

The Social Cost of Major Depression. A Systematic Review

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ABSTRACT

Major depression (MD) is a major cause of disability and a significant public health problem due to strong physical and mental impairment, possible complications for patients (including suicides), serious social and working problems to the patient and his/her family. We provide an overview of the social cost of Major depression worldwide. We conducted a systematic literature review. Two search engines were queried. Screening of records and summary of evidence was performed by two researchers blindly. The review was conducted in accordance with the standards of the PRISMA guidelines.

Twenty studies met the inclusion criteria. Despite the heterogeneity in terms of population, setting and estimation techniques, the studies showed that the largest share of the burden of disease is represented by indirect costs. Among direct healthcare costs, inpatient care represents the most significant item, followed by outpatient care. The average total direct cost of depression ranges between €508 and €24 069, depending on the jurisdiction where the analysis was run and the range of cost items included. Indirect costs range between €1963 and €27 364.

Evidence on the cost of MD in some countries is currently lacking. A deeper understanding of the drivers of the economic burden of disease is a crucial starting point for studies concerned with the cost-effectiveness of new treatment strategies.

Keywords: cost of illness, economic burden, depressive disorder, mayor depression, social cost

1. Background

Depressive disorders are part of mood disorders and include major depressive disorder (single episode or recurrent major disorder), dysthymia and depressive disorder not otherwise specified. These disorders may result from a specific triggering event such as a sudden bereavement or a financial reverse. In case of recurrent depressive episodes, generally the first episode is due to a stressful event or situation, while in later episodes' connection with a triggering factor may be less obvious or apparently absent. In some cases, the side effects of certain drugs and other pathologies, such as cardio-vascular events or cancer, may contribute to the appearance of depressive disorders. The depressive episode is characterized by symptoms such as mood swings, loss of interest in most activities of daily life, alterations in weight, appetite and sleep, agitation, decreased self-esteem, disturbances concentration, thoughts of death or suicidal behavior; to be that the psychiatric disorder has to last at least two weeks (First, 1994).

Major depressive disorder (MDD) is one of the diseases with the highest impact in Europe and worldwide, with at least 350 million people currently living with depression. According to the World Health Organization (WHO), depression is a major cause of disability and a significant public health problem resulting in strong physical and mental impairment, possible complications for patients (including suicides), serious social and working problems to the patient and his/her family, increased utilization of health care resources and direct and indirect personal and societal costs (Word Health Organization, 2012).

Evidence upon the epidemiological pattern of MDD worldwide is still ambiguous. In 2004, a large epidemiological study was run in 6 European countries, namely Belgium, France, Italy, Germany, the Netherlands, and Spain. Overall, 21425 individuals, aged 18 and older were interviewed between 2001 and 2003. Fourteen per cent of interviewees reported a lifetime history of any mood disorder, 13.6% any anxiety disorder and 5.2% a lifetime history of any alcohol disorder. Among mood disorders, major depression and specific phobia were the most common psychiatric disorders with almost 13% of patients reporting lifetime history of MDD and 4% experiencing it in the past 12 months (Alonso et al., 2004). More recently, a systematic review investigated the epidemiology of MDD worldwide estimating a point prevalence of

4.7% (4.4-5.0%), adjusted for methodological differences among the included studies and a pooled annual incidence of 3.0% (2.4-3.8%). Prevalence of MDD ranges between 8.6% (5.2-14.0) observed in South Asia and 3.7% (3.1-4.3) observed in North America. Estimates for Western Europe are slightly lower than those reported for Eastern and Central Europe (4.7 vs 5.1) (Ferrari et al., 2013).

Depressive disorders, unlike many other diseases, affect patients even at an early age and women more commonly than men, despite it is estimated that a 1.5 out of ten women become depressed postpartum, and this compromises the ability to curate the baby, by producing long term issues related to the growth and development of the child. In severe cases, depression may lead to suicide, one million people per year commit suicide, of depression and for every death are estimated about 20 failed attempts (World Health Organization, 2012; Hardt et al., 2015).

In several studies, MDD was proved to severely impair individuals' functioning in a number of ways, by negatively affecting not only mental well-being but also perceived physical functioning and bodily pain, as well as general health perception. This, in turn, threatens individuals' family and social life, often resulting in insulation (Saarijärvi, Salminen, Toikka, & Raitasalo, 2002; Riihimäki et al., 2016; Papakostas et al., 2004). For this reason, MDD induces a broad decline in patients' quality of life, which is not easily captured by traditional clinical scales but should be always taken into account through generic instrument (Rapaport, Clary, Fayyad & Endicott, 2005).

Patients with depression cannot play a "normal role" in their lives and they often have to face a hostile social environment. Typically, patients feel different and not accepted. MDD is most often associated with low self-esteem and feelings of worthlessness that induces self-discrimination (early-discrimination) (Papakostas et al., 2004).

