronic diseases and the onset of MDD

Supplemental figure Flow diagram of patients included in the case group and matched control group.



Dates (2015, 2016, 2017) represent the inclusion years. MDD, major depressive disorder.

Supplemental table 1 ICD-10 codes and other terms used to identify pre-existing diseases

Disease	ICD-10 codes and other terms
CCI-related diseases	
Myocardial infarction	I21, I22, I25.2
Cardiac failure, congestive	I43, I50, I09.9, I11.0, I25.5, I42.0, I42.5, I42.6, I42.7, I42.8, I42.9, I13.0, I13.2, P29.0
Peripheral vascular disease	I70, I71, I73.1, I73.8, I73.9, I77.1, K55.1, K55.9, Z95.8, I79.0, I79.2, K55.8, Z95.9
Cerebrovascular disease	G45, G46, I60–I69, H34.0, I72.0, I72.5, I72.6
Dementia	F00, F01, F02, F03, G30, F05.1, G31.1
Chronic lung disease (excluding asthma)	J40–J47, J60–J67, I27.8, I27.9, J68.4, J70.1, J70.3
Rheumatic disease	M05–M06, M32–M34, M31.5, M35.1, M35.3, M36.0
Peptic ulcer disease	K25–K28
Mild liver disease	B18, K73–K74, K70.0–K70.3, K70.9, K71.3, K71.4, K71.5, K71.7, K76.0, K76.2, K76.3, K76.4, K76.8, K76.9, Z94.4, K75.8
Diabetes mellitus without complications	E10.0, E10.1, E10.9, E11.0, E11.1, E11.9, E12.0, E12.1, E12.9, E13.0, E13.1, E13.9, E14.0, E14.1, E14.9
Diabetes mellitus with complications	E10.2–E10.8, E11.2, E11.3–E11.8, E12.2–E12.8, E13.2–E13.8, E14.2–E14.8
Hemiplegia or paraplegia	G81, G82, G041, G11.4, G80.1, G80.2, G83.9, G83.0–G83.4
Renal disease	N18, N19, I12.0, I13.1, N03.2–N03.7, N05.2–N05.7, N25.0, Z49.0–Z49.2, Z94.0, Z99.2
Solid tumours without metastasis	C00–C76, C80, C97
Leukaemia	C91–C96, D47.1, D47.5
Malignant lymphoma and multiple myeloma	C81–C90
Moderate or severe liver disease	I85.0, I85.9, I86.4, I98.2, K70.4, K71.1, K72.1, K72.9, K76.5–K76.7
Metastatic cancer	C77–C79
Other chronic diseases	
Angina pectoris	I20, Post-infarction angina pectoris
Dyslipidaemia (hyperlipidaemia)	E78.0–E78.2, E78.4, E78.5
Hypertensive disease	I10
Obesity	E65, E66
Atopic dermatitis	L20
Asthma	J45, J46
Thyroid disease	E01–E06, E07.0, E07.8, E07.9
Osteoarthritis	M05, M06 Other disease name with ‘osteoarthritis’
Arthritis	M00–M03, M05–M14 Other disease name with ‘arthritis’
Epilepsy	G40, G41
Headache	G43, G44, R51
Osteoporosis	M80, M81

Disease	ICD-10 codes and other terms
Parkinsonism	G20, G21
Pain	B02, F45.4, G50–G59, G64, G98, M25, M43, M45–M49, M50–M54, M79.1, M79.2, M79.6, M79.7, M89.0, R52 Diabetic neuropathic pain
Irritable bowel syndrome	K58
Chronic gastritis	K29.3, K29.4, K29.5
Chronic enteritis	K52.9
Dizziness	R42, H81, I95.1 Epidemic dizziness, psychogenic dizziness, low-tone dizziness
Autonomic nerve imbalance	G90
Attention deficit hyperactivity disorder	F90
Psychiatric disorders other than depression	F00–F99* *Except F00–F09, F20–F29, F30–F33
Sleep disorders	G47
Metabolic risk factors	
Diabetes mellitus without complications	E10.0, E10.1, E10.9, E11.0, E11.1, E11.9, E12.0, E12.1, E12.9, E13.0, E13.1, E13.9, E14.0, E14.1, E14.9
Diabetes mellitus with complications	E10.2–E10.8, E11.2–E11.8, E12.2–E12.8, E13.2–E13.8, E14.2–E14.8
Dyslipidaemia (hyperlipidaemia)	E78.0–E78.2, E78.4, E78.5
Hypertensive disease	I10
Psychiatric disorders	
Psychiatric disorders other than depression	F00–F99* *Except F00–F09, F20–F29, F30–F33
Sleep disorders	G47
MDD-related symptoms	
Headache	G43, G44, R51
Pain	B02, F45.4, G50–G59, G64, G98, M25, M43, M45–M49, M50–M54, M79.1, M79.2, M79.6, M79.7, M89.0, R52 Diabetic neuropathic pain
Autonomic nerve imbalance	G90

CCI, Charlson comorbidity index; ICD-10, International Statistical Classification of Diseases and Related Health Problems, 10th revision; MDD, major depressive disorder.

Supplemental table 2 Prevalence of diseases in the 12 months before the index date by ICD-10 code, ICD-10 name, and standard disease name in the case group and matched control group, ranked by prevalence in the case group

ICD-10 level 4 code	ICD-10 level 4 name	Standard disease name	Case group N=13,420	Control group N=134,200	Odds ratio (95% CI)
J30.4	Allergic rhinitis, unspecified	Allergic rhinitis	4782 (35.6)	37,507 (27.9)	1.4 (1.4–1.5)
J20.9	Acute bronchitis, unspecified	Acute bronchitis	4005 (29.8)	30,359 (22.6)	1.5 (1.4–1.5)
G47.0	Disorders of initiating and maintaining sleep [insomnias]	Insomnia	2836 (21.1)	4010 (3.0)	8.7 (8.3–9.2)
J06.9	Acute upper respiratory infection, unspecified	Acute infection of upper respiratory tract	2807 (20.9)	20,738 (15.5)	1.4 (1.4–1.5)
H52.2	Astigmatism	Myopic astigmatism	2784 (20.7)	26,090 (19.4)	1.1 (1.0–1.1)
K29.5	Chronic gastritis, unspecified	Chronic gastritis	2189 (16.3)	11,246 (8.4)	2.1 (2.0–2.2)
J06.0	Acute laryngopharyngitis	Acute laryngopharyngitis	2156 (16.1)	16,963 (12.6)	1.3 (1.3–1.4)
H10.1	Acute atopic conjunctivitis	Allergic conjunctivitis	1928 (14.4)	15,748 (11.7)	1.3 (1.2–1.3)
I10-	Essential (primary) hypertension	Hypertension	1903 (14.2)	14,477 (10.8)	1.4 (1.3–1.4)
J02.9	Acute pharyngitis, unspecified	Acute pharyngitis	1740 (13.0)	12,573 (9.4)	1.4 (1.4–1.5)
J45.9	Asthma, unspecified	Bronchial asthma	1689 (12.6)	11,547 (8.6)	1.5 (1.4–1.6)
M54.5	Low back pain	Low back pain	1628 (12.1)	9821 (7.3)	1.7 (1.7–1.8)
K21.0	Gastro-oesophageal reflux disease with oesophagitis	Reflux oesophagitis	1607 (12.0)	7322 (5.5)	2.4 (2.2–2.5)
K29.7	Gastritis, unspecified	Gastritis	1547 (11.5)	8762 (6.5)	1.9 (1.8–2.0)
J01.9	Acute sinusitis, unspecified	Acute sinusitis	1468 (10.9)	11,115 (8.3)	1.4 (1.3–1.4)
K29.1	Other acute gastritis	Acute gastritis	1342	8075	1.7

ICD-10 level 4 code	ICD-10 level 4 name	Standard disease name	Case group N=13,420	Control group N=134,200	Odds ratio (95% CI)
			(10.0)	(6.0)	(1.6–1.8)
R51-	Headache	Headache	1332 (9.9)	6046 (4.5)	2.3 (2.2–2.5)
F48.9	Neurotic disorder, unspecified	Neurosis	1306 (9.7)	1350 (1.0)	10.6 (9.8–11.5)
K25.9	Gastric ulcer/Unspecified as acute or chronic, without haemorrhage or perforation	Gastric ulcer	1216 (9.1)	6086 (4.5)	2.1 (2.0–2.2)
F41.1	Generalised anxiety disorder	Anxiety neurosis	1155 (8.6)	1492 (1.1)	8.4 (7.7–9.1)
E78.5	Hyperlipidaemia, unspecified	Hyperlipidaemia	1091 (8.1)	8244 (6.1)	1.4 (1.3–1.4)
J02.9	Acute pharyngitis, unspecified	Pharyngitis	1061 (7.9)	7940 (5.9)	1.4 (1.3–1.5)
L30.9	Dermatitis, unspecified	Eczema	1032 (7.7)	7799 (5.8)	1.4 (1.3–1.4)
K59.0	Constipation	Constipation	1030 (7.7)	6014 (4.5)	1.8 (1.7–1.9)
E86-	Volume depletion	Dehydration	1003 (7.5)	4825 (3.6)	2.2 (2.0–2.3)
E78.0	Pure hypercholesterolaemia	Hypercholesterolaemia	940 (7.0)	7031 (5.2)	1.4 (1.3–1.5)
R11-	Nausea and vomiting	Vomition	933 (7.0)	4031 (3.0)	2.4 (2.2–2.6)
M53.1	Cervicobrachial syndrome	Cervico-omo-brachial syndrome	905 (6.7)	3380 (2.5)	2.8 (2.6–3.0)
J00-	Acute nasopharyngitis [common cold]	Common cold	894 (6.7)	5998 (4.5)	1.5 (1.4–1.6)
A09.9	Gastroenteritis and colitis of unspecified origin	Acute gastroenteritis	873 (6.5)	5140 (3.8)	1.7 (1.6–1.9)
E14-	Unspecified diabetes mellitus	Diabetes mellitus	870 (6.5)	6285 (4.7)	1.4 (1.3–1.5)
J32.9	Chronic sinusitis, unspecified	Chronic sinusitis	818 (6.1)	5551 (4.1)	1.5 (1.4–1.6)
A09.9	Gastroenteritis and colitis of unspecified origin	Diarrhoea	781 (5.8)	4311 (3.2)	1.9 (1.7–2.0)

ICD-10 level 4 code	ICD-10 level 4 name	Standard disease name	Case group N=13,420	Control group N=134,200	Odds ratio (95% CI)
G62.9	Polyneuropathy, unspecified	Peripheral neuropathy	775 (5.8)	3374 (2.5)	2.4 (2.2–2.6)
J40-	Bronchitis, not specified as acute or chronic	Bronchitis	716 (5.3)	5644 (4.2)	1.3 (1.2–1.4)
E79.0	Hyperuricaemia without signs of inflammatory arthritis and tophaceous disease	Hyperuricaemia	700 (5.2)	5880 (4.4)	1.2 (1.1–1.3)
G43.9	Migraine, unspecified	Migraine	669 (5.0)	1917 (1.4)	3.6 (3.3–4.0)
H04.1	Other disorders of lacrimal gland	Dry eye	663 (4.9)	4312 (3.2)	1.6 (1.4–1.7)
D50.9	Iron deficiency anaemia, unspecified	Iron deficiency anaemia	650 (4.8)	4957 (3.7)	1.3 (1.2–1.4)
E78.5	Hyperlipidaemia, unspecified	Dyslipidaemia	646 (4.8)	4684 (3.5)	1.4 (1.3–1.5)
H10.9	Conjunctivitis, unspecified	Conjunctivitis	644 (4.8)	5118 (3.8)	1.3 (1.2–1.4)
H52.1	Myopia	Myopia	636 (4.7)	6292 (4.7)	1.0 (0.9–1.1)
J10.1	Influenza with other respiratory manifestations, seasonal influenza virus identified	Human influenza A	613 (4.6)	5585 (4.2)	1.1 (1.0–1.2)
M75.0	Adhesive capsulitis of shoulder	Periarthritis scapulohumeralis	605 (4.5)	3523 (2.6)	1.8 (1.6–1.9)
L20.9	Atopic dermatitis, unspecified	Atopic dermatitis	601 (4.5)	5924 (4.4)	1.0 (0.9–1.1)
L85.3	Xerosis cutis	Xerosis	596 (4.4)	4954 (3.7)	1.2 (1.1–1.3)
R42-	Dizziness and giddiness	Vertigo	585 (4.4)	1701 (1.3)	3.6 (3.2–3.9)
K76.9	Liver disease, unspecified	Hepatic dysfunction	571 (4.3)	3458 (2.6)	1.7 (1.5–1.8)
K58.9	Irritable bowel syndrome without diarrhoea	Irritable bowel syndrome	539 (4.0)	1756 (1.3)	3.2 (2.9–3.5)

ICD-10 level 4 code	ICD-10 level 4 name	Standard disease name	Case group N=13,420	Control group N=134,200	Odds ratio (95% CI)
K76.0	Fatty (change of) liver, not elsewhere classified	Hepatic steatosis	537 (4.0)	3564 (2.7)	1.5 (1.4–1.7)
J11.1	Influenza with other respiratory manifestations, virus not identified	Influenza	529 (3.9)	4256 (3.2)	1.3 (1.1–1.4)
L50.9	Urticaria, unspecified	Urticaria	524 (3.9)	3755 (2.8)	1.4 (1.3–1.5)
L85.3	Xerosis cutis	Asteatotic eczema	511 (3.8)	4328 (3.2)	1.2 (1.1–1.3)
M47.8	Other spondylosis	Cervical spondylosis	505 (3.8)	2012 (1.5)	2.6 (2.3–2.8)
J03.9	Acute tonsillitis, unspecified	Acute tonsillitis	495 (3.7)	3922 (2.9)	1.3 (1.2–1.4)
A09.9	Gastroenteritis and colitis of unspecified origin	Acute enteritis	481 (3.6)	2707 (2.0)	1.8 (1.6–2.0)
K21.0	Gastro-oesophageal reflux disease with oesophagitis	Refractory reflux oesophagitis requiring maintenance therapy	477 (3.6)	1989 (1.5)	2.4 (2.2–2.7)
E28.3	Primary ovarian failure	Ovarian insufficiency	470 (3.5)	3125 (2.3)	1.5 (1.4–1.7)
N86-	Erosion and ectropion of cervix uteri	Uterovaginal erosion	452 (3.4)	3170 (2.4)	1.4 (1.3–1.6)
A09.0	Other and unspecified gastroenteritis and colitis of infectious origin	Infectious gastroenteritis	449 (3.3)	2964 (2.2)	1.5 (1.4–1.7)
J06.0	Acute laryngopharyngitis	Laryngopharyngitis	447 (3.3)	3059 (2.3)	1.5 (1.3–1.6)
M51.9	Intervertebral disc disorder, unspecified	Lumbar vertebral discopathy	440 (3.3)	2565 (1.9)	1.7 (1.6–1.9)
F45.9	Somatoform disorder, unspecified	Psychosomatic disease	437 (3.3)	515 (0.4)	8.7 (7.7–9.9)
F43.2	Adjustment disorders	Adjustment disorder	427 (3.2)	210 (0.2)	21.0 (17.8–24.8)
J03.9	Acute tonsillitis, unspecified	Tonsillitis	413 (3.1)	2958 (2.2)	1.4 (1.3–1.6)
H52.4	Presbyopia	Presbyopia	408 (3.0)	2977 (2.2)	1.4 (1.2–1.5)

