



Impact of Depression Onset and Treatment on the Trend of Annual Medical Costs in Japan: An Exploratory, Descriptive Analysis of Employer-Based Health Insurance Claims Data

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ABSTRACT

Introduction: We aimed to clarify medical expenses in Japanese individuals before and after major depressive disorder (MDD) diagnosis, and to determine whether MDD treatment also reduces medical costs for comorbid physical conditions.

Methods: This was an exploratory, descriptive, retrospective analysis of insurance claims data from JMDC Inc. Cohort A included individuals aged 18–64 years between January 2015 and December 2019. Cohorts B and C included Cohort A individuals with diabetes/hypertension ('chronic disease'), and sleep/anxiety disorders ('high depression risk'), respectively. Individuals in Cohorts A–C with an MDD diagnosis were analyzed by year of MDD onset (Cohorts A–C_{MDD2015–2019}). Diagnoses and

median medical costs were derived from International Classification of Diseases 10 codes.

Results: Total medical and non-neuropsychiatric drug costs in MDD onset years were 170,390–182,120 and 8480–9586 yen higher, respectively, for Cohorts A_{MDD2015–2019} than for Cohort A. In Cohort A_{MDD2019}, total medical and non-neuropsychiatric drug costs increased incrementally from 2015 to 2019 (total changes: +165,130 and +7365 yen, respectively), to a greater degree than in Cohort A (+10,510 and +1246 yen, respectively). Neuropsychiatric drug costs increased in the year of MDD onset only and decreased thereafter. After MDD onset, decreases in total medical and non-neuropsychiatric drug costs were observed (Cohorts A_{MDD2015–2019}). Non-neuropsychiatric drug costs also decreased after MDD onset in the chronic disease groups (Cohorts C_{MDD2015–2019}), but not in patients with MDD recurrence.

Conclusion: Treating MDD reduces medical costs for comorbid physical conditions and may be a useful strategy for improving healthcare efficiency in Japan.

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Key Summary Points

Major depressive disorder (MDD) (diagnosed and undiagnosed) is common in Japan, particularly among highly educated individuals who make up over half of the workforce; depression-related work absenteeism costs the Japanese economy around US\$6 billion per year.

Previous data from pooled, randomized, placebo-controlled clinical trials show that treatment of MDD with antidepressants significantly improves workplace functioning.

In our exploratory, descriptive analysis, we show that total medical costs and non-neuropsychiatric drug costs are higher in patients with MDD, and start increasing well before MDD is formally diagnosed, and that MDD treatment mitigates these costs.

Health economic assessments of antidepressants should thus factor in reductions in associated costs for treating comorbid physical illnesses, in addition to established indirect benefits such as improved work productivity.

INTRODUCTION

Major depressive disorder (MDD) significantly diminishes role functioning and quality of life and is linked with high morbidity and mortality [1]. A nationwide survey conducted in Japan between 2013 and 2015 reported lifetime and 12-month prevalence estimates for MDD of 5.7% (~ 7.2 million individuals) and 2.7%, respectively [2]. In a survey of Japanese employees, high scores (≥ 16) on the Center for Epidemiologic Studies Depression Scale were

reported in 45% of participants [3]. MDD is thus common among Japanese individuals and is a significant health issue.

Both diagnosed and undiagnosed MDD have been shown to reduce the productivity of Japanese employees [4]. In a global assessment of the effects of MDD on work productivity, mean individual costs (US\$2674 per year) and aggregate costs (US\$6 billion per year) of MDD-related absenteeism were found to be the highest in Japan [5]. This was despite a relatively low proportion of employees reporting an MDD diagnosis [5], suggesting that low reporting and treatment of MDD in Japan may contribute to its high economic costs. Indeed, fewer than half of Japanese individuals with a mood disorder may seek medical treatment [2], possibly because of the stigma associated with psychiatric disorders [6]. Furthermore, MDD is more prevalent among highly educated individuals (university or above) in Japan, who comprise almost half of the working population [5, 7], and is associated with long working hours [8], which are common in the Japanese workplace [9]. A recent systematic review of randomized, double-blind, placebo-controlled trials confirmed that treatment of MDD with antidepressants significantly improves workplace functioning [10].

MDD is associated with various comorbidities [11]; individuals with sleep and anxiety disorders are at particularly high risk of developing MDD, and this relationship appears to be bidirectional [12, 13]. Furthermore, there has been substantial interest in the relationship between MDD and diabetes, with studies showing an increased risk of MDD in individuals with (vs. without) diabetes, and an increased risk of diabetes in individuals with (vs. without) MDD [14, 15]. In addition, comorbid MDD has been associated with increased healthcare costs and poorer outcomes in individuals with diabetes [16, 17], and the coexistence of diabetes and MDD has been associated with significantly increased risks of cardiovascular mortality and all-cause mortality compared with either condition alone [18]. Of particular note, treatment of MDD in patients with comorbid diabetes may reduce overall health costs (i.e., beyond those

directly attributed to MDD) compared with no treatment [19].

Healthcare costs are increasing in Japan as the population ages; maintaining efficient healthcare delivery is thus an important social issue and a key driver of health policy reform [20]. Given the associations described earlier, it is reasonable to hypothesize that individuals with MDD may have some increase in healthcare costs before a formal MDD diagnosis is made. Furthermore, treating MDD could potentially lower costs for associated comorbidities, and may therefore be an efficient way of reducing direct and indirect healthcare costs. The objectives of the current study were to clarify medical expenses in patients in Japan before and after an MDD diagnosis, including in patients with comorbid conditions. We also examined the effects of MDD treatment status (treatment duration and the presence or absence of MDD relapse) on medical costs in patients with MDD.

