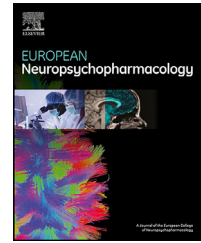




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Epidemiology and costs of depressive disorder in Spain: the EPICO study

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KEYWORDS

Depressive disorder;
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Abstract

Depressive Disorders are the most common psychiatric diagnoses in the general population. To estimate the frequency, costs associated with Depressive Disorders in usual clinical practice, and in the whole Spanish population, a longitudinal, retrospective, observational study was carried out using data from the BIG-PAC database[®]. Study population: all patients aged ≥ 18 years with a diagnosis of a Depressive Disorder in 2015–2017. Prevalence was computed as the

Abbreviations: ICD-10-CM, International Classification of Diseases (10th Edition) Clinical Modification; SD, Standard deviation; AAE, Average annual earnings; CI, Confidence intervals; INE, Spanish National Institute of Statistics; WHO, World Health Organization; EMR, Electronic medical records; SPSS, Statistical Package for the Social Sciences; DD, Depressive Disorder; MDD, Major Depressive Disorder.

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proportion of Depressive Disorder cases in the adult general population, and the incidence rate, as the number of new Depressive Disorder cases diagnosed per 1,000 person-years in the population using health services, during 2015-2017. We collected demographic variables, comorbidity, direct health costs, and indirect costs (temporary and permanent disability). Health costs related to Depressive Disorders were estimated according to the annual resource use rate (resource/patient/year). Indirect costs were calculated according to the human capital method. Using the study data and information from the Spanish National Institute of Statistics, we estimated the cost of Depressive Disorders corresponding to the Spanish adult population, including premature mortality. 69,217 Depressive Disorder patients aged ≥ 18 years who met the inclusion/exclusion criteria were studied (mean age: 56.8 years; female: 71.4%). Prevalence of Depressive Disorders in the general population was 4.73% (95% CI: 4.70-4.76%). Annual incidence rates (2015-2017) were 7.12, 7.35 and 8.02 per 1,000 person-years, respectively. Total costs observed in our Depressive Disorder patients were € 223.9 million (corresponding to a mean of € 3,235.3; mean/patient/year), of which, 18.4% were direct health care costs and 81.6%, non-health indirect costs (18% temporary occupational disability, 63.6% permanent disability). Considering also the cost of premature death, the mean cost per patient/year was € 3,402 and the estimated societal costs of Depressive Disorders in Spain were € 6,145 million. The prevalence and incidence of Depressive Disorders are consistent with other series reviewed. Resource use and total costs (especially non-health costs) were high.

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1. Introduction

According to the World Health Organization (WHO), major depressive disorder (MDD) is a mental illness that affects more than 300 million people worldwide (World Health Organization. *Depression, 2020a*). MDD is a major public health problem associated with high morbidity and mortality rates and, due to its early onset, there is a tendency to chronicity and recurrence over time (Malhi et al., 2018). MDD is a disabling disease that alters the perceived quality of life and increases health resource use (World Health Organization. *Depression, 2020a*; Malhi et al., 2018; Zivin et al., 2013). In addition, it may share symptoms with other psychiatric disorders (Corponi et al., 2020) and comorbidities, and like other mental disorders it is especially prevalent among women and is strongly associated with groups disadvantaged by personal or socioeconomic circumstances (Alonso et al., 2004, Arias de la Torre et al., 2018). Moreover, it may often be difficult to treat (McAllister-Williams et al., 2020).

It is well known that economic crisis has an impact on the prevalence of mental health disorders (World Health Organization. *Health in times of global economic crisis: implications for the WHO European Region 2009, 2009*). A study performed to compare mental health problems before and after the 2007 crisis, revealed a significant increase in the proportion of patients with mood (19.4% in major depression), anxiety, somatoform and alcohol-related disorders, particularly among families experiencing unemployment and mortgage payment difficulties (Gili et al., 2013). Nowadays, it is expected that the COVID-19 pandemic will have an impact on people's mental health as well as a big economic repercussion. Therefore, it would be ideal to have accurate and updated information on the prevalence of depression, as one of the mental disorders that most contributes to the years lived with disability.

The epidemiological information on MDD and mental disorders in the general population is limited, with signif-

icant differences between countries and regions (Alonso et al., 2004; Ferrari et al., 2013). A recent meta-analysis (years: 1994 and 2014) shows a lifetime prevalence of 10.8% and an annual prevalence of 7.2%, respectively (Lim et al., 2018). According to the European Study of the Epidemiology of Mental Disorders (ESEMeD), the prevalence in Spain is lower than that of other European countries, with a lifetime prevalence of depressive episodes of 10.6% and an annual prevalence of 4% (Gabilondo et al., 2010). The Global Health Data Exchange estimates a prevalence of Depressive Disorders in Spain of 4.13% (GHD, 2017). Other Spanish studies have shown quite variable percentages (range: approximately 4-20%), which vary depending on the methodology used, the time period, the geographical area and the subpopulation analyzed (Arias de la Torre et al., 2018; Gabilondo et al., 2012; Porras-Segovia et al., 2018; Fernández Fernández et al., 2006; Aragonès et al., 2004; Gabarrón Hortal et al., 2002).