ICD-10 level 4 code	ICD-10 level 4 name	Standard disease name	Case group N=13,420	Control group N=134,200	Odds ratio (95% CI)
R42-	Dizziness and giddiness	Dizziness	407 (3.0)	1113 (0.8)	3.7 (3.3–4.2)
N95.1	Menopausal and female climacteric states	Climacteric syndrome	399 (3.0)	1050 (0.8)	3.9 (3.5–4.4)
F41.9	Anxiety disorder, unspecified	Anxiety disorder	387 (2.9)	259 (0.2)	15.4 (13.1–18.0)
G90.9	Disorder of autonomic nervous system, unspecified	Autonomic imbalance	385 (2.9)	585 (0.4)	6.7 (5.9–7.7)
L25.9	Unspecified contact dermatitis, unspecified cause	Contact dermatitis	376 (2.8)	3018 (2.2)	1.3 (1.1–1.4)
B35.3	Tinea pedis	Foot tinea	375 (2.8)	3393 (2.5)	1.1 (1.0–1.2)
M51.2	Other specified intervertebral disc displacement	Lumbar disc herniation	375 (2.8)	2106 (1.6)	1.8 (1.6–2.0)
G44.2	Tension-type headache	Tension-type headache	372 (2.8)	1014 (0.8)	3.7 (3.3–4.2)
D25.9	Leiomyoma of uterus, unspecified	Uterus myoma	368 (2.7)	2690 (2.0)	1.4 (1.2–1.5)
H53.1	Subjective visual disturbances	Asthenopia	366 (2.7)	2355 (1.8)	1.6 (1.4–1.8)
E11-	Type 2 diabetes mellitus	Type 2 diabetes mellitus	365 (2.7)	2654 (2.0)	1.4 (1.2–1.5)
M17.9	Gonarthrosis, unspecified	Knee osteoarthritis	355 (2.6)	2589 (1.9)	1.4 (1.2–1.5)
G98-	Other disorders of nervous system, not elsewhere classified	Neuropathic pain	345 (2.6)	1011 (0.8)	3.5 (3.1–3.9)
F41.0	Panic disorder [episodic paroxysmal anxiety]	Panic disorder	341 (2.5)	198 (0.1)	17.6 (14.8–21.0)
A09.0	Other and unspecified gastroenteritis and colitis of infectious origin	Infectious enteritis	340 (2.5)	2222 (1.7)	1.5 (1.4–1.7)
H16.8	Other keratitis	Keratoconjunctivitis sicca	336 (2.5)	2509 (1.9)	1.3 (1.2–1.5)

ICD-10 level 4 code	ICD-10 level 4 name	Standard disease name	Case group N=13,420	Control group N=134,200	Odds ratio (95% CI)
R50.9	Fever, unspecified	Pyrexia	335 (2.5)	2385 (1.8)	1.4 (1.3–1.6)
G64-	Other disorders of peripheral nervous system	Peripheral neuropathic pain	334 (2.5)	1061 (0.8)	3.2 (2.8–3.6)
I20.9	Angina pectoris, unspecified	Angina pectoris	334 (2.5)	1759 (1.3)	1.9 (1.7–2.2)
J04.0	Acute laryngitis	Acute laryngitis	313 (2.3)	2428 (1.8)	1.3 (1.2–1.5)
I49.9	Cardiac arrhythmia, unspecified	Arrhythmia	307 (2.3)	1184 (0.9)	2.6 (2.3–3.0)
H81.0	Ménière disease	Ménière's disease	302 (2.3)	1066 (0.8)	2.9 (2.5–3.3)
K64.9	Haemorrhoids, unspecified	Internal haemorrhoids	300 (2.2)	1856 (1.4)	1.6 (1.4–1.8)
L21.9	Seborrheic dermatitis, unspecified	Seborrheic dermatitis	299 (2.2)	2434 (1.8)	1.2 (1.1–1.4)
J00-	Acute nasopharyngitis [common cold]	Acute rhinitis	295 (2.2)	2089 (1.6)	1.4 (1.3–1.6)
B07-	Viral warts	Verruca vulgaris	294 (2.2)	2660 (2.0)	1.1 (1.0–1.3)
L08.9	Local infection of skin and subcutaneous tissue, unspecified	Cutaneous infection	291 (2.2)	2252 (1.7)	1.3 (1.1–1.5)
N94.6	Dysmenorrhoea, unspecified	Dysmenorrhoea	290 (2.2)	1105 (0.8)	2.7 (2.3–3.0)
R63.0	Anorexia	Inappetence	290 (2.2)	826 (0.6)	3.6 (3.1–4.1)
H61.2	Impacted cerumen	Impacted cerumen	286 (2.1)	2199 (1.6)	1.3 (1.2–1.5)
H60.5	Acute otitis externa, non-infective	External ear eczema	281 (2.1)	2098 (1.6)	1.3 (1.2–1.5)
A49.8	Other bacterial infections of unspecified site	*Helicobacter pylori* infection	277 (2.1)	2222 (1.7)	1.3 (1.1–1.4)
R10.4	Other and unspecified abdominal pain	Abdominal pain	269 (2.0)	1301 (1.0)	2.1 (1.8–2.4)
G47.3	Sleep apnoea	Sleep apnoea syndrome	268 (2.0)	1335 (1.0)	2.0 (1.8–2.3)

ICD-10 level 4 code	ICD-10 level 4 name	Standard disease name	Case group N=13,420	Control group N=134,200	Odds ratio (95% CI)
N30.9	Cystitis, unspecified	Cystitis	264 (2.0)	1564 (1.2)	1.7 (1.5–1.9)
K12.1	Other forms of stomatitis	Stomatitis	262 (2.0)	1669 (1.2)	1.6 (1.4–1.8)
H52.2	Astigmatism	Hyperopic astigmatism	260 (1.9)	1851 (1.4)	1.4 (1.2–1.6)
M79.1	Myalgia	Myalgia	248 (1.8)	1226 (0.9)	2.0 (1.8–2.3)
F34.1	Dysthymia	Depressive neurosis	239 (1.8)	161 (0.1)	15.1 (12.4–18.4)
H40.9	Glaucoma, unspecified	Glaucoma	239 (1.8)	2136 (1.6)	1.1 (1.0–1.3)
H60.9	Otitis externa, unspecified	Otitis externa	239 (1.8)	1932 (1.4)	1.2 (1.1–1.4)
K63.5	Polyp of colon	Colorectal polyp	239 (1.8)	1947 (1.5)	1.2 (1.1–1.4)
A09.9	Gastroenteritis and colitis of unspecified origin	Gastroenteritis	238 (1.8)	1351 (1.0)	1.8 (1.5–2.0)
K21.0	Gastro-oesophageal reflux disease with oesophagitis	Intractable regurgitant oesophagitis	238 (1.8)	1123 (0.8)	2.1 (1.9–2.5)
N76.0	Acute vaginitis	Bacterial vaginitis	232 (1.7)	1569 (1.2)	1.5 (1.3–1.7)
M10.9	Gout, unspecified	Gout	230 (1.7)	1763 (1.3)	1.3 (1.1–1.5)
L30.9	Dermatitis, unspecified	Acute eczema	229 (1.7)	1856 (1.4)	1.2 (1.1–1.4)
H16.0	Corneal ulcer	Corneal erosion	222 (1.7)	1935 (1.4)	1.1 (1.0–1.3)
H93.1	Tinnitus	Tinnitus	217 (1.6)	672 (0.5)	3.3 (2.8–3.8)
D64.9	Anaemia, unspecified	Anaemia	216 (1.6)	1337 (1.0)	1.6 (1.4–1.9)
M47.8	Other spondylosis	Lumbar osteoarthritis	216 (1.6)	1105 (0.8)	2.0 (1.7–2.3)
H01.0	Blepharitis	Blepharitis	215 (1.6)	1665 (1.2)	1.3 (1.1–1.5)

ICD-10 level 4 code	ICD-10 level 4 name	Standard disease name	Case group N=13,420	Control group N=134,200	Odds ratio (95% CI)
H26.9	Cataract, unspecified	Cataract	214 (1.6)	1653 (1.2)	1.3 (1.1–1.5)
H52.1	Myopia	High myopia	213 (1.6)	2000 (1.5)	1.1 (0.9–1.2)
J30.1	Allergic rhinitis due to pollen	Pollinosis	210 (1.6)	1670 (1.2)	1.3 (1.1–1.5)
L30.9	Dermatitis, unspecified	Chronic eczema	210 (1.6)	1693 (1.3)	1.2 (1.1–1.4)
M81.9	Osteoporosis, unspecified	Osteoporosis	207 (1.5)	1455 (1.1)	1.4 (1.2–1.7)
R07.4	Chest pain, unspecified	Chest pain	206 (1.5)	789 (0.6)	2.6 (2.3–3.1)
J37.0	Chronic laryngitis	Chronic pharyngopharyngitis	205 (1.5)	1259 (0.9)	1.6 (1.4–1.9)
K64.9	Haemorrhoids, unspecified	Haemorrhoid	203 (1.5)	1281 (1.0)	1.6 (1.4–1.8)
J42-	Unspecified chronic bronchitis	Chronic bronchitis	201 (1.5)	1422 (1.1)	1.4 (1.2–1.6)
K29.4	Chronic atrophic gastritis	Atrophic gastritis	201 (1.5)	1503 (1.1)	1.3 (1.2–1.6)
M48.0	Spinal stenosis	Lumbar spinal canal stenosis	201 (1.5)	880 (0.7)	2.3 (2.0–2.7)
H40.0	Glaucoma suspect	Enlargement of optic disc cupping	200 (1.5)	1628 (1.2)	1.2 (1.1–1.4)
H90.5	Sensorineural hearing loss, unspecified	Sensorineural hearing loss	199 (1.5)	917 (0.7)	2.2 (1.9–2.6)
E03.9	Hypothyroidism, unspecified	Hypothyroidism	197 (1.5)	938 (0.7)	2.1 (1.8–2.5)
N40-	Hyperplasia of prostate	Prostatic hyperplasia	197 (1.5)	1098 (0.8)	1.8 (1.6–2.1)
L70.0	Acne vulgaris	Acne vulgaris	195 (1.5)	1555 (1.2)	1.3 (1.1–1.5)
L30.9	Dermatitis, unspecified	Hand eczema	193 (1.4)	1665 (1.2)	1.2 (1.0–1.3)

ICD-10 level 4 code	ICD-10 level 4 name	Standard disease name	Case group N=134,420	Control group N=134,200	Odds ratio (95% CI)
H00.0	Hordeolum and other deep inflammation of eyelid	Hordeolum	190 (1.4)	1560 (1.2)	1.2 (1.0–1.4)
M47.8	Other spondylosis	Cervical spondylosis	190 (1.4)	830 (0.6)	2.3 (2.0–2.7)
A09.9	Gastroenteritis and colitis of unspecified origin	Enterocolitis	185 (1.4)	1046 (0.8)	1.8 (1.5–2.1)
J45.9	Asthma, unspecified	Asthmatic bronchitis	185 (1.4)	1373 (1.0)	1.4 (1.2–1.6)
H16.1	Other superficial keratitis without conjunctivitis	Superficial punctate keratitis	183 (1.4)	1451 (1.1)	1.3 (1.1–1.5)
M62.8	Other specified disorders of muscle	Shoulder stiffness	181 (1.3)	755 (0.6)	2.4 (2.1–2.8)
H90.3	Sensorineural hearing loss, bilateral	Bilateral sensorineural hearing loss	176 (1.3)	590 (0.4)	3.0 (2.5–3.6)
J00-	Acute nasopharyngitis [common cold]	Acute nasopharyngitis	176 (1.3)	1291 (1.0)	1.4 (1.2–1.6)
R11-	Nausea and vomiting	Nausea	176 (1.3)	585 (0.4)	3.0 (2.6–3.6)
K31.7	Polyp of stomach and duodenum	Stomach polyp	175 (1.3)	1108 (0.8)	1.6 (1.4–1.9)
M50.2	Other cervical disc displacement	Cervical disc herniation	175 (1.3)	865 (0.6)	2.0 (1.7–2.4)
K73.9	Chronic hepatitis, unspecified	Chronic hepatitis	174 (1.3)	1179 (0.9)	1.5 (1.3–1.7)
L29.9	Pruritus, unspecified	Pruritus cutaneous	173 (1.3)	1176 (0.9)	1.5 (1.3–1.7)
N64.9	Disorder of breast, unspecified	Mastopathy	173 (1.3)	1176 (0.9)	1.5 (1.3–1.7)
H68.1	Obstruction of Eustachian tube	Stenosis of Eustachian tube	172 (1.3)	929 (0.7)	1.9 (1.6–2.2)
L81.0	Post-inflammatory hyperpigmentation	Post-inflammatory pigmentation	171 (1.3)	1272 (0.9)	1.3 (1.1–1.6)
R52.9	Pain, unspecified	Pain	169 (1.3)	904 (0.7)	1.9 (1.6–2.2)
N80.9	Endometriosis, unspecified	Endometriosis	165	872	1.9

