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

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11 5 Diseases prevalent before major depressive disorder diagnosis: a nested case-control study
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STATISTICAL SUMMARY

Abstract Text	Manuscript Text (Intro-Disc)	References	Figures / Tables
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34 **ABSTRACT**

35 **Objectives** Major depressive disorder (MDD) is often comorbid with other chronic and/or
36 serious diseases. However, little is known about the prevalence of various diseases that are
37 present before MDD onset. We examined the prevalence of all pre-existing diseases in the
38 12 months before an MDD diagnosis.

39 **Design** Nested case-control study.

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

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

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

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

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

62

ARTICLE SUMMARY**Strengths and limitations of this study**

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

74

Keywords: Administrative claims, healthcare; Comorbidity; Depressive disorder;

Epidemiology; Risk factors

77 INTRODUCTION

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

91
92 An epidemiological study conducted in Japan between 2013 and 2015 reported the lifetime
93 and 12-month prevalence rates of MDD to be 5.7% and 2.7%, respectively.⁵ However, fewer
94 than half of Japanese people with a mood disorder seek medical treatment.⁵ This reluctance
95 to seek medical treatment may be related to a perceived 'stigma' associated with psychiatric
96 disease.⁶ These factors may further reduce the detection and diagnosis of MDD in patients
97 with a chronic disease, despite the potentially increased risk of MDD in these patients.
98 However, little is known about the prevalence of underlying diseases that are comorbid with
99 MDD. Given that around 20,000 people in Japan commit suicide every year,⁷ with the highest
100 rate of about 50 per 100,000 persons in men aged 50–59 years,⁸ most of which are probably
101 related to mental disorders, additional information on factors associated with MDD that could
102 assist with early detection and treatment may help reduce the number of suicides.

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3 104 The aim of this nested case-control study of patients enrolled in a Japanese health insurance
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5 105 database was to comprehensively examine the prevalence of pre-existing diseases in the 12
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7 106 months before an MDD diagnosis. In this context, a pre-existing disease was defined as any
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9 107 diagnosis other than MDD and related mental disorders (bipolar affective disorders; organic
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11 108 mental disorders; schizophrenia, schizotypal, and delusional disorders), which could include
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13 109 conditions that are prodromal symptoms of MDD (eg, sleep disorders). In addition, we
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15 110 determined an odds ratio (OR) for the onset of MDD for each pre-existing disease to identify
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17 111 those that are most commonly associated with development of MDD and to evaluate the
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19 112 association of MDD with common lifestyle diseases.
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23 24 114 **METHODS**

25 26 115 **Study design**

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28 116 This was a nested case-control study. Data on patient demographics and diagnoses based
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30 117 on International Statistical Classification of Diseases and Related Health Problems, 10th
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32 118 revision⁹ (ICD-10) were derived from the JMDC Inc. (Tokyo, Japan) database of medical
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34 119 expense claims for company employees in Japan.¹⁰
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39 121 The study was approved by the Ethics Review Committee of the Research Institute of
40
41 122 Healthcare Data Science (Tokyo, Japan) on 6 August 2019. Only anonymised information
42
43 123 was accessible from the database; therefore, in accordance with the Ethical Guidelines for
44
45 124 Medical and Health Research Involving Human Subjects in Japan,¹¹ informed consent was
46
47 125 not required.
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51 127 **Study population**

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53 128 The study analysed data collected for the population registered in the JMDC database
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55 129 between January 2014 and December 2018 who were aged ≥ 18 years on 1 January of the
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57 130 inclusion year (2015, 2016, or 2017) and had continuous registration for the inclusion year,
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59 131 the previous year, and the subsequent year (study period). Individuals were excluded if they
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3 132 had a diagnosis of any bipolar affective disorder (ICD-10 codes F30 [manic episode], F31),
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5 133 organic mental disorder including symptomatic mental disorders (F00–F09), or
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7 134 schizophrenia, schizotypal, and delusional disorder (F20–F29) in the study period, or a
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9 135 diagnosis of MDD (ICD-10 codes F32 [‘Depressive episode’] or F33 [‘Recurrent depressive
10
11 136 disorder’]) in the year before the inclusion year, or no medical history for the year before the
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13 137 inclusion year.
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18 139 Within the study population, case patients had a diagnosis of MDD in the inclusion year (the
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20 140 date of the first MDD treatment after ≥ 1 year with no MDD diagnosis was designated as the
21
22 141 index date) and ≥ 2 months of treatment for depression within 90 days of the index date.

23
24 142 Control patients had no diagnosis of MDD in the study period and were matched 10:1
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26 143 (random sampling) to case patients according to age at index date, sex, and working status.
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30 145 **Outcomes**

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32 146 The primary end point was the proportion of patients with documented diagnosis of each pre-
33
34 147 existing disease during the 12 months before the index date (ie, before MDD diagnosis in
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36 148 case patients). An OR for the onset of MDD was calculated for each underlying disease,
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38 149 which was based on presence or absence of ICD-10 codes, Charlson comorbidity index
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40 150 (CCI)–related diseases, or other chronic diseases (online supplemental table 1).

41
42
43 151 Demographic and patient characteristics were collected, including age, sex, working status,
44
45 152 and inclusion year (2015/2016/2017).
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47 153

49 154 **Statistical analysis**

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51 155 As noted above, the proportion of patients with each pre-existing disease was determined for
52
53 156 each group and an OR for the onset of MDD was calculated. Prevalence data and ORs are
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55 157 reported for pre-existing diseases that were present in $\geq 1\%$ of the case group and $\geq 0.1\%$ of
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57 158 the control group. No inferential statistics were conducted. A post hoc analysis examined the
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59 159 possible interaction of the presence of three pre-existing disease categories that exhibited

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3 160 high ORs in the primary analysis or are common diseases: lifestyle diseases (diabetes,
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5 161 hypertension, dyslipidaemia), MDD-related symptoms (headache, pain, autonomic nerve
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7 162 imbalance), and psychiatric disorders (sleep disorders, psychiatric disorders other than
8
9 163 depression) (online supplemental table 1). A multivariate logistic regression model was used
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11 164 to determine ORs in the eight subgroups (ie, with/without lifestyle disease, MDD-related
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13 165 symptoms, and/or psychiatric disease) for the onset of MDD using the following covariates:
14
15 166 sex, age (<40 years versus ≥40 years), and working status. Netezza N2002-010 7.1.0.4.P2
16
17 167 (IBM, Armonk, NY, USA) was used as the data warehouse platform. SAS version 9.4 (SAS
18
19 168 Institute, Cary, NC, USA) was used for statistical analysis.
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23 24 170 **Patient and public involvement**

25
26 171 Patients and members of the public were not involved in the study.
27
28 172

29 30 173 **RESULTS**

31 32 174 **Demographic characteristics**

33
34 175 From more than 6.5 million people enrolled in the JMDC database between 2014 and 2018,
35
36 176 we identified 13,420 case patients who met the inclusion criteria and had MDD diagnosed in
37
38 177 2015, 2016, or 2017 (case group; online supplemental figure). From 4,212,652 control
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40 178 patients who met the inclusion criteria and did not have an MDD diagnosis in either the
41
42 179 inclusion year or the subsequent year, 134,200 were matched to case patients (control
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44 180 group; online supplemental figure). More than half (66.5%) of patients in both groups were
45
46 181 male, with a mean age of 41.9 years (**table 1**). About 40% of patients were <40 years. Most
47
48 182 (77.8%) patients were workers.
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50
51 183

184 **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

185 Data are n (%), unless otherwise noted.

186 MDD, major depressive disorder; NA, not applicable; SD, standard deviation.

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

189 CCI-related diseases and other chronic diseases

190 The prevalence of almost all chronic diseases was higher in the case group than in the
 191 control group, with most ORs between 1.3 and 2.0 (**table 2**). The highest ORs were seen for
 192 attention deficit hyperkinetic disorders (OR 12.2), psychiatric diseases except depression
 193 (OR 9.9), dementia (OR 8.7, although prevalence was ≤0.1% in both groups), sleep
 194 disorders (OR 7.2), and autonomic nerve imbalance (OR 6.5). Of these, psychiatric diseases
 195 except depression and sleep disorders were highly prevalent in the case group (30.4% and
 196 23.3%, respectively). ORs ≥2.0 were also observed (in descending order of prevalence in the
 197 case group) for pain (2.0), chronic gastritis (2.1), headache (2.7), peptic ulcer disease (2.0),
 198 dizziness (3.2), irritable bowel syndrome (3.2), angina pectoris (2.0), epilepsy (2.4), chronic
 199 enteritis (2.7), diabetes without chronic complication (2.1), metastatic solid tumour (2.2),
 200 hemiplegia or paraplegia (2.8), and Parkinson's disease (3.2).

201 **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)	2.07 (1.8–2.2)
Osteoporosis	226 (1.7)	1611 (1.2)	1.45 (1.2–1.6)
Epilepsy	177 (1.3)	729 (0.5)	2.44 (2.1–2.9)
Chronic enteritis	153 (1.1)	561 (0.4)	2.74 (2.3–3.3)
Obesity	74 (0.6)	513 (0.4)	1.47 (1.1–1.8)
Attention deficit hyperkinetic disorders	56 (0.4)	46 (<0.1)	12.20 (8.3–18.1)
Parkinson's disease	24 (0.2)	76 (0.1)	3.24 (2.0–5.0)

202 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
 203 shown ranked by prevalence in the case group. Data are n (%), unless otherwise noted.
 204 CCI, Charlson comorbidity index; CI, confidence interval.

205 **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

206 Data are n (%), unless otherwise noted.

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

208 ICD-10 blocks

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

219

220 ICD-10 codes

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

229

230 Multivariate analysis

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

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3 236 subgroups with psychiatric disorders. The odds of MDD increased significantly in subgroups
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5 237 with both MDD-related symptoms and lifestyle disease and/or psychiatric disorder. However,
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7 238 the odds of MDD decreased significantly in subgroups with both lifestyle diseases and
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9 239 psychiatric disorders (with or without MDD-related symptoms).
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240 **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	1.81 (1.71–1.91)	
				No	No	Yes	10.22 (9.58–10.91)
				No	Yes	No	13.47 (12.54–14.47)
				No	Yes	Yes	1.14 (1.06–1.23)
				Yes	No	No	2.27 (2.10–2.46)
				Yes	No	Yes	7.27 (6.61–7.99)
				Yes	Yes	Yes	11.49 (10.63–12.41)

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

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244 **DISCUSSION**

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

253
254 Our results support and extend the results of previous studies reporting a high prevalence of
255 pre-existing or comorbid diseases in patients with depression. Most previous studies have
256 been cross-sectional or small case-control studies focused on specific comorbid diseases.^{2,3}
257 ¹²⁻¹⁵ Two large case-control studies conducted in the United States, using electronic health
258 records at the Mayo Clinic,¹⁶ and South Korea, using the National Health Insurance
259 Service,¹⁷ identified pre-existing chronic physical conditions that were risk factors for the
260 development of MDD. However, these studies focused on a smaller number (24 and 19) of
261 specific chronic conditions compared with our study, which examined a broad range of both
262 chronic and acute conditions.

263
264 Stress, such as diagnosis with a chronic or serious disease, can contribute to the
265 development of MDD in vulnerable individuals.¹⁸ Further, stress can lead to psychological
266 and physiological changes that affect both mental and physical health, and may contribute
267 directly to depression.¹⁹ Psychiatric disorders can be particularly stressful and may increase
268 the chances of MDD. Depression is often comorbid with other mental disorders, particularly
269 anxiety, and may share symptoms and underlying aetiologies.²⁰⁻²³ Stress is also associated
270 with many gastrointestinal disorders,²⁴ such as irritable bowel syndrome, which were twice as
271 prevalent in the case group than in the control group.

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5 273 Depression-related symptoms (sleep disorders, pain, autonomic imbalance) may be
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7 274 diagnosed in advance of MDD and therefore may be prodromal symptoms of MDD.²⁵
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9 275 Somatic symptoms of MDD, such as fatigue, appetite loss, pain (especially headache),
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11 276 dizziness, and sleep disturbance, can be non-specific and may be attributed to physical
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13 277 illness.⁴ Doctors may first diagnose another disorder instead of MDD to avoid the stigma
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15 278 sometimes associated with depression in Japan.⁶ In addition, diagnoses based on relatively
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17 279 vague symptoms may be made for insurance purposes, eg, to permit subsidised
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19 280 prescriptions. MDD may only be diagnosed later, when symptoms worsen or other
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21 281 depression-related symptoms occur. Indeed, a significant proportion of patients with MDD
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23 282 present with only somatic symptoms.²⁶ One reason is denial of psychological symptoms,
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25 283 which is particularly prevalent in Japan.²⁶ These results support the idea that depression is
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27 284 under-recognised when patients first seek medical help in Japan, and also support our
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29 285 findings that digestive diseases, sleep disorders, and other somatic symptoms, including in
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31 286 the otological area (eg, dizziness), were highly prevalent in patients who later developed
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33 287 MDD. Interestingly, we observed that the OR for diseases of the ear and mastoid process
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35 288 was higher than for diseases of the eye and adnexa (1.8 versus 1.1). We suggest that
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37 289 physicians in otolaryngology departments may be aware of the link between somatic
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39 290 symptoms and MDD and consider psychological evaluation for patients with such symptoms.
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41 291 In contrast, physicians in ophthalmology departments may need to pay more attention to the
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43 292 risk of MDD in patients with severe visual dysfunction because both hearing loss and vision
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45 293 loss are associated with the development of depression.²⁷
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51 295 Our multivariate analysis indicated that the odds of an MDD diagnosis were significantly
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53 296 increased in patients who had depression-related symptoms (headache, pain, autonomic
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55 297 imbalance), particularly if the patient also had a sleep/psychiatric disorder or lifestyle
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57 298 disease. Interestingly, the odds of MDD decreased significantly in subgroups with lifestyle
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59 299 diseases in addition to psychiatric disorders. Although the reason for this finding is unclear, it

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3 300 may be that these patients are managed by multiple physicians who focus on treating each
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5 301 disease separately (eg, psychiatrist treating psychiatric diseases; general practitioner treating
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7 302 lifestyle diseases), with the result that MDD is not sufficiently recognised. Indeed, some
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9 303 general practitioners and other non-psychiatrist doctors in Japan fail to recognise or are
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11 304 reluctant to treat MDD,^{28 29} which may contribute to underdiagnosis of MDD in patients with
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13 305 lifestyle diseases. Psychiatrists, on the other hand, may underestimate somatic depressive
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15 306 symptoms in patients they are treating for another mental illness who also have a lifestyle-
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17 307 related illness treated by another doctor, considering fatigue and autonomic dysfunction as
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19 308 caused by the physical illness. However, depression is known to lead to treatment non-
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21 309 adherence in patients with diabetes,³⁰ which increases the risk of severe complications.³¹ In
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23 310 addition, treating lifestyle-related diseases and depression simultaneously may provide
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25 311 patients with better clinical outcomes.³² Further research is needed on the unmet needs for
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27 312 the diagnosis and treatment of depression in patients with presymptomatic depression in
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29 313 addition to lifestyle-related diseases, and on the effects of coordinated care management of
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31 314 multiple conditions.

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37 316 Many comorbidities may share underlying biological mechanisms with MDD. For example,
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39 317 inflammatory mechanisms play a role in the aetiology of many diseases, including diabetes,
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41 318 cardiovascular disease, arthritis, and asthma, as well as depression.³³⁻³⁵ Neural pathways
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43 319 and neurotransmitters that are altered in chronic pain may also affect mood, including
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45 320 depression.³⁶ Migraine and depression can both be related to specific genetic variants and/or
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47 321 neuroanatomic features.³⁷ Most of these biological mechanisms are exacerbated by stress.³
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49 322 ^{34 37} Thus, MDD may develop in parallel with certain diseases, but its diagnosis may be
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51 323 delayed compared with physical disease.

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56 325 Strengths and limitations

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58 326 Our study is strengthened by the use of a health insurance database consisting of mostly
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60 327 working-age people, which resulted in a sample size large enough to allow examination of a

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3 328 broad range of pre-existing diseases. The nested case-control design and the use of a
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5 329 database minimised selection and recall biases that may occur in other case-control studies.
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7 330 We used a strict definition of MDD onset, which required a 1-year depression-free period and
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9 331 the diagnosis for inclusion to be recorded on at least three doctor visits within 90 days; this
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11 332 definition increased our certainty that case patients had true, newly diagnosed MDD.

