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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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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 International Statistical Classification of Diseases and Related Health Problems, 10th revision 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 nationwide 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.

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 bidirectional, 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 (Tokyo, Japan) database of medical expense claims for company employees in Japan.[11]

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≤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) was used as the data warehouse platform. SAS V.9.4 (SAS Institute) 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).

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 vs 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

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	OR (95% CI)
CCI-related diseases			
Peptic ulcer disease	1431 (10.7)	7659 (5.7)	2.0 (1.9 to 2.1)
Mild liver disease	1392 (10.4)	9336 (7.0)	1.5 (1.5 to 1.6)
Chronic pulmonary disease (exc. asthma)	973 (7.3)	7381 (5.5)	1.3 (1.3 to 1.4)
Cerebrovascular disease	448 (3.3)	2378 (1.8)	1.9 (1.7 to 2.1)
Peripheral vascular disease	359 (2.7)	2237 (1.7)	1.6 (1.4 to 1.8)
Congestive heart failure	347 (2.6)	1885 (1.4)	1.9 (1.7 to 2.1)
Second solid tumour (non-metastatic)	327 (2.4)	2357 (1.8)	1.4 (1.2 to 1.6)
Diabetes with chronic complication	239 (1.8)	1758 (1.3)	1.4 (1.2 to 1.6)
Rheumatic disease	192 (1.4)	1066 (0.8)	1.8 (1.6 to 2.1)
Diabetes without chronic complication	107 (0.8)	502 (0.4)	2.1 (1.7 to 2.6)
Renal disease	77 (0.6)	708 (0.5)	1.1 (0.9 to 1.4)
Metastatic solid tumour	52 (0.4)	241 (0.2)	2.2 (1.6 to 2.9)
Myocardial infarction	46 (0.3)	338 (0.3)	1.4 (1.0 to 1.9)
Hemiplegia or paraplegia	39 (0.3)	138 (0.1)	2.8 (2.0 to 4.0)
Lymphoma/multiple myeloma	25 (0.2)	174 (0.1)	1.4 (0.9 to 2.2)
Dementia	13 (0.1)	15 (<0.1)	8.7 (4.1 to 18.2)
Leukaemia	9 (0.1)	97 (0.1)	0.9 (0.5 to 1.8)
Moderate or severe liver disease	7 (0.1)	54 (<0.1)	1.3 (0.6 to 2.8)
Other chronic diseases			
Pain	4598 (34.3)	27 452 (20.5)	2.0 (2.0 to 2.1)
Psychiatric diseases except depression	4084 (30.4)	5691 (4.2)	9.9 (9.4 to 10.3)
Sleep disorders	3128 (23.3)	5462 (4.1)	7.2 (6.8 to 7.5)
Chronic gastritis	2349 (17.5)	12 568 (9.4)	2.1 (2.0 to 2.2)
Dyslipidaemia	2286 (17.0)	17 438 (13.0)	1.4 (1.3 to 1.4)
Headache	2129 (15.9)	8634 (6.4)	2.7 (2.6 to 2.9)
Hypertensive disease	1987 (14.8)	15 052 (11.2)	1.4 (1.3 to 1.4)
Asthma	1861 (13.9)	12 923 (9.6)	1.5 (1.4 to 1.6)
Dizziness	1309 (9.8)	4345 (3.2)	3.2 (3.0 to 3.4)
Arthritis	729 (5.4)	5217 (3.9)	1.4 (1.3 to 1.5)
Osteoarthritis	654 (4.9)	4290 (3.2)	1.6 (1.4 to 1.7)
Atopic dermatitis	608 (4.5)	5984 (4.5)	1.0 (0.9 to 1.1)
Irritable bowel syndrome	588 (4.4)	1900 (1.4)	3.2 (2.9 to 3.5)
Thyroid disease	551 (4.1)	3394 (2.5)	1.7 (1.5 to 1.8)
Autonomic nerve imbalance	409 (3.0)	647 (0.5)	6.5 (5.7 to 7.4)
Angina pectoris	405 (3.0)	2058 (1.5)	2.0 (1.8 to 2.2)
Osteoporosis	226 (1.7)	1611 (1.2)	1.4 (1.2 to 1.6)
Epilepsy	177 (1.3)	729 (0.5)	2.4 (2.1 to 2.9)
Chronic enteritis	153 (1.1)	561 (0.4)	2.7 (2.3 to 3.3)
Obesity	74 (0.6)	513 (0.4)	1.4 (1.1 to 1.8)
Attention deficit hyperkinetic disorders	56 (0.4)	46 (<0.1)	12.2 (8.3 to 18.1)
Parkinson's disease	24 (0.2)	76 (0.1)	3.2 (2.0 to 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; exc., excluding; OR, odds ratio.