The relatively high prevalence of depression is directly related to the economic burden of it. The economic impact of mental disorders is high; one third of the costs are direct health costs, but indirect costs are the largest component (Gustavsson A. et al., 2011; Parés-Badell et al., 2014). In the case of treatment-resistant depression, the cost of managing the disease in these patients is even higher (Johnston et al., 2019; Shin et al., 2020). Direct health costs usually include those directly related to medical care (medical visits, hospitalization days, emergency visits, diagnostic or therapeutic requests and pharmaceutical treatments), while the non-health or indirect costs are mainly related to lost productivity. Other related costs, usually not included in these works due to the complexity to obtain the information, would be non-direct medical costs (informal care) and intangible costs (related to pain, anxiety, suffering...). The cost of affective disorders in Europe was estimated at € 113,405 million (€3,406 per person/year), with indirect costs (temporary and permanent occupational dis-

ability) being the largest cost component (63.4%). The estimated cost of mood disorders in Spain was €9.7 billion (€3,232 per person/year) (Gustavsson et al., 2011). The authors assumed that the prevalence of MDD in Spain had not changed substantially with respect to the study by Sobocki (Sobocki et al. 2006). These figures related to mood disorders were estimated slightly higher in a study specifically modelled for Spain (societal cost €10.763 billion, cost per patient: €3,584) (Parés-Badell et al., 2014). In Spain, other groups have estimated the cost of depression in specific regions. In a study carried out in Catalonia, annual costs of €735 million were estimated, 78.8% due to occupational disability (Salvador-Carulla et al., 2011). More recent unpublished data found an approximate cost of € 9-10 billion per year, which is around 1% of gross domestic product (GDP) (FEPSM, 2017). There are no more recent data estimating the costs of depression in the total population in Spain, although a more recent publication has estimated the costs of the specific population with depression that is hospitalized, being this total annual cost €44,839,196 (Darbà and Marsà et al., 2020)

Accurate figures about prevalence and costs are important when considering the necessary investment in mental health. In a global analysis of investment in mental health, a benefit-cost ratio of 3.3-5.7: 1 was estimated when both economic and health returns were considered (Chisholm, D. et al., 2016) and specific tools have been developed to assess the cost-effectiveness of scaling up preventive interventions for treating people with subclinical depression, showing that there is an 82% probability that scaling up prevention is cost-effective given a willingness-to-pay threshold of €20,000 per QALY (Lokkerbol et al., 2020). However, while there is an international call to invest in mental health (World Health Organization 2020b) the recession that usually accompanies the economic crisis frequently includes budget cuts in public spending on Mental Health Care (Hodgkin et al., 2020).

However, there are no recent published data on the prevalence and cost of Depressive Disorders in Spain (and therefore its associated costs), and data on incidence is scarce; so this study may be of interest and may provide hints on prevalence, incidence and costs that may be extrapolated to other countries and that could help in decision-making processes. The objective of the study was to assess the prevalence and incidence and health and non-health costs associated with Depressive Disorders (DD) in usual clinical practice. In addition, the cost of DD in the Spanish adult population was estimated.

2. Patients and methods

2.1. Design and study population

A retrospective, observational study was carried out. Electronic medical records (EMR) were obtained from the BIG-PAC administrative database representative of the general population (Sicras-Mainar et al., 2019) (data source: secondary; proprietor: Atrys Health; estimated population: 1.8 million patients; database registration: <http://www.encepp.eu/encepp/viewResource.htm?id=29236#>). The primary data come from the computerized medical records of seven integrated public health areas (pri-

mary care centers and hospitals) in seven Spanish autonomous communities. EMR are anonymized prior to export to BIG-PAC in compliance with Organic Law 3/2018 of 5 December on the Protection of Personal Data and guarantee of digital rights (<https://www.boe.es/eli/en/lo/2018/12/05/3>).

Patients aged ≥ 18 years with a diagnosis of a Depressive Disorder who had sought care from the healthcare system during 2015-2017 were selected. The diagnosis of Depressive Disorder was established using the International Classification of Diseases (tenth edition) Clinical Modification (ICD-10-CM; <https://eciemaps.mscbs.gob.es>), which includes the following codes: F32 [major depressive disorder, single episode], F33 [recurrent episode], F41.8 [depression with anxiety; mixed anxiety-depressive disorder], F34.1 [dysthymic disorder; includes persistent anxious depression, neurotic depression, depressive neurosis, depressive personality disorder], and F39 [unspecified mood disorder].