ICD-10 level 4 code	ICD-10 level 4 name	Standard disease name	Case group N=13,420	Control group N=134,200	Odds ratio (95% CI)
			(1.2)	(0.6)	(1.6–2.3)
H65.9	Nonsuppurative otitis media, unspecified	Otitis media with effusion	164 (1.2)	1191 (0.9)	1.4 (1.2–1.6)
J32.9	Chronic sinusitis, unspecified	Sinusitis	164 (1.2)	1146 (0.9)	1.4 (1.2–1.7)
N32.8	Other specified disorders of bladder	Overactive bladder	164 (1.2)	519 (0.4)	3.2 (2.7–3.8)
G62.9	Polyneuropathy, unspecified	Peripheral neuritis	163 (1.2)	662 (0.5)	2.5 (2.1–2.9)
L30.9	Dermatitis, unspecified	Dermatitis	163 (1.2)	1336 (1.0)	1.2 (1.0–1.4)
L70.0	Acne vulgaris	Facial common acne	162 (1.2)	1446 (1.1)	1.1 (1.0–1.3)
I50.9	Heart failure, unspecified	Chronic cardiac failure	159 (1.2)	815 (0.6)	2.0 (1.7–2.3)
G47.9	Sleep disorder, unspecified	Sleeping disturbance	157 (1.2)	205 (0.2)	7.7 (6.3–9.5)
M06.9	Rheumatoid arthritis, unspecified	Rheumatoid arthritis	155 (1.2)	830 (0.6)	1.9 (1.6–2.2)
J32.9	Chronic sinusitis, unspecified	Acute exacerbation of chronic sinusitis	153 (1.1)	1272 (0.9)	1.2 (1.0–1.4)
N20.1	Calculus of ureter	Ureterolithiasis	151 (1.1)	1139 (0.8)	1.3 (1.1–1.6)
R52.2	Other chronic pain	Chronic pain	151 (1.1)	417 (0.3)	3.7 (3.0–4.4)
R31-	Unspecified haematuria	Haematuria	149 (1.1)	1024 (0.8)	1.5 (1.2–1.7)
K76.9	Liver disease, unspecified	Liver disorder	148 (1.1)	955 (0.7)	1.6 (1.3–1.9)
R00.2	Palpitations	Palpitations	148 (1.1)	257 (0.2)	5.8 (4.7–7.1)
H10.3	Acute conjunctivitis, unspecified	Acute conjunctivitis	147 (1.1)	1212 (0.9)	1.2 (1.0–1.4)

ICD-10 level 4 code	ICD-10 level 4 name	Standard disease name	Case group N=13,420	Control group N=134,200	Odds ratio (95% CI)
J10.1	Influenza with other respiratory manifestations, seasonal influenza virus identified	Influenza B	147 (1.1)	1427 (1.1)	1.0 (0.9–1.2)
D27-	Benign neoplasm of ovary	Ovarian cystoma	141 (1.1)	967 (0.7)	1.5 (1.2–1.7)
B37.3	Candidiasis of vulva and vagina	Vulvovaginal candidiasis	140 (1.0)	930 (0.7)	1.5 (1.3–1.8)
B02.9	Zoster without complication	Herpes zoster	137 (1.0)	884 (0.7)	1.6 (1.3–1.9)
L73.9	Follicular disorder, unspecified	Folliculitis	136 (1.0)	1024 (0.8)	1.3 (1.1–1.6)
N20.0	Calculus of kidney	Nephrolithiasis	136 (1.0)	912 (0.7)	1.5 (1.2–1.8)
M47.2	Other spondylosis with radiculopathy	Cervical spondylotic radiculopathy	135 (1.0)	725 (0.5)	1.9 (1.6–2.3)

Shown are diseases with prevalence ≥1.0% in the case group and ≥0.1% in the control group. Data are n (%), unless otherwise noted.
CI, confidence interval; ICD-10, International Statistical Classification of Diseases and Related Health Problems, 10th revision.

Supplemental table 3 Number of patients in post hoc multivariate analysis subgroups

Explanatory variable	Category			Number of cases	Number of controls	Total number
Sex	Male			8924	89,240	98,164
	Female			4496	44,960	49,456
Age	<40 years			5390	53,900	59,290
	≥40 years			8030	80,300	88,330
Working status	Worker			10,447	104,470	114,917
	Non-worker			2973	29,730	32,703
Presence of metabolic risk factor, psychiatric disorder, and/or MDD-related symptoms during the 12 months before index date	Metabolic risk factor	Psychiatric disorder	MDD-related symptoms			
	No	No	No	4329	80,434	84,763
	No	No	Yes	1998	20,752	22,750
	No	Yes	No	1794	3314	5108
	No	Yes	Yes	1595	2301	3896
	Yes	No	No	901	15,660	16,561
	Yes	No	Yes	854	7588	8442
	Yes	Yes	No	675	1866	2541
	Yes	Yes	Yes	1274	2285	3559
Total				13,420	134,200	147,620

MDD, major depressive disorder.

Supplemental table 4 Multivariate logistic regression analysis for the relationship between the number of CCI-related and other chronic diseases and the onset of MDD

Dependent variable	Explanatory variable	Reference	Category	Odds ratio (95% CI)
Group (reference = control group)	Sex	Male	Female	1.08 (1.01–1.16)
	Age	<40 years	≥40 years	0.78 (0.74–0.82)
	Working status	Worker	Non-worker	0.97 (0.90–1.05)
	Number of chronic diseases	1	2	1.34 (1.27–1.42)
			3	1.51 (1.40–1.62)
			4	1.78 (1.63–1.95)
			5	2.16 (1.93–2.42)
			6	2.28 (1.95–2.66)
			7	2.21 (1.78–2.75)
			8	2.88 (2.18–3.81)
			9	3.70 (2.48–5.51)
			10	3.59 (2.03–6.35)
			≥11	3.26 (1.65–6.43)

Analysis included 8329 cases and 64,594 controls.
CCI, Charlson comorbidity index; CI, confidence interval; MDD, major depressive disorder.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *case-control studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5-6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-7
Participants	6	(a) Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	6-7
		(*b*) For matched studies, give matching criteria and the number of controls per case	7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-8
Bias	9	Describe any efforts to address potential sources of bias	NA
Study size	10	Explain how the study size was arrived at	NA
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7-8
		(*b*) Describe any methods used to examine subgroups and interactions	7-8
		(*c*) Explain how missing data were addressed	NA
		(*d*) If applicable, explain how matching of cases and controls was addressed	7
		(*e*) Describe any sensitivity analyses	NA
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8, Supplementary Figure
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	Supplementary Figure
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8, Table 1
		(b) Indicate number of participants with missing data for each variable of interest	NA
Outcome data	15*	Report numbers in each exposure category, or summary measures of exposure	8-10, Tables 2 and 3, Figure 1, Supplementary Tables
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8-10, Tables 2 and 3, Figure 1, Supplementary Tables
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8-10, Tables 2 and 3, Figure 1, Supplementary Tables
Discussion			
Key results	18	Summarise key results with reference to study objectives	10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13-14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	13-14
Other information			

Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Funding statement

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Diseases prevalent before major depressive disorder diagnosis: an exploratory nested case-control study using health insurance–based claims data

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MANUSCRIPT CATEGORY

Research Article

TITLE

Diseases prevalent before major depressive disorder diagnosis: an exploratory nested case-control study using health insurance–based claims data

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STATISTICAL SUMMARY

Abstract Text	Manuscript Text (Intro–Disc)	References	Figures / Tables
N = 291 (Limit = 300)	N = 3570 (Limit = 4000)	N = 43 (Limit = none)	N = 5 (plus 4 supplementary) (Limit = 5)

ABSTRACT

Objectives Major depressive disorder (MDD) is often comorbid with other chronic and/or serious diseases. However, little is known about the prevalence of various diseases that are present before MDD onset. We examined the prevalence of all pre-existing diseases in the 12 months before an MDD diagnosis.

Design Exploratory nested case-control study.

Setting Data, including diagnoses based on ICD-10 codes, were from a Japanese health insurance database (JMDC).

Participants Adults newly diagnosed with MDD during 2015, 2016, or 2017 (but not the preceding year) (cases) were matched (exact) 1:10 to controls by age, sex, index date, and working status.

Primary and secondary outcome measures The primary outcome was the proportion of patients in each group with each pre-existing disease during the 12 months before the index date (ie, before MDD diagnosis in cases). Odds ratios (ORs) for onset of MDD were calculated for each pre-existing disease. A post hoc multivariate analysis examined interactions of metabolic risk factors (diabetes, hypertension, dyslipidaemia), psychiatric disorders (sleep disorders, psychiatric disorders other than depression), and MDD-related symptoms (headache, pain, autonomic nerve imbalance) on MDD diagnosis.

Results There were 13,420 cases and 134,200 controls (mean age 41.9 years; 66.5% male). The prevalence of almost all pre-existing diseases was higher in cases than in controls. The highest ORs (5.8–21.0) were for psychiatric diseases and sleep disorders. Insomnia (21.1% of patients; OR 8.7) and neurosis (9.7%; OR 10.6) were particularly prevalent in the case group. The odds of MDD increased in the presence of metabolic risk factors, psychiatric disorders, and/or MDD-related symptoms.

Conclusions There is a high prevalence of pre-existing diseases in Japanese patients who develop MDD compared with matched controls without MDD. These results suggest that patients with chronic and/or serious diseases should be actively monitored for depression.

Strengths and limitations of this study

- This is the first nested case-control study to examine a broad range of pre-existing diseases in people who develop major depressive disorder (MDD) compared with people who do not.
- The use of a national health insurance database resulted in a sample size large enough to allow examination of less common pre-existing diseases.
- The nested case-control design and the use of a database minimised selection and recall biases that may occur in other case-control studies.
- Because of the nature of the database, the study did not include people aged ≥75 years, and information on the physician making the MDD diagnosis was not available.

Keywords: Administrative claims, healthcare; Comorbidity; Depressive disorder; Epidemiology; Risk factors

INTRODUCTION

Depression is frequently comorbid with other diseases, particularly chronic and/or serious diseases such as diabetes, cardiovascular/cerebrovascular disease, cancer, asthma, and arthritis.[1-3] The relationship between depression and most comorbidities is complex. For example, the temporal relationship appears to be bi-directional, in that depression can increase the risk of developing a chronic disease and vice versa.[3] In addition, the relationship with depression varies with the type, duration, and severity of disease, among other factors.[1-3] Moreover, the presence of depression in patients with pre-existing diseases is associated with worse outcomes and quality of life, and possibly decreased survival.[2] However, despite the accumulation of evidence for a link between depression and chronic illness, few studies have comprehensively compared the risk of depression in people with a broad range of pre-existing diseases.

An epidemiological study conducted in Japan between 2013 and 2015 reported the lifetime and 12-month prevalence rates of major depressive disorder (MDD) to be relatively low, at 5.7% and 2.7%, respectively.[4] Other studies have confirmed that major depressive episodes are less prevalent in Japan than in other countries.[5 6] However, fewer than half of Japanese people with a mood disorder seek medical treatment.[4] This reluctance to seek medical treatment may be related to a perceived 'stigma' associated with psychiatric disease.[7] These factors may further reduce the detection and diagnosis of MDD in patients with a chronic disease, despite the potentially increased risk of MDD in these patients. However, little is known about the prevalence of underlying diseases that are comorbid with MDD. Given that around 20,000 people in Japan commit suicide every year,[8] with the highest rate of about 50 per 100,000 persons in men aged 50–59 years,[9] most of which are probably related to mental disorders, additional information on factors associated with MDD that could assist with early detection and treatment may help reduce the number of suicides.

The aim of this exploratory nested case-control study of patients enrolled in a Japanese health insurance database was to comprehensively examine the prevalence of pre-existing diseases in the 12 months before an MDD diagnosis (defined using the International Statistical Classification of Diseases and Related Health Problems, 10th revision [ICD-10][10] codes F32 ['Depressive episode'] or F33 ['Recurrent depressive disorder']). In this context, a pre-existing disease was defined as any diagnosis other than MDD and related mental disorders (bipolar affective disorders; organic mental disorders; schizophrenia, schizotypal, and delusional disorders); the latter were excluded to avoid including patients with secondary diagnoses of MDD as cases. However, our definition of pre-existing conditions did include those that are prodromal symptoms of MDD (eg, sleep disorders), as well as psychiatric disorders that are less strongly linked to MDD. In addition, we determined an odds ratio (OR) for the onset of MDD for each pre-existing disease to identify those that are most commonly associated with development of MDD and to evaluate the association of MDD with common metabolic risk factors. We speculated that people with pre-existing diseases, including non-psychiatric diseases, might have an increased risk of subsequently developing MDD, which could be related to increased medical burden, shared underlying pathophysiological mechanisms, or other reasons.

METHODS

Study design and data source

This was a nested case-control study. Data on patient demographics and diagnoses based on ICD-10 were derived from the JMDC Inc. (Tokyo, Japan) database of medical expense claims for company employees in Japan.[11]

The study was approved by the Ethics Review Committee of the Research Institute of Healthcare Data Science (Tokyo, Japan) on 6 August 2019. Only anonymised information was accessible from the database; therefore, in accordance with the Ethical Guidelines for

Medical and Health Research Involving Human Subjects in Japan,[12] informed consent was not required.

Setting and participants

The study analysed data collected for the population registered in the JMDC database between January 2014 and December 2018 who were aged ≥18 years on 1 January of the inclusion year (2015, 2016, or 2017) and had continuous registration for the inclusion year, the previous year, and the subsequent year (study period). Individuals were excluded if they had a diagnosis of any bipolar affective disorder (ICD-10 codes F30 [manic episode], F31), organic mental disorder including symptomatic mental disorders (F00–F09), or schizophrenia, schizotypal, and delusional disorder (F20–F29) in the study period, or a diagnosis of MDD (ICD-10 codes F32 ['Depressive episode'] or F33 ['Recurrent depressive disorder']) in the year before the inclusion year, or no medical history for the year before the inclusion year.

Within the study population, case patients had a diagnosis of MDD in the inclusion year (the date of the first MDD treatment after ≥1 year with no MDD diagnosis was designated as the index date) and ≥2 months of treatment for depression within 90 days of the index date. Control patients had no diagnosis of MDD in the study period and were matched 10:1 (exact matching using random sampling) to case patients according to age at index date, sex, and working status.