In the US, MDD is the main cause of disability for individuals aged 15 and 44 years, by generating about 400 days lost for disability (DALYs), more than any other physical or mental disorder. Such a huge impact on patients' ability to function, was found to generate a huge economic burden in terms of direct and indirect costs, which was investigated in two studies focusing on the pattern of costs associated with depressive disorders between 1990 and 2000 and between 2005 and 2010, respectively (Greenberg et al., 2003; Greenberg, Fournier, Sisitsky, Pike & Kessler, 2015). In the former study, authors found that the overall weight of major depression, bipolar disorder and dysthymia in 2000 amounted to \$ 83.1 billion, of which \$ 26.1 billion for direct medical costs, \$ 5.4 billion attributable to mortality from suicide and \$ 51.5 billion of losses productivity-related absence from work or reduced work productivity, caused by the diseases (Greenberg et al., 2003; Greenberg et al., 2015). This piece of evidence was then updated by the latter study, in which authors found that the overall economic burden of MDD had been rising from 2000 to 2010 by 21.5% and that the management of comorbidities was playing a prominent role in this growth (Greenberg et al., 2015).

Despite this remarkable social and economic burden, MDD is still a strongly underdiagnosed and under treated condition. According to the WHO, only one on 10 patients with depressive disorder, receives adequate treatment and support despite the existence of many treatments to improve the patient's prognosis (World Health Organization, 2012). For instance, a large survey performed in Italy including 5.566 individuals, found that 62,7% of patients with MDD and 83,9% of those with minor depressive symptoms had never asked for a specialist advice upon their own condition. Moreover, 34,2% of patients with MDD receiving medical advice had not received any prescription, while 36,8 % had started medical treatments more than once. Furthermore, the number of consultations, of pharmacological treatments and diagnostics were three times bigger in patients with MDD compared to individuals without depressive symptoms, while the number of absences from work lasting more than one week occurring in the last 6 months was four times bigger (Battaglia, Dubini, Mannheimer & Pancheri, 2004). In existing literature, this important diagnostic and therapeutic unmet need has been attributed not only to the poor awareness, social stigma and the mistrust in pharmacological treatments, but also to the great variability in doctors' ability to correctly recognize and interpret the disease symptoms (Lasalvia et al., 2013).

On the other hand, a number of innovative treatment strategies for the management of MDD is becoming available (Thase, 2017). However, in many national settings, especially those characterized by the presence of a publicly funded health care systems, the market access of new drugs is usually conditional on the assessment of its economic impact (Paris & Belloni, 2013). As a matter of fact, in the presence of limited health care resources and potentially infinite health care needs, each decision made concerning the reimbursement of a new drug in a clinical area has a high opportunity cost, in terms of treatments forgone for other diseases. For these reason, economic evaluations of health care technologies are increasingly used also by regulatory agencies to inform decision making providing an assessment of the cost-benefit balance. However, an exhaustive assessment of a health technology (i.e. drug, procedure or medical device) cannot be performed without a deep understanding of the composition of the costs of the condition.

Cost-of-illness is the most ancient economic evaluation technique used in the health sector. Its aim is to measure the economic burden of illness to society. It is a descriptive study that can provide information to support the political process providing an estimate of the true cost of the condition to society, an analysis of the main cost components and their incidence over total costs as well as indication of the different subjects who actually bear the costs (Tarricone, 2006).

The aim of this systematic review is to provide an overview of the social cost of MDD worldwide, focusing on the composition of the overall economic burden. Looking at the cost composition, we provide insights on the current patterns and challenges in the management of these patients.

2. Materials and Methods

2.1 Data Sources & Research Strategy

In order to achieve the objectives of the study a search string was built and run on two engines, namely PubMed and EBSCOhost, including the following databases: Medline, CINAHL, Cochrane Database, Health Technology Assessments and NHS Economic Evaluation Database. The search string combined the following key words: "depressive disorder", "major depr*", depression, "economic burden", burden, cost, "cost of illness", "disease cost". Appropriate Boolean operators were utilized to combine key words together. In order to not miss any potentially relevant record, some Mesh terms were identified and looked up on Pubmed: "Depressive Disorder", "Depression", "Depressive Disorder, Major", "Cost of Illness", "Costs and Cost Analysis", "Cost Control", "Health Care Costs".

The literature search was limited to papers with full text available, published in English language during the last ten years. The study population was limited to adult humans and key words needed to be mentioned in the title and/or in the abstract.

2.2 Study Selection Process and Inclusion/Exclusion Criteria

The eligibility of the studies was ascertained by two steps: after excluding duplicates, a preliminary screening was done on the basis of title and abstract. Afterward, the studies included in this prior assessment were selected based on the full text at the second screening. Each record retrieved was assessed by two junior researchers blindly. A third reviewer intervened in case of doubt or disagreement.