2.2. Inclusion and exclusion criteria

The inclusion criteria were: a) age ≥ 18 years, b) active patients (≥ 2 contacts with the health care system) in the database during the observational period. Exclusion criteria were: a) displaced or out-of-area patients, b) permanently institutionalized patients (geriatric residences), c) terminal illness (Z51.5), dialysis (N18. 6) and a history of dementia (F01-F03, G30), bipolar depression (F31) and/or psychosis (F20-F29).

2.3. Prevalence and incidence rate

The prevalence was computed as the proportion of the total number of diagnosed cases of depressive disorders among the general population, and it was calculated for the 3-year 2015-2017 period (cumulative prevalence) and for each year separately (2015, 2016 and 2017; annual prevalence). The incidence rate was calculated as the number of new cases diagnosed with a depressive disorder per 1000 persons/year among the population attended in the health system (2015, 2016 and 2017). Standardization of the results was not necessarily due to the similarity of the population pyramid (age/sex) of the study patients with that of the Spanish population (Sicras-Mainar et al., 2019).

2.4. Demographic and comorbidity variables

We collected information on age (continuous and by range) and sex, a history of high blood pressure, diabetes mellitus, obesity, active smoking, high alcohol intake, ischemic heart disease, cerebrovascular accident, heart failure, kidney failure, anxiety and malignancies. As summary variables of general comorbidity, a the Charlson Comorbidity Index (Charlson et al., 1987) and the number of chronic comorbidities were calculated at the beginning of the study. We also measured all-cause deaths and certain variables related to suicidality or violence to others (ICD-09-CM: V62.84 [Suicidal ideation], V62.85 [Homicidal ideation], V71.89 [Suicide attempt, alleged], 300.9 [At risk for suicide], 960-979 [Poisoning by drugs, medicinal and biological substances] and E950-E959 [Suicide and self-inflicted injury]).

2.5. Resource use and general cost analysis

Resource use and the associated costs of all patients selected for the cost analysis were annualized. That is, the absolute value of each resource (Table 1) during 2015-2017 had a value proportional to the follow-up period (in days; maximum 1095 days), with the annual rate (resource/patient-year) being obtained for each resource.

Table 1 Direct and indirect unit costs in Spain, 2017.

Direct and indirect unit costs	Unit costs in € (2019)
<i>Medical visits</i>	
Primary care visit	23.19
Hospital emergency room visit	117.53
Hospitalization (one day)	420.90
Specialized care visit*	65.00
<i>Complementary tests**</i>	
Laboratory tests	32.30
Conventional radiology	28.50
Diagnostic/therapeutic tests	47.12
Computed axial tomography	96.00
Magnetic nuclear resonance	177.00
Electroconvulsive therapy***	190.00
<i>Pharmaceutical prescription</i>	
Temporary work disability (indirect costs; female-male)	Retail price AAE (€ 59.7-79.2/day)
Permanent work disability (indirect costs; female-male)	AAE (€ 61.3-81.4/day)

Source of health resources: hospital accounting and National Statistical Institute.

AAE: average annual earnings (Source: INE, 2017).

* Only in the psychiatry, psychotherapy and psychology services.

** Related to depressive disorders.

*** Does not include hospital admission, which would be counted as a day of hospitalization.

Only costs related to the depressive disorder or psychiatric treatments were considered. We estimated both the direct health costs related to care (medical visits, hospitalization days, emergencies, diagnostic or therapeutic requests, pharmaceutical prescription), and the non-health or indirect costs related to lost productivity (days of temporary and permanent work disability). ECT unit cost only considers the ECT technique to avoid double counting of hospitalizations. Cost due to premature death is not included in this analysis, as the identification of premature deaths could not be done accurately.

Costs were expressed as the mean annualized cost per patient (mean/unit/year). The study concepts and their economic valuation are shown in Table 1 (referring to Depressive Disorders, year 2109). Medical prescriptions were quantified according to the retail price per pack at the time of prescription (according to Bot Plus of the Official General Council of Colleges of Pharmacists of Spain). Days of occupational disability were considered indirect non-health costs and were estimated using average annual earnings (AAE) (Instituto Nacional de Estadística (INE), 2017). Productivity losses due to 1) temporary disability, 2) permanent disability, and 3) premature death (when estimating the total cost in the Spanish population through a simulated scenario) were estimated. The study did not include direct non-medical costs such as out-of-pocket costs or those paid by the patient/family, as they were not recorded in the database and the study design did not allow access to patients. For the same reason, indirect costs due to presenteeism or loss of unpaid productivity were neither included.