METHODS

Study Design and Data Source

This was a descriptive, retrospective, epidemiological analysis of trends over time in annual medical costs incurred by Japanese individuals before and after a diagnosis of MDD. All data for this analysis were derived from JMDC Inc. (Tokyo, Japan), which maintains a large, chronologically organized, insurance claims database that uses standardized disease classification [based on International Classification of Diseases (ICD) codes] and anonymized record linkage [21]. As of April 2020, the JMDC database included cumulative data from approximately 7.3 million Japanese individuals (~ 5.8% of the population), mainly comprising company employees and their family members [22]. The JMDC database has been used extensively as a real-world data source for epidemiological and health economic analyses [23–27].

Compliance with Ethics Guidelines

The study was approved by the Ethics Review Committee of the Research Institute of Healthcare Data Science (Tokyo, Japan; reference number RI2019004). Only anonymized information (obtained with permission from JMDC Inc.) was accessible from the database; therefore, in accordance with the Ethical Guidelines for Medical and Health Research Involving Human Subjects in Japan, informed consent was not required [28].

Study Cohorts

Individuals aged 18–64 years during the 60-month observation period (January 2015 to December 2019) were included in the analysis (Cohort A) (Fig. 1). Cohort B comprised all individuals from Cohort A who had a diabetes or hypertension diagnosis, and at least 2 months of prescriptions for these conditions, within the observation period ('chronic disease' group). Cohort C comprised all individuals from Cohort A who had a sleep or anxiety disorder diagnosis and at least 2 months of prescriptions for these conditions, without on-demand use of hypnotics or anxiety medications, within the observation period ('high risk of depression' group).

Individuals in Cohorts A–C who had an MDD diagnosis during the observation period were grouped for analysis by the year of MDD onset (2015–2019; Cohorts $A_{MDD2015-2019}$, Cohorts $B_{MDD2015-2019}$ and Cohorts $C_{MDD2015-2019}$) (Fig. 1). To be included in Cohorts $B_{MDD2015-2019}$ and Cohorts $C_{MDD2015-2019}$, individuals had to have had 'chronic disease' onset or 'high risk of depression' onset, respectively, in the year before MDD onset, which was defined as the earliest date a patient received two consecutive months of MDD treatment.

Within Cohorts $A-C_{MDD2015-2019}$, individuals who were diagnosed with MDD in 2016 were further grouped and analyzed according to the length of their first MDD treatment period and whether they had an MDD recurrence (see Table 1 for analysis group definitions).

Analysis

We conducted an exploratory, descriptive epidemiological analysis investigating annual trends—before and after the year of MDD diagnosis—in total medical costs, neuropsychiatric drug costs and non-neuropsychiatric drug costs. Data on patient demographics, medical costs and diagnoses were derived from the JMDC database based on ICD-10 codes (see S1, Electronic Supplementary Material). Total medical costs were calculated as the sum of all costs in

Japanese yen listed on the inpatient, diagnosis procedure combination, outpatient and dispensing receipts issued from January to December (inclusive) of each year. The total cost for a drug was calculated as the Drug price (as set by the Japanese National Health Insurance [NHI] [29]) \times Prescription volume per day \times Number of prescription days \times Drug price adjustment (a coefficient to adjust for the discrepancy between the standard unit and the dosage unit in the pricing system). Drug costs with or without an Anatomical Therapeutic Chemical major classification 1st level code of