Variables

The primary end point was the proportion of patients with documented diagnosis of each pre-existing disease during the 12 months before the index date (ie, before MDD diagnosis in case patients). An OR for the onset of MDD was calculated for each underlying disease, which was based on presence or absence of ICD-10 codes, Charlson comorbidity index (CCI)–related diseases, or other chronic diseases (online supplemental table 1).

Demographic and patient characteristics were collected, including age, sex, working status, and inclusion year (2015/2016/2017).

Study size

Sample size was determined by the number of cases and matched controls available in the database. Although a 4:1 matching ratio is generally considered to provide sufficient statistical power, the size of the database and the number of available controls allowed the ratio to be increased to 10:1.

Statistical methods

As noted above, the proportion of patients with each pre-existing disease was determined for each group and an OR for the onset of MDD was calculated. Prevalence data and ORs are reported for pre-existing diseases that were present in ≥1% of the case group and ≥0.1% of the control group. No inferential statistics were conducted. A post hoc analysis examined the possible interaction of the presence of three pre-existing disease categories that exhibited high ORs in the primary analysis or are common diseases: metabolic risk factors (diabetes, hypertension, dyslipidaemia), MDD-related symptoms (headache, pain, autonomic nerve imbalance), and psychiatric disorders (sleep disorders, psychiatric disorders other than depression) (online supplemental table 1). A multivariate logistic regression model was used to determine ORs in the eight subgroups (ie, with/without metabolic risk factors, MDD-related symptoms, and/or psychiatric disease) for the onset of MDD using the following covariates: sex, age (<40 years versus ≥40 years), and working status. A similar post hoc analysis was conducted to estimate ORs for the onset of MDD according to the number of low-risk ($1 \leq OR \leq 2$ in the primary analysis) CCI-related and other chronic diseases that were present during the preceding year. As above, sex, age, and working status were adjusted for in the multivariate logistic regression model. Netezza N2002-010 7.1.0.4.P2 (IBM, Armonk, NY,

USA) was used as the data warehouse platform. SAS version 9.4 (SAS Institute, Cary, NC, USA) was used for statistical analysis.

Patient and public involvement

Patients and members of the public were not involved in the study.

RESULTS

Participants

From more than 6.5 million people enrolled in the JMDC database between 2014 and 2018, we identified 13,420 case patients who met the inclusion criteria and had MDD diagnosed in 2015, 2016, or 2017 (case group; online supplemental figure). From 4,212,652 control patients who met the inclusion criteria and did not have an MDD diagnosis in either the inclusion year or the subsequent year, 134,200 were matched to case patients (control group; online supplemental figure). More than half (66.5%) of patients in both groups were male, with a mean age of 41.9 years (**table 1**). About 40% of patients were <40 years. Most (77.8%) patients were workers.

Table 1 Background and characteristics of case group

Variable	Case group N=13,420
Male sex	8924 (66.5)
Age	
Mean (SD), years	41.9 (10.4)
Median (range), years	42.0 (18–73)
<40 years	5390 (40.2)
≥40 years	8030 (59.8)
Working status	
Working	10,447 (77.8)
Non-working	2973 (22.2)
Inclusion year	
2015	3853 (28.7)
2016	4076 (30.4)
2017	5491 (40.9)
Number of beds in hospital where MDD was diagnosed	
<20	10,851 (80.9)
≥20	2569 (19.1)
Psychiatric facilities in hospital where MDD was diagnosed	
Yes	7026 (52.4)
No	6394 (47.6)

Data are n (%), unless otherwise noted.
MDD, major depressive disorder; SD, standard deviation.

Prevalence of pre-existing diseases in the year before MDD diagnosis

CCI-related diseases and other chronic diseases

The prevalence of almost all chronic diseases was higher in the case group than in the control group, with most ORs between 1.3 and 2.0 (**table 2**). The highest ORs were seen for attention deficit hyperkinetic disorders (OR 12.2), psychiatric diseases except depression (OR 9.9), dementia (OR 8.7, although prevalence was ≤0.1% in both groups), sleep disorders (OR 7.2), and autonomic nerve imbalance (OR 6.5). Of these, psychiatric diseases except depression and sleep disorders were highly prevalent in the case group (30.4% and 23.3%, respectively). ORs ≥2.0 were also observed (in descending order of prevalence in the case group) for pain (2.0), chronic gastritis (2.1), headache (2.7), peptic ulcer disease (2.0), dizziness (3.2), irritable bowel syndrome (3.2), angina pectoris (2.0), epilepsy (2.4), chronic enteritis (2.7), diabetes without chronic complication (2.1), metastatic solid tumour (2.2), hemiplegia or paraplegia (2.8), and Parkinson's disease (3.2).

Table 2 Prevalence of pre-existing diseases, ranked by prevalence in the case group

Disease	Case group N=13,420	Matched control group N=134,200	Odds ratio (95% CI)
CCI-related diseases			
Peptic ulcer disease	1431 (10.7)	7659 (5.7)	2.0 (1.9–2.1)
Mild liver disease	1392 (10.4)	9336 (7.0)	1.5 (1.5–1.6)
Chronic pulmonary disease (ex. asthma)	973 (7.3)	7381 (5.5)	1.3 (1.3–1.4)
Cerebrovascular disease	448 (3.3)	2378 (1.8)	1.9 (1.7–2.1)
Peripheral vascular disease	359 (2.7)	2237 (1.7)	1.6 (1.4–1.8)
Congestive heart failure	347 (2.6)	1885 (1.4)	1.9 (1.7–2.1)
Second solid tumour (non-metastatic)	327 (2.4)	2357 (1.8)	1.4 (1.2–1.6)
Diabetes with chronic complication	239 (1.8)	1758 (1.3)	1.4 (1.2–1.6)
Rheumatic disease	192 (1.4)	1066 (0.8)	1.8 (1.6–2.1)
Diabetes without chronic complication	107 (0.8)	502 (0.4)	2.1 (1.7–2.6)
Renal disease	77 (0.6)	708 (0.5)	1.1 (0.9–1.4)
Metastatic solid tumour	52 (0.4)	241 (0.2)	2.2 (1.6–2.9)
Myocardial infarction	46 (0.3)	338 (0.3)	1.4 (1.0–1.9)
Hemiplegia or paraplegia	39 (0.3)	138 (0.1)	2.8 (2.0–4.0)
Lymphoma/multiple myeloma	25 (0.2)	174 (0.1)	1.4 (0.9–2.2)
Dementia	13 (0.1)	15 (<0.1)	8.7 (4.1–18.2)
Leukaemia	9 (0.1)	97 (0.1)	0.9 (0.5–1.8)
Moderate or severe liver disease	7 (0.1)	54 (<0.1)	1.3 (0.6–2.8)
Other chronic diseases			
Pain	4598 (34.3)	27,452 (20.5)	2.0 (2.0–2.1)
Psychiatric diseases except depression	4084 (30.4)	5691 (4.2)	9.9 (9.4–10.3)
Sleep disorders	3128 (23.3)	5462 (4.1)	7.2 (6.8–7.5)
Chronic gastritis	2349 (17.5)	12,568 (9.4)	2.1 (2.0–2.2)
Dyslipidaemia	2286 (17.0)	17,438 (13.0)	1.4 (1.3–1.4)
Headache	2129 (15.9)	8634 (6.4)	2.7 (2.6–2.9)
Hypertensive disease	1987 (14.8)	15,052 (11.2)	1.4 (1.3–1.4)
Asthma	1861 (13.9)	12,923 (9.6)	1.5 (1.4–1.6)
Dizziness	1309 (9.8)	4345 (3.2)	3.2 (3.0–3.4)
Arthritis	729 (5.4)	5217 (3.9)	1.4 (1.3–1.5)
Osteoarthritis	654 (4.9)	4290 (3.2)	1.6 (1.4–1.7)
Atopic dermatitis	608 (4.5)	5984 (4.5)	1.0 (0.9–1.1)
Irritable bowel syndrome	588 (4.4)	1900 (1.4)	3.2 (2.9–3.5)
Thyroid disease	551 (4.1)	3394 (2.5)	1.7 (1.5–1.8)
Autonomic nerve imbalance	409 (3.0)	647 (0.5)	6.5 (5.7–7.4)

Disease	Case group N=13,420	Matched control group N=134,200	Odds ratio (95% CI)
Angina pectoris	405 (3.0)	2058 (1.5)	2.0 (1.8–2.2)
Osteoporosis	226 (1.7)	1611 (1.2)	1.4 (1.2–1.6)
Epilepsy	177 (1.3)	729 (0.5)	2.4 (2.1–2.9)
Chronic enteritis	153 (1.1)	561 (0.4)	2.7 (2.3–3.3)
Obesity	74 (0.6)	513 (0.4)	1.4 (1.1–1.8)
Attention deficit hyperkinetic disorders	56 (0.4)	46 (<0.1)	12.2 (8.3–18.1)
Parkinson's disease	24 (0.2)	76 (0.1)	3.2 (2.0–5.0)

The prevalence of CCI-related diseases and other chronic diseases in the 12 months before the index date in the case group and matched control group is shown ranked by prevalence in the case group. Data are n (%), unless otherwise noted.
CCI, Charlson comorbidity index; CI, confidence interval.

Table 3 Prevalence of pre-existing diseases in the case group and matched control group by ICD-10 block

ICD-10 block	ICD-10 block name	Case group N=13,420	Matched control group N=134,200	Odds ratio (95% CI)
A00–B99	Certain infectious and parasitic diseases	4583 (34.2)	33,852 (25.2)	1.5 (1.5–1.6)
C00–D48	Neoplasms	1575 (11.7)	12,007 (8.9)	1.4 (1.3–1.4)
D50–D89	Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	1041 (7.8)	7612 (5.7)	1.4 (1.3–1.5)
E00–E90	Endocrine, nutritional, and metabolic diseases	4477 (33.4)	32,630 (24.3)	1.6 (1.5–1.6)
F00–F99	Mental and behavioural disorders	4084 (30.4)	5691 (4.2)	9.9 (9.4–10.3)
G00–G99	Diseases of the nervous system	4965 (37.0)	14,847 (11.1)	4.7 (4.5–4.9)
H00–H59	Diseases of the eye and adnexa	5035 (37.5)	46,365 (34.5)	1.1 (1.1–1.2)
H60–H95	Diseases of the ear and mastoid process	1735 (12.9)	10,245 (7.6)	1.8 (1.7–1.9)
I00–I99	Diseases of the circulatory system	3038 (22.6)	20,545 (15.3)	1.6 (1.6–1.7)
J00–J99	Diseases of the respiratory system	9232 (68.8)	77,686 (57.9)	1.6 (1.5–1.7)
K00–K93	Diseases of the digestive system	7015 (52.3)	47,838 (35.6)	2.0 (1.9–2.0)
L00–L99	Diseases of the skin and subcutaneous tissue	4428 (33.0)	37,648 (28.1)	1.3 (1.2–1.3)
M00–M99	Diseases of the musculoskeletal system and connective tissue	5322 (39.7)	35,387 (26.4)	1.8 (1.8–1.9)
N00–N99	Diseases of the genitourinary system	2880 (21.5)	20,016 (14.9)	1.6 (1.5–1.6)
O00–O99	Pregnancy, childbirth, and the puerperium	178 (1.3)	2944 (2.2)	0.6 (0.5–0.7)
P00–P96	Certain conditions originating in the perinatal period	19 (0.1)	212 (0.2)	0.9 (0.6–1.4)
Q00–Q99	Congenital malformations, deformations, and chromosomal abnormalities	199 (1.5)	1496 (1.1)	1.3 (1.2–1.5)
R00–R99	Symptoms, signs, and abnormal clinical and laboratory findings, not elsewhere classified	5241 (39.1)	28,989 (21.6)	2.3 (2.2–2.4)
S00–T98	Injury, poisoning, and certain other consequences of external causes	2209 (16.5)	17,661 (13.2)	1.3 (1.2–1.4)
Z00–Z99	Factors influencing health status and contact with health services	252 (1.9)	1878 (1.4)	1.3 (1.2–1.5)
U00–U99	Codes for special purposes	0 (0)	1 (<0.1)	NE

Data are n (%), unless otherwise noted.

CI, confidence interval; ICD-10, International Statistical Classification of Diseases and Related Health Problems, 10th revision; NE, not estimable.

ICD-10 blocks

At the level of ICD-10 blocks, the prevalence of most pre-existing diseases in the year before MDD diagnosis was slightly higher (OR 1.1–2.0) in the case group than in the control group (**table 3**). Exceptions were blocks O00–O99 and P00–P96, which are associated with pregnancy and/or childbirth. However, the prevalence rates of mental and behavioural disorders (F00–F99) and diseases of the nervous system (G00–G99) were markedly higher in the case group, with ORs of 9.9 and 4.7, respectively. Among diseases of the circulatory system (I00–I99), respiratory system (J00–J99), and digestive system (K00–K93), the OR for digestive diseases was the highest (2.0 for digestive versus 1.6 for circulatory and respiratory). The OR for diseases of the eye and adnexa (H00–H59) was low (1.1), whereas the OR for diseases of the ear and mastoid process (H60–H95) was relatively high (1.8).

ICD-10 codes

As with the ICD-10 blocks, the prevalence of almost all pre-existing diseases based on three- or four-character ICD-10 codes in the year before MDD diagnosis was slightly higher in the case group than in the control group (**figure**; online supplemental table 2). The highest ORs for the onset of MDD were observed for psychiatric diseases and sleep disorders (**figure**). ORs >5 were seen for adjustment disorders, panic disorder, anxiety disorder, depressive neurosis, neurosis, insomnia, psychosomatic disorder, anxiety, sleeping disorder, autonomic ataxia, and palpitations. Of these comorbidities, insomnia and neurosis were particularly prevalent in the case group (21.1% and 9.7% of patients, respectively).