2.6. Calculation of temporary and permanent disability

To estimate temporary disability costs, we used 2017 AAE (Instituto Nacional de Estadística (INE), 2017). To calculate AAE, the mean age of active patients/workers with disability in the study was taken into account, according to sex: € 21,792.70 for females and € 28,912.87 for males. The individual loss of work productivity was quantified according to the days of occupational disability and the corresponding AAE. For permanent disability, the same procedure

was carried out, although in this case the days of disability were the equivalent of 365 days/year. Considering the mean age of patients with permanent work disability, the AAE was € 22,367.70 in females and € 29,711.02 in males.

2.7. Estimated cost of Depressive Disorders in the general Spanish population

The mean cost/patient/year obtained was extrapolated to the total Spanish population according to the prevalence data obtained in the study. It was not possible to estimate the cost per premature death from the study data (unnatural cause: suicide), since the cause of death is not available in the database. Therefore, for this purpose, deaths due to suicide in the general Spanish population was obtained from the INE suicide register (INE, 2017, Suicide rates by age and sex).

2.8. Estimation of the cost of premature death in Spain

To estimate the cost of premature death, we used the incidence rate, with a discounted value of the present and future costs that occur in a given year (Oliva-Moreno et al., 2009). First, suicides attributable to depression were estimated for each age group (15-29, 30-59, and 60-65 years) and sex. Based on the methodology used by Salvador-Carulla et al., (2011), 45% of suicides were considered related to depression. The final number of suicides attributable to depression was adjusted based on the percentage of employment rates (by age and sex) (INE, 2017, employment rates by age and sex). Subsequently we estimated the number of years of life lost by age and sex groups, by multiplying by the difference between the mean age of each group and 65 years (which was the official retirement age in Spain during the observational period included in the analysis). Once the total years of life lost in each group were calculated, the total earnings lost for each group was estimated, based on the mean earnings for the Spanish working population by sex and age. Different tranches (from the initial mean age, to 64 years old) have been considered for each group, each of them with different

average annual earnings, since this average annual earnings varies with age. An annual pay increase of 1% and an annual discount rate of 3% were also considered. In summary:

- Group < 30 (mean age 22 years old): Σ annual and discounted earnings of tranche 1 (22-29 years old) + tranche 2 (30-59 years old) + tranche 3 (60-64 years old)
- Group 30-59 (mean age 45 years): Σ annual and discounted earnings of tranche 1 (45-59 years old) + tranche 2 (60-64 years old)
- Group 60-64 (mean age 62 years): Σ annual and discounted earnings of tranche 1 (60-64 years old)

2.9. Confidentiality of information and ethical aspects

The study was classified by the Spanish Agency for Medicines and Health Products (EPA-OD) and subsequently approved by the research ethics committee of the Consorci Hospitalari de Terrassa (Barcelona).

2.10. Statistical analysis

The search criteria in the database were based on computer sentences (SQL script). The data were carefully reviewed, through exploratory analyses and careful data management, by observing the frequency distributions and searching for possible registration or coding errors. A descriptive univariate analysis was made. Qualitative data were analyzed using absolute and relative frequencies, and quantitative data by estimating using means, standard deviation (SD), median, percentiles 25 and 75 of the distribution (interquartile range) and 95% confidence intervals (CI) for the estimate of parameters. Analyses were carried out using SPSSWIN (version 23). Statistical significance was established as $p < 0.05$.

3. Results

Of an initial population of 1,469,659 persons aged ≥ 18 years (the population census ≥ 18 years in our database), 70,383 patients had been diagnosed with a depressive disorder according to the diagnostic criteria established in our study. To estimate the costs of prevalent cases, 69,217 subjects who met the inclusion/exclusion criteria and could be followed during the study period were analyzed (Fig. 1).

3.1. Baseline characteristics

Table 2 shows the baseline characteristics of the series studied. The mean age was 56.8 years, 71.4% were female and the mean Charlson index was 0.8 points. Anxiety (34.3%), dyslipidemia (30.2%) and high blood pressure (28.1%) were the most frequent psychiatric and medical comorbidities.

3.2. Frequency of DD (2015-2017)

The estimated mean prevalence per year during 2015-2017 was 5.43% (CI: 5.39-5.47) in the population attended and 4.73% (CI: 4.70-4.76) in the general population (reference population covered). Depressive Disorder was more prevalent among females (7.2%) than in males (3.5%), and among the 45-64 years age group (39.7%). Incidence rates in the population attended by the health system during 2015, 2016 and 2017 were 7.12, 7.35 and 8.02 per 1000 persons/year