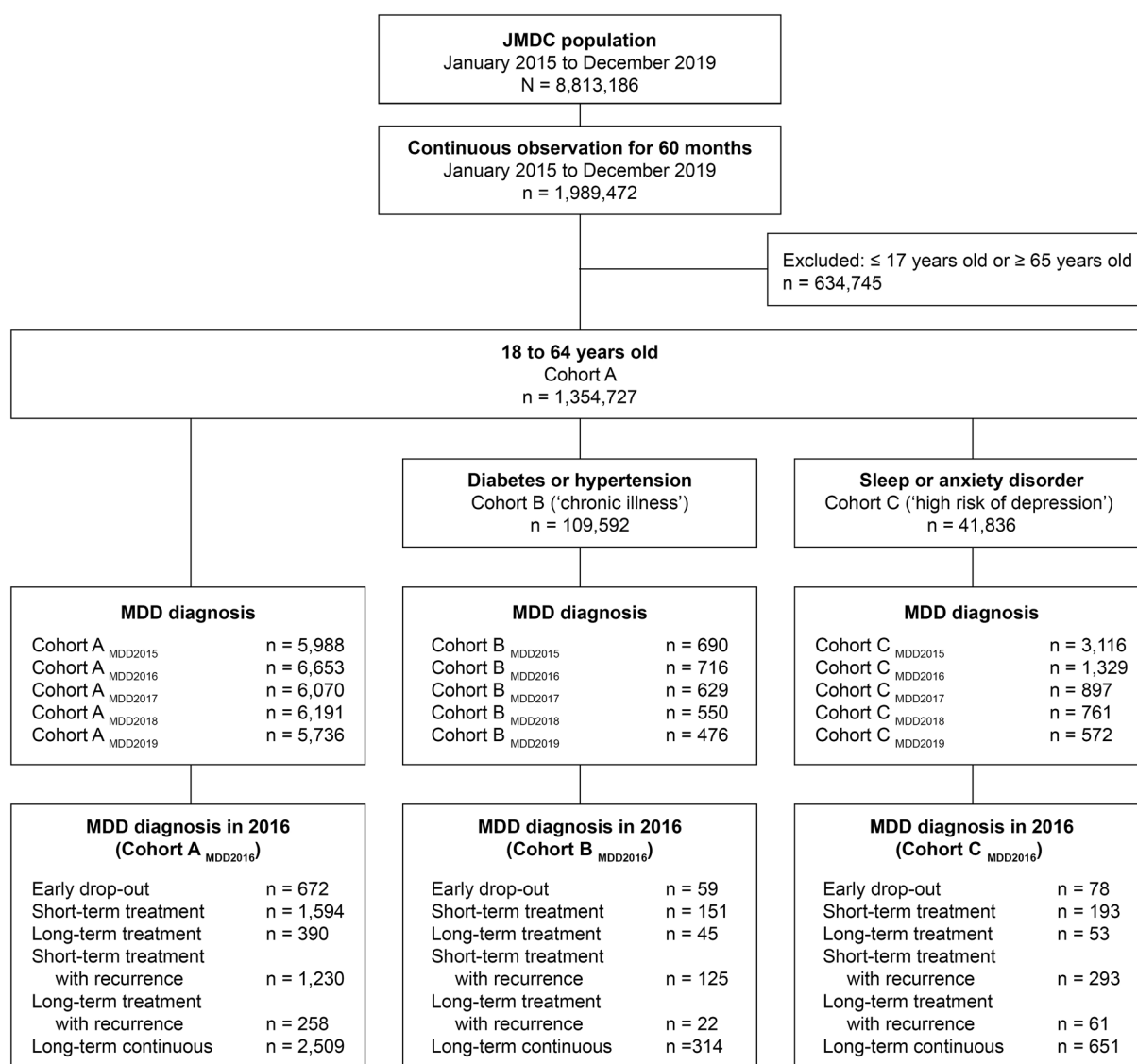


Fig. 1 Study cohort selection. *MDD*, major depressive disorder

Table 1 Treatment duration/MDD recurrence analysis group definitions (MDD onset 2016)

Group Name	First treatment period	MDD recurrence (MDD treatment > 3 months after end of first MDD treatment period)
Early drop-out	2 months	No
Short-term treatment <i>without</i> recurrence	3 to < 12 months	No
Long-term treatment <i>without</i> recurrence	12 to 17 months	No
Short-term treatment with recurrence	< 12 months	Yes
Long-term treatment with recurrence	12 to 17 months	Yes
Long-term continuous treatment	≥ 18 months	Yes and no

MDD major depressive disorder

nervous system drugs (N), which include psycholeptics and psychoanaleptics out of fourteen main anatomical or pharmacological groups, were defined as ‘neuropsychiatric’ or ‘non-neuropsychiatric’, respectively [30].

Medical costs are not normally distributed. Median values were thus used to describe medical costs over time, although means with 95% confidence intervals were also calculated for completeness (see S2 and S3, Electronic Supplementary Material). As this was an exploratory analysis designed to describe overall trends in medical costs before and after MDD onset, across cohorts with different MDD onset years, statistical testing was not performed. All analyses were conducted using SAS 9.4 software (SAS Institute, Cary, NC, USA).

RESULTS

Cohort Identification and Patient Characteristics

A summary of cohort selection for this study is presented in Fig. 1. In total, 1,354,727 individuals aged 18–64 years were enrolled in the study [Cohort A; mean age: $40 \pm$ (SD) 10 years; 39% female], of whom 30,638 (2.3%) had MDD onset during the 2015–2019 observation period (Cohorts $A_{MDD2015-2019}$). Of 109,592 individuals in Cohort A who also met criteria for inclusion in the chronic disease group (Cohort B; mean age: $50 \pm$ 7 years; 26% female), 3061 (2.8%) had an episode of MDD in the year after they met

these criteria (Cohorts $B_{MDD2015-2019}$). Of 41,836 individuals in Cohort A who also met criteria for inclusion in the ‘high risk of depression’ group (Cohort C; mean age: $44 \pm$ 9 years; 43% female), 6675 (16.0%) had an MDD episode in the year after they met these criteria (Cohorts $C_{MDD2015-2019}$).

Medical Costs: MDD Diagnosis With or Without Comorbidity

Cohort A

Median total annual medical costs for Cohort A increased slightly each year but remained under 50,000 yen for all years, and were consistently lower than in the MDD onset subgroups (Fig. 2A). Median total annual medical costs were 170,390–182,120 yen higher in the year of MDD onset in the Cohort A MDD-onset subgroups (Cohorts $A_{MDD2015-2019}$) compared with Cohort A (Fig. 2A). Furthermore, median total annual medical costs increased over time in the Cohort A MDD-onset subgroups, and to a greater degree than in Cohort A, up to and including the year of MDD onset; an increase of 165,130 yen was observed in Cohort $A_{MDD2019}$, which had the longest follow-up period (2015–2019) before MDD onset, compared with an increase of 10,510 yen in Cohort A over the same period (Fig. 2A). Over the whole study period, cumulative median total medical costs (for the year of MDD onset plus the 4 years prior to MDD onset) incurred in Cohort $A_{MDD2019}$ were 285,855 yen higher than in Cohort A.

