BMC Public Health

https://doi.org/10.1186/s12889-026-27382-5

Article in Press

The social and healthcare burden of major depressive disorder in adults: an Italian observational cohort study

Received: 18 March 2025

Accepted: 8 April 2026

Published online: 21 May 2026

Cite this article as: Cortesi P.A., Antonazzo I.C., Fornari A. *et al.* The social and healthcare burden of major depressive disorder in adults: an Italian observational cohort study. *BMC Public Health* (2026). https://doi.org/10.1186/s12889-026-27382-5

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Title: The social and healthcare burden of major depressive disorder in adults: An Italian observational cohort study.

Running title: The burden of major depressive disorders in Italy

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Abstract

Background: Major Depressive Disorder (MDD) is a leading cause of disability worldwide, with significant economic and social burden. However, studies assessing the overall socio-economic burden (direct, indirect and intangible costs) are scarce. This study aims to evaluate the socioeconomic burden imposed by MDD on patients referred to specialist medical centers in Italy.

Methods: An observational, multicenter, longitudinal cost of illness study was conducted on patients aged 18-65 years with a diagnosis of MDD starting antidepressant therapy. Healthcare resources consumption and productivity loss were collected over 1-year follow-up to estimate per-patients MDD costs. Depressive symptoms were assessed with various clinical scales. Health Related Quality of Life (HRQoL) was assessed with the EQ-5D-5L.

Results: MDD severity decreased during the observational period, as reported by all clinical scales, with a notable improvement in HRQoL scores. The main costs associated with MDD patients were indirect costs, €386.3 per patient-month at baseline, declining to €179.9 in the last 6 months. Direct medical costs peaked in the first 3 months (€155.9 per patient-month), compared to baseline (€55,09 per patient-month), then decreased. Costs were significantly associated with and increased with the number of depressive episodes (129.71;7.59-251.83) and the augmentation of Quick Inventory of Depressive Symptomatology-Self Rated (QIDS-SR16) score (7.92;2.02-13.82).

Conclusion: Our results suggest that MDD is a mental health issue with socio-economic burden that varies with symptoms severity. Indirect costs represent the main expense for MDD patients. These findings highlight the complexity and burden of MDD, emphasizing the importance of prioritizing depressive disorders in public health.

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Keywords: Costs, Major Depressive Disorder, Health-Related Quality of Life, Mental Health, Burden of Disease, Longitudinal Studies

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Introduction

Major depressive disorder (MDD) is a common psychiatric condition characterized by functional and interpersonal deficits manifested through cognitive, behavioral, somatic and affective impairments, leading to functional and interpersonal deficits.[1] Depressive episodes can occur at any age, with higher prevalence in women than in men.[2] Depression markedly reduces quality of life by affecting daily activities, work routine, and social interaction.[3] The associated disability and the costs (i.e., direct and indirect costs) make MDD a significant public health issue.[4,5] Depression is an important public health concern due to its bidirectional relationship with other comorbidities, such as cardiovascular, neurological, metabolic, and psychiatric diseases, among others.[6,7] The coexistence of depression with other medical conditions poses significant clinical challenges in patients management, owing to potential impairment of the therapeutic alliance, the occurrence of drug-drug interactions, and an increased risk of adverse events.[6,8] Previous studies suggested that the presence of depression alongside other comorbidities is associated with significantly greater presenteeism and absenteeism compared with depression alone.[9–11] Patients affected by both depression and other comorbidities also experienced a lower quality of life.[12,13] All these aspects contribute to increased complexity and potentially higher healthcare costs related to patients management. In this context, treatment adherence represents an important driver of costs among patients with depression.[14–16] Non-adherence to treatment may be associated with an increased risk of disease relapse and recurrence, higher rates of hospitalization and emergency department visits, and increases disease severity, all of which contribute to increase both healthcare and non-healthcare costs.[14–16] The Global Burden of Disease identified depression and anxiety disorders as two of the most disabling mental disorders, ranking among the top 25 leading causes of global burden worldwide in 2019.[17] It has been estimated that over 350 million people suffer from depression worldwide, a number steadily increasing each year.[17] Despite compelling evidence supporting interventions aimed at reducing MDD's impact, neither its global burden nor its prevalence has declined since 1990.[18]

The COVID-19 pandemic in 2020, along with subsequent SARS-CoV-2 containment measures, raised concerns regarding their direct and long-term

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psychological, economic, and societal effects on mental health.[19] Social restriction, lockdowns, school and business closures, job losses, economic downturns, and shifting government priorities to control COVID-19 outbreaks may have negatively affected mental health, leading to new cases of depression and anxiety disorders as well as worsening of symptoms in individuals with pre-existing conditions.[20]