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16 334 Despite these strengths, some caveats do apply when interpreting our results. For example,
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18 335 our data set did not include an older population aged ≥ 75 years. Patients with chronic
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20 336 diseases are likely to visit their physicians frequently, increasing the opportunity for detection
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22 337 and diagnosis of MDD. Further, patients with pre-existing psychiatric disorders are likely to
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24 338 be treated by psychiatrists, who may be better at diagnosing MDD than other physicians,
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26 339 which might lead to higher ORs for psychiatric diseases than for physical diseases; however,
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28 340 MDD diagnosis by general practitioners is also higher in patients with psychiatric comorbidity
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30 341 than in those with physical comorbidity.³⁸ Nevertheless, MDD is often under-recognised and
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32 342 underdiagnosed, and this is probably even more true in patients with chronic disease as
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34 343 physicians focus on the disease and may attribute non-specific symptoms to the physical
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36 344 illness.³⁹ We only assessed disease prevalence, and not incidence, during the year before
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38 345 the inclusion year; therefore, we do not know if the disease was diagnosed during that year
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40 346 or in a previous year. This limitation could potentially result in a disproportionate number of
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42 347 people in the control group who had longer-term diseases and were not vulnerable to MDD.
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44 348 For some high-stress diseases such as cancer or stroke, MDD often occurs soon after
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46 349 diagnosis^{40 41}; hence, less vulnerable patients who did not develop MDD would have
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48 350 remained within the control group, leading to lower ORs for those diseases than might be
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50 351 expected. Although comparing ORs for the onset of MDD across a broad range of pre-
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52 352 existing diseases can help develop hypotheses regarding possible underlying mechanisms,
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54 353 the risk of MDD occurring in specific diseases should be investigated on an individual basis.
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3 355 **CONCLUSIONS**
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5 356 This large, nested case-control study has documented the high prevalence of pre-existing
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7 357 diseases in Japanese patients with MDD compared with matched controls without MDD. The
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9 358 high prevalence of pre-existing diseases in patients who develop MDD reflects the complex
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11 359 relationship between physical and mental disorders and indicates a high medical burden for
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13 360 these patients. These results confirm that patients with chronic and/or serious diseases
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15 361 should be monitored for depressive symptoms, and pre-existing diseases should be taken
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17 362 into consideration when prescribing treatment for MDD.
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370

371 **Author contributions**

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

375

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380 data collection, data analysis, preparation of the manuscript, and decision to submit the
381 manuscript for publication.

382

383 **Data availability statement**

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

388

389 **Ethics approval and consent to participate**

390 Not applicable.

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5 392 **Patient consent for publication**
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7 393 Not applicable.
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11 395 **Competing interests**
12
13 396 Dr Cho reports grants from Shionogi & Co., Ltd. and Otsuka Pharmaceutical Co., Ltd., and
14
15 397 personal fees from Shionogi & Co., Ltd., Otsuka Pharmaceutical Co., Ltd., Eli Lilly Japan
16
17 398 K.K., Kyowa Kirin Co. Ltd., Pfizer Japan Inc., Meiji Seika Pharma Co., Ltd., Mitsubishi
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20
21 400 MSD K.K., Takeda Pharmaceutical Company Limited, and Lundbeck Japan K.K., outside the
22
23 401 submitted work. Drs Mishiro, Akaki, Akimoto, and Fujikawa report personal fees from Takeda
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25 402 Pharmaceutical Company Limited, outside the submitted work.
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403 **REFERENCES**

- 404 1 Clarke DM, Currie KC. Depression, anxiety and their relationship with chronic
405 diseases: a review of the epidemiology, risk and treatment evidence. *Med J Aust*
406 2009;190:S54–60.
- 407 2 Evans DL, Charney DS, Lewis L, et al. Mood disorders in the medically ill: scientific
408 review and recommendations. *Biol Psychiatry* 2005;58:175–89.
- 409 3 Katon WJ. Epidemiology and treatment of depression in patients with chronic medical
410 illness. *Dialogues Clin Neurosci* 2011;13:7–23.
- 411 4 Kapfhammer HP. Somatic symptoms in depression. *Dialogues Clin Neurosci*
412 2006;8:227–39.
- 413 5 Ishikawa H, Tachimori H, Takeshima T, et al. Prevalence, treatment, and the
414 correlates of common mental disorders in the mid 2010's in Japan: the results of the
415 World Mental Health Japan 2nd Survey. *J Affect Disord* 2018;241:554–62.
- 416 6 Ando S, Yamaguchi S, Aoki Y, et al. Review of mental-health-related stigma in Japan.
417 *Psychiatry Clin Neurosci* 2013;67:471–82.
- 418 7 Ministry of Health, Labour and Welfare. Vital statistics of Japan, 2017. Available:
419 <https://www.mhlw.go.jp/english/database/db-hw/dl/81-1a2en.pdf> [Accessed 16
420 January 2020].
- 421 8 Snowdon J, Phillips J, Zhong B, et al. Changes in age patterns of suicide in Australia,
422 the United States, Japan and Hong Kong. *J Affect Disord* 2017;211:12–9.
- 423 9 International Statistical Classification of Diseases and Related Health Problems, 10th
424 Revision, 2016. Available: <https://icd.who.int/browse10/2016/en> [Accessed 16
425 January 2020].
- 426 10 Kimura S, Sato T, Ikeda S, et al. Development of a database of health insurance
427 claims: standardization of disease classifications and anonymous record linkage. *J*
428 *Epidemiol* 2010;20:413–9.
- 429 11 Ministry of Health, Labour and Welfare. Ethical guidelines for medical and health
430 research involving human subjects, 2015. Available: [Comorbidity and MDD review only - <http://bmjopen.bmj.com/site/about/guidelines.xhtml> Page 23 of 27](https://www.mhlw.go.jp/file/06-</p></div><div data-bbox=)

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2
3 431 Seisakujouhou-10600000-Daijinkanboukouseikagakuka/0000080278.pdf [Accessed
4
5 432 16 January 2020].
6
7 433 12 Daré LO, Bruand P-E, Gérard D, et al. Co-morbidities of mental disorders and chronic
8
9 434 physical diseases in developing and emerging countries: a meta-analysis. *BMC*
10
11 435 *Public Health* 2019;19:304.
12
13 436 13 Park SJ, Hong S, Jang H, et al. The prevalence of chronic physical diseases
14
15 437 comorbid with depression among different sex and age groups in South Korea: a
16
17 438 population-based study, 2007-2014. *Psychiatry Investig* 2018;15:370–5.
18
19 439 14 Patten SB. Long-term medical conditions and major depression in a Canadian
20
21 440 population study at waves 1 and 2. *J Affect Disord* 2001;63:35–41.
22
23 441 15 Young JQ, Kline-Simon AH, Mordecai DJ, et al. Prevalence of behavioral health
24
25 442 disorders and associated chronic disease burden in a commercially insured health
26
27 443 system: findings of a case-control study. *Gen Hosp Psychiatry* 2015;37:101–8.
28
29 444 16 Ryu E, Chamberlain AM, Pendegraft RS, et al. Quantifying the impact of chronic
30
31 445 conditions on a diagnosis of major depressive disorder in adults: a cohort study using
32
33 446 linked electronic medical records. *BMC Psychiatry* 2016;16:114.
34
35 447 17 Han KM, Kim MS, Kim A, et al. Chronic medical conditions and metabolic syndrome
36
37 448 as risk factors for incidence of major depressive disorder: a longitudinal study based
38
39 449 on 4.7 million adults in South Korea. *J Affect Disord* 2019;257:486–94.
40
41 450 18 de Kloet ER, Joëls M, Holsboer F. Stress and the brain: from adaptation to disease.
42
43 451 *Nat Rev Neurosci* 2005;6:463–75.
44
45 452 19 Yang L, Zhao Y, Wang Y, et al. The effects of psychological stress on depression.
46
47 453 *Curr Neuropharmacol* 2015;13:494–504.
48
49 454 20 Birk JL, Kronish IM, Moise N, et al. Depression and multimorbidity: considering
50
51 455 temporal characteristics of the associations between depression and multiple chronic
52
53 456 diseases. *Health Psychol* 2019;38:802–11.
54
55 457 21 Gorman JM, Coplan JD. Comorbidity of depression and panic disorder. *J Clin*
56
57 458 *Psychiatry* 1996;57:34–41; discussion 2–3.

- 1
2
3 459 22 Hölzel L, Härter M, Reese C, et al. Risk factors for chronic depression — a systematic
4 review. *J Affect Disord* 2011;129:1–13.
5 460
6
7 461 23 Pollack MH. Comorbid anxiety and depression. *J Clin Psychiatry* 2005;66:22–9.
8
9 462 24 Konturek PC, Brzozowski T, Konturek SJ. Stress and the gut: pathophysiology,
10 clinical consequences, diagnostic approach and treatment options. *J Physiol*
11 463
12
13 464
14
15 465 25 Fava GA, Tossani E. Prodromal stage of major depression. *Early Interv Psychiatry*
16 466
17 2007;1:9–18.
18
19 467 26 Simon GE, VonKorff M, Piccinelli M, et al. An international study of the relation
20 468
21 between somatic symptoms and depression. *N Engl J Med* 1999;341:1329–35.
22
23 469 27 McDonnall MC. The effects of developing a dual sensory loss on depression in older
24 470
25 adults: a longitudinal study. *J Aging Health* 2009;21:1179–99.
26
27 471 28 Ohtsuki T, Inagaki M, Oikawa Y, et al. Multiple barriers against successful care
28 472
29 provision for depressed patients in general internal medicine in a Japanese rural
30 473
31 hospital: a cross-sectional study. *BMC Psychiatry* 2010;10:30.
32
33 474 29 Ohtsuki T, Kodaka M, Sakai R, et al. Attitudes toward depression among Japanese
34 475
35 non-psychiatric medical doctors: a cross-sectional study. *BMC Res Notes*
36 476
37 2012;5:441.
38
39 477 30 Gonzalez JS, Peyrot M, McCarl LA, et al. Depression and diabetes treatment
40 478
41 nonadherence: a meta-analysis. *Diabetes Care* 2008;31:2398–403.
42
43 479 31 Chen AJ, Hwang V, Law PY, et al. Factors associated with non-compliance for
44 480
45 diabetic retinopathy follow-up in an urban safety-net hospital. *Ophthalmic Epidemiol*
46 481
47 2018;25:443–50.
48
49 482 32 Katon WJ, Lin EH, Von Korff M, et al. Collaborative care for patients with depression
50 483
51 and chronic illnesses. *N Engl J Med* 2010;363:2611–20.
52
53 484 33 Dantzer R, O'Connor JC, Freund GG, et al. From inflammation to sickness and
54 485
55 depression: when the immune system subjugates the brain. *Nat Rev Neurosci*
56 486
57 2008;9:46–56.
58
59
60

- 1
2
3 487 34 Iwata M, Ota KT, Duman RS. The inflammasome: pathways linking psychological
4
5 488 stress, depression, and systemic illnesses. *Brain Behav Immun* 2013;31:105–14.
6
7 489 35 Raison CL, Capuron L, Miller AH. Cytokines sing the blues: inflammation and the
8
9 490 pathogenesis of depression. *Trends Immunol* 2006;27:24–31.
10
11 491 36 Bair MJ, Robinson RL, Katon W, et al. Depression and pain comorbidity: a literature
12
13 492 review. *Arch Intern Med* 2003;163:2433–45.
14
15 493 37 Baksa D, Gonda X, Juhasz G. Why are migraineurs more depressed? A review of the
16
17 494 factors contributing to the comorbidity of migraine and depression.
18
19 495 *Neuropsychopharmacol Hung* 2017;19:37–44.
20
21 496 38 Nuyen J, Volkens AC, Verhaak PF, et al. Accuracy of diagnosing depression in
22
23 497 primary care: the impact of chronic somatic and psychiatric co-morbidity. *Psychol*
24
25 498 *Med* 2005;35:1185–95.
26
27 499 39 Cepoiu M, McCusker J, Cole MG, et al. Recognition of depression by non-psychiatric
28
29 500 physicians--a systematic literature review and meta-analysis. *J Gen Intern Med*
30
31 501 2008;23:25–36.
32
33 502 40 Hackett ML, Pickles K. Part I: frequency of depression after stroke: an updated
34
35 503 systematic review and meta-analysis of observational studies. *Int J Stroke*
36
37 504 2014;9:1017–25.
38
39 505 41 Lu D, Andersson TML, Fall K, et al. Clinical diagnosis of mental disorders
40
41 506 immediately before and after cancer diagnosis: a nationwide matched cohort study in
42
43 507 Sweden. *JAMA Oncol* 2016;2:1188–96.
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3 509 **FIGURE LEGEND**
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7 511 **Figure A**, Diseases with prevalence >8% in the case group in the 12 months before MDD

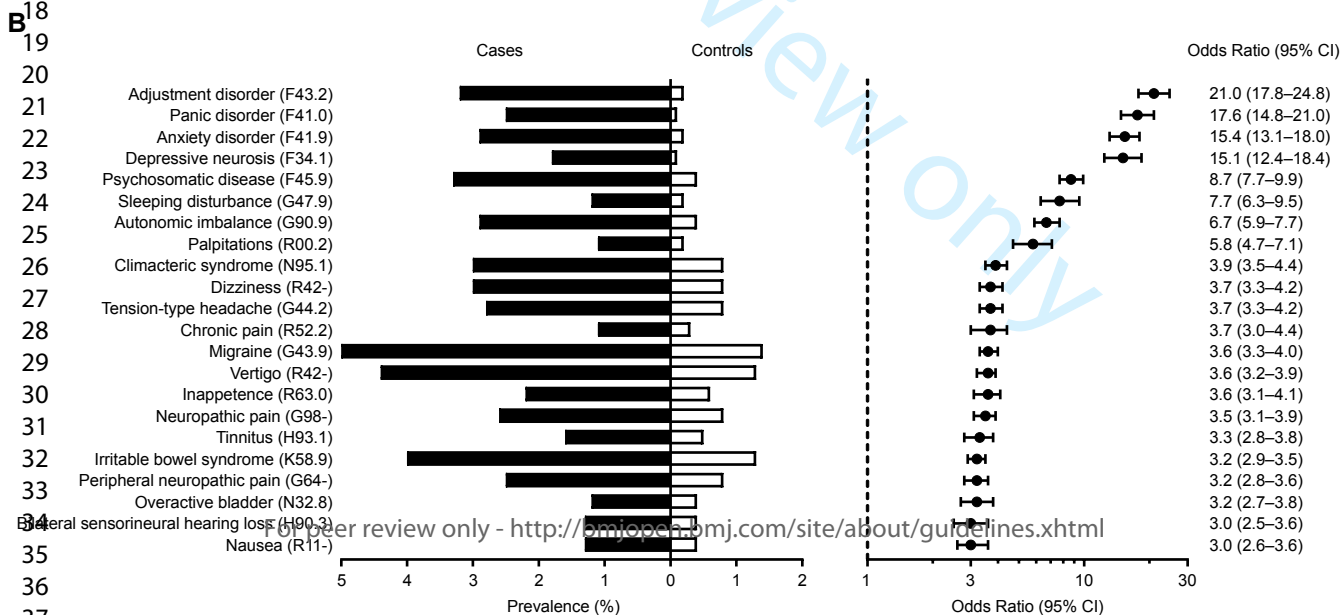
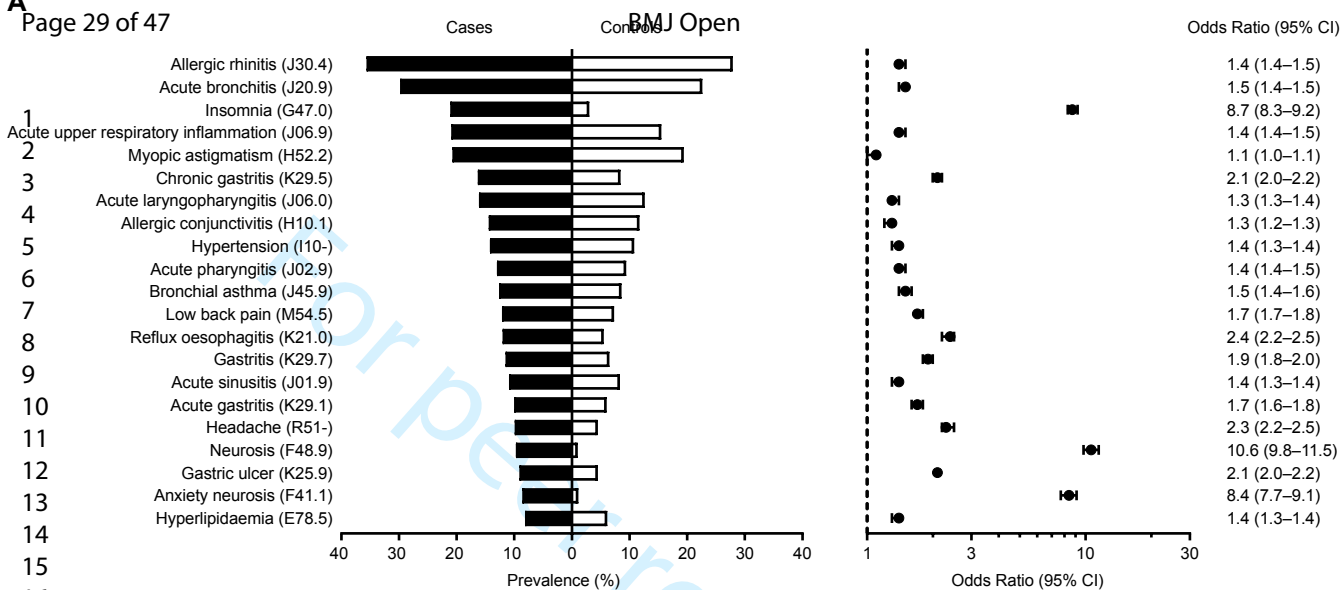
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9 512 diagnosis. B, Diseases with odds ratio >3.0. Shown are the prevalence rates in the case

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11 513 group and in the matched control group, as well as the odds ratio (95% CI). CI, confidence

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13 514 interval; MDD, major depressive disorder.