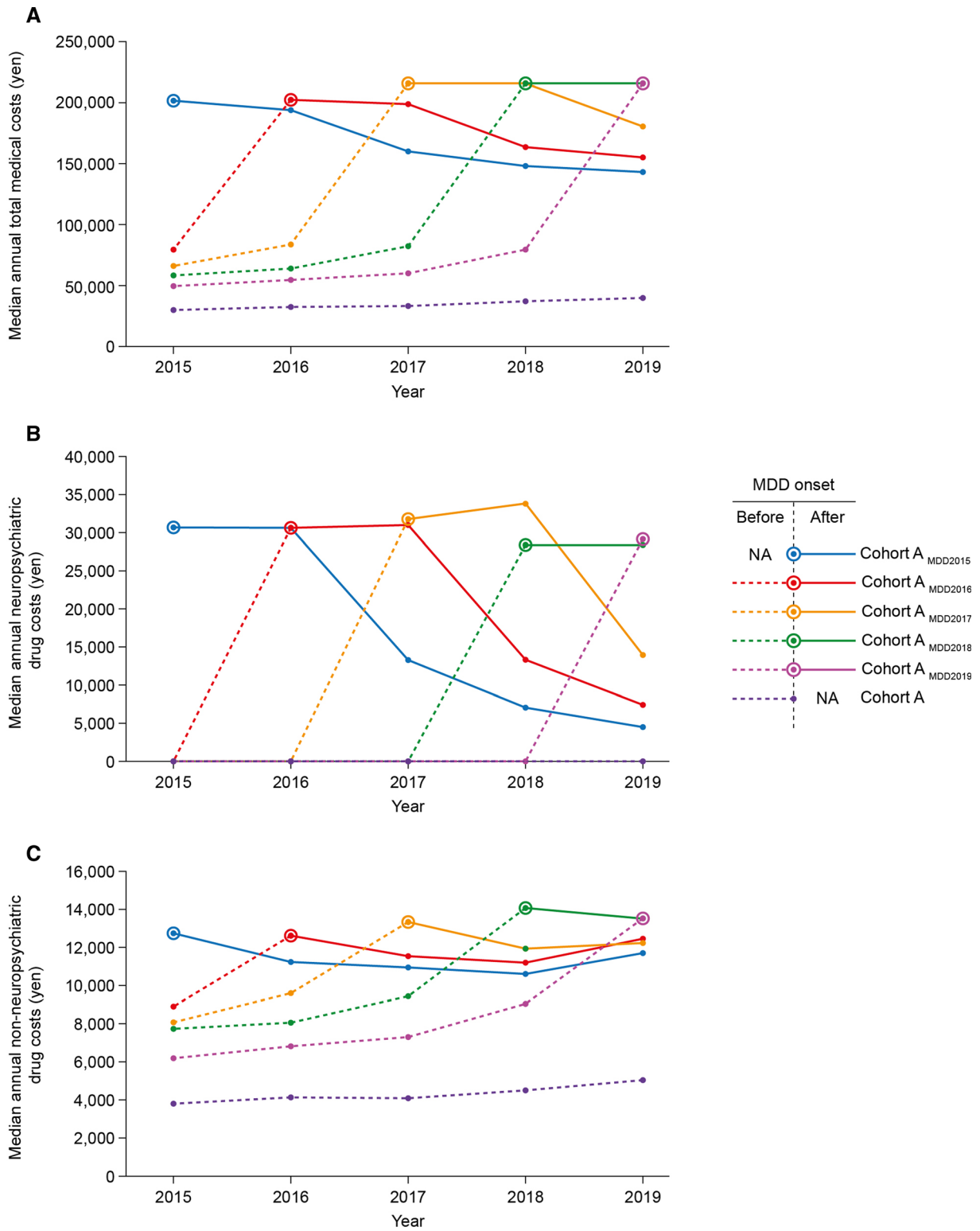


Fig. 2 Median annual **a** total medical costs, **b** neuropsychiatric drug costs, and **c** non-neuropsychiatric drug costs, by year of MDD onset for Cohort A. *MDD* major depressive disorder, *NA* not applicable

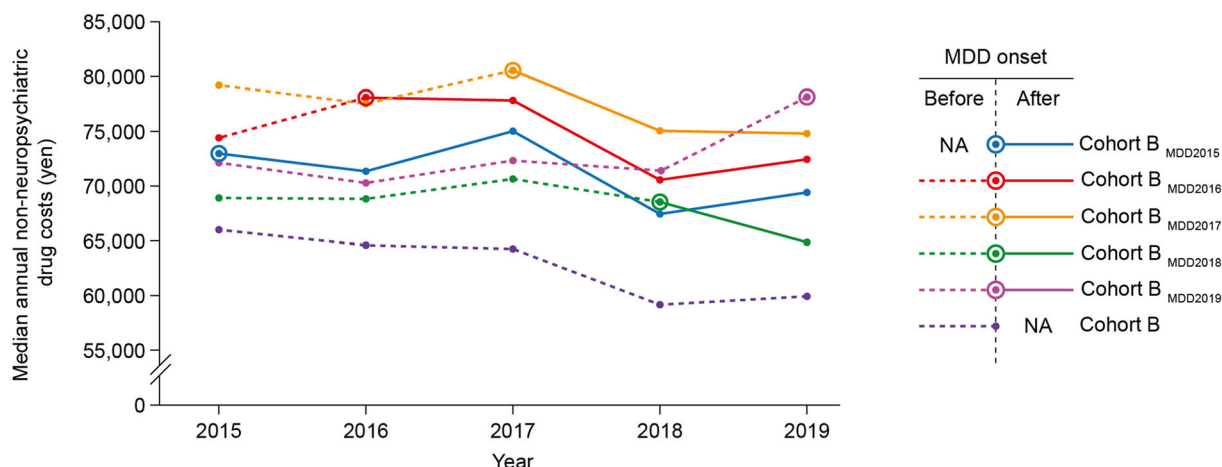


Fig. 3 Median annual non-neuropsychiatric drug costs by year of MDD onset for Cohort B [diabetes or hypertension prior to MDD onset (‘chronic illness’ group)]. *MDD* major depressive disorder, *NA* not applicable