It has been estimated that in the United States, the cost of depression has risen significantly over time, from 83.1 billion dollars in 2000 to 173.2 billion in 2005, 210.5 billion in 2010, and 326.2 billion in 2018.[21–23] The 2018 cost estimate includes 35% for direct treatment costs, 4% for suicide-related costs, and 61% for indirect workplace costs.[23] Tanner and colleagues estimated an annual excess cost of $7,232 in healthcare and $1,012 in social services among individuals with depression compared with the general population, corresponding to approximately $12 million per year when extrapolated to the Canadian population.[24] Similar findings were reported by Chiu and colleagues, who estimated an excess cost of $210 million for individuals with MDD compared with control subjects.[25] In a systematic review, König and colleagues highlighted significantly higher excess costs associated with depression, encompassing both direct and indirect components. Their findings indicated increased costs of depression management across all age groups (adults, older adults, and adolescents), as well as among individuals with comorbidities.[26] Another review by Cicchetti reported that, for MDD, direct costs ranged from €508 to €24,069, while indirect costs ranged from €1,963 to €27,364, depending on national jurisdiction.[27] Elevated costs of MDD management have also been documented in Europe. A study conducted in Switzerland by Tomonaga estimated total annual direct and indirect costs of approximately €8.3 billion euros per year, while costs in Germany were estimated at €15.6 billion in Germany.[28,29] In Italy, costs associated with MDD, including treatment-resistant depression, reaching up to €2,654 per patient in direct costs, €615 per patient in out-of-pocket expenses, and €7,140 per patient in social cost.[30]

Considering the increasing global prevalence of depression, it can be supposed that the economic burden of MDD will continue to rise in the coming years, making it a condition with substantial clinical and economic demands.

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Therefore, economic evaluations of the MDD burden are essential to provide evidence-based insights for clinicians and policymakers, thereby supporting the development of public health strategies aimed at mitigating its impact on patients, caregivers and society. Therefore, this study aims to assess the associated healthcare costs, productivity loss, and Health related quality of life (HRQoL) impairment in adults diagnosed with MDD referred to specialist medical centers in Italy.

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Materials and Methods

Study design and data source

We conducted an observational, multicenter, longitudinal cost-of-illness study to evaluate the socio-economic burden of MDD in adults. The study was carried out at two centers: Department of Neuroscience and Mental Health, Hospital Fatebenefratelli Sacco in Milan; and the Department of Mental Health (DSM) and complex structure of Psychiatry of Hospital San Gerardo in Monza.

The study was conducted in accordance with the Declaration of Helsinki, and the protocol and informed consent form were approved by Institutional Ethics Committees of Fatebenefratelli (number/ID: 549_2016bis; Date: 11/10/2026) and San Gerardo hospital (number/ID: Carico Socio-Sanitario Depressione Maggiore; Date: 15/12/2016). The study protocol agrees with the principles established by the 18th World Medical Assembly.[31]

Inclusion and exclusion criteria

Adults aged 18-65 years old with a diagnosis of MDD according to the Diagnostic and Statistical Manual of Mental Disorders, 5th ed. (DSM-5),[32] who started a new antidepressant therapy (new users or switchers) and had a clinical visit between January 1st, 2016 and December 31st, 2019, were enrolled in the study. Disease classification was based on the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM). Patients who were unable to understand or sign the informed consent form were excluded from the study.

Participants were followed-up for 12 months after enrolment, with scheduled follow-up visit at 3-, 6- and 12 months. Data were collected at each visit.

Data collection

Demographic, clinical, and socio-economic data were collected by using a specifically designed case report form (CRF). CRF data was linked to the Lombardy Region administrative database “Psiche web” to estimate the economic burden of the disease.[33–36]

During the enrollment visit, socio-demographic characteristics (i.e., sex, age, educational level, working status), medical history (i.e., time from symptoms’ onset to the visit, disease duration, comorbidities, use of antidepressants and

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other medications), loss of productivity, healthcare resources utilization and non-healthcare costs (i.e., home nurse) related to the previous 3 months were collected.

Information on depression and depressive symptoms was assessed using the following scales: the Clinical Global Impression - Severity (CGI-S) scale; this scale assesses the symptoms severity within 7 days before the clinical assessment (score range from 1-no symptoms to 7-most severe symptoms);[37] the Hamilton Rating Scale for Depression (HRSD) to assess depressive symptoms in adults (a score ≤7 indicates absence of disease, 8-7 mild disease, 18-24 moderate disease and ≥25 severe depression) (Hamilton 1960); and 16-article version of the Quick Inventory of Depressive Symptomatology-Self Rated (QIDS-SR16), generally used to assess depressive symptoms severity and frequency in the period prior, during and after treatment.[38]

Information on patient health-related quality of life was assessed using the self-assessed, health-related, quality of life questionnaire (EQ-5D-5L).[39] This questionnaire encompasses of the EQ-5D descriptive system and a Visual Analogue Scale (EQ-VAS). The first part of the questionnaire has five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each of the dimension has five response levels: no problems, slight problems, moderate problems, severe problems, and unable to/extreme problems. The second part (EQ-VAS) is a standard, vertical, 20 cm visual scale which ranges from 100 (the best health state one can imagine) to 0 (the worst health one can imagine).[38,40]

During the follow-up visits, results of clinical scales, data on antidepressant therapies, HRQoL, productivity loss, medical and non-medical resources consumption, and productivity loss associated with MDD were collected.