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For peer review only



Supplemental Material

TITLE

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

AUTHORS

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Izumi MISHIRO

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Takafumi AKIMOTO

Keita FUJIKAWA

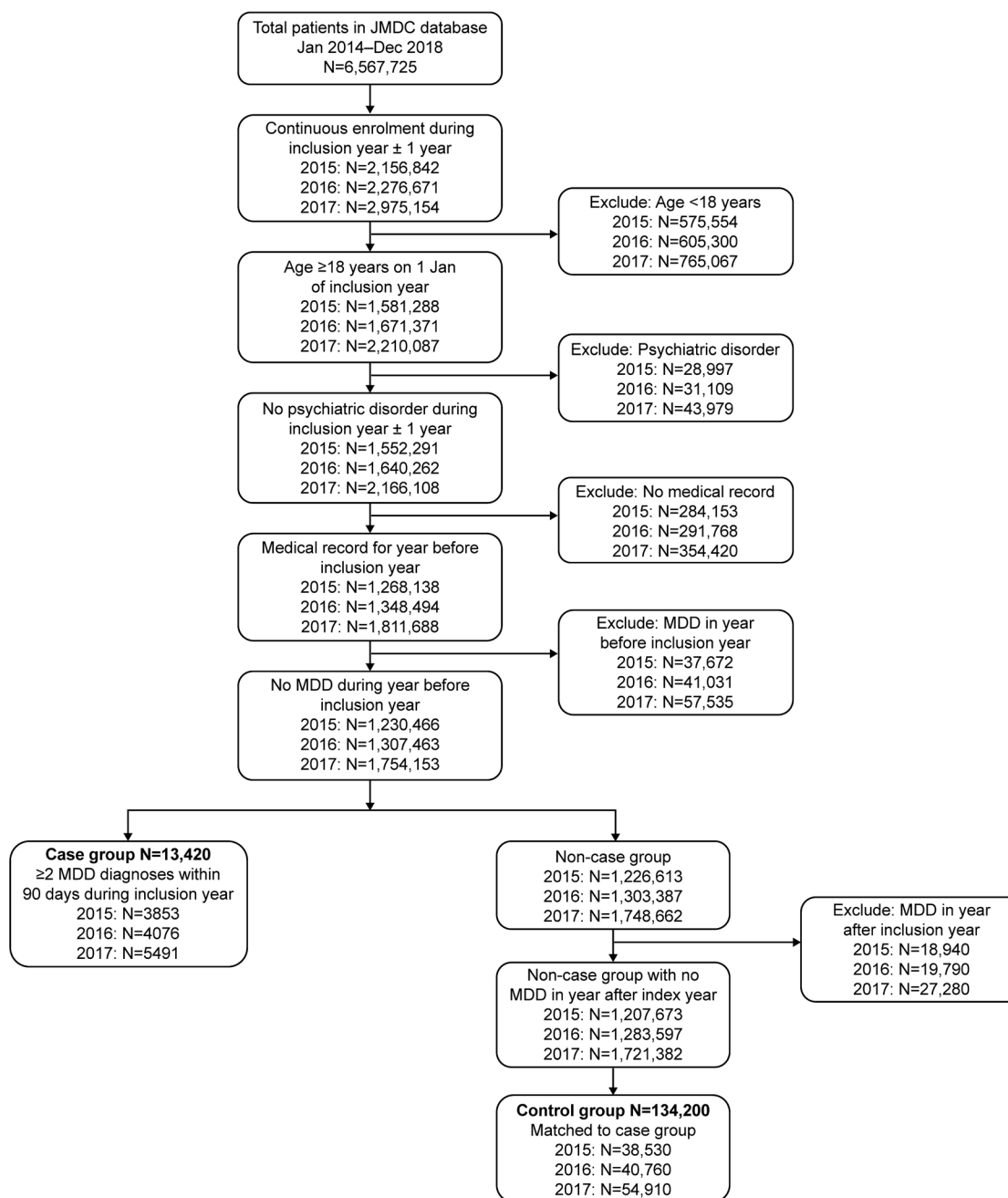
Supplemental figure Flow diagram of patients included in the case group and matched control group. Dates (2015, 2016, 2017) represent the inclusion years. MDD, major depressive disorder.

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
<i>CCI-related diseases</i>	
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
<i>Other chronic diseases</i>	
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
Arthritis	Other disease name with 'osteoarthritis' M00–M03, M05–M14
Epilepsy	Other disease name with 'arthritis' 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
Irritable bowel syndrome	Diabetic neuropathic pain K58
Chronic gastritis	K29.3, K29.4, K29.5
Chronic enteritis	K52.9
Dizziness	R42, H81, I95.1
Autonomic nerve imbalance	Epidemic dizziness, psychogenic dizziness, low-tone dizziness G90
Attention deficit hyperactivity disorder	F90
Psychiatric disorders other than depression	F00–F99*
Sleep disorders	*Except F00–F09, F20–F29, F30–F33 G47
<i>Lifestyle diseases</i>	
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
<i>Psychiatric disorders</i>	
Psychiatric disorders other than depression	F00–F99*
Sleep disorders	*Except F00–F09, F20–F29, F30–F33 G47
<i>MDD-related symptoms</i>	
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
Autonomic nerve imbalance	Diabetic neuropathic pain 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=13,920	Control group N=134,200	Odds ratio (95% CI)
			(10.0)	(6.0)	(1.6–1.8)
R51-	Headache	Headache	1332	6046	2.3
F48.9	Neurotic disorder, unspecified	Neurosis	1306	1350	10.6
K25.9	Gastric ulcer/Unspecified as acute or chronic, without haemorrhage or perforation	Gastric ulcer	1216	6086	2.1
F41.1	Generalised anxiety disorder	Anxiety neurosis	1155	1492	8.4
E78.5	Hyperlipidaemia, unspecified	Hyperlipidaemia	1091	8244	1.4
J02.9	Acute pharyngitis, unspecified	Pharyngitis	1061	7940	1.4
L30.9	Dermatitis, unspecified	Eczema	1032	7799	1.4
K59.0	Constipation	Constipation	1030	6014	1.8
E86-	Volume depletion	Dehydration	1003	4825	2.2
E78.0	Pure hypercholesterolaemia	Hypercholesterolaemia	940	7031	1.4
R11-	Nausea and vomiting	Vomition	933	4031	2.4
M53.1	Cervicobrachial syndrome	Cervico-omo-brachial syndrome	905	3380	2.8
J00-	Acute nasopharyngitis [common cold]	Common cold	894	5998	1.5
A09.9	Gastroenteritis and colitis of unspecified origin	Acute gastroenteritis	873	5140	1.7
E14-	Unspecified diabetes mellitus	Diabetes mellitus	870	6285	1.4
J32.9	Chronic sinusitis, unspecified	Chronic sinusitis	818	5551	1.5
A09.9	Gastroenteritis and colitis of unspecified origin	Diarrhoea	781	4311	1.9
			(5.8)	(3.2)	(1.7–2.0)

ICD-10 level 4 code	ICD-10 level 4 name	Standard disease name	Case group N=13,920	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=13,942	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=13,920	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=13,920	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	<i>Helicobacter pylori</i> 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=13,920	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)

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ICD-10 level 4 code	ICD-10 level 4 name	Standard disease name	Case group N=13,920	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=13,920	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=13,920	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	1191	1.4
J32.9	Chronic sinusitis, unspecified	Sinusitis	164	1146	1.4
N32.8	Other specified disorders of bladder	Overactive bladder	164	519	3.2
G62.9	Polyneuropathy, unspecified	Peripheral neuritis	163	662	2.5
L30.9	Dermatitis, unspecified	Dermatitis	163	1336	1.2
L70.0	Acne vulgaris	Facial common acne	162	1446	1.1
I50.9	Heart failure, unspecified	Chronic cardiac failure	159	815	2.0
G47.9	Sleep disorder, unspecified	Sleeping disturbance	157	205	7.7
M06.9	Rheumatoid arthritis, unspecified	Rheumatoid arthritis	155	830	1.9
J32.9	Chronic sinusitis, unspecified	Acute exacerbation of chronic sinusitis	153	1272	1.2
N20.1	Calculus of ureter	Ureterolithiasis	151	1139	1.3
R52.2	Other chronic pain	Chronic pain	151	417	3.7
R31-	Unspecified haematuria	Haematuria	149	1024	1.5
K76.9	Liver disease, unspecified	Liver disorder	148	955	1.6
R00.2	Palpitations	Palpitations	148	257	5.8
H10.3	Acute conjunctivitis, unspecified	Acute conjunctivitis	147	1212	1.2
			(1.1)	(0.9)	(1.0–1.4)

ICD-10 level 4 code	ICD-10 level 4 name	Standard disease name	Case group N=13,920	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 $\geq 1.0\%$ in the case group and $\geq 0.1\%$ 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
	No	No	Yes	1998	20,752	22,750
	No	Yes	No	1794	33,171	5108
	No	Yes	Yes	1595	23,095	3896
	Yes	No	No	901	15,660	16,561
	Yes	No	Yes	854	7,589	8442
	Yes	Yes	No	675	18,664	2541
Yes	Yes	Yes	1274	22,855	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
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*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.

BMJ Open

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

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Keywords:	EPIDEMIOLOGY, GENERAL MEDICINE (see Internal Medicine), MEDICAL HISTORY, Depression & mood disorders < PSYCHIATRY

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3 1 **MANUSCRIPT CATEGORY**

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5 2 Research Article
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9 4 **TITLE**

10 5 Diseases prevalent before major depressive disorder diagnosis: an exploratory nested case-
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12 6 control study using health insurance-based claims data
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STATISTICAL SUMMARY

Abstract Text	Manuscript Text (Intro-Disc)	References	Figures / Tables
N = 300 (Limit = 300)	N = 3379 (Limit = 4000)	N = 43 (Limit = none)	N = 5 (plus 4 supplementary) (Limit = 5)

32

For peer review only

1
2
3 34 **ABSTRACT**
4

5 35 **Objectives** Major depressive disorder (MDD) is often comorbid with other chronic and/or
6
7 36 serious diseases. However, little is known about the prevalence of various diseases that are
8
9 37 present before MDD onset. We examined the prevalence of all pre-existing diseases in the
10
11 38 12 months before an MDD diagnosis.
12

13
14 39 **Design** Exploratory nested case-control study.
15

16 40 **Setting** Data, including diagnoses based on ICD-10 codes, were from a Japanese health
17
18 41 insurance database (JMDC).
19

20 42 **Participants** Adults newly diagnosed with MDD during 2015, 2016, or 2017 (but not the
21
22 43 preceding year) (cases) were matched (exact) 1:10 to controls by age, sex, index date, and
23
24 44 working status.
25

26 45 **Primary and secondary outcome measures** The primary outcome was the proportion of
27
28 46 patients in each group with each pre-existing disease during the 12 months before the index
29
30 47 date (ie, before MDD diagnosis in cases). Odds ratios (ORs) for onset of MDD were
31
32 48 calculated for each pre-existing disease. A post hoc multivariate analysis examined
33
34 49 interactions of metabolic risk factors (diabetes, hypertension, dyslipidaemia), psychiatric
35
36 50 disorders (sleep disorders, psychiatric disorders other than depression), and MDD-related
37
38 51 symptoms (headache, pain, autonomic nerve imbalance) on MDD diagnosis.
39

40
41 52 **Results** There were 13,420 cases and 134,200 controls (mean age 41.9 years; 66.5%
42
43 53 male). The prevalence of almost all pre-existing diseases was higher in cases than in
44
45 54 controls. The highest ORs (5.8–21.0) were for psychiatric diseases and sleep disorders.
46
47 55 Insomnia (21.1% of patients; OR 8.7) and neurosis (9.7%; OR 10.6) were particularly
48
49 56 prevalent in the case group. The odds of MDD increased in the presence of metabolic risk
50
51 57 factors, psychiatric disorders, and/or MDD-related symptoms.
52

53
54 58 **Conclusions** The high ORs of pre-existing diseases and/or prodromal symptoms in patients
55
56 59 who develop MDD indicate a high medical burden for these patients. Patients with chronic
57
58 60 and/or serious diseases should be monitored for depressive symptoms, and pre-existing
59
60 61 diseases should be considered when prescribing MDD treatment.
61

62

Strengths and limitations of this study

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

73

74 **Keywords:** Administrative claims, healthcare; Comorbidity; Depressive disorder;

75 Epidemiology; Risk factors

76 INTRODUCTION

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

88
89 An epidemiological study conducted in Japan between 2013 and 2015 reported the lifetime
90 and 12-month prevalence rates of major depressive disorder (MDD) to be relatively low, at
91 5.7% and 2.7%, respectively.⁴ Other studies have confirmed that major depressive episodes
92 are less prevalent in Japan than in other countries.^{5,6} However, fewer than half of Japanese
93 people with a mood disorder seek medical treatment.⁴ This reluctance to seek medical
94 treatment may be related to a perceived 'stigma' associated with psychiatric disease.⁷ These
95 factors may further reduce the detection and diagnosis of MDD in patients with a chronic
96 disease, despite the potentially increased risk of MDD in these patients. However, little is
97 known about the prevalence of underlying diseases that are comorbid with MDD. Given that
98 around 20,000 people in Japan commit suicide every year,⁸ with the highest rate of about 50
99 per 100,000 persons in men aged 50–59 years,⁹ most of which are probably related to
100 mental disorders, additional information on factors associated with MDD that could assist
101 with early detection and treatment may help reduce the number of suicides.

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3 103 The aim of this exploratory nested case-control study of patients enrolled in a Japanese
4
5 104 health insurance database was to comprehensively examine the prevalence of pre-existing
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7 105 diseases in the 12 months before an MDD diagnosis (defined using the International
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9 106 Statistical Classification of Diseases and Related Health Problems, 10th revision [ICD-10]¹⁰
10
11 107 codes F32 ['Depressive episode'] or F33 ['Recurrent depressive disorder']). In this context, a
12
13 108 pre-existing disease was defined as any diagnosis other than MDD and related mental
14
15 109 disorders (bipolar affective disorders; organic mental disorders; schizophrenia, schizotypal,
16
17 110 and delusional disorders); the latter were excluded to avoid including patients with secondary
18
19 111 diagnoses of MDD as cases. However, our definition of pre-existing conditions did include
20
21 112 those that are prodromal symptoms of MDD (eg, sleep disorders). In addition, we determined
22
23 113 an odds ratio (OR) for the onset of MDD for each pre-existing disease to identify those that
24
25 114 are most commonly associated with development of MDD and to evaluate the association of
26
27 115 MDD with common metabolic risk factors.
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116

117 **METHODS**

118 **Study design**

119 This was a nested case-control study. Data on patient demographics and diagnoses based
120 on ICD-10 were derived from the JMDC Inc. (Tokyo, Japan) database of medical expense
121 claims for company employees in Japan.¹¹
122

123

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

129

129 **Study population**

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3 130 The study analysed data collected for the population registered in the JMDC database
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5 131 between January 2014 and December 2018 who were aged ≥ 18 years on 1 January of the
6
7 132 inclusion year (2015, 2016, or 2017) and had continuous registration for the inclusion year,
8
9 133 the previous year, and the subsequent year (study period). Individuals were excluded if they
10
11 134 had a diagnosis of any bipolar affective disorder (ICD-10 codes F30 [manic episode], F31),
12
13 135 organic mental disorder including symptomatic mental disorders (F00–F09), or
14
15 136 schizophrenia, schizotypal, and delusional disorder (F20–F29) in the study period, or a
16
17 137 diagnosis of MDD (ICD-10 codes F32 [‘Depressive episode’] or F33 [‘Recurrent depressive
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19 138 disorder’]) in the year before the inclusion year, or no medical history for the year before the
20
21 139 inclusion year.
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26 141 Within the study population, case patients had a diagnosis of MDD in the inclusion year (the
27
28 142 date of the first MDD treatment after ≥ 1 year with no MDD diagnosis was designated as the
29
30 143 index date) and ≥ 2 months of treatment for depression within 90 days of the index date.
31
32 144 Control patients had no diagnosis of MDD in the study period and were matched 10:1 (exact
33
34 145 matching using random sampling) to case patients according to age at index date, sex, and
35
36 146 working status.
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39 147

40 148 **Outcomes**

41
42
43 149 The primary end point was the proportion of patients with documented diagnosis of each pre-
44
45 150 existing disease during the 12 months before the index date (ie, before MDD diagnosis in
46
47 151 case patients). An OR for the onset of MDD was calculated for each underlying disease,
48
49 152 which was based on presence or absence of ICD-10 codes, Charlson comorbidity index
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51 153 (CCI)–related diseases, or other chronic diseases (online supplemental table 1).
52
53 154 Demographic and patient characteristics were collected, including age, sex, working status,
54
55 155 and inclusion year (2015/2016/2017).
56
57
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60

157 **Statistical analysis**

158 As noted above, the proportion of patients with each pre-existing disease was determined for
159 each group and an OR for the onset of MDD was calculated. Prevalence data and ORs are
160 reported for pre-existing diseases that were present in $\geq 1\%$ of the case group and $\geq 0.1\%$ of
161 the control group. No inferential statistics were conducted. A post hoc analysis examined the
162 possible interaction of the presence of three pre-existing disease categories that exhibited
163 high ORs in the primary analysis or are common diseases: metabolic risk factors (diabetes,
164 hypertension, dyslipidaemia), MDD-related symptoms (headache, pain, autonomic nerve
165 imbalance), and psychiatric disorders (sleep disorders, psychiatric disorders other than
166 depression) (online supplemental table 1). A multivariate logistic regression model was used
167 to determine ORs in the eight subgroups (ie, with/without metabolic risk factors, MDD-related
168 symptoms, and/or psychiatric disease) for the onset of MDD using the following covariates:
169 sex, age (<40 years versus ≥ 40 years), and working status. A similar post hoc analysis was
170 conducted to estimate ORs for the onset of MDD according to the number of low-risk ($1 \leq \text{OR}$
171 ≤ 2 in the primary analysis) CCI-related and other chronic diseases that were present during
172 the preceding year. As above, sex, age, and working status were adjusted for in the
173 multivariate logistic regression model. Netezza N2002-010 7.1.0.4.P2 (IBM, Armonk, NY,
174 USA) was used as the data warehouse platform. SAS version 9.4 (SAS Institute, Cary, NC,
175 USA) was used for statistical analysis.