Eligibility was assessed against the following criteria: *i)* Study type: primary report of original research; reviews, systematic reviews, editorials and protocol papers were excluded. *ii)* Type of analysis: cost of illness, economic studies, clinical studies analyzing costs based on either retrospective administrative data or surveys were deemed eligible. *iii)* Data reported: eligible papers had to include enough detail on cost data and their sources; *iv)* Full text availability: the full text of eligible papers needed to be available to reviewers; corresponding authors were contacted where necessary. The Consolidated Health Economic Evaluation Reporting Standards (CHEERS) 24-item checklist was used to evaluate the quality of the studies reviewed (Husereau et al., 2013).

2.3 Data Extraction, Analysis and Reporting

Standardized data extraction forms were used. Each record yielded by the search strategy was attached a progressive ID number, in order to be easily tracked. For each paper, regardless of its subsequent inclusion in the review, first author, title, source and study design were recorded.

For included studies, information on population, study design, cost data sources estimates of direct and indirect costs were collected. After careful reading, cost items were classified into more general cost categories in order to allow for comparisons across studies. Costs of different currencies have been converted to Euros 2015 and adjusted by the consumer price index. Where possible, values have been presented per patient per year.

The reporting was compliant with the standards of the "Preferred Reporting Items for Systematic Reviews and Met-Analyses" (PRISMA) guidelines (Liberati et al., 2015).

3. Results

3.1 Search Results

Overall, the search strategy yielded 12 910 records. After the removal of 4271 duplicates, another 3412 papers were considered not relevant based on the reading of the title. The remaining 956 abstracts were assessed for eligibility. Of these, 793 were excluded for not complying with eligibility criteria and 163 full texts were reviewed. The reading of full texts led to the exclusion of 143 articles have been excluded for the following reasons: 84 reported cost-effectiveness analyses and not original cost analysis assessments, 39 referred to populations not relevant to the aim of the current review, and 21 focused on clinical and/or epidemiological aspects of MDD. Twenty records eventually met our inclusion criteria (Greenberg et al., 2015; Birnbaum et al., 2010; Stensland, Jacobson & Nyhuis, 2007; Ivanova et al., 2011; Unützer et al., 2009; Olchanski et al., 2013; François, Despiéglé, Maman, Saragoussi & Auquier, 2010; Vasiliadis et al., 2013; Lepine, Moreno, Campos & Couttolenc, 2012; Tomonaga et al., 2013; Sobocki, LeKander, Borgström, Ström & Runeson, 2007; von Knorring, Akerblad, Bengtsson, Carlsson, & Ekselius, 2006; Ekman, Granström, Omérov, Jacob & Landén, 2013; Salvador-Carulla et al., 2011; Kleine-Budde et al., 2013; Bosmans et al., 2010; Sado et al., 2011; Hu, He, Zhang & Chen, 2007; Ho, Mak, Chua, Ho, Mak, 2013; Chang, Hong & Cho, 2012).

The study selection process is depicted in Figure 1.