Direct and indirect costs

The study was conducted adopting the societal perspective, encompassing both direct costs incurred by the National Health Service (NHS) and all costs (direct and indirect) incurred by patients and caregivers. Healthcare resources consumption data were collected using an ad hoc CRF and the administrative database “Psiche-web”. Treatment information at baseline and during follow-up was obtained through the CRF. Specifically, the CRF included data on the

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prescribed drug/brand name and therapeutic regimen. Data on various healthcare resources (i.e., general practitioner visits, specialist visits, psychotherapy, examinations, diagnostic tests, hospital admissions due to disease or residential care admissions), and other resources (i.e., nurse home visits, transportation and travel-related service) were retrieved form the "Psyche-web" database. Treatment costs were estimated based on the ex-factory price for the Italian NHS.[34] The cost associated to hospitalization (it included costs for psychiatric conditions based on the diagnosis-related group), medical visits, and specialist visits were calculated by multiplying the number of healthcare resources utilized by patients with the respective unit costs per resource as reported in the Italian tariff.[33] The costs associated with psychotherapy were calculated by multiplying the number of psychotherapy sessions by unit cost for the Italian NHS.[35,36] The costs related to residential care admissions were estimated by multiplying the number of individuals who use the service, by the number of days of utilization and the unit cost per day.[35] Costs associated with productivity loss due to MDD for patients and caregivers were quantified by using the Human Capital Approach method. Specifically, indirect costs, associated with productivity days-lost, were calculated by multiplying the number of work days lost due to the disease by the average wage (90€ per day) reported by the Italian general population statistics-ISTAT.[41]

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Statistical analysis

Demographic, clinical and quality of life data were summarized using frequency and percentage for categorical variables and mean and standard deviation (SD)/95% confidence intervals (95%CI) or median and interquartile range (IQR) for continuous variables.

The healthcare resources utilization was summarized as frequency, mean and median across the different time-points: enrolment (baseline), visit 1 (after 3 months), visit 2 (after 6 months) and visit 3 (after 12 months). Difference across the time-points were assessed by using non-parametric Friedman test (p-value <0.005).

Direct and indirect costs were reported across the different time points as mean €/patient-month. Indirect costs were reported as mean days of productivity loss

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per patient-month or caregiver-month. The analysis was conducted on the entire cohort and stratified according to treatment adherence (switchers Vs non-switchers).

The association between demographic and clinical variables at baseline and costs were assessed by using univariate and multivariate regression models with a stepwise selection approach, therefore variables that showed a significant association in the univariate model were included in the multivariate model. In the model, demographic and clinical characteristics as well as quality of life scales at baseline were used as predictive variables. All the analyses were performed by using STATA version 13.1 software.

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Results

Sample description

A total of 137 participants were enrolled. Over the study period, 124 patients completed visit 1, 116 visit2, and 103 visit 3. Among the 137 patients, 24 patients (25%) were lost during follow-up.

Demographic and clinical characteristics as well as HRQoL data at baseline, were presented in tables 1 and 2, supplementary material. Most patients were female (64.96%), with a mean age of 47.96 (SD: 11.56) years. 67.15% of the subjects were employed, and 54.01% were married or in common-law partnership. Smoking was reported by 31.39% of the subjects, with an average of 13 cigarettes per day. Additionally, 27.74% consumed alcohol, and 20.44% reported cannabis use.

At baseline, 64.23% of patients had recurrent MDD episodes. Among the investigated mental comorbidities, 55.47% had anxiety disorders, 27.01% had sleep disorders, and 13.14% personality disorders. The majority of patients (89.78%) had no history of suicide attempts, while 8.03% had one prior attempt. Regarding comorbidities, 23.36% had metabolic diseases, 22.63% had cardiovascular diseases, 8.03% had gastrointestinal diseases, and fewer than 5% had other conditions (see supplementary material, Table 2). Almost all patients reported a CGI-scale score between 3 and 5, a mean Hamilton score of 19.64, and a mean QIDS-SR16 score of 18.23. The analysis of patients' quality of life showed a mean EQ-5D utility score of 0.78 (0.11) and a mean VAS score of 43.72 (21.12) (supplementary material, Table 2).

As shown in figure 1, patients reported decreased CGI-S and Hamilton score compared to baseline during the follow-up period. Specifically, the HRDS score decreased from 19.64 (18.37;20.91) at baseline visit to 8.68 (6.97;10.39) at the last follow-up visit ($p < 0.0001$) (Figure 1). Similarly, the QIDS-R means changed from 18.23 (16.88;19.57) during the first visit to 8.04 (6.51;9.57) during the last visit ($p<0.0001$) (Figure 1). Conversely, the EQ-5D VAS and EQ-5D utility score showed an increasing trend during the study period (Figure 1). The mean score of EQ-5D utility increased from 0.78 (0.76;0.80) at baseline to 0.89 (0.87;0.91) at the end of follow-up ($p<0.0001$). A similar trend was observed for EQ-5D VAS score (supplementary material, figure 1). Patients experienced an improvement

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in all assessed domains of the EQ-5D utility scale during follow-up, as reported in figure 2 in the supplementary material.