Multivariate analysis

A post hoc multivariate analysis indicated that the odds of developing MDD were lower in women than in men, in patients ≥40 years than in younger patients, and in non-workers than in workers (**table 4**). The odds of MDD also increased in subgroups with metabolic risk factors, psychiatric disorders, and/or MDD-related symptoms, relative to 84,763 individuals without any of these diseases (online supplemental table 3). The highest ORs (>10) were

seen in subgroups with psychiatric disorders. Compared with subgroups with MDD-related symptoms only, the odds of MDD were increased in subgroups who also had metabolic risk factors or psychiatric disorders. However, the odds of MDD decreased in subgroups who had both metabolic risk factors and psychiatric disorders relative to subgroups with only one of these factors (with or without MDD-related symptoms). Finally, we identified 72,923 people (8329 cases with MDD and 64,594 controls) who had at least one low-risk (1≤OR≤2) pre-existing CCI-related or other chronic disease (**table 2**) and categorised them based on the number of diseases from one (N=36,993) to 11–13 (N=46). Relative to people with only one pre-existing disease, the OR for MDD increased with the number of pre-existing chronic diseases, from 1.34 in people with two pre-existing diseases to more than three in people with nine or more comorbidities (online supplemental table 4).

Table 4 Multivariate logistic regression analysis for the onset of MDD

Dependent variable	Explanatory variable	Reference	Category			Odds ratio (95% CI)
Group (reference = control group)	Sex	Male	Female			0.93 (0.89–0.98)
	Age	<40 years	≥40 years			0.80 (0.77–0.83)
	Working status	Worker	Non-worker			0.92 (0.86–0.97)
	Presence of metabolic risk factor, psychiatric disorder, and/or MDD-related symptoms during the 12 months before index date	None	Metabolic risk factor	Psychiatric disorder	MDD-related symptoms	
			No	No	Yes	1.81 (1.71–1.91)
			No	Yes	No	10.22 (9.58–10.91)
			No	Yes	Yes	13.47 (12.54–14.47)
			Yes	No	No	1.14 (1.06–1.23)
			Yes	No	Yes	2.27 (2.10–2.46)
			Yes	Yes	No	7.27 (6.61–7.99)
			Yes	Yes	Yes	11.49 (10.63–12.41)

'Metabolic risk factors' included diabetes, hypertension, and dyslipidaemia; 'psychiatric disorders' included sleep disorders and psychiatric diseases other than depression; 'MDD-related symptoms' included headache, pain, and autonomic nerve imbalance (online supplemental table 1).
CI, confidence interval; MDD, major depressive disorder.

DISCUSSION

This is the first nested case-control study to demonstrate that a broad range of pre-existing diseases are more prevalent in people who develop MDD than in those who do not. These results indicate that most patients have complex health conditions before starting treatment for MDD. The highest ORs were seen for sleep disorders and psychiatric diseases other than depression, which were also among the most prevalent pre-existing diseases in the case group. Other common diseases that were more prevalent in the case group included pain, headache, autonomic disturbances, gastrointestinal diseases, and metabolic risk factors, such as dyslipidaemia, hypertension, and diabetes.

Our results support and extend the results of previous studies reporting a high prevalence of pre-existing or comorbid diseases in patients with depression. Most previous studies have been cross-sectional or small case-control studies focused on specific comorbid diseases.[2 3 13-16] Two large case-control studies conducted in the United States, using electronic health records at the Mayo Clinic,[17] and South Korea, using the National Health Insurance Service,[18] identified pre-existing chronic physical conditions that were risk factors for the development of MDD. However, these studies focused on a smaller number (24 and 19) of specific chronic conditions compared with our study, which examined a broad range of both chronic and acute conditions.

Stress, such as diagnosis with a chronic or serious disease, can contribute to the development of MDD in vulnerable individuals.[19] Further, stress can lead to psychological and physiological changes that affect both mental and physical health, and may contribute directly to depression.[20] Psychiatric disorders can be particularly stressful and may increase the chances of MDD. Depression is often comorbid with other mental disorders, particularly anxiety, and may share symptoms and underlying aetiologies.[21-24] Our results support this link and further suggest that depression may be present in patients with other psychiatric disorders but may not be diagnosed as MDD until symptoms become severe. Stress is also

associated with many gastrointestinal disorders,[25] such as irritable bowel syndrome, which were twice as prevalent in the case group than in the control group.

Depression-related symptoms (sleep disorders, pain, autonomic imbalance) may be diagnosed in advance of MDD and therefore may be prodromal symptoms of MDD.[26] Somatic symptoms of MDD, such as fatigue, appetite loss, pain (especially headache), dizziness, and sleep disturbance, can be non-specific and may be attributed to physical illness.[27] Indeed, a significant proportion of patients with MDD present with only somatic symptoms.[28] One reason is denial of psychological symptoms, which is particularly prevalent in Japan.[28] These results support the idea that depression is under-recognised when patients first seek medical help in Japan, and also support our findings that digestive diseases, sleep disorders, and other somatic symptoms, including in the otological area (eg, dizziness), were highly prevalent in patients who later developed MDD. Interestingly, we observed that the OR for diseases of the ear and mastoid process was higher than for diseases of the eye and adnexa (1.8 versus 1.1). We suggest that physicians in otolaryngology departments may be aware of the link between somatic symptoms and MDD and consider psychological evaluation for patients with such symptoms. In contrast, physicians in ophthalmology departments may need to pay more attention to the risk of MDD in patients with severe visual dysfunction because both hearing loss and vision loss are associated with the development of depression.[29]

Our multivariate analysis indicated that the odds of an MDD diagnosis were increased in patients who had depression-related symptoms (headache, pain, autonomic imbalance), particularly if the patient also had a sleep/psychiatric disorder or metabolic risk factor. Interestingly, the odds of MDD decreased in subgroups with metabolic risk factors in addition to psychiatric disorders. Although the reason for this finding is unclear, it may be that these patients are managed by multiple physicians who focus on treating each disease separately (eg, psychiatrist treating psychiatric diseases; general practitioner treating metabolic risk

factors), with the result that MDD is not sufficiently recognised. Indeed, some general practitioners and other non-psychiatrist doctors in Japan fail to recognise or are reluctant to treat MDD,[30 31] which may contribute to underdiagnosis of MDD in patients with metabolic risk factors. Psychiatrists, on the other hand, may underestimate somatic depressive symptoms in patients they are treating for another mental illness who also have a metabolic-related illness treated by another doctor, considering fatigue and autonomic dysfunction as caused by the physical illness. However, depression is known to lead to treatment non-adherence in patients with diabetes,[32] which increases the risk of severe complications.[33] In addition, treating metabolic-related diseases and depression simultaneously may provide patients with better clinical outcomes.[34] Further research is needed on the unmet needs for the diagnosis and treatment of depression in patients with presymptomatic depression in addition to metabolic-related diseases, and on the effects of coordinated care management of multiple conditions.

We also found that the risk of MDD increased with increasing number of relatively low-risk (OR≤2) CCI-related and other chronic diseases. Thus, increased medical burden appears to be associated with greater risk of depression among working-age people, consistent with a recent study conducted in Denmark.[35]

Many comorbidities may share underlying biological mechanisms with MDD. For example, inflammatory mechanisms play a role in the aetiology of many diseases, including diabetes, cardiovascular disease, arthritis, and asthma, as well as depression.[36-38] Neural pathways and neurotransmitters that are altered in chronic pain may also affect mood, including depression.[39] Migraine and depression can both be related to specific genetic variants and/or neuroanatomic features.[40] Most of these biological mechanisms are exacerbated by stress.[3 37 40] Thus, MDD may develop in parallel with certain diseases, but its diagnosis may be delayed compared with physical disease.

Strengths and limitations

Our study is strengthened by the use of a health insurance database consisting of mostly working-age people, which resulted in a sample size large enough to allow examination of a broad range of pre-existing diseases. The nested case-control design and the use of a database minimised selection and recall biases that may occur in other case-control studies. We used a strict definition of MDD onset, which required a 1-year depression-free period and the diagnosis for inclusion to be recorded on at least three doctor visits within 90 days; this definition increased our certainty that case patients had true, newly diagnosed MDD. In addition, our inclusion criteria meant that people in both the control and case groups needed to have visited a doctor at least once to have a medical record within the observation period. Because of the comprehensive insurance available in Japan, medical care is readily accessible, and consultations for relatively minor concerns are common. Therefore, the controls in our study can essentially be considered as representative of the general population, except for the absence of people aged 75 years or older, who are covered by government-administered insurance, and the relatively low proportion of people aged 65–74 years, many of whom would be retired from work.

Despite these strengths, some caveats do apply when interpreting our results. As with any claims database study, the data were not collected specifically for the purpose of the study. As such, we could not evaluate variables like socioeconomic factors or severity/history of MDD. Further, errors in ICD-10 coding may have occurred, although equally in cases and controls. Patients with chronic diseases are likely to visit their physicians frequently, increasing the opportunity for detection and diagnosis of MDD. Further, patients with pre-existing psychiatric disorders are likely to be treated by psychiatrists, who may be better at diagnosing MDD than other physicians, which might lead to higher ORs for psychiatric diseases than for physical diseases; however, MDD diagnosis by general practitioners is also higher in patients with psychiatric comorbidity than in those with physical comorbidity.[41] Nevertheless, MDD is often under-recognised and underdiagnosed, which may mean that

the control group included patients who actually had depression or depressive symptoms. We only assessed disease prevalence, and not incidence, during the year before the inclusion year; therefore, we do not know if the disease was diagnosed during that year or in a previous year. This limitation could potentially result in a disproportionate number of people in the control group who had longer-term diseases and were not vulnerable to MDD. For some high-stress diseases such as cancer or stroke, MDD often occurs soon after diagnosis[42 43]; hence, less vulnerable patients who did not develop MDD would have remained within the control group, leading to lower ORs for those diseases than might be expected. Further, the nature of the database made it difficult to exclude patients with an MDD diagnosis more than a year previously; consequently, our cases could have included patients with recurrent MDD as well as those diagnosed for the first time. The use of standard logistic regression instead of conditional logistic regression may also have resulted in the underestimation of ORs. Finally, the relatively short observation period limits our ability to look at the long-term relationship between MDD, which can re-occur multiple times in a patient's life, and other chronic conditions. Although comparing ORs for the onset of MDD across a broad range of pre-existing diseases can help develop hypotheses regarding possible underlying mechanisms, the risk of MDD occurring in specific diseases should be investigated on an individual basis.

CONCLUSIONS

This large, preliminary, nested case-control study has documented the high prevalence of pre-existing diseases in Japanese patients with MDD compared with matched controls without MDD. The high prevalence of pre-existing diseases in patients who develop MDD reflects the complex relationship between physical and mental disorders and indicates a high medical burden for these patients. These results confirm that patients with chronic and/or serious diseases, including prodromal symptoms that are not always recognised as related to MDD, should be monitored for depressive symptoms, and pre-existing diseases should be taken into consideration when prescribing treatment for MDD.

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Contributors

Yoshinori Cho designed the study and data collection, interpreted the study results, and participated in the drafting, critical revision, and approval of the final version of the manuscript. Izumi Mishiro designed the study and data collection, wrote the statistical analysis plan, interpreted the study results, and participated in the drafting, critical revision, and approval of the final version of the manuscript. Tsuyoshi Akaki designed the study and data collection, interpreted the study results, and participated in the drafting, critical revision, and approval of the final version of the manuscript. Takafumi Akimoto designed the study and data collection, interpreted the study results, and participated in the drafting, critical revision, and approval of the final version of the manuscript. Keita Fujiwara designed the study and data collection, interpreted the study results, and participated in the drafting, critical revision, and approval of the final version of the manuscript.

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Data availability statement

The data that support the findings of this study are available from JMDC Inc. but were used under licence for the current study; therefore, restrictions apply and the data are not publicly available. For inquiries about access to the data set used in this study, please contact JMDC (https://www.jmdc.co.jp).

Competing interests

Dr Cho reports grants from Shionogi & Co., Ltd. and Otsuka Pharmaceutical Co., Ltd., and personal fees from Shionogi & Co., Ltd., Otsuka Pharmaceutical Co., Ltd., Eli Lilly Japan K.K., Kyowa Kirin Co. Ltd., Pfizer Japan Inc., Meiji Seika Pharma Co., Ltd., Mitsubishi Tanabe Pharma Corporation, Sumitomo Dainippon Pharma Co., Ltd., Astellas Pharma Inc., MSD K.K., Takeda Pharmaceutical Company Limited, and Lundbeck Japan K.K., outside the submitted work. Drs Mishiro, Akaki, Akimoto, and Fujikawa report personal fees from Takeda Pharmaceutical Company Limited, outside the submitted work.

Ethics statements

Ethics approval

The study was approved by the Ethics Review Committee of the Research Institute of Healthcare Data Science (Tokyo, Japan) on 6 August 2019 (approval number RI2019004). Only anonymised information was accessible from the database; therefore, in accordance with the Ethical Guidelines for Medical and Health Research Involving Human Subjects in Japan, informed consent was not required.

Patient consent for publication

Not applicable.