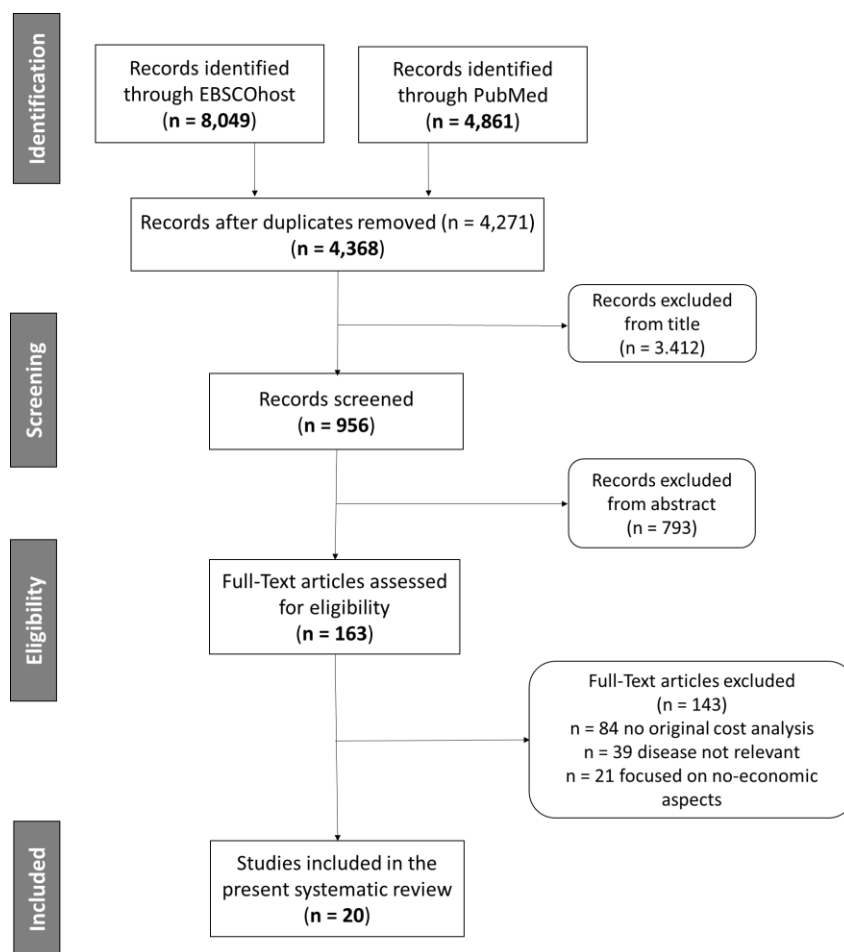


Figure 1. Flow chart of systematic literature review

Nine of the studies included in the current review were conducted in America, 7 in Europe and 4 in Asia. General features of the studies are listed in Table 1 reporting the study year (i.e. the year that data refer to), the size and age of the study population, the case definition, the study perspective and the cost data sources.

Fourteen out of 20 studies observed patients for a time span longer than one year (Greenberg et al., 2015; Birnbaum et al., 2010; Ivanova et al., 2011; Unützer et al., 2009; Olchanski et al., 2013; François et al., 2010; Vasiliadis et al., 2013; Lepine et al., 2013; Tomonaga et al., 2013; von Knorring et al., 2006; Ekman et al., 2013; Kleine-Budde et al., 2013; Bosmans et al., 2010; Ho et al., 2013). Only in 3 out of 20 studies (Birnbaum et al., 2010; Vasiliadis et al., 2013; Hu et al., 2007), eligible patients were selected through physician diagnosis, whereas in the remaining cases diagnosis-related classifications were used.

Eleven studies (Birnbaum et al., 2010; Greenberg et al., 2015; Tomonaga et al., 2013; Sobocki et al., 2005; von Knorring et al., 2006; Ekman et al., 2013; Salvador-Carulla, 2011; Sado et al., 2011; Hu et al., 2007; Ho et al., 2013; Chang et al., 2012) adopted either a patient or societal perspective, including estimation of both health care direct costs and productivity losses. The remaining papers investigated the cost of MDD under the third party payer perspective. Of these, 3 (Unützer et al., 2009; Vasiliadis et al., 2013; Lepine et al., 2012) adopted the public payer point of view and 6 adopted the insurer perspective (Stensland et al., 2004; Ivanova et al., 2011; Olchanski et al., 2013; François et al., 2010; Kleine-Budde et al., 2013; Bosmans et al., 2010).

All the studies included assessed direct costs (i.e. costs directly related to the MD treatment) exhaustively, by organizing them in the following labels: inpatient costs, outpatient costs, depressive drugs, non-depressive drugs and ancillary care. Inpatient costs have been aggregated from the following cost items: hospital, hospital stays, hospitalizations whereas outpatient costs involve ambulatory, day hospital, primary care, specialized care, general practice and psychiatric consultations. Finally, ancillary care includes diagnostic (e.g. laboratory tests, radiology, genetic testing, diagnostic imaging), therapeutic (rehabilitation to physical and occupational therapy, massage, chiropractic services, speech therapy), and custodial services (hospice care, long-term acute care, nursing facilities and urgent care).

Indirect costs (i.e. costs to the society generated by the inability to work due to the disease) were evaluated in terms of

suicides and loss of work productivity generated by either presentism or absenteeism. The loss of productivity was always calculated through the human capital approach. Despite the heterogeneity in terms of population and geographical location and the difference in costs estimation techniques, all the included studies show an important weight of indirect costs within the overall economic burden. Detail on cost data is reported in Table 2 including values per patient per year.

Table 1. Main characteristics of included and relevant studies.

Continent	Country	First Author, year	Study Year	N (Age)	Case Definition	Study Perspective	Cost Data Sources
America	USA	Birnbaum, 2009	2001-2	4.465 (18+)	Physician's Diagnosis	Patient	National Survey
	USA	Stensland, 2006	2004	60.643 (18 - 64)	ICD-9-CM	Third Party Payer	Administrative Database
	USA	Greenberg, 2015	2005-10	44.241 (18 - 64)	ICD-9-CM	Societal	Insurance Database
	USA	Ivanova, 2011	1999-2007	18.834 (18 - 64)	ICD-9-CM	Third Party Payer	Administrative Database
	USA	Unutzer, 2009	2004-6	2.108 (18+)	ICD-9-CM	Public Payer	Administrative and Insurance Database
	USA	Olchanski, 2012	2001-9	58.697 (21+)	ICD-9-CM	Third Party Payer	Administrative Database
	USA	Francois, 2010	2002-5	599.624 (18+)	ICD-9-CM	Third Party Payer	Administrative Database
	Canada	Vasiliadis, 2012	2005-6	150 (65+)	Physician's Diagnosis	Public Payer	Regional Survey
	Brazil	Lepine, 2012	1997-2002	212 (18+)*	ICD-10	Public Payer	Administrative Database
	Switzerland	Tomonaga, 2013	2007-8	556 (18 - 65)	ICD-10	Societal	Administrative Database
Europe	Sweden	Sobocki, 2007	2005	-	ICD-10	Societal	Hospital Database
	Sweden	Von Knorring, 2006	1999-2003	1031 (18+)	DSM-IV	Societal	RCT
	Sweden	Ekman, 2013	2006-8	10.430 (18+)	ICD-10	Societal	Hospital Database
	Spain	Salvador-Carulla, 2011	2006	1.619 (18+)	ICD-10	Societal	Regional Survey
	Germany	Kleine-Budde, 2013	2007-9	117.220 (18+)	ICD-10	Third Party Payer	Insurance Database
	Netherlands	Bosmans, 2010	2002-4	7128 (18+)	ICD-10	Third Party Payer	Administrative Database
	Japan	Sado, 2011	2005	900.000 (20+)	ICD-10	Societal	National Survey
	Japan				DSM-IV		
Asia	China	Hu, 2007	2002	-	Physician's Diagnosis	Societal	National Survey
	Singapore	Ho, 2013	2007-8	49 (18 - 60)	ICD-10	Societal	Clinical Database
	Korea	Chang, 2012	2005	885.700 (18+)	ICD-11	Societal	Insurance Database