Health care resource consumption and loss of productivity/usual daily activities

During the observation period, patients were mainly treated with SSRIs, including sertraline, escitalopram, and citalopram. Over follow-up visits, therapy switches occurred in 13.7%, 10.3% and 8.7% of treated individuals at visit 1, 2, and 3, respectively. In the same time frame, 64.5%-70.9% of patients required dose adjustment across these visits. Dose modifications or therapy switches were prompted by the onset of adverse events (8.8% at visit 1; 13.8% at visit 2; 63.6% at visit 3) or treatment inefficacy (88.2 at visit 1; 69% at visit 2; 9.1% at visit 3).

As indicated in table 1, the follow-up period witnessed a decline in the number of patients attending GPs or specialist visits (from 21.17% at baseline to 3.0% during visit 3). Conversely, the number of patients undergoing psychotherapy sessions increased during the first (41.94%) and second (38.79%) and third (38.83%) visits of follow-up compared to the baseline (31.39%).

The number of hospitalizations and the utilization of other healthcare resources (i.e., meeting/discussion with their family members, individual intervention on basic ability, drug administration) showed an increase during the follow-up, aligned with the percentage of patients utilizing these resources (Table 1). The number of hospitalizations/Day hospital rose from enrollment (3.65%) to the first visit (11.29%) and subsequently decreased during follow-up.

In the study period, there was a reduction in the number of patients experiencing lost workdays or being unable to perform daily activities. Specifically, the percentage of patients losing at least one day of productivity decreased from 51.91% to 18.99% from baseline to the end of follow-up. The overall cohort’s productivity loss decreased from 4.73 days/patient-month to 1.34 days/patient-months. Among patients reporting productivity loss during follow-up, it was 13.49 at baseline and 13.80 at the end of follow-up, with a peak of 21.28 at visit 2. Detailed information on productivity loss (i.e., presenteeism) was reported in table 3 in the supplementary material. Regarding the ability to perform daily activities, a decrease was observed in the percentage of patients

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experiencing routine activities impairment, from 57.78% to 24.27%, and the mean number of days/patient-month decreased from 8.88 to 2.31 (Table 1). A similar pattern was observed for caregivers during follow-up.

Costs

In the study period, the overall costs of MDD patients decreased from € 441,37 at baseline to € 218,36 at visit 3 (table 2).

Among the various components contributing to the economic burden of patients with MDD, indirect costs were the main cost driver. The indirect costs accounted for 87% of the overall cost at baseline, 63% at visit 1, 61% at visit 2 and 50% at visit 3. The indirect costs reported a reduction from € 386.28 per patient-month at baseline to € 109.48 at the end of follow-up.

Among direct costs, those related to residential care, diagnostic tests, and treatment emerged as the predominant components. The cost related to residential care constituted 4% of the overall direct costs at baseline, increasing to 26% at the end of follow-up. Diagnostic test-related costs constituted 42.66% of the overall direct costs per patient at baseline, diminishing to 17.17% at the end of follow-up. Similar trends were observed for direct costs linked to clinical visits and psychotherapy. Treatment costs showed marginal increase from 13.94% after 3 months of follow-up to 19.07% at the end of the follow-up. As reported in table 4 in the supplementary material, at visits 1 and 2 the treatment costs were significantly higher in switcher patients compared with non-switchers (p-value <0.05). From visits 2, switchers reported higher total costs than non-switch patients (342€ Vs 280€ at visit 3 and 297€ Vs 181€ at visit 3) (table 4 supplementary material).

Table 3 showed factors associated with the economic burden of MDD. In the model, both the number of depressive episodes (129.71; 7.59-251.83) and the QIDS-SR16 score (7.92; 2.02-13.82) were significantly associated with increased costs in the study population.

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Discussion

The rising costs of health systems around the world have emerged as a pivotal concern for health managers and policymakers, primarily attributable to the surging prevalence of non-communicable and chronic diseases such as MDD. The financial burden associated with MDD, encompassing both medical and non-medical costs, has experienced rapid growth in recent years, as highlighted by various studies.[21–23,42] This study aimed to evaluate the burden imposed by MDD on patients referred to specialist medical centers in Italy and to quantify the associated costs.

Our study delineated notable heterogeneity in the utilization and pattern of therapeutic approaches during follow-up. Among prominently prescribed drugs were SSRIs such as sertraline, escitalopram and citalopram. Although the drug choices was consistent with current guideline recommendations,[43] the observed alterations in the treatment and dosage adjustment underscore the challenges with the existing therapeutic options.[20] The management of depression remains a challenge for healthcare providers and society at large.[44] A previous study investigated the economic burden associated with unsuccessful antidepressant therapy during the first 12 months after treatment initiation reported significantly higher costs among patients requiring additional lines of pharmacotherapy compared with those who successfully completing treatment with a single line of therapy.[45] The integration of a multidisciplinary approach encompassing pharmacotherapy, psychotherapy, and other interventions may help alleviate symptoms and, consequently, reduce the overall disease burden for patients, caregiver and society.