176

177 **Patient and public involvement**

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

179

180 **RESULTS**

181 **Demographic characteristics**

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

184 2015, 2016, or 2017 (case group; online supplemental figure). From 4,212,652 control
 185 patients who met the inclusion criteria and did not have an MDD diagnosis in either the
 186 inclusion year or the subsequent year, 134,200 were matched to case patients (control
 187 group; online supplemental figure). More than half (66.5%) of patients in both groups were
 188 male, with a mean age of 41.9 years (**table 1**). About 40% of patients were <40 years. Most
 189 (77.8%) patients were workers.

190 **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)

191 Data are n (%), unless otherwise noted.

192 MDD, major depressive disorder; SD, standard deviation.

193

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

195 CCI-related diseases and other chronic diseases

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

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2
3 202 23.3%, respectively). ORs ≥ 2.0 were also observed (in descending order of prevalence in the
4
5 203 case group) for pain (2.0), chronic gastritis (2.1), headache (2.7), peptic ulcer disease (2.0),
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7 204 dizziness (3.2), irritable bowel syndrome (3.2), angina pectoris (2.0), epilepsy (2.4), chronic
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9 205 enteritis (2.7), diabetes without chronic complication (2.1), metastatic solid tumour (2.2),
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11 206 hemiplegia or paraplegia (2.8), and Parkinson's disease (3.2).
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For peer review only

207 **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)	12.0 (8.3–18.1)
Parkinson's disease	24 (0.2)	76 (0.1)	3.2 (2.0–5.0)

208 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
 209 shown ranked by prevalence in the case group. Data are n (%), unless otherwise noted.
 210 CCI, Charlson comorbidity index; CI, confidence interval.

211 **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 (0.1)	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

212 Data are n (%), unless otherwise noted.

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

214 ICD-10 blocks

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

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226 ICD-10 codes

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

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236 Multivariate analysis

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

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3 242 seen in subgroups with psychiatric disorders. Compared with subgroups with MDD-related
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5 243 symptoms only, the odds of MDD were increased in subgroups who also had metabolic risk
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7 244 factors or psychiatric disorders. However, the odds of MDD decreased in subgroups who had
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9 245 both metabolic risk factors and psychiatric disorders relative to subgroups with only one of
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11 246 these factors (with or without MDD-related symptoms). Finally, we identified 72,923 people
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13 247 (8329 cases with MDD and 64,594 controls) who had at least one low-risk ($1 \leq OR \leq 2$) pre-
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15 248 existing CCI-related or other chronic disease (**table 2**) and categorised them based on the
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17 249 number of diseases from one (N=36,993) to 11–13 (N=46). Relative to people with only one
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19 250 pre-existing disease, the OR for MDD increased with the number of pre-existing chronic
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21 251 diseases, from 1.34 in people with two pre-existing diseases to more than three in people
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23 252 with nine or more comorbidities (online supplemental table 4).
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253 **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)				

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

257 **DISCUSSION**

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

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

276
277 Stress, such as diagnosis with a chronic or serious disease, can contribute to the
278 development of MDD in vulnerable individuals.¹⁹ Further, stress can lead to psychological
279 and physiological changes that affect both mental and physical health, and may contribute
280 directly to depression.²⁰ Psychiatric disorders can be particularly stressful and may increase
281 the chances of MDD. Depression is often comorbid with other mental disorders, particularly
282 anxiety, and may share symptoms and underlying aetiologies.²¹⁻²⁴ Stress is also associated
283 with many gastrointestinal disorders,²⁵ such as irritable bowel syndrome, which were twice as
284 prevalent in the case group than in the control group.

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3 313 treat MDD,^{30 31} which may contribute to underdiagnosis of MDD in patients with metabolic risk
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5 314 factors. Psychiatrists, on the other hand, may underestimate somatic depressive symptoms
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7 315 in patients they are treating for another mental illness who also have a metabolic-related
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9 316 illness treated by another doctor, considering fatigue and autonomic dysfunction as caused
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11 317 by the physical illness. However, depression is known to lead to treatment non-adherence in
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13 318 patients with diabetes,³² which increases the risk of severe complications.³³ In addition,
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15 319 treating metabolic-related diseases and depression simultaneously may provide patients with
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17 320 better clinical outcomes.³⁴ Further research is needed on the unmet needs for the diagnosis
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19 321 and treatment of depression in patients with presymptomatic depression in addition to
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21 322 metabolic-related diseases, and on the effects of coordinated care management of multiple
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23 323 conditions.
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28 325 We also found that the risk of MDD increased with increasing number of relatively low-risk
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30 326 (OR \leq 2) CCI-related and other chronic diseases. Thus, increased medical burden appears to
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32 327 be associated with greater risk of depression among working-age people, consistent with a
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34 328 recent study conducted in Denmark.³⁵
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39 330 Many comorbidities may share underlying biological mechanisms with MDD. For example,
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41 331 inflammatory mechanisms play a role in the aetiology of many diseases, including diabetes,
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43 332 cardiovascular disease, arthritis, and asthma, as well as depression.³⁶⁻³⁸ Neural pathways
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45 333 and neurotransmitters that are altered in chronic pain may also affect mood, including
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47 334 depression.³⁹ Migraine and depression can both be related to specific genetic variants and/or
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49 335 neuroanatomic features.⁴⁰ Most of these biological mechanisms are exacerbated by stress.³
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51 336 ^{37 40} Thus, MDD may develop in parallel with certain diseases, but its diagnosis may be
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53 337 delayed compared with physical disease.
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58 339 Our study is strengthened by the use of a health insurance database consisting of mostly
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60 340 working-age people, which resulted in a sample size large enough to allow examination of a

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3 341 broad range of pre-existing diseases. The nested case-control design and the use of a
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5 342 database minimised selection and recall biases that may occur in other case-control studies.
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7 343 We used a strict definition of MDD onset, which required a 1-year depression-free period and
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9 344 the diagnosis for inclusion to be recorded on at least three doctor visits within 90 days; this
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11 345 definition increased our certainty that case patients had true, newly diagnosed MDD. In
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13 346 addition, our inclusion criteria meant that people in both the control and case groups needed
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15 347 to have visited a doctor at least once to have a medical record within the observation period.
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17 348 Because of the comprehensive insurance available in Japan, medical care is readily
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19 349 accessible, and consultations for relatively minor concerns are common. Therefore, the
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21 350 controls in our study can essentially be considered as representative of the general
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23 351 population, except for the absence of people aged 75 years or older, who are covered by
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25 352 government-administered insurance, and the relatively low proportion of people aged 65–74
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27 353 years, many of whom would be retired from work.
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31 355 Despite these strengths, some caveats do apply when interpreting our results. As with any
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33 356 claims database study, the data were not collected specifically for the purpose of the study.
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35 357 As such, we could not evaluate variables like socioeconomic factors or severity/history of
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37 358 MDD. Further, errors in ICD-10 coding may have occurred, although equally in cases and
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39 359 controls. Patients with chronic diseases are likely to visit their physicians frequently,
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41 360 increasing the opportunity for detection and diagnosis of MDD. Further, patients with pre-
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43 361 existing psychiatric disorders are likely to be treated by psychiatrists, who may be better at
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45 362 diagnosing MDD than other physicians, which might lead to higher ORs for psychiatric
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47 363 diseases than for physical diseases; however, MDD diagnosis by general practitioners is also
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49 364 higher in patients with psychiatric comorbidity than in those with physical comorbidity.⁴¹
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51 365 Nevertheless, MDD is often under-recognised and underdiagnosed, which may mean that
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53 366 the control group included patients who actually had depression or depressive symptoms.
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55 367 We only assessed disease prevalence, and not incidence, during the year before the
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57 368 inclusion year; therefore, we do not know if the disease was diagnosed during that year or in

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3 369 a previous year. This limitation could potentially result in a disproportionate number of people
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5 370 in the control group who had longer-term diseases and were not vulnerable to MDD. For
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7 371 some high-stress diseases such as cancer or stroke, MDD often occurs soon after
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9 372 diagnosis^{42 43}; hence, less vulnerable patients who did not develop MDD would have
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11 373 remained within the control group, leading to lower ORs for those diseases than might be
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13 374 expected. Finally, the relatively short observation period limits our ability to look at the long-
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15 375 term relationship between MDD, which can re-occur multiple times in a patient's life, and
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17 376 other chronic conditions. Although comparing ORs for the onset of MDD across a broad
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19 377 range of pre-existing diseases can help develop hypotheses regarding possible underlying
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21 378 mechanisms, the risk of MDD occurring in specific diseases should be investigated on an
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23 379 individual basis.
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27 28 381 **CONCLUSIONS**

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30 382 This large, preliminary, nested case-control study has documented the high prevalence of
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32 383 pre-existing diseases in Japanese patients with MDD compared with matched controls
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34 384 without MDD. The high prevalence of pre-existing diseases in patients who develop MDD
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36 385 reflects the complex relationship between physical and mental disorders and indicates a high
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38 386 medical burden for these patients. These results confirm that patients with chronic and/or
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40 387 serious diseases, including prodromal symptoms that are not always recognised as related to
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42 388 MDD, should be monitored for depressive symptoms, and pre-existing diseases should be
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44 389 taken into consideration when prescribing treatment for MDD.
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397

398 **Contributors**

399 Yoshinori Cho designed the study and data collection, interpreted the study results, and
400 participated in the drafting, critical revision, and approval of the final version of the
401 manuscript. Izumi Mishiro designed the study and data collection, wrote the statistical
402 analysis plan, interpreted the study results, and participated in the drafting, critical revision,
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408 study and data collection, interpreted the study results, and participated in the drafting,
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3 418 **Data availability statement**
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5 419 The data that support the findings of this study are available from JMDC Inc. but were used
6
7 420 under licence for the current study; therefore, restrictions apply and the data are not publicly
8
9 421 available. For inquiries about access to the data set used in this study, please contact JMDC
10
11 422 (<https://www.jmdc.co.jp>).
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16 424 **Competing interests**

17
18 425 Dr Cho reports grants from Shionogi & Co., Ltd. and Otsuka Pharmaceutical Co., Ltd., and
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35 433 **Ethics statements**

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37 434 **Ethics approval**

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39 435 The study was approved by the Ethics Review Committee of the Research Institute of
40
41 436 Healthcare Data Science (Tokyo, Japan) on 6 August 2019 (approval number RI2019004).
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43 437 Only anonymised information was accessible from the database; therefore, in accordance
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45 438 with the Ethical Guidelines for Medical and Health Research Involving Human Subjects in
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47 439 Japan, informed consent was not required.
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52 441 **Patient consent for publication**

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54 442 Not applicable.
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444 **REFERENCES**

- 445 1 Clarke DM, Currie KC. Depression, anxiety and their relationship with chronic
446 diseases: a review of the epidemiology, risk and treatment evidence. *Med J Aust*
447 2009;190:S54–60.
- 448 2 Evans DL, Charney DS, Lewis L, et al. Mood disorders in the medically ill: scientific
449 review and recommendations. *Biol Psychiatry* 2005;58:175–89.
- 450 3 Katon WJ. Epidemiology and treatment of depression in patients with chronic medical
451 illness. *Dialogues Clin Neurosci* 2011;13:7–23.
- 452 4 Ishikawa H, Tachimori H, Takeshima T, et al. Prevalence, treatment, and the
453 correlates of common mental disorders in the mid 2010's in Japan: the results of the
454 World Mental Health Japan 2nd Survey. *J Affect Disord* 2018;241:554–62.
- 455 5 Andrade L, Caraveo-Anduaga JJ, Berglund P, et al. The epidemiology of major
456 depressive episodes: results from the International Consortium of Psychiatric
457 Epidemiology (ICPE) Surveys. *Int J Methods Psychiatr Res* 2003;12:3–21.
- 458 6 Bromet E, Andrade LH, Hwang I, et al. Cross-national epidemiology of DSM-IV major
459 depressive episode. *BMC Med* 2011;9:90.
- 460 7 Ando S, Yamaguchi S, Aoki Y, et al. Review of mental-health-related stigma in Japan.
461 *Psychiatry Clin Neurosci* 2013;67:471–82.
- 462 8 Ministry of Health, Labour and Welfare. Vital statistics of Japan, 2017. Available:
463 <https://www.mhlw.go.jp/english/database/db-hw/dl/81-1a2en.pdf> [Accessed 16
464 January 2020].
- 465 9 Snowden J, Phillips J, Zhong B, et al. Changes in age patterns of suicide in Australia,
466 the United States, Japan and Hong Kong. *J Affect Disord* 2017;211:12–9.
- 467 10 International Statistical Classification of Diseases and Related Health Problems, 10th
468 Revision, 2016. Available: <https://icd.who.int/browse10/2016/en> [Accessed 16
469 January 2020].

- 1
2
3 470 11 Kimura S, Sato T, Ikeda S, et al. Development of a database of health insurance
4
5 471 claims: standardization of disease classifications and anonymous record linkage. *J*
6
7 472 *Epidemiol* 2010;20:413–9.
8
9 473 12 Ministry of Health, Labour and Welfare. Ethical guidelines for medical and health
10
11 474 research involving human subjects, 2015. Available: <https://www.mhlw.go.jp/file/06->
12
13 475 [Seisakujouhou-10600000-Daijinkanboukouseikagakuka/0000080278.pdf](https://www.mhlw.go.jp/file/06-Seisakujouhou-10600000-Daijinkanboukouseikagakuka/0000080278.pdf) [Accessed
14
15 476 16 January 2020].
16
17 477 13 Daré LO, Bruand P-E, Gérard D, et al. Co-morbidities of mental disorders and chronic
18
19 478 physical diseases in developing and emerging countries: a meta-analysis. *BMC*
20
21 479 *Public Health* 2019;19:304.
22
23 480 14 Park SJ, Hong S, Jang H, et al. The prevalence of chronic physical diseases
24
25 481 comorbid with depression among different sex and age groups in South Korea: a
26
27 482 population-based study, 2007-2014. *Psychiatry Investig* 2018;15:370–5.
28
29 483 15 Patten SB. Long-term medical conditions and major depression in a Canadian
30
31 484 population study at waves 1 and 2. *J Affect Disord* 2001;63:35–41.
32
33 485 16 Young JQ, Kline-Simon AH, Mordecai DJ, et al. Prevalence of behavioral health
34
35 486 disorders and associated chronic disease burden in a commercially insured health
36
37 487 system: findings of a case-control study. *Gen Hosp Psychiatry* 2015;37:101–8.
38
39 488 17 Ryu E, Chamberlain AM, Pendegraft RS, et al. Quantifying the impact of chronic
40
41 489 conditions on a diagnosis of major depressive disorder in adults: a cohort study using
42
43 490 linked electronic medical records. *BMC Psychiatry* 2016;16:114.
44
45 491 18 Han KM, Kim MS, Kim A, et al. Chronic medical conditions and metabolic syndrome
46
47 492 as risk factors for incidence of major depressive disorder: a longitudinal study based
48
49 493 on 4.7 million adults in South Korea. *J Affect Disord* 2019;257:486–94.
50
51 494 19 de Kloet ER, Joëls M, Holsboer F. Stress and the brain: from adaptation to disease.
52
53 495 *Nat Rev Neurosci* 2005;6:463–75.
54
55 496 20 Yang L, Zhao Y, Wang Y, et al. The effects of psychological stress on depression.
56
57 497 *Curr Neuropharmacol* 2015;13:494–504.
58
59
60