Table 2. MDD direct and indirect costs per patient/year

First author, Year, Country	Direct health care costs (€)						Indirect costs (€)			Total	Suicide
	Inpatient	Outpatient	Depression drugs	Other drugs	Ancillary Care	Total direct Health care costs	Absenteeism	Presenteeism	Total indirect costs		
Birnbaum, 2009, US	1183	215	186	N/A	347	1931	2211	N/A	2211	4142	N/A
Stensland, 2006, US	2619	1158	439	82	N/A	4298	N/A	N/A	N/A	N/A	N/A
Greenberg, 2015, US	2509	1226	1019	1540	483	6777	11 977	1963	13 941	20 718	478390
Ivanova, 2011, US	4364	8260	2720	2614	N/A	17 960	N/A	N/A	N/A	N/A	N/A
Unutzer, 2009, US	9454	8470	N/A	N/A	6145	24 069	N/A	N/A	N/A	N/A	N/A
Olchanski, 2012, US	902	5415	931	1409	N/A	8656	N/A	N/A	N/A	N/A	N/A
François, 2010, US	2650	2682	903	N/A	284	6518	N/A	N/A	N/A	N/A	N/A
Vasiliadis, 2012, Canada	618	1459	1224	N/A	N/A	3302	N/A	N/A	N/A	N/A	N/A
Lepine, 2012, Brazil	323	137	1171	N/A	778	2409	N/A	N/A	N/A	N/A	N/A
Tomonaga, 2013, Switzerland	8701	1903	877	N/A	N/A	11 482	N/A	14 359	14 359	25 841	N/A
Sobocki, 2007, Sweden	342	401	1757	N/A	N/A	2501	N/A	5136	5136	7637	439705
von Knorring, 2006, Sweden	641	1471	308	711	N/A	3131	N/A	20 585	20 585	23 717	N/A
Ekman, 2013, Sweden	792	1115	286	N/A	N/A	2193	N/A	16 330	16 331	18 524	N/A
Salvador-Carulla, 2011, Spain	3704	453	21	N/A	N/A	4178	6046	21 318	27 364	31 542	401635
Kleine-Budde, 2013, Germany	224	129	155	N/A	N/A	508	N/A	N/A	N/A	N/A	N/A
Bosmans, 2010, Netherlands	N/A	2.312	571	599	N/A	3482	N/A	N/A	N/A	N/A	N/A
Sado, 2011, Japan	470	658	8564	N/A	N/A	1692	8647	N/A	8647	10339	439705
Hu, 2007, China	113	221	75	N/A	179	588	138	133	272	860	2.650
Ho, 2013, Singapore	575	202	480	N/A	192	1449	3058	3121	6178	7628	N/A
Chang, 2012, Korea	84	349	35	N/A	N/A	468	6046	21 318	27 364	27 833	401635

3.2 Direct Health Care Costs

Nine out of 20 studies were performed in America (Greenberg et al., 2015; Birnbaum et al., 2010; Stensland et al., 2004; Ivanova et al., 2011; Unutzer et al., 2009; Olchanski et al., 2013; François et al., 2010; Vasiliadis et al., 2013; Lepine et al., 2012). Of these, 7 (Greenberg et al., 2015; Birnbaum et al., 2010; Stensland et al., 2004; Ivanova et al., 2011; Unutzer et al., 2009; Olchanski et al., 2013; François et al., 2010) were conducted in the US, 1 in Canada (Vasiliadis et al., 2013) and one in Brazil (Lepine et al., 2012). In these studies, among direct health care costs, inpatient care and outpatient care represent the most significant items, equaling on average € 2751 (€ 460- € 9454, SD=€ 2813) and € 3406 (€ 215 - € 8470, SD= € 3167), respectively. The weight of inpatient care is heavier than that of outpatient care in five studies (Greenberg et al., 2015; Birnbaum et al., 2010; Stensland et al., 2004; Unutzer et al., 2009; Lepine et al., 2012).