Findings of this study showed that adults with MDD impose a sizable economic burden on society, amounting to approximately 1,400 €/year per patient. This estimate is consistent with findings from other European countries, where the total costs per patient range from 1,171€ to 16,581€.[46] Over the one-year follow-up, up to 70% of total costs were attributable to indirect costs; with a maximum of 86% at baseline. The limited evidence available in Italy regarding the economic burden of depression in the general population, combined with methodological variability among studies, complicates direct result comparisons.[47,48] Nevertheless, our results corroborate previous findings from other European studies showing that approximately 81.6% of total costs are

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attributable to indirect costs.[49] Remarkably, the direct costs associated with treating MDD accounted for 30%, with therapy-related costs comprising less than 20%. These findings align with previous literature advocating for integrative and collaborative approaches to mitigate the economic burden on adults with MDD.[50–52] A recent U.S. study revealed that for every dollar spent on direct costs of MDD, an additional 2.30 dollars were expended on MDD-related indirect costs, and another 5.61 dollars were spent on direct and indirect comorbidity costs.[23]

Key drivers of this economic burden included the number of depressive episodes and QIDS-SR16 and Hamilton score. Consistent with our study, a prior study showed that depression correlates with low quality of life in term of subjective health, mood, relationship with friends and family, financial satisfaction, and overall life satisfaction. These factors contribute to an increased burden of disease, necessitating significant healthcare resource utilization and subsequently escalating costs.[53–55]

Findings suggest a more severe clinical condition of patients at baseline compared to the subsequent follow-up period. For instance, at baseline, patients exhibited a higher prevalence of treatment switch, lower quality of life, impairment in routine activities, and more than half of patients reported at least one day of productivity loss, compared to the end of follow-up, leading to a higher cost at baseline compared with the end of follow-up (441€ Vs 218€). The findings indicate a simultaneously decrease in both the number of therapy switches and costs, especially indirect costs, during follow-up, suggesting that patient's engagement during follow-up, resulting in improved therapy compliance and consequently reduced impact of the disease on daily activities. In this context, previous studies have shown that treatment adherence and resistance influence the likelihood of work leave for patients with MDD.[56–58] Specifically, low treatment adherence or resistance increases productivity loss in MDD patients:[56–58] therefore, it is plausible to speculate, that antidepressant treatments, particularly during the acute phase and relapses, improve quality of life and work productivity, ultimately leading to a reduction in overall costs.[56–58] In fact, from a clinical perspective, both pharmacological and psychotherapeutic interventions are crucial in alleviating clinical symptoms of depression and addressing psychological aspects such as negative ideation and

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self-defeating behaviors in MDD patients, leading to improve quality of life and reduced productivity loss.[56]

Results also highlighted a positive correlation between quality-of-life scale (i.e., QIDS-SR-16) and costs, with lower quality of life being associated with higher patient's costs. In our study, we observed an improvement in patients' quality of life and a reduction in costs during follow-up, as evidenced by various scales. The impact of patients'quality of life extends to their social relationship and work productivity. Thus, it is plausible that patients with lower quality of life are likely to consume more healthcare resources and experience greater productivity losses (i.e., absenteeism and presenteeism), leading to higher overall costs associated with MDD.[56] This supports the hypothesis that enhanced patient engagement through both pharmacological and non-pharmacological interventions may lead to improvements in quality of life and subsequent reduction in disease-associated costs.[56,59]

The study has limitations that should be considered. First, the analysis did not stratify the patients due to sample size. In fact, in the study, no stratified analyses were performed apart from the descriptive comparison between patients who switched therapy and those who did not. Furthermore, the study focused on costs associated with patients' management in two centers during the first year of follow-up this might limit generatability of findings. To overcome these limitations, future studies with greater sample size and longer follow-up are needed. Considering the nature of the study, potential selection bias cannot be completely ruled out, as participants who chose to engage in the study may exhibit greater compliance with therapy, potentially impacting the generalizability of results to the broader MDD population. Additionally, the inclusion of patients more predisposed to compliance with physician's prescriptions may result in an underestimation of costs. Furthermore, the study included both new antidepressant users and patients who switched treatment. Although the aim was to estimate the economic burden of MDD, the exclusion of prevalent users may have led to an underestimation of the overall burden of MDD. Future studies are warranted to further evaluate differences in MDD between prevalent and incident users, as well as between patients initiating antidepressant therapy for the first time and those who switch treatment. In addition, the follow-up duration was limited to 1 year, offering new insights into

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the clinical and economic impacts of MDD. However, future study with extended follow-up period could provide estimations of medium and longer disease impact. The study included data from two specialist centers, which may limit the generalizability of the results, as differences in disease management across other centers/setting could lead to different cost estimates. Furthermore, the exclusive focus on specialist centers may have resulted in a potential underestimation of costs; it is plausible that inclusion of patients treated in private settings would yield even higher estimates. However, Italy operates a tax-based healthcare system, making it likely that the majority of patients receive care within publicly reimbursed facilities. Additionally, only individuals aged 18–65 years were included, which may further limit the generalizability of the findings to the entire population. However, it should be noted that including patients older than 65 years might have introduced bias in cost estimates due to potential nursing home residence and unavailable data on patient management during residency. For this reason, future studies without age restrictions should be conducted to estimate MDD-related costs across working-age adults, older individuals, and younger populations, while also accounting for caregiver burden.