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	OR (95% CI)
A00–B99	Certain infectious and parasitic diseases	4583 (34.2)	33 852 (25.2)	1.5 (1.5 to 1.6)
C00–D48	Neoplasms	1575 (11.7)	12 007 (8.9)	1.4 (1.3 to 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 to 1.5)
E00–E90	Endocrine, nutritional and metabolic diseases	4477 (33.4)	32 630 (24.3)	1.6 (1.5 to 1.6)
F00–F99	Mental and behavioural disorders	4084 (30.4)	5691 (4.2)	9.9 (9.4 to 10.3)
G00–G99	Diseases of the nervous system	4965 (37.0)	14 847 (11.1)	4.7 (4.5 to 4.9)
H00–H59	Diseases of the eye and adnexa	5035 (37.5)	46 365 (34.5)	1.1 (1.1 to 1.2)
H60–H95	Diseases of the ear and mastoid process	1735 (12.9)	10 245 (7.6)	1.8 (1.7 to 1.9)
I00–I99	Diseases of the circulatory system	3038 (22.6)	20 545 (15.3)	1.6 (1.6 to 1.7)
J00–J99	Diseases of the respiratory system	9232 (68.8)	77 686 (57.9)	1.6 (1.5 to 1.7)
K00–K93	Diseases of the digestive system	7015 (52.3)	47 838 (35.6)	2.0 (1.9 to 2.0)
L00–L99	Diseases of the skin and subcutaneous tissue	4428 (33.0)	37 648 (28.1)	1.3 (1.2 to 1.3)
M00–M99	Diseases of the musculoskeletal system and connective tissue	5322 (39.7)	35 387 (26.4)	1.8 (1.8 to 1.9)
N00–N99	Diseases of the genitourinary system	2880 (21.5)	20 016 (14.9)	1.6 (1.5 to 1.6)
O00–O99	Pregnancy, childbirth and the puerperium	178 (1.3)	2944 (2.2)	0.6 (0.5 to 0.7)
P00–P96	Certain conditions originating in the perinatal period	19 (0.1)	212 (0.2)	0.9 (0.6 to 1.4)
Q00–Q99	Congenital malformations, deformations and chromosomal abnormalities	199 (1.5)	1496 (1.1)	1.3 (1.2 to 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 to 2.4)
S00–T98	Injury, poisoning and certain other consequences of external causes	2209 (16.5)	17 661 (13.2)	1.3 (1.2 to 1.4)
Z00–Z99	Factors influencing health status and contact with health services	252 (1.9)	1878 (1.4)	1.3 (1.2 to 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; OR, odds ratio.

(figure 1; online supplemental table 2). The highest ORs for the onset of MDD were observed for psychiatric diseases and sleep disorders (figure 1). 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