Studies performed in Europe showed a similar pattern of direct health care costs, and even if the amounts are different the relative impact of cost items is comparable to the one observed for the American studies. Four out of 7 articles reported a value of inpatient costs higher than outpatient costs (Tomonaga et al., 2013; Salvador-Carulla et al., 2011; Klein-Budde et al., 2013; Bosmans et al., 2010), while in the remaining 3 studies the trend is opposite (Sobocki et al.,

2007; von Knorring et al., 2006; Ekman et al., 2013). The inpatient costs have on average a value of € 2089 (range: € 207-€ 8701) with a standard deviation of € 3573. The outpatient costs have on average a value of € 1438 with a standard deviation of € 838, range between € 128 and € 2312.

In absolute terms, studies conducted in Asia show a lower burden of disease in terms of direct health care costs compared with Occidental countries, probably due to differences in the patient management strategies. The inpatient costs average € 376 with a standard deviation of € 258 (range: € 84-€ 575), while the outpatient costs average € 373 with a standard deviation of € 248 (range between € 202 and € 658) (Sado et al., 2011; Hu et al., 2007; Ho et al., 2013; Chang et al., 2012).

Pharmaceuticals represent worldwide a share of 24% on the total direct costs of illness. Among studies performed in Northern America, the incidence of the cost of drugs on the overall cost of illness is very heterogeneous. Three studies (Greenberg et al., 2015; Ivanova et al., 2011; Vasiliadis et al., 2013) report a cost of anti-depressive and non-anti-depressive drugs which accounts for more than 30% of the overall cost per patient. Two of these studies refer to the US setting (Greenberg et al., 2015; Ivanova et al., 2011) the third one was performed in Canada (Vasiliadis et al., 2013). In another 3 studies the cost of drugs accounts more 15% (Birnbaum et al., 2010; Stensland et al., 2004; François et al., 2010).

In Europe, on average, the impact of drugs on the overall cost of disease is 20,32%, with only two studies reporting a figure higher than 30% (von Knorring et al., 2006; Klein-Budde et al., 2013). In the studies focusing on the European setting such value is below 16% (Tomonaga et al., 2013; Ekman et al., 2013; Bosmans et al., 2010).

Studies performed in Asia report a relatively high incidence of pharmaceuticals on the total direct cost. Pharmaceuticals account for more than 30% in Sado et al. (2011), where the cost of drugs is € 564 on a total direct costs of € 1692, as well as in Ho et al. (2013) where the cost of medicines is €480 on a total direct costs of € 1449. In Chang et al. (2012) the incidence of pharmaceuticals on the overall cost is near to 10%.

The supportive care is a costs item extremely complex and articulated, including different types of care aimed at improving the patients' quality of life, preventing or treating as early as possible the symptoms of disease, managing side effects caused by the treatment, and providing psychological, social, and spiritual support. Worldwide the supportive care costs represent, on average, the 14.25% of the total direct costs, ranging between 4% and 26%. However, only six studies took this cost item into account (Greenberg et al., 2015; Birnbaum et al., 2010; Unützer et al., 2009; François et al., 2010; Bosmans et al., 2010; Ho et al., 2013).

Nonetheless, such a cost item deserves careful attention since supportive care plays a central role in the management of a disease like depression, for whom the support service activities outside of health care structures and the presence and support of a caregiver is essential for patient, both from the physical and the psychological point of view.

The average total direct cost of depression, in America ranges between € 1931 and €24 069, in Europe between € 508 and € 11 482 and in Asia between € 380 and € 1 692; the variation in range depending on the jurisdiction where the analysis was run and the range of cost items included by the authors.

3.3 Indirect Costs

The indirect costs were gathered from every article and were organized and tabulated in three cost labels: suicides, directly linked with depressive illness, and loss of work productivity, in terms of presentism (i.e. productivity loss on the work place due to poor health conditions) and in terms of absenteeism (i.e. productivity losses due to absence from work due to depression).

Only two studies performed in America have dealt with indirect costs (Greenberg et al., 2015; Birnbaum et al., 2010). Birnbaum et al. (2010) investigated, in a sample of 4465 US workforce, the presentism costs by assessing a loss of productivity per person of € 2211. There was a significant correlation between MD severity and treatment usage and costs, as well as between treatment adequacy and severity. Disability increased with MD severity, while work performance decreased with MD severity. Greenberg et al. (2015) evaluated the indirect costs in term of absenteeism, by identifying a significant weight of loss of productivity on the economic burden of MD. The injury, illness and disability generated an absenteeism cost of € 1963 per person, which have contributed to the increase economic impact of MD in USA (Greenberg et al., 2015).