Multicenter studies involving a larger number of sites from both public and private settings are warranted to generate additional evidence (such as the impact of suicide attempts on costs, the analysis of costs across subpopulations, and costs across different treatment settings) in order to inform stakeholders.

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Conclusion

During the study period, the estimated burden of depression in Italy was approximately 1400€ per patients. The predominant factors of these costs were attributed to indirect costs (i.e., workdays lost). Over the observed period, there was a reduction in indirect costs per treated individual, whereas direct costs exhibited a marginal increase. These findings suggest that both pharmacological and non-pharmacological therapies may exert a positive influence on the psychiatric burden of disease, consequently mitigating factors that adversely affect indirect costs. This study underscores the importance of managing not only the acute phase of MDD but also the entire period of

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symptoms ‘resolution. Given the escalating trend in the incidence of MDD and considering the social and economic burden associated with depression, the study emphasizes the necessity to designate MDD as public-health priority. In this context, future studies are warranted to evaluate the long-term clinical and economic impact of different pharmacological and non-pharmacological treatments across the different levels of disease severity.

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Author contributions

Conceptualization, P.A.C., P.C., and L.G.M; Methodology: P.A.C., and P.C; data analysis: A.F., and P.C; writing—original draft preparation: I.C.A., and P.A.C; writing—review and editing: all authors. All authors have read and agreed to the published version of the manuscript

Conflict of interest

P.A.C, I.C.A, A.F, P.C, AF, A.P, M.B, V.V, F.C, V.S, P.R, C.Z, G.C, G.C, G.C, M.C, C, M have no conflicts of interest.

L.G.M. reports receiving grants from Bayer, Daiiki-Sankyo, and Boehringer Ingelheim outside the
submitted work and speaker fees from Pfizer and Bayer.

Data Availability Statement

The data used in the preparation of this article are available upon reasonable request.

Ethics Statement and Consent to Participate declarations

The study was conducted in accordance with the Declaration of Helsinki, and the protocol and informed consent form were approved by Institutional Ethics Committees of Fatebenefratelli (number/ID: 549_2016bis; Date: 11/10/2026) and San Gerardo hospital (number/ID: Carico Socio-Sanitario Depressione Maggiore; Date: 15/12/2016). All participants provided written informed consent at enrollment after receiving comprehensive information regarding the study objectives and their right to withdraw at any time without any consequences.

Consent to Publish declaration

Not applicable.

Clinical trial number

Not applicable

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Funding

This work has been supported by an unrestricted research grant from Angelini (Rome, Italy). The funding source had no involvement in the data collection, data analysis, or data interpretation.

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Key points

- Major Depressive Disorder (MDD) is a leading cause of disabilities worldwide, with significant economic and social impacts.
- During the study period, MDD severity decreased as reported by clinical scales and an improvement of HRQoL was observed.
- Economic burden was driven by indirect costs. As regard, the direct medical costs, these increased during the first 3 months and then decreased overtime.
- The number of depressive episodes and the increase in QIDS-SR16 score were factors that significantly influenced the disease costs.
- MDD is associated with high socio-economic burden, emphasizing the importance of including MDD as a public-health priority.

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Table 1. Health care resources utilization and loss of productivity.

	Baseline (N=137)	Visit 1 (N=124)	Visit 2 (N=116)	Visit 3 (N=103)
Health care resources				
Specialist visits				
Patients N (%)	29 (21.17)	10 (8.06)	7 (6.03)	3 (2.91)
Mean [95% CI]	0.58 [0.16;0.99]	0.11 [-0.04;0.26]	0.11 [-0.06;0.28]	0.01 [0.00;0.02]
Median (IQR)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)
General practitioner visits[1]				
Patients N (%)	5 (3.65)	1 (0.81)	0 (0.00)	0 (0.00)
Mean [95% CI]	0.06 [0.00;0.12]	0.00 [0.00;0.01]	0.00 [0.00;0.00]	0.00 [0.00;0.00]
Median (IQR)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)
Psychotherapy sessions (Any Type)				
Patients N (%)	43 (31.39)	52 (41.94)	45 (38.79)	40 (38.83)
Mean [95% CI]	2.15 [1.47;2.83]	1.38 [0.64;2.13]	1.05 [0.74;1.35]	0.94 [0.65;1.22]
Median (IQR)	0.00 (0.00-2.00)	0.00 (0.00-1.33)	0.00 (0.00-2.00)	0.00 (0.00-1.67)
Psychotherapy sessions (Individual, group, familiar psychotherapy)				
Patients N (%)	3 (2.19)	1 (0.81)	4 (3.45)	2 (1.94)
Mean [95% CI]	0.01 [0.00;0.03]	0 [0.00;0.01]	0.01 [0.00;0.02]	0.01 [0.00;0.03]
Median (IQR)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)
Diagnostic tests[2]				
Patients N (%)	49 (35.77)	28 (22.58)	13 (11.21)	7 (6.80)
Mean [95% CI]	0.43 [0.32;0.54]	0.09 [0.06;0.13]	0.04 [0.02;0.06]	0.01 [0.00;0.02]
Median (IQR)	0.00 (0.00-1.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)
Visits undertaken[3]				
Patients N (%)	58 (42.34)	92 (74.19)	66 (56.90)	63 (61.17)
Mean [95% CI]	0.34 [0.24;0.45]	0.8 [0.57;1.02]	0.51 [0.37;0.65]	0.52 [0.38;0.65]
Median (IQR)	0.00 (0.00-0.33)	0.67 (0.00-1.00)	0.33 (0.00-0.67)	0.33 (0.00-0.67)
Other healthcare resources[4]				
Patients N (%)	13 (9.49)	19 (15.32)	15 (12.93)	14 (13.59)
Mean [95% CI]	0.07 [0.01;0.12]	0.16 [0.06;0.27]	0.11 [0.03;0.19]	0.09 [0.00;0.17]
Median (IQR)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)
Hospitalization/Day hospital[5]				
Patients N (%)	5 (3.65)	14 (11.29)	6 (5.17)	5 (4.85)
Mean [95% CI]	0.10 [-0.01;0.21]	0.40 [0.12;0.68]	0.22 [0.03;0.42]	0.13 [-0.02;0.28]
Median (IQR)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)
Loss of productivity/usual daily activities				
Patients losing≥1 day of productivity				
N (%)	54 (51.91)	33 (36.26)	13 (16.05)	15 (18.99)
Mean days/patient-month of productivity loss[7]	4.73	3.20	2.20	1.34