Median total medical costs declined in all MDD-onset subgroups in the years after MDD onset; a decrease of 59,360 yen was observed from 2015 to 2019 in Cohort A_{MDD2015}, which had the longest follow-up after MDD onset (Fig. 2a). The cumulative cost savings in the years after MDD onset in Cohort A_{MDD2015} would be equivalent to 163,250 yen per patient from 2016 to 2019, using the 2015 (MDD onset year) costs as a baseline. This is based on the conservative assumption (given the upward trend in total medical costs up to and including MDD diagnosis) that median total annual medical costs in Cohort A_{MDD2015} would at least have remained stable if MDD were not diagnosed and treated.

The median neuropsychiatric drug cost in Cohort A was 0 yen for all years. In contrast, median neuropsychiatric drug costs in the year of MDD onset were 28,509–31,870 yen in the Cohort A MDD-onset subgroups. These costs decreased from the second year onwards after MDD onset, with a decrease of 26,012 yen observed from 2015 to 2019 in Cohort A_{MDD2015} (Fig. 2b).

Median non-neuropsychiatric drug costs for Cohort A increased slightly each year but remained under 5100 yen, and were consistently lower than in the MDD onset subgroups (Fig. 2c). Median non-neuropsychiatric drug costs in the year of MDD onset were 8480–9586 yen higher in the Cohort A MDD-onset

subgroups than in Cohort A (Fig. 2c). Median non-neuropsychiatric drug costs increased over time in the Cohort A MDD-onset subgroups, and to a greater degree than in Cohort A, up to and including the year of MDD onset; an increase of 7365 yen was observed from 2015 to 2019 in Cohort A_{MDD2019}, compared with an increase of 1246 yen in Cohort A over the same period (Fig. 2C). After MDD onset, median non-neuropsychiatric drug costs decreased before partially rebounding (Fig. 2c).

Total annual medical costs, neuropsychiatric drug costs and non-neuropsychiatric drug costs were also analyzed by sex and age (< 40 years vs. ≥ 40 years). However, no notable differences were observed when stratifying by these variables (data not shown).

Cohorts B and C

In patients with chronic disease onset in the year before MDD onset (Cohorts B_{MDD2015–2019}), median non-neuropsychiatric drug costs were 6828–18,087 yen higher than in Cohort B (Fig. 3). In addition, non-neuropsychiatric drug costs in the Cohort B_{MDD2015–2019} onset subgroups were stable or increased up to and including the year of MDD onset; an increase of 5984 yen was observed in Cohort B_{MDD2019}, which had the longest follow-up (2015 to 2019) before MDD onset (Fig. 3). In contrast, median non-neuropsychiatric drug costs decreased by

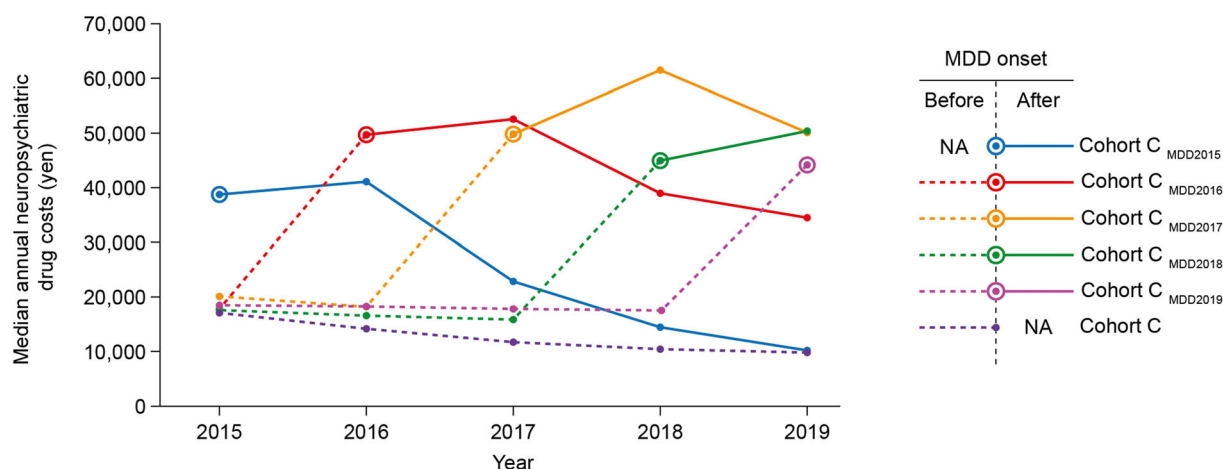


Fig. 4 Median annual neuropsychiatric drug costs by year of MDD onset for Cohort C [sleep or anxiety disorders prior to MDD onset ('high risk of depression' group)]. *MDD* major depressive disorder, *NA* not applicable

6067 yen in Cohort B over the same period, and were lower than in the MDD onset subgroups for all years. After MDD onset, median non-neuropsychiatric drug costs decreased over time (Fig. 3).