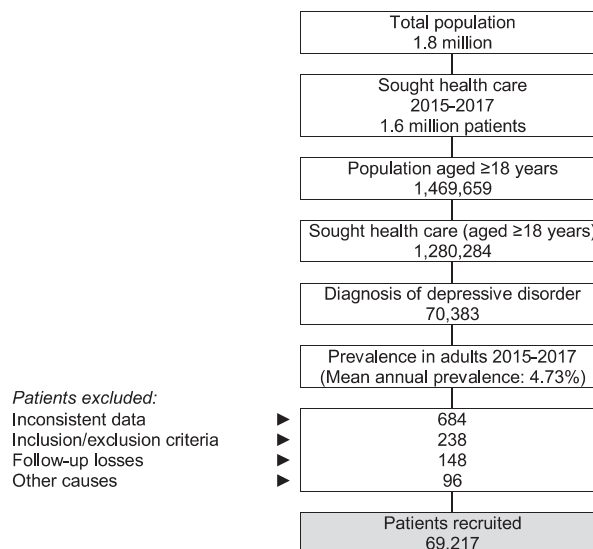


Fig. 1 Study flow diagram.

respectively (mean incidence 7,5 per 1000 persons/year) (Table 3).

3.3. Use of direct health resources and indirect non-health costs

The main components of health resource use (mean use/patient/year) were primary care visits 7.9 (SD: 7.2), specialist visits 0.6 (SD: 2.2) and days of hospital stay 0.3 (SD: 13.8). Diagnostic tests had no marked impact. Indirect non-health costs showed the mean days of temporary disability were 8.8 (SD: 37.8). In patients with ≥ 1 days of work disability, the median was 27 days, and the mean, 53.5 days (minimum-maximum values 2-365). 8.6% of patients had permanent work disability. Table 4 shows the direct health and indirect non-health costs of depressive disorders as the mean/patient-year (in €). The total cost (health and non-health) was € 223.9 million (69,217 patients x € 3,235.3), of which 18.4% corresponded to direct health costs and 81.6% to indirect non-health costs. The share of non-health costs was 18% for temporal work disability and 63.6% for permanent disability. The largest components of the health cost were primary care visits (5.7%; € 183), antidepressant treatments (4.8%; € 155.8) and hospital admissions (4%; € 130.6). The mean cost/patient/year, not including the cost of premature death, was € 3235.

3.4. Cost of depressive disorders in Spain

Table 5 shows the estimated societal cost of depressive disorders in Spain population (INE, 2017, population aged ≥ 18 years). A prevalence of 4.73% was assumed in the general population. According to this prevalence and a population ≥ 18 years old of 38,158,732 people in 2017, 1,806,180 patients with depressive disorder were estimated in the Spanish population. The health costs were € 594 and non-health costs were € 582 due to temporary work disability plus 2059 due to permanent disability. The cost of premature death

Table 2 Baseline characteristics of patients with Major Depressive Disorder (MDD).

Variables	N= 69,217
<i>Demographics</i>	
Mean age, years (SD)	56.8 (17.0)
Ranges: 18-44 years	18,561 (26.8%)
45-64 years	27,476 (39.7%)
65-74 years	11,537 (16.7%)
≥ 75 years	11,643 (16.8%)
Sex (female)	49,392 (71.4%)
<i>General comorbidity</i>	
Mean chronic diagnoses (SD)	1.5 (1.3)
Mean Charlson Index (SD)	0.8 (1.2)
0	41,733 (60.3%)
1	15,117 (21.8%)
2	4,349 (6.3%)
3+	8,018 (12.0%)
<i>Associated comorbidities, N (%)</i>	
High blood pressure	19,429 (28.1%)
Diabetes mellitus	6,831 (9.9%)
Dyslipidemia	20,871 (30.2%)
Obesity	8,424 (12.2%)
Active smoker	6,572 (9.5%)
Alcoholism	748 (1.1%)
Ischemic heart disease	2,018 (2.9%)
Cerebrovascular accident	1,938 (2.8%)
Heart failure	1,812 (2.6%)
Kidney failure	2,232 (3.2%)
Anxiety	23,750 (34.3%)
Neoplasms	7,410 (10.7%)

Values expressed as percentages (N, %) or mean (SD: standard deviation)

Table 4 Yearly health (direct) and non-health (indirect) costs (in €) of Depressive Disorders per patient (study population, N = 69,217).

Cost components	€ (mean/patient/year)
Primary care visits	183.0 (166.2)
Hospital emergency room visits	15 (121.4)
Specialist visits	40.5 (141.2)
Hospital stays	130.6 (5.792.4)
Laboratory tests	24.5 (31.7)
Conventional radiology	6.0 (24.1)
Axial tomography	0.6 (5.4)
Magnetic nuclear resonance	1.7 (13.3)
Other complementary tests	27.2 (465.2)
Electroconvulsive therapy	9.5 (1.1)
Anti-depressant medication	155.8 (449.3)
<i>Health costs</i>	594.2 (6.031.5)
<i>Non-health costs</i>	
- Temporary disability (days of occupational disability)	582.3 (2.493.1)
- Permanent disability	2,058.8 (6,711.7)
<i>Total cost</i>	3,235.3 (10,606.7)

Values are expressed as means (SD: standard deviation)

The cost of premature death could not be estimated, as the exact cause was not available.

was € 301,571,055. Therefore, the societal cost of depressive disorders also including the cost of premature death in the Spanish population, was estimated at € 6,145 million. The mean cost per patient/year with was € 3402 (Fig. 2).