- 1
2
3 498 21 Birk JL, Kronish IM, Moise N, et al. Depression and multimorbidity: considering
4
5 499 temporal characteristics of the associations between depression and multiple chronic
6
7 500 diseases. *Health Psychol* 2019;38:802–11.
8
9 501 22 Gorman JM, Coplan JD. Comorbidity of depression and panic disorder. *J Clin*
10
11 502 *Psychiatry* 1996;57:34–41; discussion 2–3.
12
13 503 23 Hölzel L, Härter M, Reese C, et al. Risk factors for chronic depression — a systematic
14
15 504 review. *J Affect Disord* 2011;129:1–13.
16
17 505 24 Pollack MH. Comorbid anxiety and depression. *J Clin Psychiatry* 2005;66:22–9.
18
19 506 25 Konturek PC, Brzozowski T, Konturek SJ. Stress and the gut: pathophysiology,
20
21 507 clinical consequences, diagnostic approach and treatment options. *J Physiol*
22
23 508 *Pharmacol* 2011;62:591–9.
24
25 509 26 Fava GA, Tossani E. Prodromal stage of major depression. *Early Interv Psychiatry*
26
27 510 2007;1:9–18.
28
29 511 27 Kapfhammer HP. Somatic symptoms in depression. *Dialogues Clin Neurosci*
30
31 512 2006;8:227–39.
32
33 513 28 Simon GE, VonKorff M, Piccinelli M, et al. An international study of the relation
34
35 514 between somatic symptoms and depression. *N Engl J Med* 1999;341:1329–35.
36
37 515 29 McDonnell MC. The effects of developing a dual sensory loss on depression in older
38
39 516 adults: a longitudinal study. *J Aging Health* 2009;21:1179–99.
40
41 517 30 Ohtsuki T, Inagaki M, Oikawa Y, et al. Multiple barriers against successful care
42
43 518 provision for depressed patients in general internal medicine in a Japanese rural
44
45 519 hospital: a cross-sectional study. *BMC Psychiatry* 2010;10:30.
46
47 520 31 Ohtsuki T, Kodaka M, Sakai R, et al. Attitudes toward depression among Japanese
48
49 521 non-psychiatric medical doctors: a cross-sectional study. *BMC Res Notes*
50
51 522 2012;5:441.
52
53 523 32 Gonzalez JS, Peyrot M, McCarl LA, et al. Depression and diabetes treatment
54
55 524 nonadherence: a meta-analysis. *Diabetes Care* 2008;31:2398–403.
56
57
58
59
60

- 1
2
3 525 33 Chen AJ, Hwang V, Law PY, et al. Factors associated with non-compliance for
4 526 diabetic retinopathy follow-up in an urban safety-net hospital. *Ophthalmic Epidemiol*
5 527 2018;25:443–50.
6
7
8
9 528 34 Katon WJ, Lin EH, Von Korff M, et al. Collaborative care for patients with depression
10 529 and chronic illnesses. *N Engl J Med* 2010;363:2611–20.
11
12
13 530 35 Köhler-Forsberg O, Petersen L, Ishtiak-Ahmed K, et al. Medical diseases prior to first-
14 531 time depression diagnosis and subsequent risk of admissions for depression: a
15 532 nationwide study of 117,585 patients. *J Affect Disord* 2020;276:1030–7.
16
17
18 533 36 Dantzer R, O'Connor JC, Freund GG, et al. From inflammation to sickness and
19 534 depression: when the immune system subjugates the brain. *Nat Rev Neurosci*
20 535 2008;9:46–56.
21
22
23 536 37 Iwata M, Ota KT, Duman RS. The inflammasome: pathways linking psychological
24 537 stress, depression, and systemic illnesses. *Brain Behav Immun* 2013;31:105–14.
25
26
27 538 38 Raison CL, Capuron L, Miller AH. Cytokines sing the blues: inflammation and the
28 539 pathogenesis of depression. *Trends Immunol* 2006;27:24–31.
29
30
31 540 39 Bair MJ, Robinson RL, Katon W, et al. Depression and pain comorbidity: a literature
32 541 review. *Arch Intern Med* 2003;163:2433–45.
33
34
35 542 40 Baksa D, Gonda X, Juhasz G. Why are migraineurs more depressed? A review of the
36 543 factors contributing to the comorbidity of migraine and depression.
37 544 *Neuropsychopharmacol Hung* 2017;19:37–44.
38
39
40 545 41 Nuyen J, Volkens AC, Verhaak PF, et al. Accuracy of diagnosing depression in
41 546 primary care: the impact of chronic somatic and psychiatric co-morbidity. *Psychol*
42 547 *Med* 2005;35:1185–95.
43
44
45 548 42 Hackett ML, Pickles K. Part I: frequency of depression after stroke: an updated
46 549 systematic review and meta-analysis of observational studies. *Int J Stroke*
47 550 2014;9:1017–25.
48
49
50
51
52
53
54
55
56
57
58
59
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6
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42
43
44
45
46
47
48
49
50
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52
53
54
55
56
57
58
59
60

551 43 Lu D, Andersson TML, Fall K, et al. Clinical diagnosis of mental disorders
552 immediately before and after cancer diagnosis: a nationwide matched cohort study in
553 Sweden. *JAMA Oncol* 2016;2:1188–96.
554

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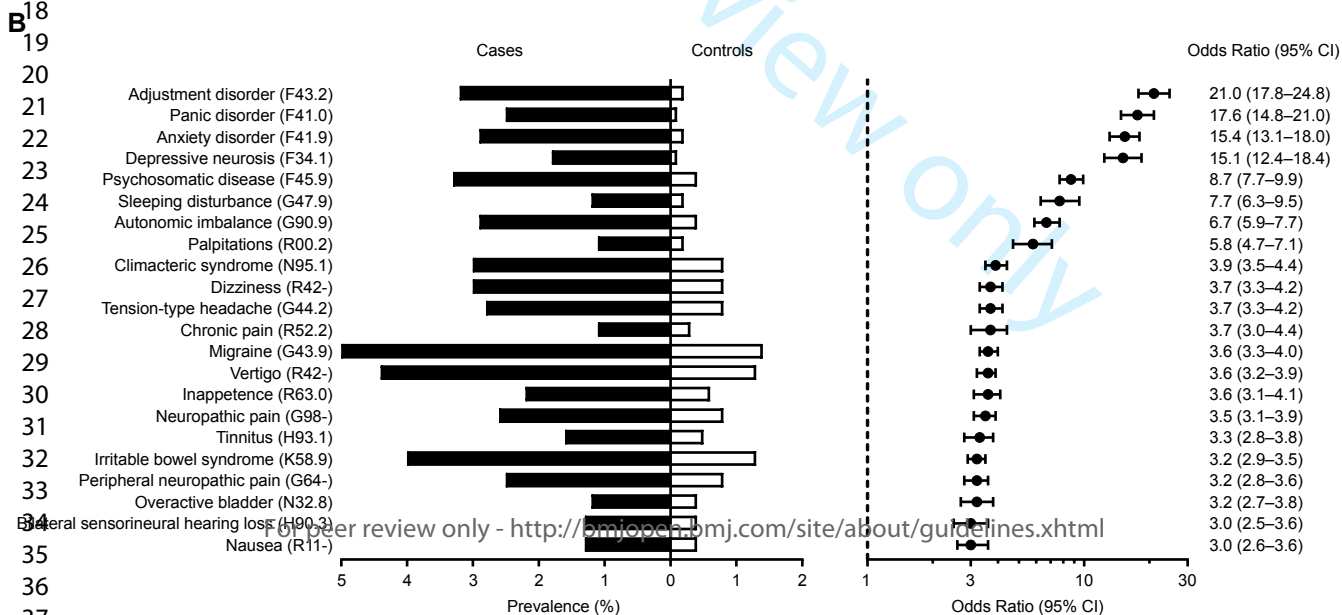
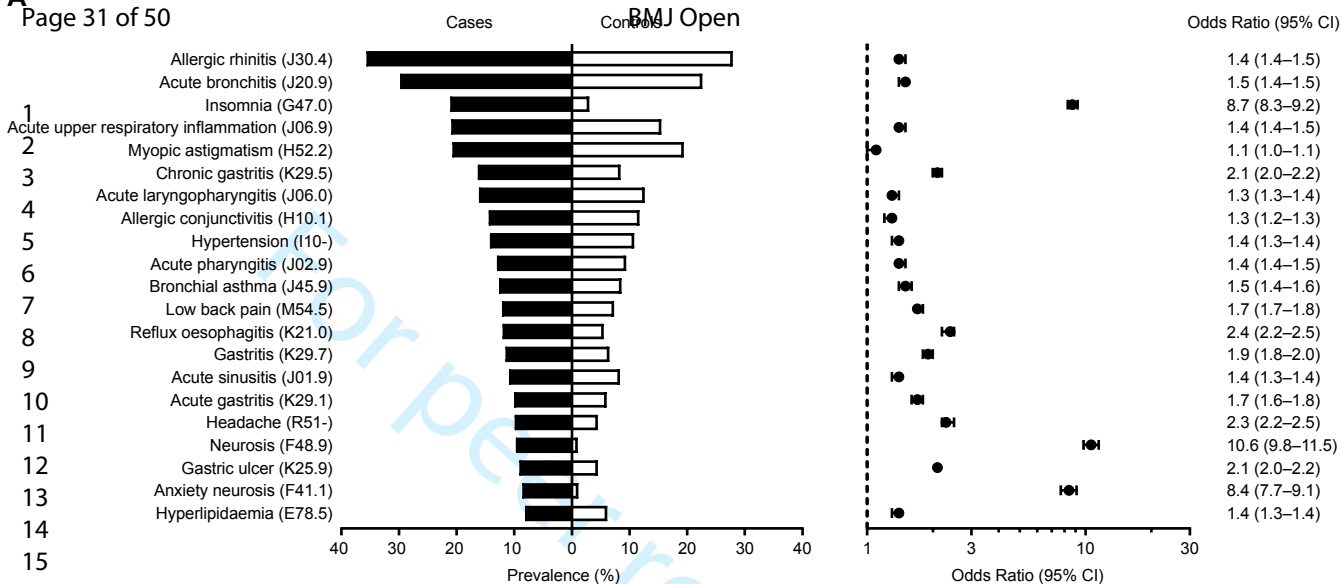
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3 555 **FIGURE LEGEND**
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7 557 **Figure A**, Diseases with prevalence >8% in the case group in the 12 months before MDD
8 diagnosis. B, Diseases with odds ratio >3.0. Shown are the prevalence rates in the case
9 558 group and in the matched control group, as well as the odds ratio (95% CI). CI, confidence
10 559 interval; MDD, major depressive disorder.
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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.

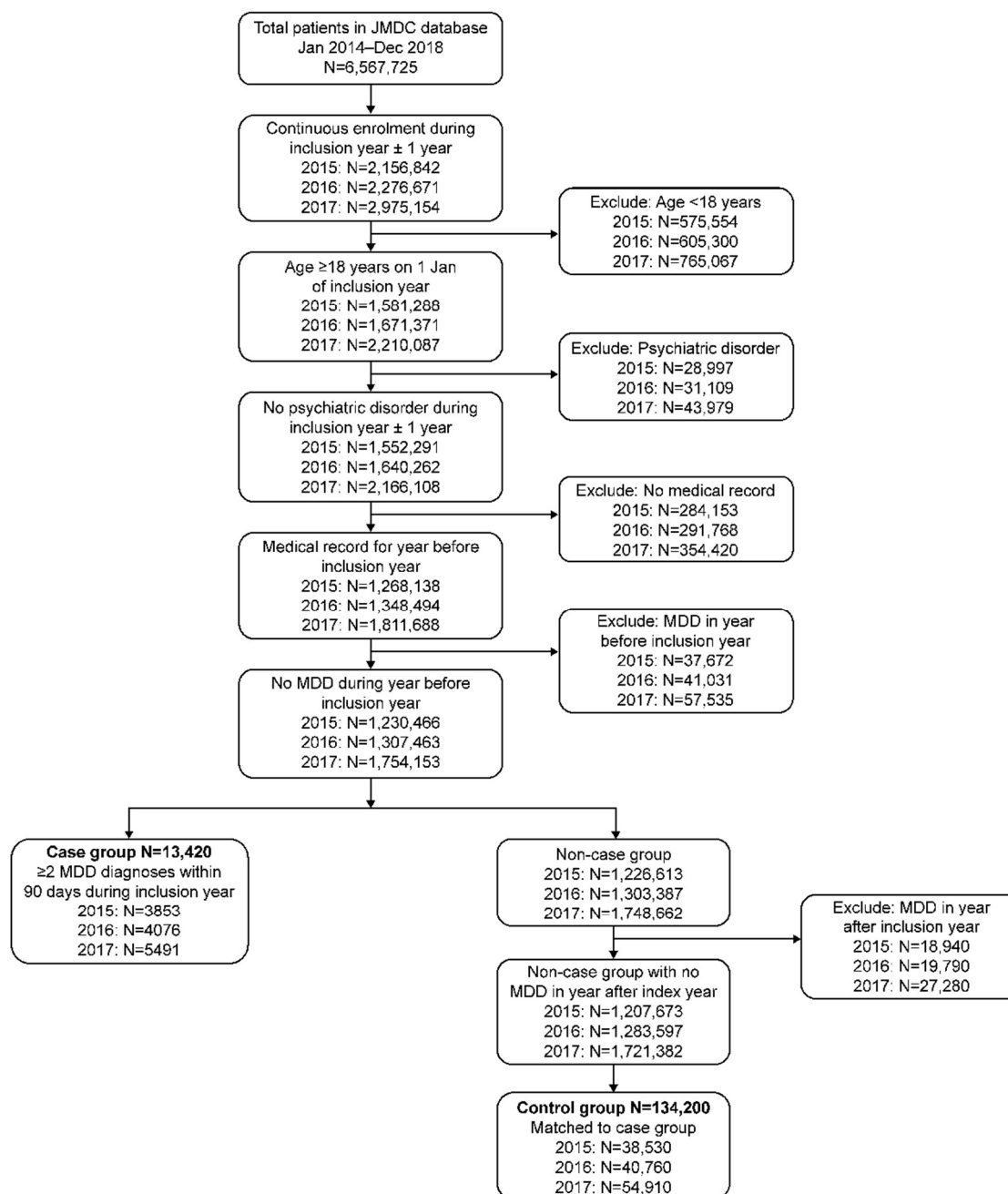
Supplemental table 1 ICD-10 codes and other terms used to identify pre-existing diseases

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
<i>CCI-related diseases</i>	
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
<i>Other chronic diseases</i>	
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
Arthritis	Other disease name with 'osteoarthritis' M00–M03, M05–M14
Epilepsy	Other disease name with 'arthritis' 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
Irritable bowel syndrome	Diabetic neuropathic pain K58
Chronic gastritis	K29.3, K29.4, K29.5
Chronic enteritis	K52.9
Dizziness	R42, H81, I95.1
Autonomic nerve imbalance	Epidemic dizziness, psychogenic dizziness, low-tone dizziness G90
Attention deficit hyperactivity disorder	F90
Psychiatric disorders other than depression	F00–F99*
Sleep disorders	*Except F00–F09, F20–F29, F30–F33 G47
<i>Metabolic risk factors</i>	
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
<i>Psychiatric disorders</i>	
Psychiatric disorders other than depression	F00–F99*
Sleep disorders	*Except F00–F09, F20–F29, F30–F33 G47
<i>MDD-related symptoms</i>	
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
Autonomic nerve imbalance	Diabetic neuropathic pain 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	6046	2.3
F48.9	Neurotic disorder, unspecified	Neurosis	1306	1350	10.6
K25.9	Gastric ulcer/Unspecified as acute or chronic, without haemorrhage or perforation	Gastric ulcer	1216	6086	2.1
F41.1	Generalised anxiety disorder	Anxiety neurosis	1155	1492	8.4
E78.5	Hyperlipidaemia, unspecified	Hyperlipidaemia	1091	8244	1.4
J02.9	Acute pharyngitis, unspecified	Pharyngitis	1061	7940	1.4
L30.9	Dermatitis, unspecified	Eczema	1032	7799	1.4
K59.0	Constipation	Constipation	1030	6014	1.8
E86-	Volume depletion	Dehydration	1003	4825	2.2
E78.0	Pure hypercholesterolaemia	Hypercholesterolaemia	940	7031	1.4
R11-	Nausea and vomiting	Vomition	933	4031	2.4
M53.1	Cervicobrachial syndrome	Cervico-omo-brachial syndrome	905	3380	2.8
J00-	Acute nasopharyngitis [common cold]	Common cold	894	5998	1.5
A09.9	Gastroenteritis and colitis of unspecified origin	Acute gastroenteritis	873	5140	1.7
E14-	Unspecified diabetes mellitus	Diabetes mellitus	870	6285	1.4
J32.9	Chronic sinusitis, unspecified	Chronic sinusitis	818	5551	1.5
A09.9	Gastroenteritis and colitis of unspecified origin	Diarrhoea	781	4311	1.9
			(5.8)	(3.2)	(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=13,920	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	<i>Helicobacter pylori</i> 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	1191	1.4
			(1.2)	(0.9)	(1.2–1.6)
J32.9	Chronic sinusitis, unspecified	Sinusitis	164	1146	1.4
			(1.2)	(0.9)	(1.2–1.7)
N32.8	Other specified disorders of bladder	Overactive bladder	164	519	3.2
			(1.2)	(0.4)	(2.7–3.8)
G62.9	Polyneuropathy, unspecified	Peripheral neuritis	163	662	2.5
			(1.2)	(0.5)	(2.1–2.9)
L30.9	Dermatitis, unspecified	Dermatitis	163	1336	1.2
			(1.2)	(1.0)	(1.0–1.4)
L70.0	Acne vulgaris	Facial common acne	162	1446	1.1
			(1.2)	(1.1)	(1.0–1.3)
I50.9	Heart failure, unspecified	Chronic cardiac failure	159	815	2.0
			(1.2)	(0.6)	(1.7–2.3)
G47.9	Sleep disorder, unspecified	Sleeping disturbance	157	205	7.7
			(1.2)	(0.2)	(6.3–9.5)
M06.9	Rheumatoid arthritis, unspecified	Rheumatoid arthritis	155	830	1.9
			(1.2)	(0.6)	(1.6–2.2)
J32.9	Chronic sinusitis, unspecified	Acute exacerbation of chronic sinusitis	153	1272	1.2
			(1.1)	(0.9)	(1.0–1.4)
N20.1	Calculus of ureter	Ureterolithiasis	151	1139	1.3
			(1.1)	(0.8)	(1.1–1.6)
R52.2	Other chronic pain	Chronic pain	151	417	3.7
			(1.1)	(0.3)	(3.0–4.4)
R31-	Unspecified haematuria	Haematuria	149	1024	1.5
			(1.1)	(0.8)	(1.2–1.7)
K76.9	Liver disease, unspecified	Liver disorder	148	955	1.6
			(1.1)	(0.7)	(1.3–1.9)
R00.2	Palpitations	Palpitations	148	257	5.8
			(1.1)	(0.2)	(4.7–7.1)
H10.3	Acute conjunctivitis, unspecified	Acute conjunctivitis	147	1212	1.2
			(1.1)	(0.9)	(1.0–1.4)