In patients at high risk of depression in the year before MDD onset (Cohorts $C_{MDD2015-2019}$), neuropsychiatric drug costs were 21,449–37,878 yen higher than in Cohort C after MDD onset and decreased from the second year after MDD onset (Fig. 4). Neuropsychiatric drug costs in Cohort C were lower than those in the MDD onset subgroups for all years.

Medical Costs: MDD Treatment Length and Relapse Status

Cohort A

In individuals from Cohort A who had MDD onset in 2016 (Cohort $A_{MDD2016}$), median total medical costs decreased after MDD onset regardless of MDD treatment duration/relapse status and were lowest overall in the early drop-out group and the short treatment without an MDD recurrence group (Fig. 5a). Similar patterns were observed for neuropsychiatric drug costs (Fig. 5b). However, median non-neuropsychiatric drug costs increased after MDD onset in both MDD recurrence subgroups (short and long treatment), decreased in both subgroups without an MDD recurrence (short and

long treatment) and in the early drop-out group, and were stable after MDD onset in the long-term continuous treatment subgroup (Fig. 5c).

Cohorts B and C

In patients with chronic disease onset in the year before an MDD onset that occurred in 2016 (Cohort $B_{MDD2016}$), non-neuropsychiatric drug costs decreased after MDD onset in all MDD treatment duration/relapse status subgroups except for those with long treatment without an MDD recurrence (Fig. 6). In patients at high risk of depression in the year before an MDD onset that occurred in 2016 (Cohort $C_{MDD2016}$), non-neuropsychiatric drug costs increased after MDD onset in both subgroups with an MDD recurrence, but decreased in the subgroups without an MDD recurrence, and in the long-term continuous treatment subgroup (Fig. 7). In the early drop-out subgroup, non-neuropsychiatric drug costs increased sharply in the third year after MDD onset (Fig. 7).

DISCUSSION

In this descriptive, epidemiological analysis of real-world data from a Japanese medical insurance claims database (the JMDC), we show that total medical costs and non-neuropsychiatric drug costs in patients with MDD are