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Mean days/patient-month of productivity loss[8]	13.49	15.27	21.28	13.80
Patients losing≥1 day of usual daily activities				
N (%)	78 (57.78)	51 (41.13)	28 (24.14)	25 (24.27)
Mean days/patient-month of usual activities loss[7]	8.88	5.72	3.59	2.31
Mean days/patient-month of usual activities loss[9]	17.62	16.13	15.43	11.31
Caregivers losing ≥1 day of productivity				
N (%)	9 (6.67)	3 (2.42)	1 (0.86)	0 (0.00)
Mean days/caregivers-month of productivity loss[7]	0.16	0.05	0.01	0.00
Mean days/caregivers-month of productivity loss[10]	2.79	2.00	1.00	-
Caregivers with paid work, N (%)	8 (88.89)	3 (100.00)	1 (100.00)	0 (0.00)
Use of caregivers' work permit, N (%)	2 (22.22)	1 (33.33)	0 (0.00)	0 (0.00)

1 More often Neurologist, Cardiologist and Psychiatrist.
2 Blood tests and/or instrumental tests.
3 With Psychiatrist or other healthcare professionals.
4 Colloquy with family member; individual intervention on basic ability; meeting with healthcare unit/other unit; meeting on clinical cases within the unit; drug administration.
5 Day hospital, Hospitalization, Residential or semi residential care
6 Estimated including only patients with at least one hospital admission
7 Estimated in all sample.
8 Among patients losing productivity.
9 Among patients losing days of usual activities.
10 Among caregivers losing days of productivity.

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Table 2. Estimated direct and indirect costs per patient/month (€).

Direct medical costs				
Cost item	**Baseline (N=137)**	**Visit 1 (N=124)**	**Visit 2 (N=116)**	**Visit 3 (N=103)**
Total direct costs	**55.09 (12.49%)**	**154.95 (37.20%)**	**114.71 (38.94%)**	**108.88 (49.86%)**
Hospital admissions	*1.15 (0.26%)*	*2.53 (0.61%)*	*0 (0.00%)*	*0 (0.00%)*
Day hospital	*6.24 (1.41%)*	*27.07 (6.50%)*	*11.94 (4.05%)*	*1.08 (0.49%)*
Residential care	*16.04 (3.63%)*	*51.91 (12.46%)*	*45.45 (15.43%)*	*56.4 (25.83%)*
Treatment	*NA**	*21.60 (13.94%)*	*20.86 (18.18%)*	*20.76 (19.07%)*
Diagnostic tests	*23.50 (42.66%)*	*33.07 (21.34%)*	*24.20 (21.10%)*	*18.69 (17.17%)*
Clinical visits and psychotherapy	*8.16 (14.81%)*	*18.87 (12.18%)*	*12.26 (10.69%)*	*11.96 (10.98%)*
Total indirect costs	**386.28 (87.51%)**	**261.60 (62.80%)**	**179.86 (61.06%)**	**109.48 (50.14%)**
Total costs	**441.37 (100.00%)**	**416.55 (100.00%)**	**294.57 (100.00%)**	**218.36 (100.00%)**