Table 3 Frequency of DD (2015-2017).

Annual prevalence (Population attended)	Population aged ≥ 18 years attended	Depressive Disorder patients aged ≥ 18 years	Prevalence
2015	1,279,532	68,462	5.40%
2016	1,280,196	69,090	5.40%
2017	1,281,125	69,886	5.50%
Average annual prevalence (mean, 95% CI)	1,280,284	69,146	5.43% (95% CI: 5.39-5.47)
<i>Annual prevalence (General population 2015-2017)</i>			
2015	1,468,795	68,462	4.70%
2016	1,469,559	69,090	4.70%
2017	1,470,624	69,886	4.80%
Mean annual prevalence (95% CI)	1,469,659	69,146	4.73% (95% CI: 4.70-4.76)
<i>Incidence rate (per 1,000 persons/year)</i>			
2015	1,279,532	9,116	7.12‰
2016	1,280,196	9,408	7.35‰
2017	1,281,125	10,272	8.02‰

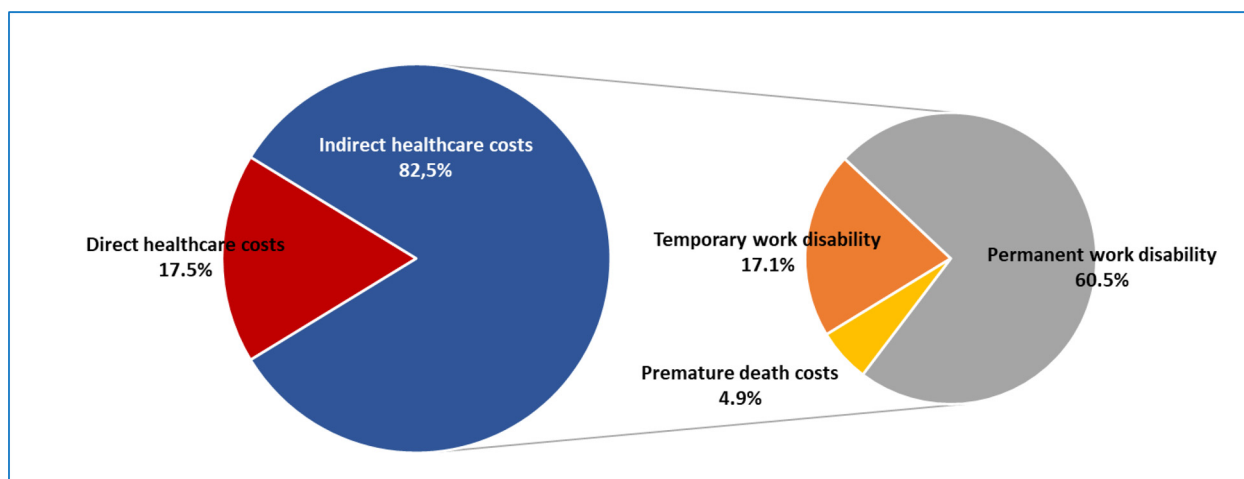
CI: confidence intervals

Table 5 Estimated societal costs of Depressive Disorders in Spain, 2017 (in €).

Study concepts	Study results (2015-2017)	Spanish population* (simulated scenario)	
<i>Epidemiological data</i>	<i>N, %</i>	<i>Demographic data</i>	
General population	1,801,072	46,515,845	
Population aged ≥ 18 years	1,469,659	38,158,732	
Population attended aged ≥ 18 years	1,280,284		
With DD diagnosis	70,383	1,806,180	
Recruitment - DD (study)	69,217		
Prevalence in adults (aged ≥ 18 years)	4.73%		
<i>Costs 2015-2017/annualized-adults</i>	<i>Mean/patient-year</i>	<i>Cost components</i>	<i>%</i>
Health	€594	€1,073,232,145	17.5%
Temporary work disability	€582	€1,051,738,603	17.1%
Permanent disability	€2,059	€3,718,563,346	60.5%
Estimate for premature death**	—	€301,571,055	4.9%
Total cost DD - Spain	€3,235	€6,145,105,149	100%
Cost/patient/year - Spain		€3,402	
Cost per capita (population aged ≥ 18 years)		€161	

*Source: INE (Spanish population pyramid, 2017).

**Costs for premature death include those related to suicide during 2017.



Cost estimation considering direct health-care costs related to the depressive disorder or psychiatric treatments, indirect costs related to temporary and permanent disability, and suicide-related premature death.