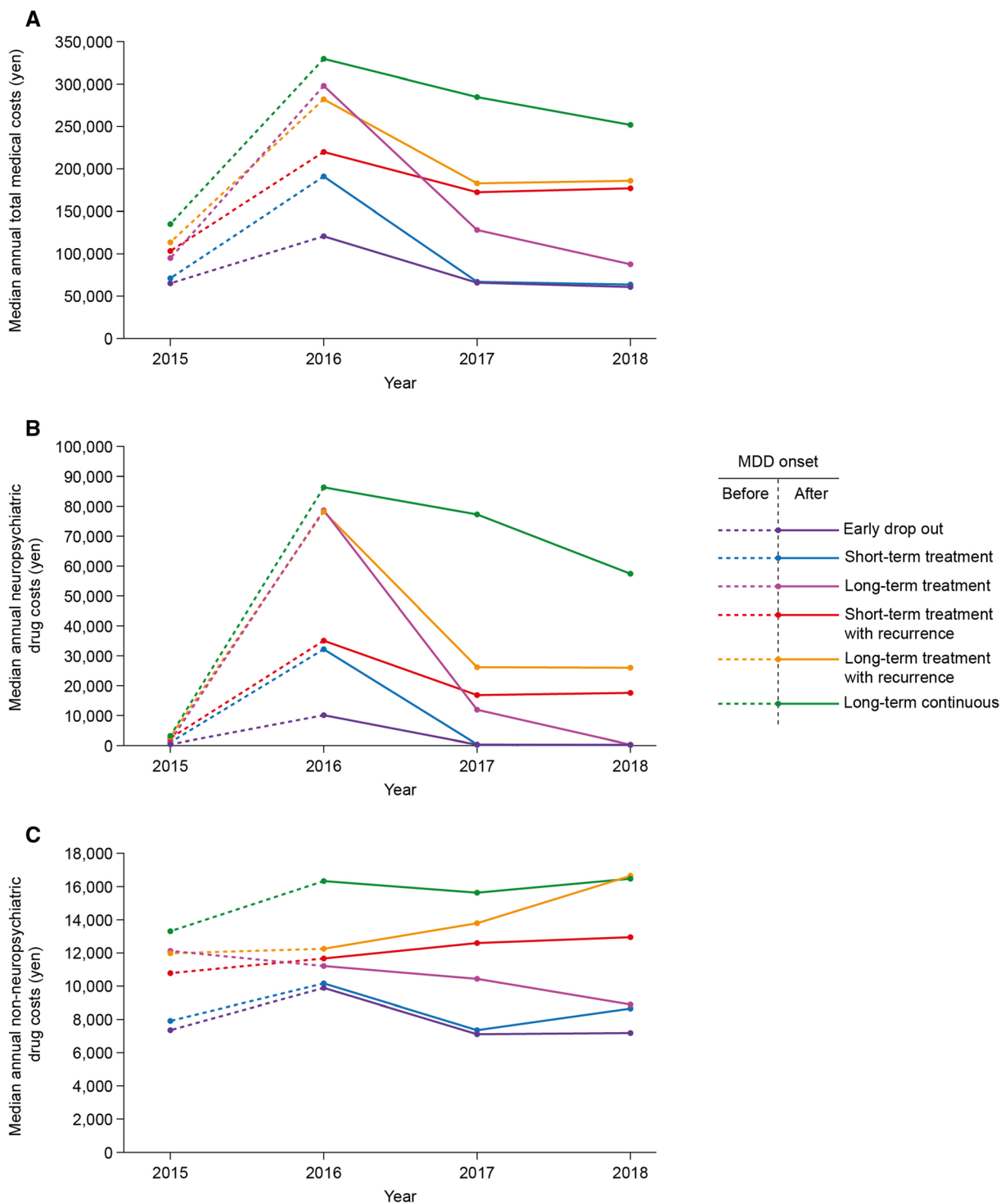


Fig. 5 Median annual **a** total medical costs, **b** neuropsychiatric drug costs, and **c** non-neuropsychiatric drug costs, by MDD treatment duration and recurrence in patients from Cohort A with MDD onset in 2016. *MDD* major depressive disorder

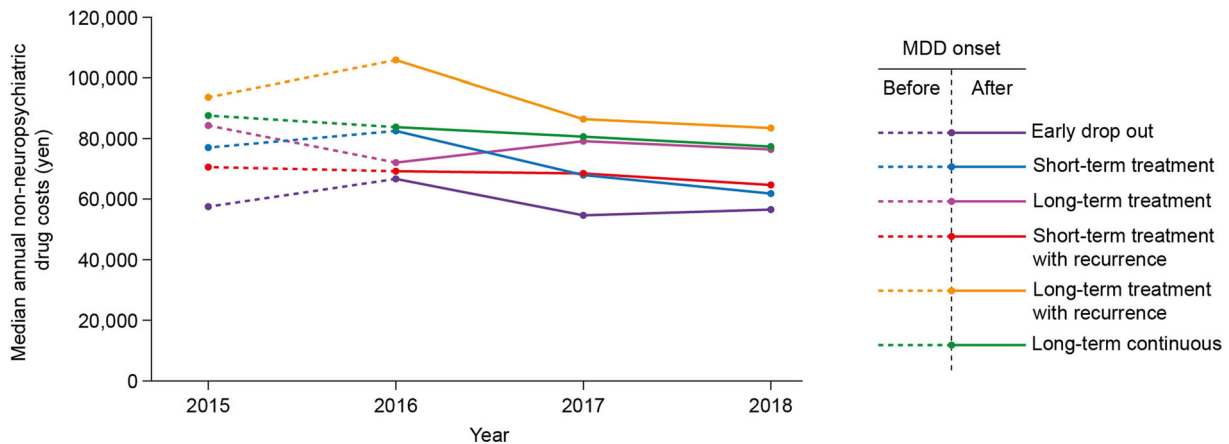


Fig. 6 Median annual non-neuropsychiatric drug costs by MDD treatment duration and recurrence status in patients from Cohort B [diabetes or hypertension prior to MDD

onset ('chronic illness' group)] with MDD onset in 2016. *MDD* major depressive disorder

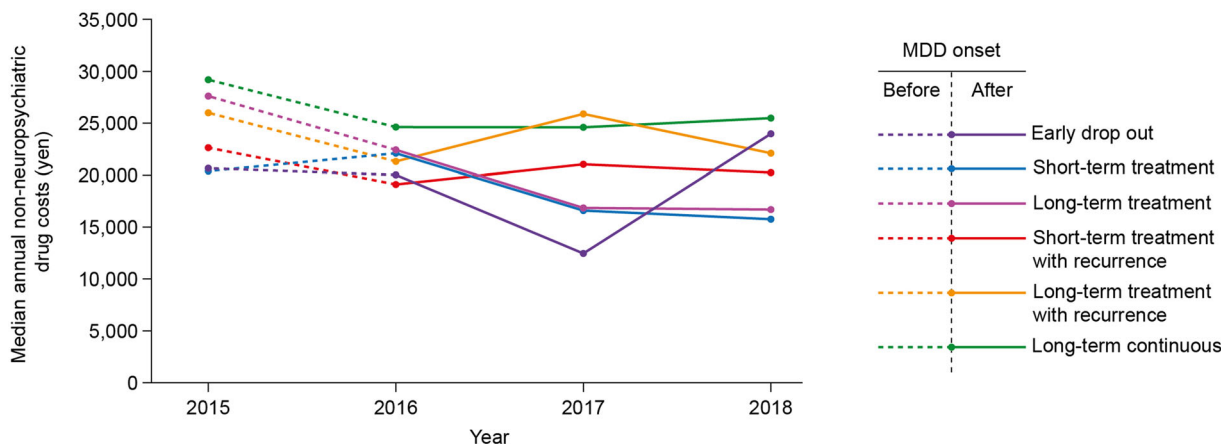


Fig. 7 Median annual non-neuropsychiatric drug costs by MDD treatment duration and recurrence status in patients from Cohort C [sleep or anxiety disorders prior to MDD

onset ('high-risk of depression' group)] with MDD onset in 2016. *MDD* major depressive disorder

substantially higher than in patients without MDD, including in the years before a formal diagnosis is made. Furthermore, these costs increase gradually in the years leading up to MDD onset, and to a greater degree over time, than in patients without MDD. Neuropsychiatric drug costs are also substantially higher in patients with MDD than in those without, but are absent before MDD onset (except in patients with pre-existing sleep or anxiety disorders), consistent with these costs being mainly attributed to MDD treatment.