Among the studies performed in Europe, 5 investigated also the indirect costs; the absenteeism costs averaged € 14 330 with a standard deviation of € 6104 (range: between € 6046-€ 20 585), (Tomonaga et al., 2013; Sobocki et al., 2007; von Knorring et al., 2006; Ekman et al., 2013; ; Salvador-Carulla et al., 2011; Klein-Budde et al., 2013). Tomonaga et al. (2013) assessed the economic burden of depression in Switzerland, the loss of productivity was significantly associated with severity of depression, increased unemployment, disability and reduced work performance, in terms of workdays lost. The enormous impact of depression on patients' ability to work was shown, by the authors, with unemployment and

employment rates of 25.8% and 59.2%, respectively, with almost 50 workdays lost per year and an absenteeism value near to the European average. Von Knorring et al. (2006) emphasized the importance of the attention on the indirect costs and highlighted potential cost savings from a reduction in absences from work for patients responding to medical treatment, substantially lowering the indirect costs associated with the disease. Such a result is particularly relevant to the context where the study was performed, since costs for sickness absence in Sweden are high and increasing, and psychiatric disorders are the second most common reason for sick leave. In this setting, the absenteeism cost is more than € 20 000 per person. Another Swedish study of 2013 assessed the impact of indirect costs on the overall economic burden of MD (Ekman et al., 2013); the authors computed an absenteeism value of € 16 331. The indirect cost due to sick leave and early retirement was by far the largest cost item for patients with depression; treatment improvements that can bring back more patients to work, therefore, have the potential to lead to substantial cost offsets from the societal perspective. In Spain, Salvador-Carulla et al. (2011) calculated the absenteeism value with a particular attention on the difference between temporary and permanent disability. The value taken into account through this review is € 6046 of absenteeism for temporary disability, instead the loss of productivity due to permanent disability has a higher cost which amounted to € 21 318.

Concerning studies performed in the Asian setting, Sado et al. (2011) assessed the presentism cost around € 8647 per person. In Japan, the productivity loss of patients with depression who continue to work is enormous. In this situation, early interventions, such as effective screening along with access to appropriate treatment, could contain the social implications of this lack of productivity and work activity. The study conducted by Ho et al. (2013), in Singapore, evaluated the loss of productivity of a medium worker such as € 3058 per absenteeism and € 3121 per presentism. In this study, the weight of indirect cost is very relevant, representing approximately 80% of total costs per MD patient. Chang et al. (2012) estimated a social cost for morbidity of € 2859 for absenteeism and € 4498 for presentism for South Korea.

Among indirect cost, suicides, directly related to depressive illness, represent a tremendous burden for society. In the US, Greenberg et al. (2015) assessed the value of suicides in € 478 390 per patient, while in Spain and in Sweden the suicide cost was estimated in € 401 635 and € 454 334, respectively. In Japan, the cost per depression-related death was estimated in € 439 705; however, the suicide rate here is two and four times higher than in the US and in the UK, respectively (Sado et al., 2011). Considering that approximately half of the total costs of depression in Japan can be attributed to mortality costs, effective interventions to prevent suicides should be implemented. Regardless of the geographical location and the reference healthcare setting of the study, the economic burden of the suicides related to depression, exceeds € 400 000 per person, except for South Korea where a cost of about € 190 000/ suicide was computed (Chang et al., 2012).

Most of the studies included in this review concluded that the indirect cost is the most relevant share of the overall economic burden of major depression. Access to health care services, as well as, adequacy of the treatment received have been found to be strongly related to lower disability rates and avoidance of losses of productivity, measured in terms of absenteeism and presentism. Among indirect costs, the suicides have a significant and tremendous social impact and economic burden on the welfare system. Therefore, the investments in health and health plans related to depression may have a significant impact on social and economic system.

Figures 2 and 3 show the composition of the overall cost per patient with MD. In particular, Figure 2 only includes studies run under the third party payer perspective and, for this reason only focuses on direct health care costs. Figure 3 includes studies with a societal perspective, which focus also on indirect costs. The white dot on the secondary y axes represents the incidence of the total indirect cost (i.e. presentism + absenteeism) on the overall cost per patient.