ICD-10 level 4 code	ICD-10 level 4 name	Standard disease name	Case group N=13,920	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 $\geq 1.0\%$ in the case group and $\geq 0.1\%$ 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
	No	No	Yes	1998	20,752	22,750
	No	Yes	No	1794	33,179	34,973
	No	Yes	Yes	1595	23,076	24,671
	Yes	No	No	901	15,060	15,961
	Yes	No	Yes	854	7,589	8,443
	Yes	Yes	No	675	18,675	19,350
	Yes	Yes	Yes	1274	22,811	24,085
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
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*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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BMJ Open

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

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Manuscript ID	bmjopen-2020-048233.R2
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Secondary Subject Heading:	Mental health
Keywords:	EPIDEMIOLOGY, GENERAL MEDICINE (see Internal Medicine), MEDICAL HISTORY, Depression & mood disorders < PSYCHIATRY

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3 **1 MANUSCRIPT CATEGORY**

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5 2 Research Article
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10 **4 TITLE**

11 5 Diseases prevalent before major depressive disorder diagnosis: an exploratory nested case-
12 control study using health insurance-based claims data
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STATISTICAL SUMMARY

Abstract Text	Manuscript Text (Intro-Disc)	References	Figures / Tables
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3 34 **ABSTRACT**
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5 35 **Objectives** Major depressive disorder (MDD) is often comorbid with other chronic and/or
6
7 36 serious diseases. However, little is known about the prevalence of various diseases that are
8
9 37 present before MDD onset. We examined the prevalence of all pre-existing diseases in the
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11 38 12 months before an MDD diagnosis.
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14 39 **Design** Exploratory nested case-control study.
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16 40 **Setting** Data, including diagnoses based on ICD-10 codes, were from a Japanese health
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18 41 insurance database (JMDC).
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20 42 **Participants** Adults newly diagnosed with MDD during 2015, 2016, or 2017 (but not the
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22 43 preceding year) (cases) were matched (exact) 1:10 to controls by age, sex, index date, and
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24 44 working status.
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26 45 **Primary and secondary outcome measures** The primary outcome was the proportion of
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28 46 patients in each group with each pre-existing disease during the 12 months before the index
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30 47 date (ie, before MDD diagnosis in cases). Odds ratios (ORs) for onset of MDD were
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32 48 calculated for each pre-existing disease. A post hoc multivariate analysis examined
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34 49 interactions of metabolic risk factors (diabetes, hypertension, dyslipidaemia), psychiatric
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36 50 disorders (sleep disorders, psychiatric disorders other than depression), and MDD-related
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38 51 symptoms (headache, pain, autonomic nerve imbalance) on MDD diagnosis.
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41 52 **Results** There were 13,420 cases and 134,200 controls (mean age 41.9 years; 66.5%
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43 53 male). The prevalence of almost all pre-existing diseases was higher in cases than in
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45 54 controls. The highest ORs (5.8–21.0) were for psychiatric diseases and sleep disorders.
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47 55 Insomnia (21.1% of patients; OR 8.7) and neurosis (9.7%; OR 10.6) were particularly
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49 56 prevalent in the case group. The odds of MDD increased in the presence of metabolic risk
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51 57 factors, psychiatric disorders, and/or MDD-related symptoms.
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54 58 **Conclusions** There is a high prevalence of pre-existing diseases in Japanese patients who
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56 59 develop MDD compared with matched controls without MDD. These results suggest that
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58 60 patients with chronic and/or serious diseases should be actively monitored for depression.
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3 62 **Strengths and limitations of this study**
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- 5 63 • This is the first nested case-control study to examine a broad range of pre-existing
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7 64 diseases in people who develop major depressive disorder (MDD) compared with
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9 65 people who do not.
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11 66 • The use of a national health insurance database resulted in a sample size large
12
13 67 enough to allow examination of less common pre-existing diseases.
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15 68 • The nested case-control design and the use of a database minimised selection and
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17 69 recall biases that may occur in other case-control studies.
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20 70 • Because of the nature of the database, the study did not include people aged ≥ 75
21
22 71 years, and information on the physician making the MDD diagnosis was not available.
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26 73 **Keywords:** Administrative claims, healthcare; Comorbidity; Depressive disorder;
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28 74 Epidemiology; Risk factors
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75 INTRODUCTION

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

87
88 An epidemiological study conducted in Japan between 2013 and 2015 reported the lifetime
89 and 12-month prevalence rates of major depressive disorder (MDD) to be relatively low, at
90 5.7% and 2.7%, respectively.⁴ Other studies have confirmed that major depressive episodes
91 are less prevalent in Japan than in other countries.^{5,6} However, fewer than half of Japanese
92 people with a mood disorder seek medical treatment.⁴ This reluctance to seek medical
93 treatment may be related to a perceived 'stigma' associated with psychiatric disease.⁷ These
94 factors may further reduce the detection and diagnosis of MDD in patients with a chronic
95 disease, despite the potentially increased risk of MDD in these patients. However, little is
96 known about the prevalence of underlying diseases that are comorbid with MDD. Given that
97 around 20,000 people in Japan commit suicide every year,⁸ with the highest rate of about 50
98 per 100,000 persons in men aged 50–59 years,⁹ most of which are probably related to
99 mental disorders, additional information on factors associated with MDD that could assist
100 with early detection and treatment may help reduce the number of suicides.

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3 102 The aim of this exploratory nested case-control study of patients enrolled in a Japanese
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5 103 health insurance database was to comprehensively examine the prevalence of pre-existing
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7 104 diseases in the 12 months before an MDD diagnosis (defined using the International
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9 105 Statistical Classification of Diseases and Related Health Problems, 10th revision [ICD-10]¹⁰
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11 106 codes F32 ['Depressive episode'] or F33 ['Recurrent depressive disorder']). In this context, a
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13 107 pre-existing disease was defined as any diagnosis other than MDD and related mental
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15 108 disorders (bipolar affective disorders; organic mental disorders; schizophrenia, schizotypal,
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17 109 and delusional disorders); the latter were excluded to avoid including patients with secondary
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19 110 diagnoses of MDD as cases. However, our definition of pre-existing conditions did include
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21 111 those that are prodromal symptoms of MDD (eg, sleep disorders), as well as psychiatric
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23 112 disorders that are less strongly linked to MDD. In addition, we determined an odds ratio (OR)
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25 113 for the onset of MDD for each pre-existing disease to identify those that are most commonly
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27 114 associated with development of MDD and to evaluate the association of MDD with common
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29 115 metabolic risk factors. We speculated that people with pre-existing diseases, including non-
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31 116 psychiatric diseases, might have an increased risk of subsequently developing MDD, which
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33 117 could be related to increased medical burden, shared underlying pathophysiological
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35 118 mechanisms, or other reasons.
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41 120 **METHODS**

43 121 **Study design and data source**

45 122 This was a nested case-control study. Data on patient demographics and diagnoses based
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47 123 on ICD-10 were derived from the JMDC Inc. (Tokyo, Japan) database of medical expense
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49 124 claims for company employees in Japan.¹¹
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53 126 The study was approved by the Ethics Review Committee of the Research Institute of
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55 127 Healthcare Data Science (Tokyo, Japan) on 6 August 2019. Only anonymised information
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57 128 was accessible from the database; therefore, in accordance with the Ethical Guidelines for
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3 129 Medical and Health Research Involving Human Subjects in Japan,¹² informed consent was
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5 130 not required.
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9 132 **Setting and participants**

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11 133 The study analysed data collected for the population registered in the JMDC database
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13 134 between January 2014 and December 2018 who were aged ≥ 18 years on 1 January of the
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15 135 inclusion year (2015, 2016, or 2017) and had continuous registration for the inclusion year,
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17 136 the previous year, and the subsequent year (study period). Individuals were excluded if they
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19 137 had a diagnosis of any bipolar affective disorder (ICD-10 codes F30 [manic episode], F31),
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21 138 organic mental disorder including symptomatic mental disorders (F00–F09), or
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23 139 schizophrenia, schizotypal, and delusional disorder (F20–F29) in the study period, or a
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25 140 diagnosis of MDD (ICD-10 codes F32 [‘Depressive episode’] or F33 [‘Recurrent depressive
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27 141 disorder’]) in the year before the inclusion year, or no medical history for the year before the
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29 142 inclusion year.
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34 144 Within the study population, case patients had a diagnosis of MDD in the inclusion year (the
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36 145 date of the first MDD treatment after ≥ 1 year with no MDD diagnosis was designated as the
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38 146 index date) and ≥ 2 months of treatment for depression within 90 days of the index date.

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40 147 Control patients had no diagnosis of MDD in the study period and were matched 10:1 (exact
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42 148 matching using random sampling) to case patients according to age at index date, sex, and
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44 149 working status.
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48 49 151 **Variables**

50
51 152 The primary end point was the proportion of patients with documented diagnosis of each pre-
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53 153 existing disease during the 12 months before the index date (ie, before MDD diagnosis in
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55 154 case patients). An OR for the onset of MDD was calculated for each underlying disease,
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57 155 which was based on presence or absence of ICD-10 codes, Charlson comorbidity index
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59 156 (CCI)–related diseases, or other chronic diseases (online supplemental table 1).
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157 Demographic and patient characteristics were collected, including age, sex, working status,
158 and inclusion year (2015/2016/2017).

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160 **Study size**

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

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166 **Statistical methods**

167 As noted above, the proportion of patients with each pre-existing disease was determined for
168 each group and an OR for the onset of MDD was calculated. Prevalence data and ORs are
169 reported for pre-existing diseases that were present in $\geq 1\%$ of the case group and $\geq 0.1\%$ of
170 the control group. No inferential statistics were conducted. A post hoc analysis examined the
171 possible interaction of the presence of three pre-existing disease categories that exhibited
172 high ORs in the primary analysis or are common diseases: metabolic risk factors (diabetes,
173 hypertension, dyslipidaemia), MDD-related symptoms (headache, pain, autonomic nerve
174 imbalance), and psychiatric disorders (sleep disorders, psychiatric disorders other than
175 depression) (online supplemental table 1). A multivariate logistic regression model was used
176 to determine ORs in the eight subgroups (ie, with/without metabolic risk factors, MDD-related
177 symptoms, and/or psychiatric disease) for the onset of MDD using the following covariates:
178 sex, age (<40 years versus ≥ 40 years), and working status. A similar post hoc analysis was
179 conducted to estimate ORs for the onset of MDD according to the number of low-risk ($1 \leq \text{OR}$
180 ≤ 2 in the primary analysis) CCI-related and other chronic diseases that were present during
181 the preceding year. As above, sex, age, and working status were adjusted for in the
182 multivariate logistic regression model. Netezza N2002-010 7.1.0.4.P2 (IBM, Armonk, NY,

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

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186 Patient and public involvement

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

188

189 RESULTS

190 Participants

191 From more than 6.5 million people enrolled in the JMDC database between 2014 and 2018,
192 we identified 13,420 case patients who met the inclusion criteria and had MDD diagnosed in
193 2015, 2016, or 2017 (case group; online supplemental figure). From 4,212,652 control
194 patients who met the inclusion criteria and did not have an MDD diagnosis in either the
195 inclusion year or the subsequent year, 134,200 were matched to case patients (control
196 group; online supplemental figure). More than half (66.5%) of patients in both groups were
197 male, with a mean age of 41.9 years (**table 1**). About 40% of patients were <40 years. Most
198 (77.8%) patients were workers.

199 **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)

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3 200 Data are n (%), unless otherwise noted.
4 201 MDD, major depressive disorder; SD, standard deviation.
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7 203 **Prevalence of pre-existing diseases in the year before MDD diagnosis**

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9 204 CCI-related diseases and other chronic diseases

10
11 205 The prevalence of almost all chronic diseases was higher in the case group than in the
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13 206 control group, with most ORs between 1.3 and 2.0 (**table 2**). The highest ORs were seen for
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15 207 attention deficit hyperkinetic disorders (OR 12.2), psychiatric diseases except depression
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17 208 (OR 9.9), dementia (OR 8.7, although prevalence was $\leq 0.1\%$ in both groups), sleep
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19 209 disorders (OR 7.2), and autonomic nerve imbalance (OR 6.5). Of these, psychiatric diseases
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21 210 except depression and sleep disorders were highly prevalent in the case group (30.4% and
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23 211 23.3%, respectively). ORs ≥ 2.0 were also observed (in descending order of prevalence in the
24
25 212 case group) for pain (2.0), chronic gastritis (2.1), headache (2.7), peptic ulcer disease (2.0),
26
27 213 dizziness (3.2), irritable bowel syndrome (3.2), angina pectoris (2.0), epilepsy (2.4), chronic
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29 214 enteritis (2.7), diabetes without chronic complication (2.1), metastatic solid tumour (2.2),
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31 215 hemiplegia or paraplegia (2.8), and Parkinson's disease (3.2).
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216 **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)	2.07 (1.8–2.2)
Osteoporosis	226 (1.7)	1611 (1.2)	1.45 (1.2–1.6)
Epilepsy	177 (1.3)	729 (0.5)	2.44 (2.1–2.9)
Chronic enteritis	153 (1.1)	561 (0.4)	2.74 (2.3–3.3)
Obesity	74 (0.6)	513 (0.4)	1.44 (1.1–1.8)
Attention deficit hyperkinetic disorders	56 (0.4)	46 (<0.1)	12.20 (8.3–18.1)
Parkinson's disease	24 (0.2)	76 (0.1)	3.24 (2.0–5.0)

217 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
 218 shown ranked by prevalence in the case group. Data are n (%), unless otherwise noted.
 219 CCI, Charlson comorbidity index; CI, confidence interval.