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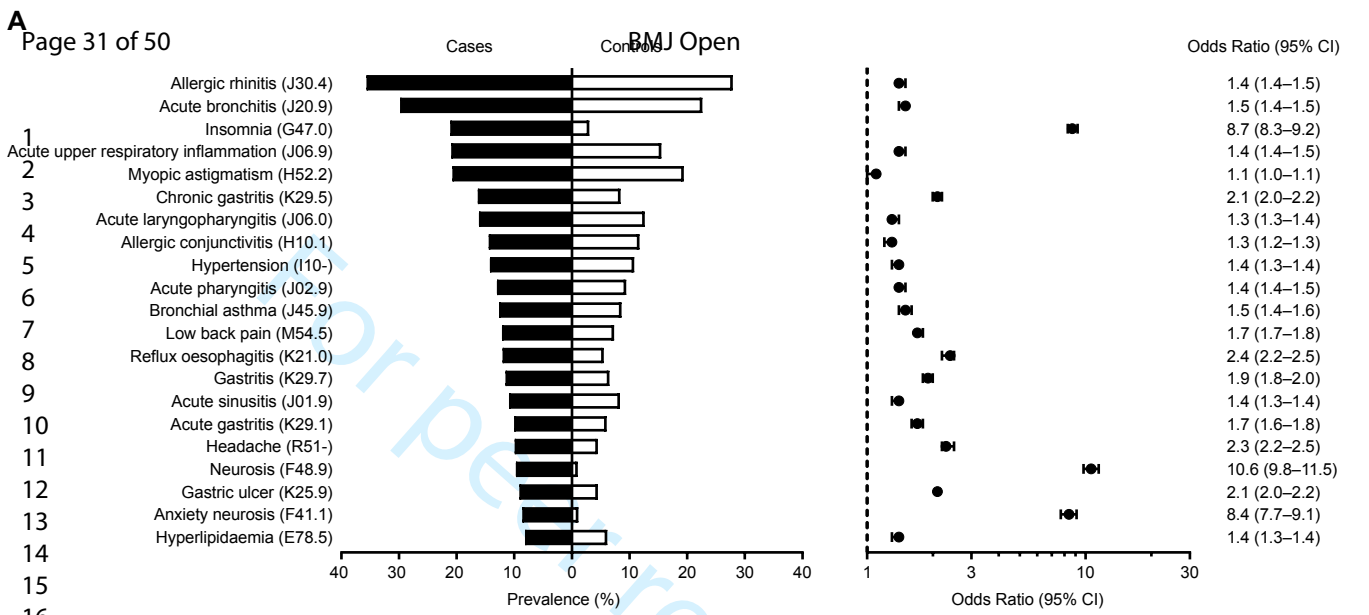
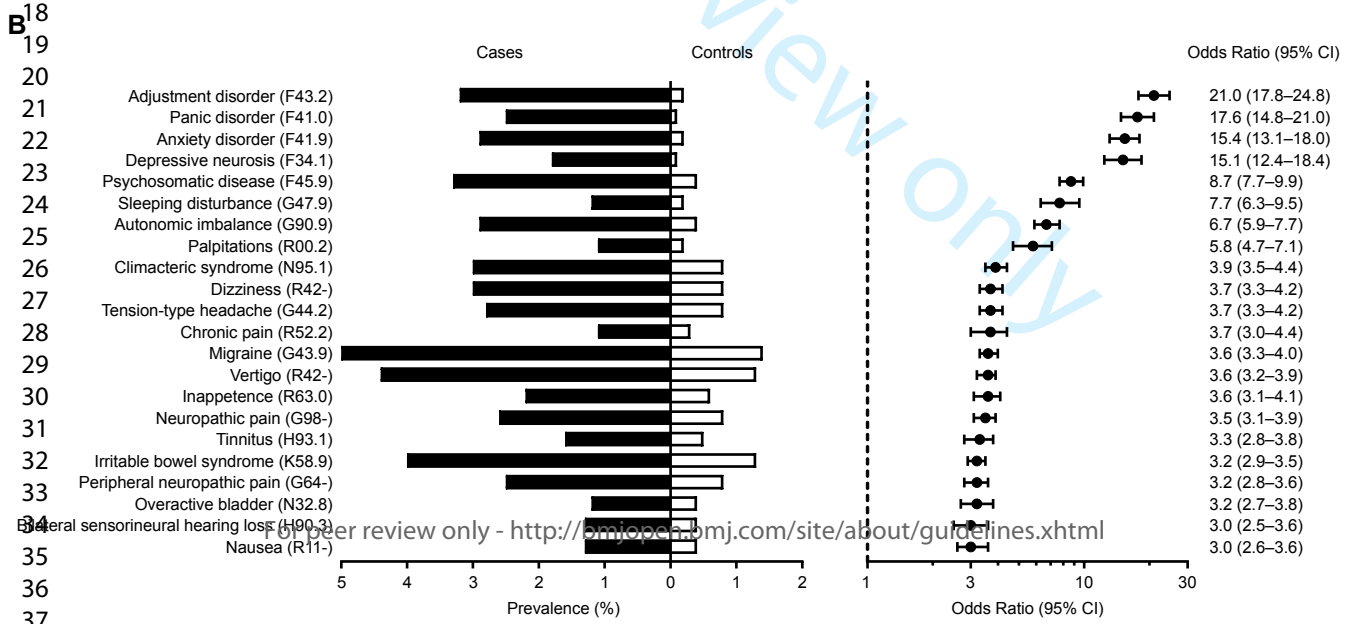
FIGURE LEGEND

Figure A, Diseases with prevalence >8% in the case group in the 12 months before MDD diagnosis. B, Diseases with odds ratio >3.0. Shown are the prevalence rates in the case group and in the matched control group, as well as the odds ratio (95% CI). CI, confidence interval; MDD, major depressive disorder.





Supplemental Material

TITLE

Diseases prevalent before major depressive disorder diagnosis: an exploratory nested case-control study using health insurance–based claims data

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Supplemental figure Flow diagram of patients included in the case group and matched control group. Dates (2015, 2016, 2017) represent the inclusion years. MDD, major depressive disorder.

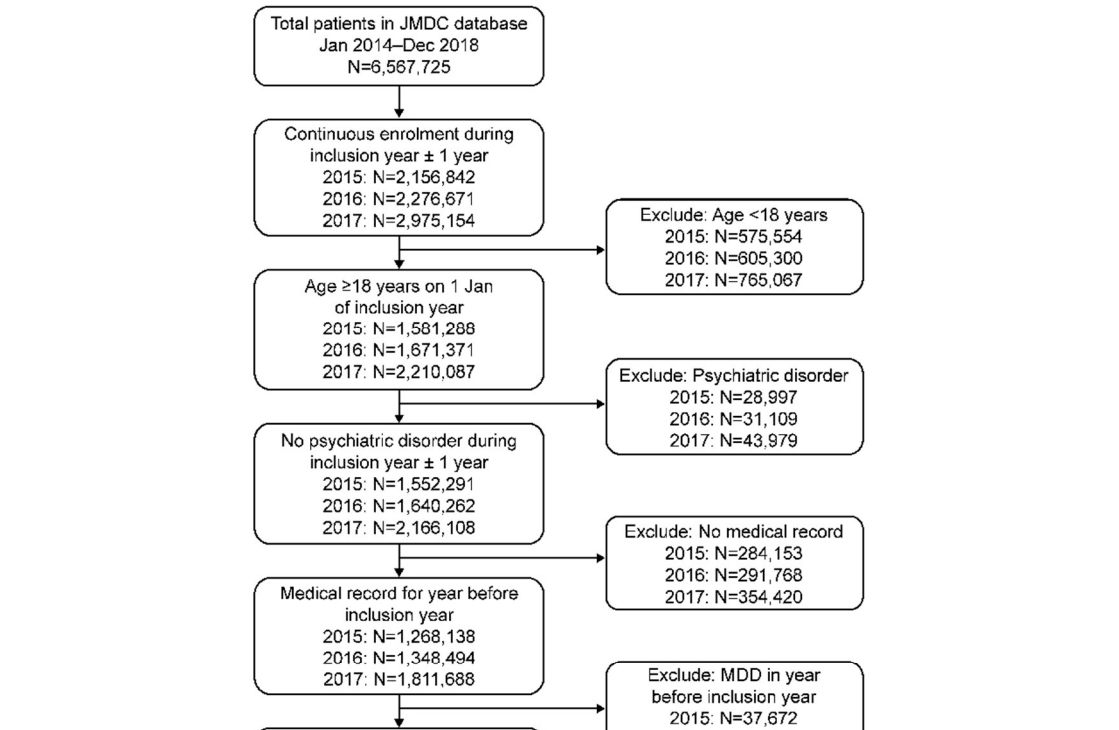
Supplemental table 1 ICD-10 codes and other terms used to identify pre-existing diseases

Supplemental table 2 Prevalence of diseases in the 12 months before the index date by ICD-10 code, ICD-10 name, and standard disease name in the case group and matched control group, ranked by prevalence in the case group

Supplemental table 3 Number of patients in post hoc multivariate analysis subgroups

Supplemental table 4 Multivariate logistic regression analysis for the relationship between the number of CCI-related and other chronic diseases and the onset of MDD

Supplemental figure Flow diagram of patients included in the case group and matched control group.



Dates (2015, 2016, 2017) represent the inclusion years. MDD, major depressive disorder.

Supplemental table 1 ICD-10 codes and other terms used to identify pre-existing diseases

Disease	ICD-10 codes and other terms
CCI-related diseases	
Myocardial infarction	I21, I22, I25.2
Cardiac failure, congestive	I43, I50, I09.9, I11.0, I25.5, I42.0, I42.5, I42.6, I42.7, I42.8, I42.9, I13.0, I13.2, P29.0
Peripheral vascular disease	I70, I71, I73.1, I73.8, I73.9, I77.1, K55.1, K55.9, Z95.8, I79.0, I79.2, K55.8, Z95.9
Cerebrovascular disease	G45, G46, I60–I69, H34.0, I72.0, I72.5, I72.6
Dementia	F00, F01, F02, F03, G30, F05.1, G31.1
Chronic lung disease (excluding asthma)	J40–J47, J60–J67, I27.8, I27.9, J68.4, J70.1, J70.3
Rheumatic disease	M05–M06, M32–M34, M31.5, M35.1, M35.3, M36.0
Peptic ulcer disease	K25–K28
Mild liver disease	B18, K73–K74, K70.0–K70.3, K70.9, K71.3, K71.4, K71.5, K71.7, K76.0, K76.2, K76.3, K76.4, K76.8, K76.9, Z94.4, K75.8
Diabetes mellitus without complications	E10.0, E10.1, E10.9, E11.0, E11.1, E11.9, E12.0, E12.1, E12.9, E13.0, E13.1, E13.9, E14.0, E14.1, E14.9
Diabetes mellitus with complications	E10.2–E10.8, E11.2, E11.3–E11.8, E12.2–E12.8, E13.2–E13.8, E14.2–E14.8
Hemiplegia or paraplegia	G81, G82, G041, G11.4, G80.1, G80.2, G83.9, G83.0–G83.4
Renal disease	N18, N19, I12.0, I13.1, N03.2–N03.7, N05.2–N05.7, N25.0, Z49.0–Z49.2, Z94.0, Z99.2
Solid tumours without metastasis	C00–C76, C80, C97
Leukaemia	C91–C96, D47.1, D47.5
Malignant lymphoma and multiple myeloma	C81–C90
Moderate or severe liver disease	I85.0, I85.9, I86.4, I98.2, K70.4, K71.1, K72.1, K72.9, K76.5–K76.7
Metastatic cancer	C77–C79
Other chronic diseases	
Angina pectoris	I20, Post-infarction angina pectoris
Dyslipidaemia (hyperlipidaemia)	E78.0–E78.2, E78.4, E78.5
Hypertensive disease	I10
Obesity	E65, E66
Atopic dermatitis	L20
Asthma	J45, J46
Thyroid disease	E01–E06, E07.0, E07.8, E07.9
Osteoarthritis	M05, M06 Other disease name with ‘osteoarthritis’
Arthritis	M00–M03, M05–M14 Other disease name with ‘arthritis’
Epilepsy	G40, G41
Headache	G43, G44, R51
Osteoporosis	M80, M81

Disease	ICD-10 codes and other terms
Parkinsonism	G20, G21
Pain	B02, F45.4, G50–G59, G64, G98, M25, M43, M45–M49, M50–M54, M79.1, M79.2, M79.6, M79.7, M89.0, R52 Diabetic neuropathic pain
Irritable bowel syndrome	K58
Chronic gastritis	K29.3, K29.4, K29.5
Chronic enteritis	K52.9
Dizziness	R42, H81, I95.1 Epidemic dizziness, psychogenic dizziness, low-tone dizziness
Autonomic nerve imbalance	G90
Attention deficit hyperactivity disorder	F90
Psychiatric disorders other than depression	F00–F99* *Except F00–F09, F20–F29, F30–F33
Sleep disorders	G47
Metabolic risk factors	
Diabetes mellitus without complications	E10.0, E10.1, E10.9, E11.0, E11.1, E11.9, E12.0, E12.1, E12.9, E13.0, E13.1, E13.9, E14.0, E14.1, E14.9
Diabetes mellitus with complications	E10.2–E10.8, E11.2–E11.8, E12.2–E12.8, E13.2–E13.8, E14.2–E14.8
Dyslipidaemia (hyperlipidaemia)	E78.0–E78.2, E78.4, E78.5
Hypertensive disease	I10
Psychiatric disorders	
Psychiatric disorders other than depression	F00–F99* *Except F00–F09, F20–F29, F30–F33
Sleep disorders	G47
MDD-related symptoms	
Headache	G43, G44, R51
Pain	B02, F45.4, G50–G59, G64, G98, M25, M43, M45–M49, M50–M54, M79.1, M79.2, M79.6, M79.7, M89.0, R52 Diabetic neuropathic pain
Autonomic nerve imbalance	G90

CCI, Charlson comorbidity index; ICD-10, International Statistical Classification of Diseases and Related Health Problems, 10th revision; MDD, major depressive disorder.