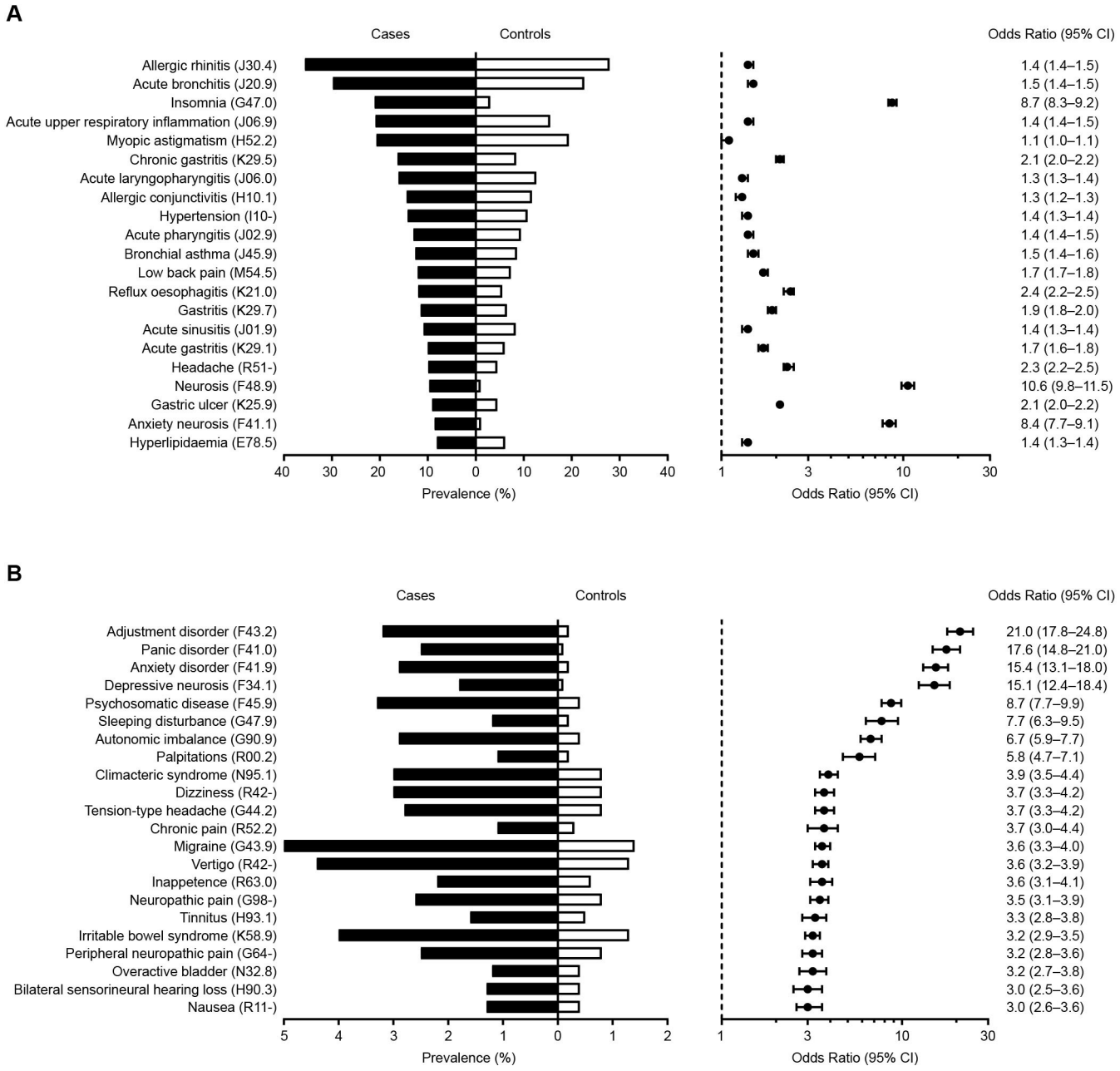

Figure 1 (A) Diseases with prevalence >8% in the case group in the 12 months before MDD diagnosis. (B) Diseases with OR >3.0. Shown are the prevalence rates in the case group and in the matched control group, as well as the OR (95% CI). CI, confidence interval; MDD, major depressive disorder; OR, odds ratio.

three in people with nine or more comorbidities (online supplemental table 4).

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 12–15] Two large case–control studies conducted in the USA, using electronic health records at the Mayo Clinic[16] and South Korea, using the National Health Insurance Service,[17] identified pre-existing chronic

Table 4 Multivariate logistic regression analysis for the onset of MDD

Dependent variable	Explanatory variable	Reference	Category			OR (95% CI)
Group (reference=control group)	Sex	Male	Female			0.93 (0.89 to 0.98)
	Age	<40 years	≥40 years			0.80 (0.77 to 0.83)
	Working status	Worker	Non-worker			0.92 (0.86 to 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 to 1.91)
			No	Yes	No	10.22 (9.58 to 10.91)
			No	Yes	Yes	13.47 (12.54 to 14.47)
			Yes	No	No	1.14 (1.06 to 1.23)
			Yes	No	Yes	2.27 (2.10 to 2.46)
			Yes	Yes	No	7.27 (6.61 to 7.99)
			Yes	Yes	Yes	11.49 (10.63 to 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; OR, odds ratio.

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] 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,[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.[26] Indeed, a significant proportion of patients with MDD present with only somatic symptoms.[27] One reason is denial of psychological symptoms, which is particularly prevalent in Japan.[27] 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 vs 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.[28]

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,[29 30] 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,[31] which increases the risk of severe complications.[32] In addition, treating metabolic-related diseases

and depression simultaneously may provide patients with better clinical outcomes.[33] 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.[34]

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.[35–37] Neural pathways and neurotransmitters that are altered in chronic pain may also affect mood, including depression.[38] Migraine and depression can both be related to specific genetic variants and/or neuroanatomic features.[39] Most of these biological mechanisms are exacerbated by stress.[3 36 39] 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.[40] 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[41 42]; 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 reoccur 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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Data availability statement Data may be obtained from a third party and are not publicly available. The data that support the findings of this study are available from JMDC 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).

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