Fig. 2 Cost of depressive disorders in Spain.

4. Discussion

This study shows that the prevalence of depressive disorders is very close to 5% and the annual incidence rate of diagnosed depressive disorders in Spain is 7-8 cases/1000 persons/year. Resource use and the total costs (especially indirect costs) associated with depressive disorders are high. Most Spanish studies on this subject have used methodologies based on interviews or questionnaires, whereas there is a lack of observational studies using population based EMR. This different methodology used makes it difficult to compare our results, and at the same time support the interest and need for this type of studies.

Available published data suggests that a large percentage of the population may develop MDD over their lifetime

(Malhi et al., 2018). The literature review showed significant variations in the estimated prevalence and a scarcity of data in recent years, especially in the Spanish population. This may be related to the design of the study, including the time period, the subpopulations analyzed (geographical areas, specific subgroups, selected diagnostic codes), the methodology and the instruments used to measure MDD (population interview vs registered diagnoses) or other aspects that may have an impact on the results (Wang et al., 2017; Ferrari et al., 2013; Kessler et al., 2003).

In our study, the prevalence/year of Depressive Disorder was 4.73% in the general population and the incidence rate was 7-8/1000 patients/year. Llorente, in a cohort of 62,804 patients attended by primary care during 2010, found a prevalence of depression of 5.67%, a mean age of 59 years

and a higher proportion of females (female-male ratio: 3:1) (Lorente et al., 2018). Arias de la Torre found a current depressive disorder prevalence of MDD of > 8% in females and 4% in males (data obtained from the European Health Survey [PHQ-8]). The authors found the prevalence in Spain was high, especially among females, and was strongly associated with personal and socioeconomic variables (Arias de la Torre et al., 2018). Gabilondo, using Spanish data from the ESEMeD, found a prevalence of major depressive episodes (assessed using the Composite International Diagnostic Interview Version 3.0) of 4%. The authors concluded that the prevalence of MDD in Spain is lower than in other Western countries and that, together, the results provide a complex picture of the epidemiology of MDD in Spain compared with other European countries (Gabilondo et al., 2010). Researchers from the ODIN international study of 8,764 subjects found an overall prevalence of depressive episodes or major depression of 8.6%, with a higher prevalence in Ireland and the United Kingdom. The authors showed that these disorders are highly prevalent in Europe. The main finding was the large difference in the prevalence in the centers analyzed (Ayuso-Mateos et al., 2001).

Other Spanish studies found a prevalence of depressive disorders in primary care patients of 20.2% and highlighted subclinical depressive disorders, especially in females and older patients (Roca et al., 2009; Gabarrón Hortal et al., 2002). Compared with other European or international studies, our results show slightly lower rates as might be expected in a study on the prevalence of diagnosed depression compared with prevalence studies using specific interviews conducted in the general population (Alonso et al., 2004). As epidemiological studies have found that 31% of MDD patients with severe depression would not have used health-care resources in the previous 12 months. (Gabilondo et al., 2011), our study could be underestimating this prevalence of depressive disorder. One of the reasons that would explain the higher prevalence of depressive disorders found in studies performed in primary care settings than the prevalence shown in this study is that, in Spain, depressive disorders are primary attended in primary care settings, which would significantly increase the prevalence in this specific population.

For example, a US study in 10,257 subjects aged > 20 years found a prevalence of depressive symptoms of 8% between 2015 and 2020 (according to a PHQ-9 score of ≥ 10), and 19.7% of adults surveyed reported feeling depressed at least once a month (Cao et al., 2020). Allowing for the methodological limitations of the studies reviewed, our results are in line with the population-based estimates described above, although the results in the population receiving medical care might be slightly higher. In Spain, based on reported data, about 1.8 million adults could have some type of depressive disorder annually (simulated prevalence scenario).

Total direct and indirect costs were € 223.9 million (69,217 patients \times €3,235; mean/patient/year). The cost components were (a) direct health costs: 18.4%; (b) indirect costs: 81.6% [temporary occupational disability: 18.0%; permanent disability: 63.6%], without taking into account the cost of premature deaths due to suicide. There is little available evidence in Spain on the cost of depression in the general population, and methodological variations make

it difficult to compare the results. However, studies consistently show that MDD is a public health problem and results in a high economic burden (health, non-health and social; disability and reduced quality of life) in patients, caregivers and society at large (Zivin et al et al., 2013; Darbá and Marsá, 2020; Lépine and Briley, 2011).