Supplemental table 2 Prevalence of diseases in the 12 months before the index date by ICD-10 code, ICD-10 name, and standard disease name in the case group and matched control group, ranked by prevalence in the case group

ICD-10 level 4 code	ICD-10 level 4 name	Standard disease name	Case group N=13,420	Control group N=134,200	Odds ratio (95% CI)
J30.4	Allergic rhinitis, unspecified	Allergic rhinitis	4782 (35.6)	37,507 (27.9)	1.4 (1.4–1.5)
J20.9	Acute bronchitis, unspecified	Acute bronchitis	4005 (29.8)	30,359 (22.6)	1.5 (1.4–1.5)
G47.0	Disorders of initiating and maintaining sleep [insomnias]	Insomnia	2836 (21.1)	4010 (3.0)	8.7 (8.3–9.2)
J06.9	Acute upper respiratory infection, unspecified	Acute infection of upper respiratory tract	2807 (20.9)	20,738 (15.5)	1.4 (1.4–1.5)
H52.2	Astigmatism	Myopic astigmatism	2784 (20.7)	26,090 (19.4)	1.1 (1.0–1.1)
K29.5	Chronic gastritis, unspecified	Chronic gastritis	2189 (16.3)	11,246 (8.4)	2.1 (2.0–2.2)
J06.0	Acute laryngopharyngitis	Acute laryngopharyngitis	2156 (16.1)	16,963 (12.6)	1.3 (1.3–1.4)
H10.1	Acute atopic conjunctivitis	Allergic conjunctivitis	1928 (14.4)	15,748 (11.7)	1.3 (1.2–1.3)
I10-	Essential (primary) hypertension	Hypertension	1903 (14.2)	14,477 (10.8)	1.4 (1.3–1.4)
J02.9	Acute pharyngitis, unspecified	Acute pharyngitis	1740 (13.0)	12,573 (9.4)	1.4 (1.4–1.5)
J45.9	Asthma, unspecified	Bronchial asthma	1689 (12.6)	11,547 (8.6)	1.5 (1.4–1.6)
M54.5	Low back pain	Low back pain	1628 (12.1)	9821 (7.3)	1.7 (1.7–1.8)
K21.0	Gastro-oesophageal reflux disease with oesophagitis	Reflux oesophagitis	1607 (12.0)	7322 (5.5)	2.4 (2.2–2.5)
K29.7	Gastritis, unspecified	Gastritis	1547 (11.5)	8762 (6.5)	1.9 (1.8–2.0)
J01.9	Acute sinusitis, unspecified	Acute sinusitis	1468 (10.9)	11,115 (8.3)	1.4 (1.3–1.4)
K29.1	Other acute gastritis	Acute gastritis	1342	8075	1.7

ICD-10 level 4 code	ICD-10 level 4 name	Standard disease name	Case group N=13,420	Control group N=134,200	Odds ratio (95% CI)
			(10.0)	(6.0)	(1.6–1.8)
R51-	Headache	Headache	1332 (9.9)	6046 (4.5)	2.3 (2.2–2.5)
F48.9	Neurotic disorder, unspecified	Neurosis	1306 (9.7)	1350 (1.0)	10.6 (9.8–11.5)
K25.9	Gastric ulcer/Unspecified as acute or chronic, without haemorrhage or perforation	Gastric ulcer	1216 (9.1)	6086 (4.5)	2.1 (2.0–2.2)
F41.1	Generalised anxiety disorder	Anxiety neurosis	1155 (8.6)	1492 (1.1)	8.4 (7.7–9.1)
E78.5	Hyperlipidaemia, unspecified	Hyperlipidaemia	1091 (8.1)	8244 (6.1)	1.4 (1.3–1.4)
J02.9	Acute pharyngitis, unspecified	Pharyngitis	1061 (7.9)	7940 (5.9)	1.4 (1.3–1.5)
L30.9	Dermatitis, unspecified	Eczema	1032 (7.7)	7799 (5.8)	1.4 (1.3–1.4)
K59.0	Constipation	Constipation	1030 (7.7)	6014 (4.5)	1.8 (1.7–1.9)
E86-	Volume depletion	Dehydration	1003 (7.5)	4825 (3.6)	2.2 (2.0–2.3)
E78.0	Pure hypercholesterolaemia	Hypercholesterolaemia	940 (7.0)	7031 (5.2)	1.4 (1.3–1.5)
R11-	Nausea and vomiting	Vomition	933 (7.0)	4031 (3.0)	2.4 (2.2–2.6)
M53.1	Cervicobrachial syndrome	Cervico-omo-brachial syndrome	905 (6.7)	3380 (2.5)	2.8 (2.6–3.0)
J00-	Acute nasopharyngitis [common cold]	Common cold	894 (6.7)	5998 (4.5)	1.5 (1.4–1.6)
A09.9	Gastroenteritis and colitis of unspecified origin	Acute gastroenteritis	873 (6.5)	5140 (3.8)	1.7 (1.6–1.9)
E14-	Unspecified diabetes mellitus	Diabetes mellitus	870 (6.5)	6285 (4.7)	1.4 (1.3–1.5)
J32.9	Chronic sinusitis, unspecified	Chronic sinusitis	818 (6.1)	5551 (4.1)	1.5 (1.4–1.6)
A09.9	Gastroenteritis and colitis of unspecified origin	Diarrhoea	781 (5.8)	4311 (3.2)	1.9 (1.7–2.0)

ICD-10 level 4 code	ICD-10 level 4 name	Standard disease name	Case group N=13,420	Control group N=134,200	Odds ratio (95% CI)
G62.9	Polyneuropathy, unspecified	Peripheral neuropathy	775 (5.8)	3374 (2.5)	2.4 (2.2–2.6)
J40-	Bronchitis, not specified as acute or chronic	Bronchitis	716 (5.3)	5644 (4.2)	1.3 (1.2–1.4)
E79.0	Hyperuricaemia without signs of inflammatory arthritis and tophaceous disease	Hyperuricaemia	700 (5.2)	5880 (4.4)	1.2 (1.1–1.3)
G43.9	Migraine, unspecified	Migraine	669 (5.0)	1917 (1.4)	3.6 (3.3–4.0)
H04.1	Other disorders of lacrimal gland	Dry eye	663 (4.9)	4312 (3.2)	1.6 (1.4–1.7)
D50.9	Iron deficiency anaemia, unspecified	Iron deficiency anaemia	650 (4.8)	4957 (3.7)	1.3 (1.2–1.4)
E78.5	Hyperlipidaemia, unspecified	Dyslipidaemia	646 (4.8)	4684 (3.5)	1.4 (1.3–1.5)
H10.9	Conjunctivitis, unspecified	Conjunctivitis	644 (4.8)	5118 (3.8)	1.3 (1.2–1.4)
H52.1	Myopia	Myopia	636 (4.7)	6292 (4.7)	1.0 (0.9–1.1)
J10.1	Influenza with other respiratory manifestations, seasonal influenza virus identified	Human influenza A	613 (4.6)	5585 (4.2)	1.1 (1.0–1.2)
M75.0	Adhesive capsulitis of shoulder	Periarthritis scapulohumeralis	605 (4.5)	3523 (2.6)	1.8 (1.6–1.9)
L20.9	Atopic dermatitis, unspecified	Atopic dermatitis	601 (4.5)	5924 (4.4)	1.0 (0.9–1.1)
L85.3	Xerosis cutis	Xerosis	596 (4.4)	4954 (3.7)	1.2 (1.1–1.3)
R42-	Dizziness and giddiness	Vertigo	585 (4.4)	1701 (1.3)	3.6 (3.2–3.9)
K76.9	Liver disease, unspecified	Hepatic dysfunction	571 (4.3)	3458 (2.6)	1.7 (1.5–1.8)
K58.9	Irritable bowel syndrome without diarrhoea	Irritable bowel syndrome	539 (4.0)	1756 (1.3)	3.2 (2.9–3.5)

ICD-10 level 4 code	ICD-10 level 4 name	Standard disease name	Case group N=13,420	Control group N=134,200	Odds ratio (95% CI)
K76.0	Fatty (change of) liver, not elsewhere classified	Hepatic steatosis	537 (4.0)	3564 (2.7)	1.5 (1.4–1.7)
J11.1	Influenza with other respiratory manifestations, virus not identified	Influenza	529 (3.9)	4256 (3.2)	1.3 (1.1–1.4)
L50.9	Urticaria, unspecified	Urticaria	524 (3.9)	3755 (2.8)	1.4 (1.3–1.5)
L85.3	Xerosis cutis	Asteatotic eczema	511 (3.8)	4328 (3.2)	1.2 (1.1–1.3)
M47.8	Other spondylosis	Cervical spondylosis	505 (3.8)	2012 (1.5)	2.6 (2.3–2.8)
J03.9	Acute tonsillitis, unspecified	Acute tonsillitis	495 (3.7)	3922 (2.9)	1.3 (1.2–1.4)
A09.9	Gastroenteritis and colitis of unspecified origin	Acute enteritis	481 (3.6)	2707 (2.0)	1.8 (1.6–2.0)
K21.0	Gastro-oesophageal reflux disease with oesophagitis	Refractory reflux oesophagitis requiring maintenance therapy	477 (3.6)	1989 (1.5)	2.4 (2.2–2.7)
E28.3	Primary ovarian failure	Ovarian insufficiency	470 (3.5)	3125 (2.3)	1.5 (1.4–1.7)
N86-	Erosion and ectropion of cervix uteri	Uterovaginal erosion	452 (3.4)	3170 (2.4)	1.4 (1.3–1.6)
A09.0	Other and unspecified gastroenteritis and colitis of infectious origin	Infectious gastroenteritis	449 (3.3)	2964 (2.2)	1.5 (1.4–1.7)
J06.0	Acute laryngopharyngitis	Laryngopharyngitis	447 (3.3)	3059 (2.3)	1.5 (1.3–1.6)
M51.9	Intervertebral disc disorder, unspecified	Lumbar vertebral discopathy	440 (3.3)	2565 (1.9)	1.7 (1.6–1.9)
F45.9	Somatoform disorder, unspecified	Psychosomatic disease	437 (3.3)	515 (0.4)	8.7 (7.7–9.9)
F43.2	Adjustment disorders	Adjustment disorder	427 (3.2)	210 (0.2)	21.0 (17.8–24.8)
J03.9	Acute tonsillitis, unspecified	Tonsillitis	413 (3.1)	2958 (2.2)	1.4 (1.3–1.6)
H52.4	Presbyopia	Presbyopia	408 (3.0)	2977 (2.2)	1.4 (1.2–1.5)

ICD-10 level 4 code	ICD-10 level 4 name	Standard disease name	Case group N=13,420	Control group N=134,200	Odds ratio (95% CI)
R42-	Dizziness and giddiness	Dizziness	407 (3.0)	1113 (0.8)	3.7 (3.3–4.2)
N95.1	Menopausal and female climacteric states	Climacteric syndrome	399 (3.0)	1050 (0.8)	3.9 (3.5–4.4)
F41.9	Anxiety disorder, unspecified	Anxiety disorder	387 (2.9)	259 (0.2)	15.4 (13.1–18.0)
G90.9	Disorder of autonomic nervous system, unspecified	Autonomic imbalance	385 (2.9)	585 (0.4)	6.7 (5.9–7.7)
L25.9	Unspecified contact dermatitis, unspecified cause	Contact dermatitis	376 (2.8)	3018 (2.2)	1.3 (1.1–1.4)
B35.3	Tinea pedis	Foot tinea	375 (2.8)	3393 (2.5)	1.1 (1.0–1.2)
M51.2	Other specified intervertebral disc displacement	Lumbar disc herniation	375 (2.8)	2106 (1.6)	1.8 (1.6–2.0)
G44.2	Tension-type headache	Tension-type headache	372 (2.8)	1014 (0.8)	3.7 (3.3–4.2)
D25.9	Leiomyoma of uterus, unspecified	Uterus myoma	368 (2.7)	2690 (2.0)	1.4 (1.2–1.5)
H53.1	Subjective visual disturbances	Asthenopia	366 (2.7)	2355 (1.8)	1.6 (1.4–1.8)
E11-	Type 2 diabetes mellitus	Type 2 diabetes mellitus	365 (2.7)	2654 (2.0)	1.4 (1.2–1.5)
M17.9	Gonarthrosis, unspecified	Knee osteoarthritis	355 (2.6)	2589 (1.9)	1.4 (1.2–1.5)
G98-	Other disorders of nervous system, not elsewhere classified	Neuropathic pain	345 (2.6)	1011 (0.8)	3.5 (3.1–3.9)
F41.0	Panic disorder [episodic paroxysmal anxiety]	Panic disorder	341 (2.5)	198 (0.1)	17.6 (14.8–21.0)
A09.0	Other and unspecified gastroenteritis and colitis of infectious origin	Infectious enteritis	340 (2.5)	2222 (1.7)	1.5 (1.4–1.7)
H16.8	Other keratitis	Keratoconjunctivitis sicca	336 (2.5)	2509 (1.9)	1.3 (1.2–1.5)

ICD-10 level 4 code	ICD-10 level 4 name	Standard disease name	Case group N=13,420	Control group N=134,200	Odds ratio (95% CI)
R50.9	Fever, unspecified	Pyrexia	335 (2.5)	2385 (1.8)	1.4 (1.3–1.6)
G64-	Other disorders of peripheral nervous system	Peripheral neuropathic pain	334 (2.5)	1061 (0.8)	3.2 (2.8–3.6)
I20.9	Angina pectoris, unspecified	Angina pectoris	334 (2.5)	1759 (1.3)	1.9 (1.7–2.2)
J04.0	Acute laryngitis	Acute laryngitis	313 (2.3)	2428 (1.8)	1.3 (1.2–1.5)
I49.9	Cardiac arrhythmia, unspecified	Arrhythmia	307 (2.3)	1184 (0.9)	2.6 (2.3–3.0)
H81.0	Ménière disease	Ménière's disease	302 (2.3)	1066 (0.8)	2.9 (2.5–3.3)
K64.9	Haemorrhoids, unspecified	Internal haemorrhoids	300 (2.2)	1856 (1.4)	1.6 (1.4–1.8)
L21.9	Seborrheic dermatitis, unspecified	Seborrheic dermatitis	299 (2.2)	2434 (1.8)	1.2 (1.1–1.4)
J00-	Acute nasopharyngitis [common cold]	Acute rhinitis	295 (2.2)	2089 (1.6)	1.4 (1.3–1.6)
B07-	Viral warts	Verruca vulgaris	294 (2.2)	2660 (2.0)	1.1 (1.0–1.3)
L08.9	Local infection of skin and subcutaneous tissue, unspecified	Cutaneous infection	291 (2.2)	2252 (1.7)	1.3 (1.1–1.5)
N94.6	Dysmenorrhoea, unspecified	Dysmenorrhoea	290 (2.2)	1105 (0.8)	2.7 (2.3–3.0)
R63.0	Anorexia	Inappetence	290 (2.2)	826 (0.6)	3.6 (3.1–4.1)
H61.2	Impacted cerumen	Impacted cerumen	286 (2.1)	2199 (1.6)	1.3 (1.2–1.5)
H60.5	Acute otitis externa, non-infective	External ear eczema	281 (2.1)	2098 (1.6)	1.3 (1.2–1.5)
A49.8	Other bacterial infections of unspecified site	*Helicobacter pylori* infection	277 (2.1)	2222 (1.7)	1.3 (1.1–1.4)
R10.4	Other and unspecified abdominal pain	Abdominal pain	269 (2.0)	1301 (1.0)	2.1 (1.8–2.4)
G47.3	Sleep apnoea	Sleep apnoea syndrome	268 (2.0)	1335 (1.0)	2.0 (1.8–2.3)