These trends indicate that patients with MDD may experience declines in both physical and mental health prior to an MDD diagnosis. This may be due to a combination of late diagnosis of MDD in patients already meeting these criteria, and a gradual escalation over time of depression symptoms towards the threshold for MDD in individuals not yet meeting these criteria. Given the bidirectionality of the relationship between MDD and some of its comorbidities, it is possible that this association is explained by the deterioration of existing comorbid physical conditions, leading to

exacerbation of MDD symptoms, and thus concomitant increases in neuropsychiatric and non-neuropsychiatric drug costs. However, total medical costs and non-neuropsychiatric drug costs decreased after MDD onset, arresting upward trends in these expenses that were observed prior to MDD onset, and indicating that these cost reductions were due to MDD treatment. Improvements in MDD symptoms were thus likely responsible for the reduced drug costs observed for physical conditions, indicating some directionality for the association. Neuropsychiatric costs also decreased after MDD onset, most likely because of patients coming off antidepressants over time. This may increase the risk of MDD recurrence in some patients, potentially explaining the partial rebound in non-neuropsychiatric costs that occurred over time after MDD onset in Cohorts A_{MDD2015–2019}. Indeed, we found that non-neuropsychiatric drug costs continued to increase after initial MDD onset in patients who had an MDD recurrence, while decreasing in patients who did not have an MDD recurrence.

The results of our study are consistent with reductions in healthcare costs in patients with comorbid diabetes after MDD treatment observed in at least one other study [19]. However, to our knowledge, the current study is the first to observe a similar relationship in Japanese individuals. At least for diabetes, it is likely that a significant proportion of improved outcomes achieved with MDD treatment is due to altered behaviors. Specifically, patients with diabetes who also have MDD are more likely than those without MDD to have poor self-care (e.g. lower adherence to diabetes medication, reduced physical exercise) and thus poor glycemic control, leading to an increased risk of complications [31]. Similar relationships are likely to exist with other chronic conditions, such as hypertension, that require a high degree of adherence to medication and/or behavioral routines to be effectively controlled. In addition, biological mechanisms, such as increased cortisol levels, oxidative stress and inflammation are likely to predispose patients with MDD to poorer overall physical health [32–35]. It is therefore not surprising that treating symptoms of MDD may improve complications, and

therefore costs, associated with physical conditions.

It is worth noting that the ‘control’ population in our study likely still included many patients with undiagnosed MDD. Indeed, fewer than half of Japanese people with a mood disorder seek medical treatment [2], and many non-psychiatric physicians do not diagnose or treat psychiatric conditions even when present. As such, the differences in medical costs between those diagnosed with MDD and those without an MDD diagnosis are likely an underestimate. This may have also contributed to the relatively low number of newly diagnosed MDD cases identified each year in our study (~ 6000 in a population of 1.345 million).

There are some limitations of this study that must be acknowledged. First, our analysis was exploratory and designed to be descriptive in nature, and thus did not include formal statistical comparisons. Second, sample sizes for some of the subgroups analyzed were low, increasing variability, and the possibility of spurious observations. Nevertheless, our results are consistent with our stated hypothesis and (as described earlier) there is a strong rationale to explain our findings. However, given the scarcity of research on this topic, further validation with additional studies is recommended. In addition, effects of factors (not able to be assessed in the current study) on trends in medical costs, such as early- versus late-onset MDD, or socioeconomic variables, would be worthy of future exploration.

CONCLUSION

This study shows that MDD onset is associated with increased medical costs in Japanese patients, and that these costs are reduced with MDD treatment. In addition to previously demonstrated improvements in workplace functioning, antidepressants also reduce medical costs associated with comorbid physical conditions in Japanese individuals, which may start accumulating well in advance of a formal MDD diagnosis. Early diagnosis and treatment of MDD, and monitoring of potential recurrences (which also incur greater costs), are thus of key

importance in neutralizing the spiraling healthcare expenses that may eventuate with MDD. In addition to pharmacological treatment, ways of minimizing factors that predispose individuals to MDD in the workplace, such as long work hours and low job satisfaction [8], should be explored, as well as education to increase awareness of the signs and impacts of MDD. These may be useful strategies for improving the efficiency of healthcare delivery in Japan.

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Authors' Contributions. Yoshinori Cho, Izumi Mishiro and Shinji Fujimoto were involved in the planning and design of the study. Izumi Mishiro and Tadashi Nakajima contributed to and/or supervised the acquisition and analysis of the data. All authors contributed to the interpretation of the data analysis, revised the manuscript for important intellectual content, and approved the final version for submission.

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Takeda Pharmaceuticals, Kyowa, Dainippon-Sumitomo, Lundbeck Japan, Viartis, Shionogi, Janssen Pharmaceutical, Tanabe-Mitsubishi, Astellas, Otsuka and Yoshitomiya and personnel fees as an occupational physician from Shionogi.

Compliance with Ethics Guidelines. The study was approved by the Ethics Review Committee of the Research Institute of Healthcare Data Science (Tokyo, Japan, reference number RI2019004). Only anonymized information (obtained with permission from JMDC Inc.) was accessible from the database; therefore, in accordance with the Ethical Guidelines for Medical and Health Research Involving Human Subjects in Japan, informed consent was not required.

Data Availability. Individual deidentified participant data and additional study-related documents will not be available.

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