220 **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

221 Data are n (%), unless otherwise noted.

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

223 ICD-10 blocks

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

234

235 ICD-10 codes

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

244

245 Multivariate analysis

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

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3 251 seen in subgroups with psychiatric disorders. Compared with subgroups with MDD-related
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5 252 symptoms only, the odds of MDD were increased in subgroups who also had metabolic risk
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7 253 factors or psychiatric disorders. However, the odds of MDD decreased in subgroups who had
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9 254 both metabolic risk factors and psychiatric disorders relative to subgroups with only one of
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11 255 these factors (with or without MDD-related symptoms). Finally, we identified 72,923 people
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13 256 (8329 cases with MDD and 64,594 controls) who had at least one low-risk ($1 \leq OR \leq 2$) pre-
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15 257 existing CCI-related or other chronic disease (**table 2**) and categorised them based on the
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17 258 number of diseases from one (N=36,993) to 11–13 (N=46). Relative to people with only one
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19 259 pre-existing disease, the OR for MDD increased with the number of pre-existing chronic
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21 260 diseases, from 1.34 in people with two pre-existing diseases to more than three in people
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24 261 with nine or more comorbidities (online supplemental table 4).
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262 **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)				

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

266 DISCUSSION

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

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

285

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

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3 294 associated with many gastrointestinal disorders,²⁵ such as irritable bowel syndrome, which
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5 295 were twice as prevalent in the case group than in the control group.
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9 297 Depression-related symptoms (sleep disorders, pain, autonomic imbalance) may be
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11 298 diagnosed in advance of MDD and therefore may be prodromal symptoms of MDD.²⁶

13 299 Somatic symptoms of MDD, such as fatigue, appetite loss, pain (especially headache),
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15 300 dizziness, and sleep disturbance, can be non-specific and may be attributed to physical
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17 301 illness.²⁷ Indeed, a significant proportion of patients with MDD present with only somatic
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19 302 symptoms.²⁸ One reason is denial of psychological symptoms, which is particularly prevalent
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21 303 in Japan.²⁸ These results support the idea that depression is under-recognised when patients
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23 304 first seek medical help in Japan, and also support our findings that digestive diseases, sleep
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25 305 disorders, and other somatic symptoms, including in the otological area (eg, dizziness), were
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27 306 highly prevalent in patients who later developed MDD. Interestingly, we observed that the OR
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29 307 for diseases of the ear and mastoid process was higher than for diseases of the eye and
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31 308 adnexa (1.8 versus 1.1). We suggest that physicians in otolaryngology departments may be
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33 309 aware of the link between somatic symptoms and MDD and consider psychological
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35 310 evaluation for patients with such symptoms. In contrast, physicians in ophthalmology
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37 311 departments may need to pay more attention to the risk of MDD in patients with severe visual
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39 312 dysfunction because both hearing loss and vision loss are associated with the development
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41 313 of depression.²⁹
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47 315 Our multivariate analysis indicated that the odds of an MDD diagnosis were increased in
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49 316 patients who had depression-related symptoms (headache, pain, autonomic imbalance),
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51 317 particularly if the patient also had a sleep/psychiatric disorder or metabolic risk factor.

53 318 Interestingly, the odds of MDD decreased in subgroups with metabolic risk factors in addition
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55 319 to psychiatric disorders. Although the reason for this finding is unclear, it may be that these
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57 320 patients are managed by multiple physicians who focus on treating each disease separately
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59 321 (eg, psychiatrist treating psychiatric diseases; general practitioner treating metabolic risk

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3 322 factors), with the result that MDD is not sufficiently recognised. Indeed, some general
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5 323 practitioners and other non-psychiatrist doctors in Japan fail to recognise or are reluctant to
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7 324 treat MDD,^{30 31} which may contribute to underdiagnosis of MDD in patients with metabolic risk
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9 325 factors. Psychiatrists, on the other hand, may underestimate somatic depressive symptoms
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11 326 in patients they are treating for another mental illness who also have a metabolic-related
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13 327 illness treated by another doctor, considering fatigue and autonomic dysfunction as caused
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15 328 by the physical illness. However, depression is known to lead to treatment non-adherence in
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17 329 patients with diabetes,³² which increases the risk of severe complications.³³ In addition,
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19 330 treating metabolic-related diseases and depression simultaneously may provide patients with
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21 331 better clinical outcomes.³⁴ Further research is needed on the unmet needs for the diagnosis
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23 332 and treatment of depression in patients with presymptomatic depression in addition to
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25 333 metabolic-related diseases, and on the effects of coordinated care management of multiple
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27 334 conditions.
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33 336 We also found that the risk of MDD increased with increasing number of relatively low-risk
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35 337 (OR \leq 2) CCI-related and other chronic diseases. Thus, increased medical burden appears to
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37 338 be associated with greater risk of depression among working-age people, consistent with a
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39 339 recent study conducted in Denmark.³⁵
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43 341 Many comorbidities may share underlying biological mechanisms with MDD. For example,
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45 342 inflammatory mechanisms play a role in the aetiology of many diseases, including diabetes,
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47 343 cardiovascular disease, arthritis, and asthma, as well as depression.³⁶⁻³⁸ Neural pathways
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49 344 and neurotransmitters that are altered in chronic pain may also affect mood, including
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51 345 depression.³⁹ Migraine and depression can both be related to specific genetic variants and/or
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53 346 neuroanatomic features.⁴⁰ Most of these biological mechanisms are exacerbated by stress.³
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55 347 ^{37 40} Thus, MDD may develop in parallel with certain diseases, but its diagnosis may be
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57 348 delayed compared with physical disease.
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350 **Strengths and limitations**

351 Our study is strengthened by the use of a health insurance database consisting of mostly
352 working-age people, which resulted in a sample size large enough to allow examination of a
353 broad range of pre-existing diseases. The nested case-control design and the use of a
354 database minimised selection and recall biases that may occur in other case-control studies.
355 We used a strict definition of MDD onset, which required a 1-year depression-free period and
356 the diagnosis for inclusion to be recorded on at least three doctor visits within 90 days; this
357 definition increased our certainty that case patients had true, newly diagnosed MDD. In
358 addition, our inclusion criteria meant that people in both the control and case groups needed
359 to have visited a doctor at least once to have a medical record within the observation period.
360 Because of the comprehensive insurance available in Japan, medical care is readily
361 accessible, and consultations for relatively minor concerns are common. Therefore, the
362 controls in our study can essentially be considered as representative of the general
363 population, except for the absence of people aged 75 years or older, who are covered by
364 government-administered insurance, and the relatively low proportion of people aged 65–74
365 years, many of whom would be retired from work.
366
367 Despite these strengths, some caveats do apply when interpreting our results. As with any
368 claims database study, the data were not collected specifically for the purpose of the study.
369 As such, we could not evaluate variables like socioeconomic factors or severity/history of
370 MDD. Further, errors in ICD-10 coding may have occurred, although equally in cases and
371 controls. Patients with chronic diseases are likely to visit their physicians frequently,
372 increasing the opportunity for detection and diagnosis of MDD. Further, patients with pre-
373 existing psychiatric disorders are likely to be treated by psychiatrists, who may be better at
374 diagnosing MDD than other physicians, which might lead to higher ORs for psychiatric
375 diseases than for physical diseases; however, MDD diagnosis by general practitioners is also
376 higher in patients with psychiatric comorbidity than in those with physical comorbidity.⁴¹
377 Nevertheless, MDD is often under-recognised and underdiagnosed, which may mean that

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3 378 the control group included patients who actually had depression or depressive symptoms.
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5 379 We only assessed disease prevalence, and not incidence, during the year before the
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7 380 inclusion year; therefore, we do not know if the disease was diagnosed during that year or in
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9 381 a previous year. This limitation could potentially result in a disproportionate number of people
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11 382 in the control group who had longer-term diseases and were not vulnerable to MDD. For
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13 383 some high-stress diseases such as cancer or stroke, MDD often occurs soon after
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15 384 diagnosis^{42 43}; hence, less vulnerable patients who did not develop MDD would have
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17 385 remained within the control group, leading to lower ORs for those diseases than might be
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19 386 expected. Further, the nature of the database made it difficult to exclude patients with an
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21 387 MDD diagnosis more than a year previously; consequently, our cases could have included
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23 388 patients with recurrent MDD as well as those diagnosed for the first time. The use of
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25 389 standard logistic regression instead of conditional logistic regression may also have resulted
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27 390 in the underestimation of ORs. Finally, the relatively short observation period limits our ability
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29 391 to look at the long-term relationship between MDD, which can re-occur multiple times in a
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31 392 patient's life, and other chronic conditions. Although comparing ORs for the onset of MDD
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33 393 across a broad range of pre-existing diseases can help develop hypotheses regarding
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35 394 possible underlying mechanisms, the risk of MDD occurring in specific diseases should be
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37 395 investigated on an individual basis.
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42 43 397 **CONCLUSIONS**

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45 398 This large, preliminary, nested case-control study has documented the high prevalence of
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47 399 pre-existing diseases in Japanese patients with MDD compared with matched controls
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49 400 without MDD. The high prevalence of pre-existing diseases in patients who develop MDD
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51 401 reflects the complex relationship between physical and mental disorders and indicates a high
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53 402 medical burden for these patients. These results confirm that patients with chronic and/or
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55 403 serious diseases, including prodromal symptoms that are not always recognised as related to
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57 404 MDD, should be monitored for depressive symptoms, and pre-existing diseases should be
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59 405 taken into consideration when prescribing treatment for MDD.
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413

414 **Contributors**

415 Yoshinori Cho designed the study and data collection, interpreted the study results, and
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417 manuscript. Izumi Mishiro designed the study and data collection, wrote the statistical
418 analysis plan, interpreted the study results, and participated in the drafting, critical revision,
419 and approval of the final version of the manuscript. Tsuyoshi Akaki designed the study and
420 data collection, interpreted the study results, and participated in the drafting, critical revision,
421 and approval of the final version of the manuscript. Takafumi Akimoto designed the study
422 and data collection, interpreted the study results, and participated in the drafting, critical
423 revision, and approval of the final version of the manuscript. Keita Fujiwara designed the
424 study and data collection, interpreted the study results, and participated in the drafting,
425 critical revision, and approval of the final version of the manuscript.

426

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432 manuscript for publication.

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3 434 **Data availability statement**
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5 435 The data that support the findings of this study are available from JMDC Inc. but were used
6
7 436 under licence for the current study; therefore, restrictions apply and the data are not publicly
8
9 437 available. For inquiries about access to the data set used in this study, please contact JMDC
10
11 438 (<https://www.jmdc.co.jp>).
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16 440 **Competing interests**

17
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19
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21
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24 444 Tanabe Pharma Corporation, Sumitomo Dainippon Pharma Co., Ltd., Astellas Pharma Inc.,
25
26 445 MSD K.K., Takeda Pharmaceutical Company Limited, and Lundbeck Japan K.K., outside the
27
28 446 submitted work. Drs Mishiro, Akaki, Akimoto, and Fujikawa report personal fees from Takeda
29
30 447 Pharmaceutical Company Limited, outside the submitted work.
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35 449 **Ethics statements**

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37 450 **Ethics approval**

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39 451 The study was approved by the Ethics Review Committee of the Research Institute of
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41 452 Healthcare Data Science (Tokyo, Japan) on 6 August 2019 (approval number RI2019004).
42
43 453 Only anonymised information was accessible from the database; therefore, in accordance
44
45 454 with the Ethical Guidelines for Medical and Health Research Involving Human Subjects in
46
47 455 Japan, informed consent was not required.
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52 457 **Patient consent for publication**

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54 458 Not applicable.
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460 **REFERENCES**

- 461 1 Clarke DM, Currie KC. Depression, anxiety and their relationship with chronic
462 diseases: a review of the epidemiology, risk and treatment evidence. *Med J Aust*
463 2009;190:S54–60.
- 464 2 Evans DL, Charney DS, Lewis L, et al. Mood disorders in the medically ill: scientific
465 review and recommendations. *Biol Psychiatry* 2005;58:175–89.
- 466 3 Katon WJ. Epidemiology and treatment of depression in patients with chronic medical
467 illness. *Dialogues Clin Neurosci* 2011;13:7–23.
- 468 4 Ishikawa H, Tachimori H, Takeshima T, et al. Prevalence, treatment, and the
469 correlates of common mental disorders in the mid 2010's in Japan: the results of the
470 World Mental Health Japan 2nd Survey. *J Affect Disord* 2018;241:554–62.
- 471 5 Andrade L, Caraveo-Anduaga JJ, Berglund P, et al. The epidemiology of major
472 depressive episodes: results from the International Consortium of Psychiatric
473 Epidemiology (ICPE) Surveys. *Int J Methods Psychiatr Res* 2003;12:3–21.
- 474 6 Bromet E, Andrade LH, Hwang I, et al. Cross-national epidemiology of DSM-IV major
475 depressive episode. *BMC Med* 2011;9:90.
- 476 7 Ando S, Yamaguchi S, Aoki Y, et al. Review of mental-health-related stigma in Japan.
477 *Psychiatry Clin Neurosci* 2013;67:471–82.
- 478 8 Ministry of Health, Labour and Welfare. Vital statistics of Japan, 2017. Available:
479 <https://www.mhlw.go.jp/english/database/db-hw/dl/81-1a2en.pdf> [Accessed 16
480 January 2020].
- 481 9 Snowden J, Phillips J, Zhong B, et al. Changes in age patterns of suicide in Australia,
482 the United States, Japan and Hong Kong. *J Affect Disord* 2017;211:12–9.
- 483 10 International Statistical Classification of Diseases and Related Health Problems, 10th
484 Revision, 2016. Available: <https://icd.who.int/browse10/2016/en> [Accessed 16
485 January 2020].

- 1
2
3 486 11 Kimura S, Sato T, Ikeda S, et al. Development of a database of health insurance
4
5 487 claims: standardization of disease classifications and anonymous record linkage. *J*
6
7 488 *Epidemiol* 2010;20:413–9.
8
9 489 12 Ministry of Health, Labour and Welfare. Ethical guidelines for medical and health
10
11 490 research involving human subjects, 2015. Available: <https://www.mhlw.go.jp/file/06->
12
13 491 [Seisakujouhou-10600000-Daijinkanboukouseikagakuka/0000080278.pdf](https://www.mhlw.go.jp/file/06-Seisakujouhou-10600000-Daijinkanboukouseikagakuka/0000080278.pdf) [Accessed
14
15 492 16 January 2020].
16
17 493 13 Daré LO, Bruand P-E, Gérard D, et al. Co-morbidities of mental disorders and chronic
18
19 494 physical diseases in developing and emerging countries: a meta-analysis. *BMC*
20
21 495 *Public Health* 2019;19:304.
22
23 496 14 Park SJ, Hong S, Jang H, et al. The prevalence of chronic physical diseases
24
25 497 comorbid with depression among different sex and age groups in South Korea: a
26
27 498 population-based study, 2007-2014. *Psychiatry Investig* 2018;15:370–5.
28
29 499 15 Patten SB. Long-term medical conditions and major depression in a Canadian
30
31 500 population study at waves 1 and 2. *J Affect Disord* 2001;63:35–41.
32
33 501 16 Young JQ, Kline-Simon AH, Mordecai DJ, et al. Prevalence of behavioral health
34
35 502 disorders and associated chronic disease burden in a commercially insured health
36
37 503 system: findings of a case-control study. *Gen Hosp Psychiatry* 2015;37:101–8.
38
39 504 17 Ryu E, Chamberlain AM, Pendegraft RS, et al. Quantifying the impact of chronic
40
41 505 conditions on a diagnosis of major depressive disorder in adults: a cohort study using
42
43 506 linked electronic medical records. *BMC Psychiatry* 2016;16:114.
44
45 507 18 Han KM, Kim MS, Kim A, et al. Chronic medical conditions and metabolic syndrome
46
47 508 as risk factors for incidence of major depressive disorder: a longitudinal study based
48
49 509 on 4.7 million adults in South Korea. *J Affect Disord* 2019;257:486–94.
50
51 510 19 de Kloet ER, Joëls M, Holsboer F. Stress and the brain: from adaptation to disease.
52
53 511 *Nat Rev Neurosci* 2005;6:463–75.
54
55 512 20 Yang L, Zhao Y, Wang Y, et al. The effects of psychological stress on depression.
56
57 513 *Curr Neuropharmacol* 2015;13:494–504.
58
59
60

- 1
2
3 514 21 Birk JL, Kronish IM, Moise N, et al. Depression and multimorbidity: considering
4
5 515 temporal characteristics of the associations between depression and multiple chronic
6
7 516 diseases. *Health Psychol* 2019;38:802–11.
8
9 517 22 Gorman JM, Coplan JD. Comorbidity of depression and panic disorder. *J Clin*
10
11 518 *Psychiatry* 1996;57:34–41; discussion 2–3.
12
13 519 23 Hölzel L, Härter M, Reese C, et al. Risk factors for chronic depression — a systematic
14
15 520 review. *J Affect Disord* 2011;129:1–13.
16
17 521 24 Pollack MH. Comorbid anxiety and depression. *J Clin Psychiatry* 2005;66:22–9.
18
19 522 25 Konturek PC, Brzozowski T, Konturek SJ. Stress and the gut: pathophysiology,
20
21 523 clinical consequences, diagnostic approach and treatment options. *J Physiol*
22
23 524 *Pharmacol* 2011;62:591–9.
24
25 525 26 Fava GA, Tossani E. Prodromal stage of major depression. *Early Interv Psychiatry*
26
27 526 2007;1:9–18.
28
29 527 27 Kapfhammer HP. Somatic symptoms in depression. *Dialogues Clin Neurosci*
30
31 528 2006;8:227–39.
32
33 529 28 Simon GE, VonKorff M, Piccinelli M, et al. An international study of the relation
34
35 530 between somatic symptoms and depression. *N Engl J Med* 1999;341:1329–35.
36
37 531 29 McDonnell MC. The effects of developing a dual sensory loss on depression in older
38
39 532 adults: a longitudinal study. *J Aging Health* 2009;21:1179–99.
40
41 533 30 Ohtsuki T, Inagaki M, Oikawa Y, et al. Multiple barriers against successful care
42
43 534 provision for depressed patients in general internal medicine in a Japanese rural
44
45 535 hospital: a cross-sectional study. *BMC Psychiatry* 2010;10:30.
46
47 536 31 Ohtsuki T, Kodaka M, Sakai R, et al. Attitudes toward depression among Japanese
48
49 537 non-psychiatric medical doctors: a cross-sectional study. *BMC Res Notes*
50
51 538 2012;5:441.
52
53 539 32 Gonzalez JS, Peyrot M, McCarl LA, et al. Depression and diabetes treatment
54
55 540 nonadherence: a meta-analysis. *Diabetes Care* 2008;31:2398–403.
56
57
58
59
60