ICD-10 level 4 code	ICD-10 level 4 name	Standard disease name	Case group N=13,420	Control group N=134,200	Odds ratio (95% CI)
N30.9	Cystitis, unspecified	Cystitis	264 (2.0)	1564 (1.2)	1.7 (1.5–1.9)
K12.1	Other forms of stomatitis	Stomatitis	262 (2.0)	1669 (1.2)	1.6 (1.4–1.8)
H52.2	Astigmatism	Hyperopic astigmatism	260 (1.9)	1851 (1.4)	1.4 (1.2–1.6)
M79.1	Myalgia	Myalgia	248 (1.8)	1226 (0.9)	2.0 (1.8–2.3)
F34.1	Dysthymia	Depressive neurosis	239 (1.8)	161 (0.1)	15.1 (12.4–18.4)
H40.9	Glaucoma, unspecified	Glaucoma	239 (1.8)	2136 (1.6)	1.1 (1.0–1.3)
H60.9	Otitis externa, unspecified	Otitis externa	239 (1.8)	1932 (1.4)	1.2 (1.1–1.4)
K63.5	Polyp of colon	Colorectal polyp	239 (1.8)	1947 (1.5)	1.2 (1.1–1.4)
A09.9	Gastroenteritis and colitis of unspecified origin	Gastroenteritis	238 (1.8)	1351 (1.0)	1.8 (1.5–2.0)
K21.0	Gastro-oesophageal reflux disease with oesophagitis	Intractable regurgitant oesophagitis	238 (1.8)	1123 (0.8)	2.1 (1.9–2.5)
N76.0	Acute vaginitis	Bacterial vaginitis	232 (1.7)	1569 (1.2)	1.5 (1.3–1.7)
M10.9	Gout, unspecified	Gout	230 (1.7)	1763 (1.3)	1.3 (1.1–1.5)
L30.9	Dermatitis, unspecified	Acute eczema	229 (1.7)	1856 (1.4)	1.2 (1.1–1.4)
H16.0	Corneal ulcer	Corneal erosion	222 (1.7)	1935 (1.4)	1.1 (1.0–1.3)
H93.1	Tinnitus	Tinnitus	217 (1.6)	672 (0.5)	3.3 (2.8–3.8)
D64.9	Anaemia, unspecified	Anaemia	216 (1.6)	1337 (1.0)	1.6 (1.4–1.9)
M47.8	Other spondylosis	Lumbar osteoarthritis	216 (1.6)	1105 (0.8)	2.0 (1.7–2.3)
H01.0	Blepharitis	Blepharitis	215 (1.6)	1665 (1.2)	1.3 (1.1–1.5)

ICD-10 level 4 code	ICD-10 level 4 name	Standard disease name	Case group N=13,420	Control group N=134,200	Odds ratio (95% CI)
H26.9	Cataract, unspecified	Cataract	214 (1.6)	1653 (1.2)	1.3 (1.1–1.5)
H52.1	Myopia	High myopia	213 (1.6)	2000 (1.5)	1.1 (0.9–1.2)
J30.1	Allergic rhinitis due to pollen	Pollinosis	210 (1.6)	1670 (1.2)	1.3 (1.1–1.5)
L30.9	Dermatitis, unspecified	Chronic eczema	210 (1.6)	1693 (1.3)	1.2 (1.1–1.4)
M81.9	Osteoporosis, unspecified	Osteoporosis	207 (1.5)	1455 (1.1)	1.4 (1.2–1.7)
R07.4	Chest pain, unspecified	Chest pain	206 (1.5)	789 (0.6)	2.6 (2.3–3.1)
J37.0	Chronic laryngitis	Chronic pharyngopharyngitis	205 (1.5)	1259 (0.9)	1.6 (1.4–1.9)
K64.9	Haemorrhoids, unspecified	Haemorrhoid	203 (1.5)	1281 (1.0)	1.6 (1.4–1.8)
J42-	Unspecified chronic bronchitis	Chronic bronchitis	201 (1.5)	1422 (1.1)	1.4 (1.2–1.6)
K29.4	Chronic atrophic gastritis	Atrophic gastritis	201 (1.5)	1503 (1.1)	1.3 (1.2–1.6)
M48.0	Spinal stenosis	Lumbar spinal canal stenosis	201 (1.5)	880 (0.7)	2.3 (2.0–2.7)
H40.0	Glaucoma suspect	Enlargement of optic disc cupping	200 (1.5)	1628 (1.2)	1.2 (1.1–1.4)
H90.5	Sensorineural hearing loss, unspecified	Sensorineural hearing loss	199 (1.5)	917 (0.7)	2.2 (1.9–2.6)
E03.9	Hypothyroidism, unspecified	Hypothyroidism	197 (1.5)	938 (0.7)	2.1 (1.8–2.5)
N40-	Hyperplasia of prostate	Prostatic hyperplasia	197 (1.5)	1098 (0.8)	1.8 (1.6–2.1)
L70.0	Acne vulgaris	Acne vulgaris	195 (1.5)	1555 (1.2)	1.3 (1.1–1.5)
L30.9	Dermatitis, unspecified	Hand eczema	193 (1.4)	1665 (1.2)	1.2 (1.0–1.3)

ICD-10 level 4 code	ICD-10 level 4 name	Standard disease name	Case group N=134,420	Control group N=134,200	Odds ratio (95% CI)
H00.0	Hordeolum and other deep inflammation of eyelid	Hordeolum	190 (1.4)	1560 (1.2)	1.2 (1.0–1.4)
M47.8	Other spondylosis	Cervical spondylosis	190 (1.4)	830 (0.6)	2.3 (2.0–2.7)
A09.9	Gastroenteritis and colitis of unspecified origin	Enterocolitis	185 (1.4)	1046 (0.8)	1.8 (1.5–2.1)
J45.9	Asthma, unspecified	Asthmatic bronchitis	185 (1.4)	1373 (1.0)	1.4 (1.2–1.6)
H16.1	Other superficial keratitis without conjunctivitis	Superficial punctate keratitis	183 (1.4)	1451 (1.1)	1.3 (1.1–1.5)
M62.8	Other specified disorders of muscle	Shoulder stiffness	181 (1.3)	755 (0.6)	2.4 (2.1–2.8)
H90.3	Sensorineural hearing loss, bilateral	Bilateral sensorineural hearing loss	176 (1.3)	590 (0.4)	3.0 (2.5–3.6)
J00-	Acute nasopharyngitis [common cold]	Acute nasopharyngitis	176 (1.3)	1291 (1.0)	1.4 (1.2–1.6)
R11-	Nausea and vomiting	Nausea	176 (1.3)	585 (0.4)	3.0 (2.6–3.6)
K31.7	Polyp of stomach and duodenum	Stomach polyp	175 (1.3)	1108 (0.8)	1.6 (1.4–1.9)
M50.2	Other cervical disc displacement	Cervical disc herniation	175 (1.3)	865 (0.6)	2.0 (1.7–2.4)
K73.9	Chronic hepatitis, unspecified	Chronic hepatitis	174 (1.3)	1179 (0.9)	1.5 (1.3–1.7)
L29.9	Pruritus, unspecified	Pruritus cutaneous	173 (1.3)	1176 (0.9)	1.5 (1.3–1.7)
N64.9	Disorder of breast, unspecified	Mastopathy	173 (1.3)	1176 (0.9)	1.5 (1.3–1.7)
H68.1	Obstruction of Eustachian tube	Stenosis of Eustachian tube	172 (1.3)	929 (0.7)	1.9 (1.6–2.2)
L81.0	Post-inflammatory hyperpigmentation	Post-inflammatory pigmentation	171 (1.3)	1272 (0.9)	1.3 (1.1–1.6)
R52.9	Pain, unspecified	Pain	169 (1.3)	904 (0.7)	1.9 (1.6–2.2)
N80.9	Endometriosis, unspecified	Endometriosis	165	872	1.9

ICD-10 level 4 code	ICD-10 level 4 name	Standard disease name	Case group N=13,420	Control group N=134,200	Odds ratio (95% CI)
			(1.2)	(0.6)	(1.6–2.3)
H65.9	Nonsuppurative otitis media, unspecified	Otitis media with effusion	164 (1.2)	1191 (0.9)	1.4 (1.2–1.6)
J32.9	Chronic sinusitis, unspecified	Sinusitis	164 (1.2)	1146 (0.9)	1.4 (1.2–1.7)
N32.8	Other specified disorders of bladder	Overactive bladder	164 (1.2)	519 (0.4)	3.2 (2.7–3.8)
G62.9	Polyneuropathy, unspecified	Peripheral neuritis	163 (1.2)	662 (0.5)	2.5 (2.1–2.9)
L30.9	Dermatitis, unspecified	Dermatitis	163 (1.2)	1336 (1.0)	1.2 (1.0–1.4)
L70.0	Acne vulgaris	Facial common acne	162 (1.2)	1446 (1.1)	1.1 (1.0–1.3)
I50.9	Heart failure, unspecified	Chronic cardiac failure	159 (1.2)	815 (0.6)	2.0 (1.7–2.3)
G47.9	Sleep disorder, unspecified	Sleeping disturbance	157 (1.2)	205 (0.2)	7.7 (6.3–9.5)
M06.9	Rheumatoid arthritis, unspecified	Rheumatoid arthritis	155 (1.2)	830 (0.6)	1.9 (1.6–2.2)
J32.9	Chronic sinusitis, unspecified	Acute exacerbation of chronic sinusitis	153 (1.1)	1272 (0.9)	1.2 (1.0–1.4)
N20.1	Calculus of ureter	Ureterolithiasis	151 (1.1)	1139 (0.8)	1.3 (1.1–1.6)
R52.2	Other chronic pain	Chronic pain	151 (1.1)	417 (0.3)	3.7 (3.0–4.4)
R31-	Unspecified haematuria	Haematuria	149 (1.1)	1024 (0.8)	1.5 (1.2–1.7)
K76.9	Liver disease, unspecified	Liver disorder	148 (1.1)	955 (0.7)	1.6 (1.3–1.9)
R00.2	Palpitations	Palpitations	148 (1.1)	257 (0.2)	5.8 (4.7–7.1)
H10.3	Acute conjunctivitis, unspecified	Acute conjunctivitis	147 (1.1)	1212 (0.9)	1.2 (1.0–1.4)

ICD-10 level 4 code	ICD-10 level 4 name	Standard disease name	Case group N=13,420	Control group N=134,200	Odds ratio (95% CI)
J10.1	Influenza with other respiratory manifestations, seasonal influenza virus identified	Influenza B	147 (1.1)	1427 (1.1)	1.0 (0.9–1.2)
D27-	Benign neoplasm of ovary	Ovarian cystoma	141 (1.1)	967 (0.7)	1.5 (1.2–1.7)
B37.3	Candidiasis of vulva and vagina	Vulvovaginal candidiasis	140 (1.0)	930 (0.7)	1.5 (1.3–1.8)
B02.9	Zoster without complication	Herpes zoster	137 (1.0)	884 (0.7)	1.6 (1.3–1.9)
L73.9	Follicular disorder, unspecified	Folliculitis	136 (1.0)	1024 (0.8)	1.3 (1.1–1.6)
N20.0	Calculus of kidney	Nephrolithiasis	136 (1.0)	912 (0.7)	1.5 (1.2–1.8)
M47.2	Other spondylosis with radiculopathy	Cervical spondylotic radiculopathy	135 (1.0)	725 (0.5)	1.9 (1.6–2.3)

Shown are diseases with prevalence ≥1.0% in the case group and ≥0.1% in the control group. Data are n (%), unless otherwise noted.
CI, confidence interval; ICD-10, International Statistical Classification of Diseases and Related Health Problems, 10th revision.

Supplemental table 3 Number of patients in post hoc multivariate analysis subgroups

Explanatory variable	Category			Number of cases	Number of controls	Total number
Sex	Male			8924	89,240	98,164
	Female			4496	44,960	49,456
Age	<40 years			5390	53,900	59,290
	≥40 years			8030	80,300	88,330
Working status	Worker			10,447	104,470	114,917
	Non-worker			2973	29,730	32,703
Presence of metabolic risk factor, psychiatric disorder, and/or MDD-related symptoms during the 12 months before index date	Metabolic risk factor	Psychiatric disorder	MDD-related symptoms			
	No	No	No	4329	80,434	84,763
	No	No	Yes	1998	20,752	22,750
	No	Yes	No	1794	3314	5108
	No	Yes	Yes	1595	2301	3896
	Yes	No	No	901	15,660	16,561
	Yes	No	Yes	854	7588	8442
	Yes	Yes	No	675	1866	2541
	Yes	Yes	Yes	1274	2285	3559
Total				13,420	134,200	147,620

MDD, major depressive disorder.

Supplemental table 4 Multivariate logistic regression analysis for the relationship between the number of CCI-related and other chronic diseases and the onset of MDD

Dependent variable	Explanatory variable	Reference	Category	Odds ratio (95% CI)
Group (reference = control group)	Sex	Male	Female	1.08 (1.01–1.16)
	Age	<40 years	≥40 years	0.78 (0.74–0.82)
	Working status	Worker	Non-worker	0.97 (0.90–1.05)
	Number of chronic diseases	1	2	1.34 (1.27–1.42)
			3	1.51 (1.40–1.62)
			4	1.78 (1.63–1.95)
			5	2.16 (1.93–2.42)
			6	2.28 (1.95–2.66)
			7	2.21 (1.78–2.75)
			8	2.88 (2.18–3.81)
			9	3.70 (2.48–5.51)
			10	3.59 (2.03–6.35)
			≥11	3.26 (1.65–6.43)

Analysis included 8329 cases and 64,594 controls.
CCI, Charlson comorbidity index; CI, confidence interval; MDD, major depressive disorder.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *case-control studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5-6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-7
Participants	6	(a) Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	6-7
		(*b*) For matched studies, give matching criteria and the number of controls per case	7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-8
Bias	9	Describe any efforts to address potential sources of bias	NA
Study size	10	Explain how the study size was arrived at	NA
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7-8
		(*b*) Describe any methods used to examine subgroups and interactions	7-8
		(*c*) Explain how missing data were addressed	NA
		(*d*) If applicable, explain how matching of cases and controls was addressed	7
		(*e*) Describe any sensitivity analyses	NA
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8, Supplementary Figure
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	Supplementary Figure
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8, Table 1
		(b) Indicate number of participants with missing data for each variable of interest	NA
Outcome data	15*	Report numbers in each exposure category, or summary measures of exposure	8-10, Tables 2 and 3, Figure 1, Supplementary Tables
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8-10, Tables 2 and 3, Figure 1, Supplementary Tables
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8-10, Tables 2 and 3, Figure 1, Supplementary Tables
Discussion			
Key results	18	Summarise key results with reference to study objectives	10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13-14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	13-14
Other information			

Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Funding statement

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.