**NA= Not available. Baseline total is not including drug treatment costs.*

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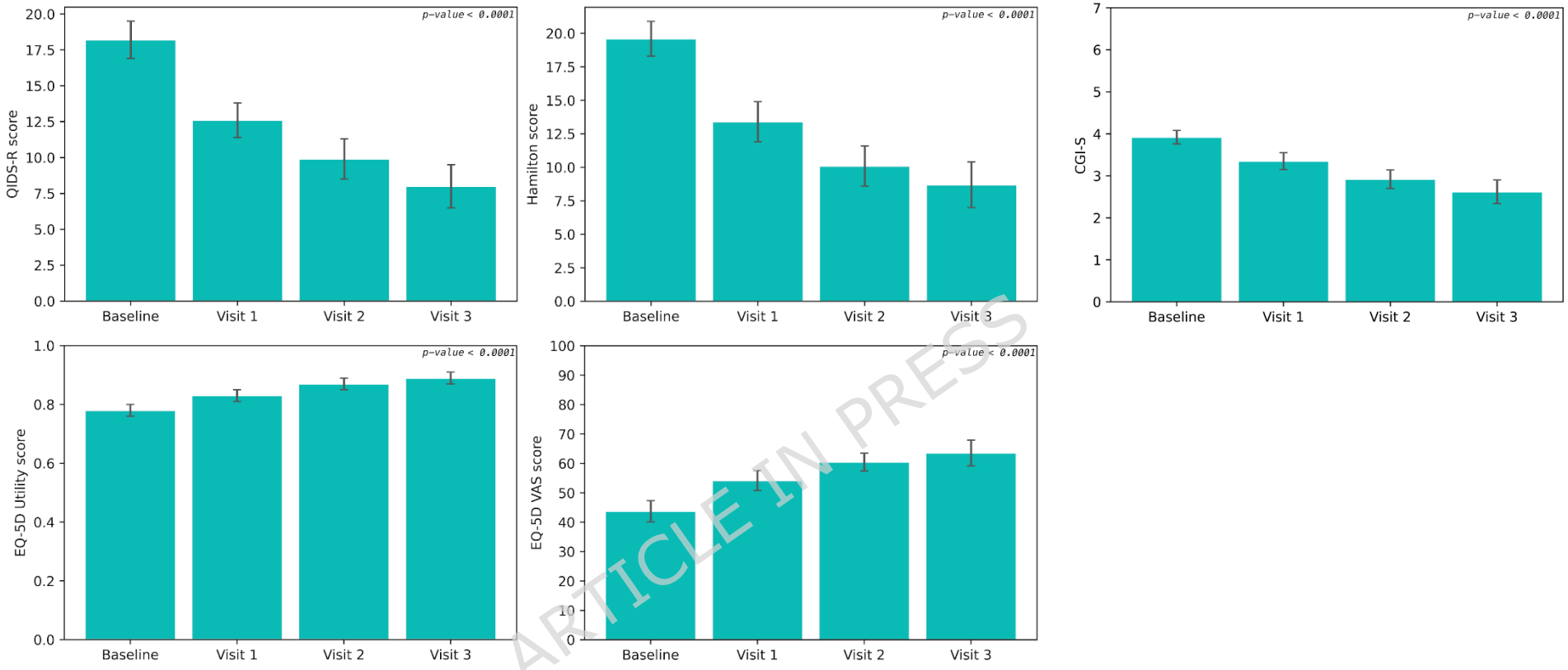
Table 3. Univariate and multivariate analysis to assess association between demographic and clinical as well as QoL factors and patient's costs.

Variable	Univariate regression models		Multivariate stepwise regression	
	Coefficient [95% CI]	***p-value***	***Coefficient [95% CI]***	***p-value***
Age	2.10 [-2.11; 6.31]	0.326		
Sex (Male vs. Female)	20.71 [-81.31; 122.73]	0.689		
Recurrent vs. Single episode	75.85 [-24.93; 176.64]	0.139		
Anxiety disorders	-55.50 [-153.03; 42.04]	0.262		
Sleep disorders	66.27 [-42.84; 175.38]	0.232		
Personality disorders	102.11 [-41.00; 245.22]	0.161		
Symptoms onset (6-1yr vs >6yr)	-11.36 [-141.31; 118.59]	0.863		
Symptoms onset (1yr-6m vs >6yr)	-86.64 [-203.70; 30.42]	0.146		
Number of episodes (1-3 vs 0)	5.92 [-116.53; 128.36]	0.924	10.14 [-109.68; 129.96]	0.867
Number of episodes (>4 vs 0)	**129.61 [4.77; 254.44]**	**0.042**	**129.71 [7.59; 251.83]**	**0.038**
CGI 2 vs 1	-25.23 [-538.75; 488.29]	0.923		
CGI 3 vs 1	-26.63 [-435.30; 382.04]	0.898		
CGI 4 vs 1	52.45 [-351.30; 456.21]	0.798		
CGI 5 vs 1	5.90 [-408.81; 420.60]	0.978		
CGI 6 vs 1	283.83 [-167.20; 734.86]	0.215		
QIDS-SR16 score	**8.05 [2.06; 14.03]**	**0.009**	**7.92 [2.02; 13.82]**	**0.009**
Hamilton score	**7.70 [1.33; 14.07]**	**0.018**		
EQ-5D VAS	-1.36 [-3.70; 0.97]	0.251		

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Figure 1. Clinical scales, EQ-5D-VAS and EQ-5D-utility scores at different visits during follow-up.



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