- 1
2
3 541 33 Chen AJ, Hwang V, Law PY, et al. Factors associated with non-compliance for
4 542 diabetic retinopathy follow-up in an urban safety-net hospital. *Ophthalmic Epidemiol*
5 543 2018;25:443–50.
6
7
8
9 544 34 Katon WJ, Lin EH, Von Korff M, et al. Collaborative care for patients with depression
10 545 and chronic illnesses. *N Engl J Med* 2010;363:2611–20.
11
12
13 546 35 Köhler-Forsberg O, Petersen L, Ishtiak-Ahmed K, et al. Medical diseases prior to first-
14 547 time depression diagnosis and subsequent risk of admissions for depression: a
15 548 nationwide study of 117,585 patients. *J Affect Disord* 2020;276:1030–7.
16
17
18 549 36 Dantzer R, O'Connor JC, Freund GG, et al. From inflammation to sickness and
19 550 depression: when the immune system subjugates the brain. *Nat Rev Neurosci*
20 551 2008;9:46–56.
21
22
23 552 37 Iwata M, Ota KT, Duman RS. The inflammasome: pathways linking psychological
24 553 stress, depression, and systemic illnesses. *Brain Behav Immun* 2013;31:105–14.
25
26
27 554 38 Raison CL, Capuron L, Miller AH. Cytokines sing the blues: inflammation and the
28 555 pathogenesis of depression. *Trends Immunol* 2006;27:24–31.
29
30
31 556 39 Bair MJ, Robinson RL, Katon W, et al. Depression and pain comorbidity: a literature
32 557 review. *Arch Intern Med* 2003;163:2433–45.
33
34
35 558 40 Baksa D, Gonda X, Juhasz G. Why are migraineurs more depressed? A review of the
36 559 factors contributing to the comorbidity of migraine and depression.
37 560 *Neuropsychopharmacol Hung* 2017;19:37–44.
38
39
40 561 41 Nuyen J, Volkers AC, Verhaak PF, et al. Accuracy of diagnosing depression in
41 562 primary care: the impact of chronic somatic and psychiatric co-morbidity. *Psychol*
42 563 *Med* 2005;35:1185–95.
43
44
45 564 42 Hackett ML, Pickles K. Part I: frequency of depression after stroke: an updated
46 565 systematic review and meta-analysis of observational studies. *Int J Stroke*
47 566 2014;9:1017–25.
48
49
50
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59
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567 43 Lu D, Andersson TML, Fall K, et al. Clinical diagnosis of mental disorders
568 immediately before and after cancer diagnosis: a nationwide matched cohort study in
569 Sweden. *JAMA Oncol* 2016;2:1188–96.
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3 571 **FIGURE LEGEND**
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7 573 **Figure A**, Diseases with prevalence >8% in the case group in the 12 months before MDD

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9 574 diagnosis. B, Diseases with odds ratio >3.0. Shown are the prevalence rates in the case

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11 575 group and in the matched control group, as well as the odds ratio (95% CI). CI, confidence

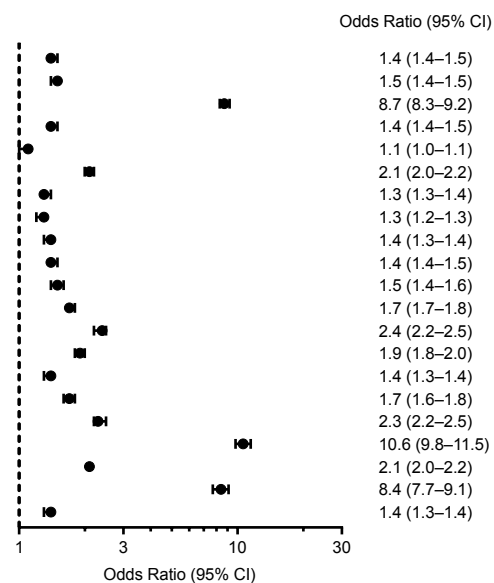
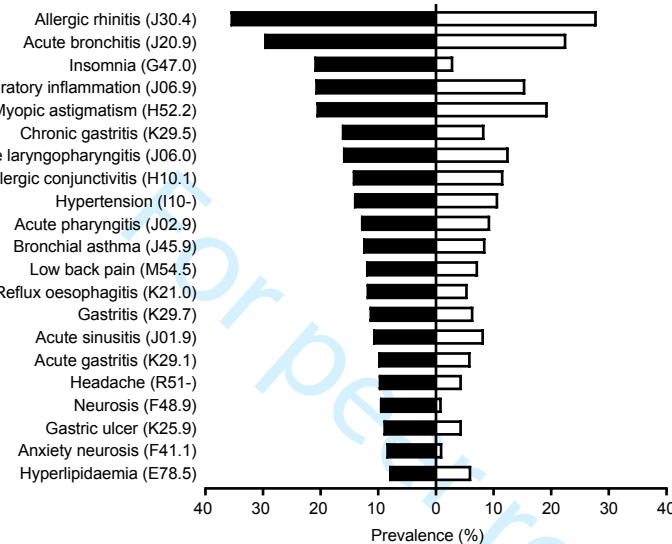
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13 576 interval; MDD, major depressive disorder.
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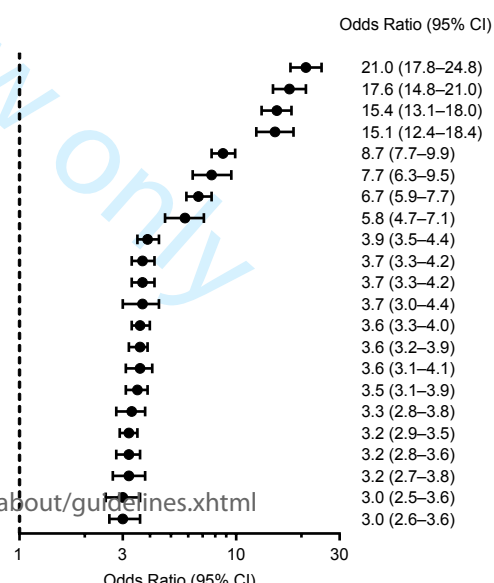
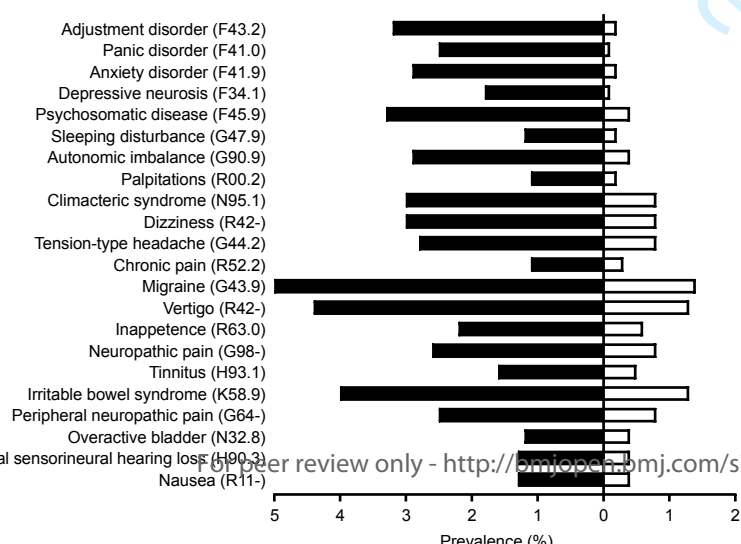
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Cases Controls



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.

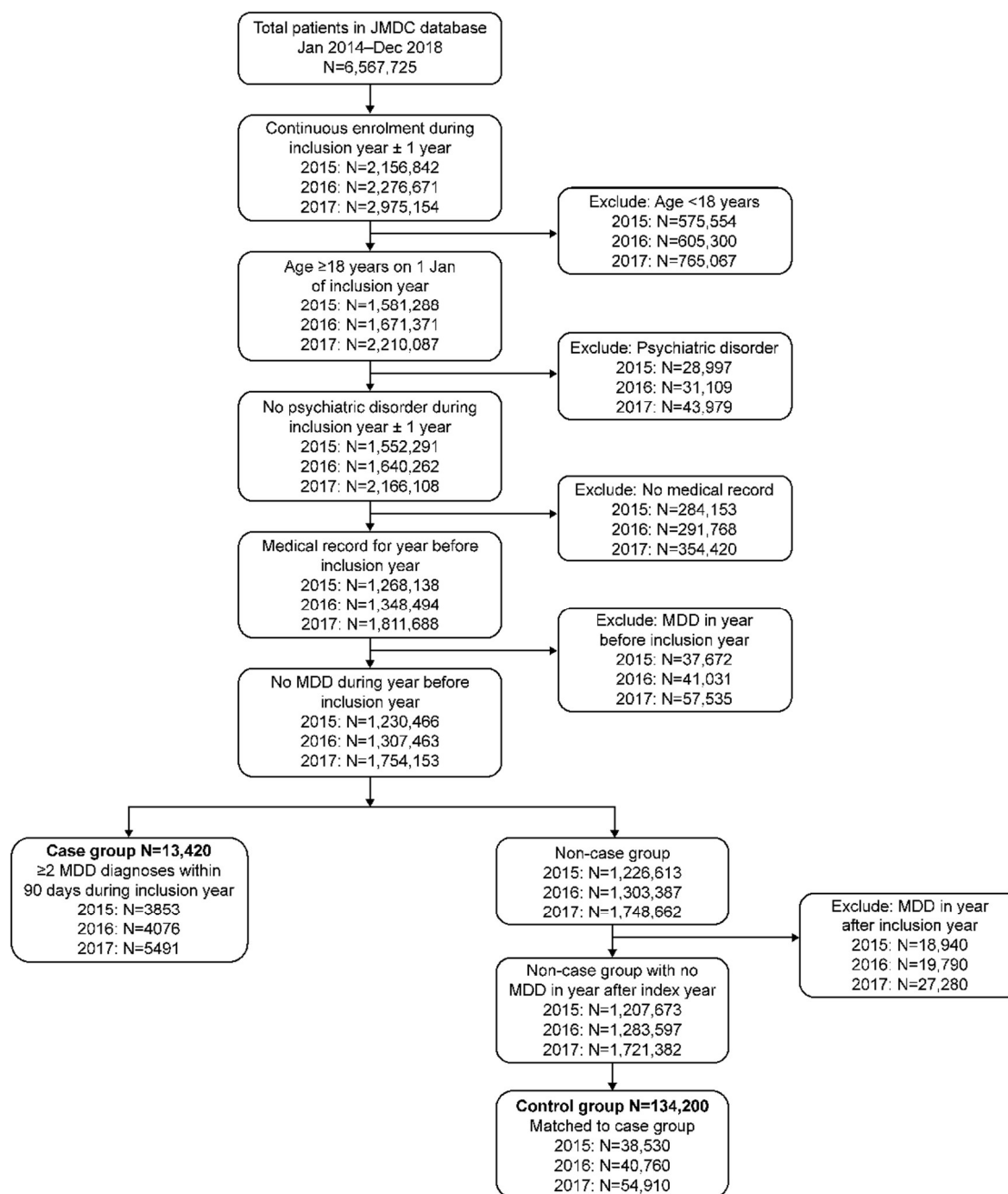
Supplemental table 1 ICD-10 codes and other terms used to identify pre-existing diseases

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
<i>CCI-related diseases</i>	
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
<i>Other chronic diseases</i>	
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
Arthritis	Other disease name with 'osteoarthritis' M00–M03, M05–M14
Epilepsy	Other disease name with 'arthritis' 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
Irritable bowel syndrome	Diabetic neuropathic pain K58
Chronic gastritis	K29.3, K29.4, K29.5
Chronic enteritis	K52.9
Dizziness	R42, H81, I95.1
Autonomic nerve imbalance	Epidemic dizziness, psychogenic dizziness, low-tone dizziness G90
Attention deficit hyperactivity disorder	F90
Psychiatric disorders other than depression	F00–F99*
Sleep disorders	*Except F00–F09, F20–F29, F30–F33 G47
<i>Metabolic risk factors</i>	
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
<i>Psychiatric disorders</i>	
Psychiatric disorders other than depression	F00–F99*
Sleep disorders	*Except F00–F09, F20–F29, F30–F33 G47
<i>MDD-related symptoms</i>	
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
Autonomic nerve imbalance	Diabetic neuropathic pain 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	6046	2.3
F48.9	Neurotic disorder, unspecified	Neurosis	1306	1350	10.6
K25.9	Gastric ulcer/Unspecified as acute or chronic, without haemorrhage or perforation	Gastric ulcer	1216	6086	2.1
F41.1	Generalised anxiety disorder	Anxiety neurosis	1155	1492	8.4
E78.5	Hyperlipidaemia, unspecified	Hyperlipidaemia	1091	8244	1.4
J02.9	Acute pharyngitis, unspecified	Pharyngitis	1061	7940	1.4
L30.9	Dermatitis, unspecified	Eczema	1032	7799	1.4
K59.0	Constipation	Constipation	1030	6014	1.8
E86-	Volume depletion	Dehydration	1003	4825	2.2
E78.0	Pure hypercholesterolaemia	Hypercholesterolaemia	940	7031	1.4
R11-	Nausea and vomiting	Vomition	933	4031	2.4
M53.1	Cervicobrachial syndrome	Cervico-omo-brachial syndrome	905	3380	2.8
J00-	Acute nasopharyngitis [common cold]	Common cold	894	5998	1.5
A09.9	Gastroenteritis and colitis of unspecified origin	Acute gastroenteritis	873	5140	1.7
E14-	Unspecified diabetes mellitus	Diabetes mellitus	870	6285	1.4
J32.9	Chronic sinusitis, unspecified	Chronic sinusitis	818	5551	1.5
A09.9	Gastroenteritis and colitis of unspecified origin	Diarrhoea	781	4311	1.9
			(5.8)	(3.2)	(1.7–2.0)

ICD-10 level 4 code	ICD-10 level 4 name	Standard disease name	Case group N=13,942	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=13,920	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	<i>Helicobacter pylori</i> 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	1191	1.4
			(1.2)	(0.9)	(1.2–1.6)
J32.9	Chronic sinusitis, unspecified	Sinusitis	164	1146	1.4
			(1.2)	(0.9)	(1.2–1.7)
N32.8	Other specified disorders of bladder	Overactive bladder	164	519	3.2
			(1.2)	(0.4)	(2.7–3.8)
G62.9	Polyneuropathy, unspecified	Peripheral neuritis	163	662	2.5
			(1.2)	(0.5)	(2.1–2.9)
L30.9	Dermatitis, unspecified	Dermatitis	163	1336	1.2
			(1.2)	(1.0)	(1.0–1.4)
L70.0	Acne vulgaris	Facial common acne	162	1446	1.1
			(1.2)	(1.1)	(1.0–1.3)
I50.9	Heart failure, unspecified	Chronic cardiac failure	159	815	2.0
			(1.2)	(0.6)	(1.7–2.3)
G47.9	Sleep disorder, unspecified	Sleeping disturbance	157	205	7.7
			(1.2)	(0.2)	(6.3–9.5)
M06.9	Rheumatoid arthritis, unspecified	Rheumatoid arthritis	155	830	1.9
			(1.2)	(0.6)	(1.6–2.2)
J32.9	Chronic sinusitis, unspecified	Acute exacerbation of chronic sinusitis	153	1272	1.2
			(1.1)	(0.9)	(1.0–1.4)
N20.1	Calculus of ureter	Ureterolithiasis	151	1139	1.3
			(1.1)	(0.8)	(1.1–1.6)
R52.2	Other chronic pain	Chronic pain	151	417	3.7
			(1.1)	(0.3)	(3.0–4.4)
R31-	Unspecified haematuria	Haematuria	149	1024	1.5
			(1.1)	(0.8)	(1.2–1.7)
K76.9	Liver disease, unspecified	Liver disorder	148	955	1.6
			(1.1)	(0.7)	(1.3–1.9)
R00.2	Palpitations	Palpitations	148	257	5.8
			(1.1)	(0.2)	(4.7–7.1)
H10.3	Acute conjunctivitis, unspecified	Acute conjunctivitis	147	1212	1.2
			(1.1)	(0.9)	(1.0–1.4)

ICD-10 level 4 code	ICD-10 level 4 name	Standard disease name	Case group N=13,920	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 $\geq 1.0\%$ in the case group and $\geq 0.1\%$ 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
	No	No	Yes	1998	20,752	22,750
	No	Yes	No	1794	33,179	34,973
	No	Yes	Yes	1595	23,075	24,670
	Yes	No	No	901	15,060	15,961
	Yes	No	Yes	854	7,588	8,442
	Yes	Yes	No	675	18,675	19,350
	Yes	Yes	Yes	1274	22,822	24,096
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
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*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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