The cost of depressive disorders in the Spanish population was estimated at € 6,145 million. The mean cost per patient/year was € 3,402 (cost per capita in persons aged ≥ 18 years: € 161). A 2006 study estimated the total cost of depression in Europe at € 118 billion, with 61% due to the indirect costs of occupational disability and lost productivity. Likewise, the estimated economic burden of depression in Spain in 2005 was about € 5 billion per year, with a distribution of resource use very similar to that found in Europe as a whole (Sobocki et al., 2006). In Catalonia, in 2006, depression had a direct health cost of € 155 million (21%), which rose to € 735 million (79%) when lost productivity was included (temporary disability: 27%; permanent: 48%). Premature mortality was 4%. The authors concluded that inefficiencies can be found in the overuse of medicines and in the criteria of occupational disability (Salvador-Carulla et al., 2011). Another Spanish study found that the direct public cost of depression in the city of Sabadell (Barcelona, Spain) was € 9,155,620 in 2007 and € 9,304,706 in 2008 (Pamias Massana et al., 2012). The relative weight of primary care visits and drug use accounted for more than 85% of the direct cost. In both cases, the weight corresponding to temporary work disability was the most relevant. Other authors have estimated the total cost of mental illness in Spain at about €7,019 million. Direct medical costs accounted for 39.6% of the total cost and 7.3% of total public health spending in Spain. Informal care costs accounted for 17.7% of the total costs and lost productivity for 42.7%. The authors concluded that the cost of mental illness in Spain has a considerable economic impact from a social perspective (Oliva-Moreno et al., 2009). And it is important to mention that most of these works do not include other important matters such as the burden of caregivers. In a recent study it has been shown that it showed that the caregivers' rejective attitude toward their patients was determined by their level of depressive symptoms, perceived reassurance seeking, and subjective feeling of sadness and anger, rather than by their objective burden (Yu et al., 2020).

Our results show that the total cost of depression, in absolute terms, was higher than the costs found in other Spanish studies. Despite making conservative estimates of the Spanish population, the data reviewed came from older studies and may be far from the current reality. In relative terms, our results were similar to those of a Catalanian study that included the cost of premature deaths, although these accounted for only 4% of the total cost. One notable aspect of our study is the shorter time of temporary work disability and the relatively greater weight of long-term or permanent occupational disability. This may be due to better management by health professionals or the health administration that currently regulates these processes, resulting in a reduction in the mean cost per patient of occupational disability in the working population. Despite the significant social and economic burden of depressive disorders, some studies suggest that only a minority of patients receive adequate minimum treatment: 1 in 5 people in high-

income countries and 1 in 27 in low- and middle-income countries (Thornicroft et al., 2017).

The strengths of our study include a large sample size and its representativeness of the general population (Sicras-Mainar et al., 2019). Nevertheless, some limitations of the study deserve discussion. 1) First, as a retrospective and observational design study, the potential disease under-recording (frequencies based on diagnosed cases) which could reflect a prevalence below that expected considering other methodologies (based on interviews to general population). This possible limitation of under-diagnosis is also a strength of the study, permitting a contrast between the prevalence of diagnosed Depressive Disorder in our study and the epidemiological data from other methodologies based on population studies. 2) The possible inaccuracy of diagnostic coding in terms of the diagnosis of depressive disorders may also be a limitation of this study. To avoid loss of sensitivity in the result and taking into account this variability when assigning a certain diagnostic code, it was decided to include different depression related diagnostic codes. 3) The lack of variables in the database that could influence the final results (socioeconomic level, occupational status [unemployed, housewives, etc.], demographic situation) is also a possible limitation. However, to overcome this limitation when estimating the cost of depressive disorder in the total population, mean average salaries and occupational status were taken into account. 4) The total costs could be underestimated, as only direct costs related to public health and the area of influence of the patient were accounted for (while other different costs related to specific comorbidities or potential conditions in these patients such as drug abuse were not included (Roncero et al., 2015). In the same way, occupational disability may be a limited indicator of indirect costs as they underestimate self-employment. Likewise, the costs of lost productivity due to presenteeism or to unpaid productivity were not included. The results and conclusions regarding the costs of this analysis are limited to direct costs in the public health system, as well as indirect costs due to productivity losses (work disabilities and premature death), so it should not be understood as the totality of the costs of depression. Finally, it should be considered that there are different methodologies that can be followed when carrying out this type of cost-of-illness analysis. Despite these limitations, the analysis of this study allows us to conclude that the prevalence and incidence of depressive disorder in Spain is high, having important economic consequences due to the costs derived from the loss of productivity.

Role of the founding source

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Declaration of Competing Interest

TH and BH are full-time employees of Janssen-Cilag S.A. ASM and ASN are independent consultants at Atrys Health regarding the development of this study.

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Author contributions

The conception and design of the manuscript were made by all authors; data collection and statistical analysis by ASM, ASN and BH; preparation of the first draft by ASM, and interpretation of the data, critical review and approval of the manuscript submitted by all authors.

Data availability

The data supporting the study findings are available on request from the corresponding author, AS. The data are not publicly available as they contain information that could contain potentially identifying or sensitive patient information.

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