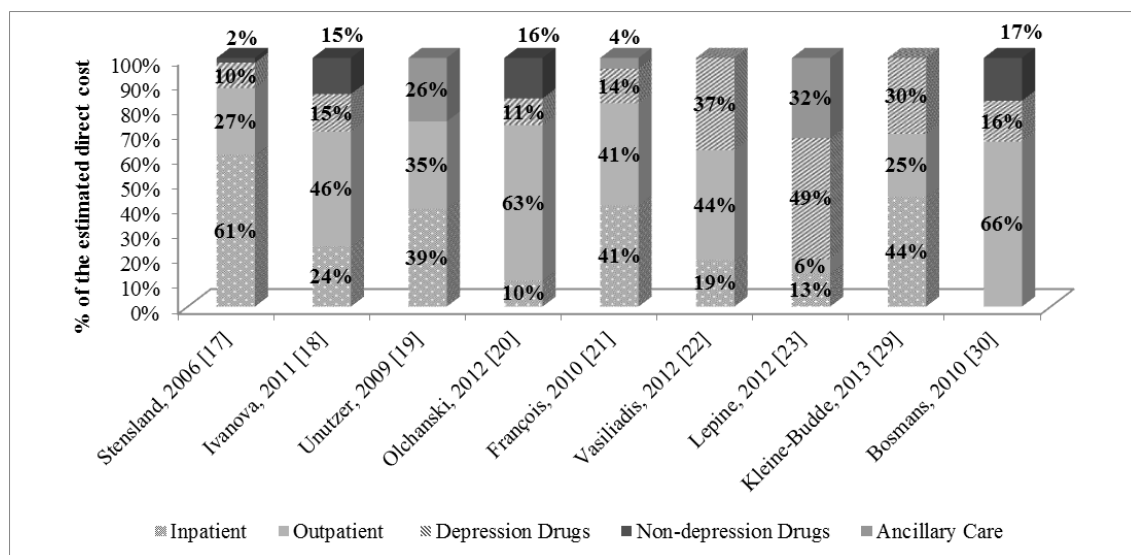


Figure 2. Direct health care cost in studies adopting the third party payer perspective.

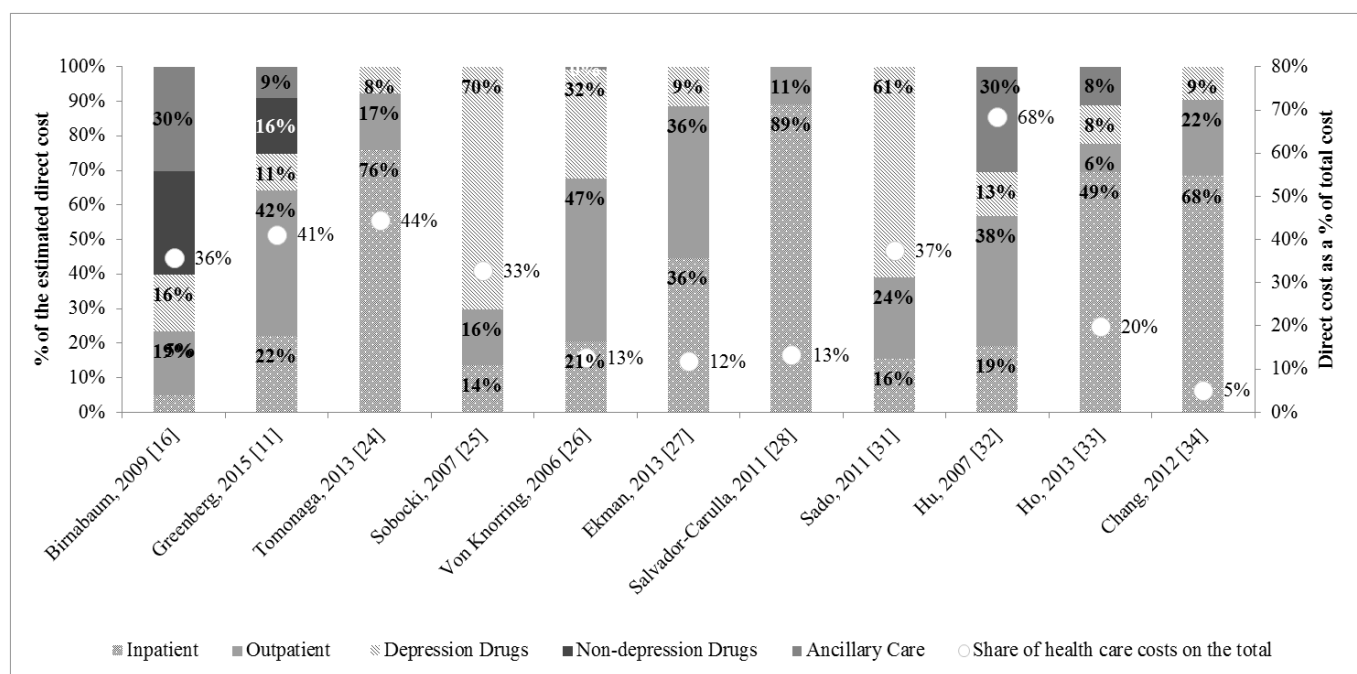


Figure 3. Direct health care cost in studies adopting the societal perspective.

4. Discussion

Depression is a health problem of paramount importance under the clinical, societal and economic point of view. Despite its severity, the evidence shows that depression is a severely under diagnosed disease in many countries and, very often, even when diagnosed, it is not properly treated.

The current review shed light on the societal cost of major depression worldwide. When indirect costs are taken into account, they represent the most significant share of the total cost of depression. These costs include loss of productivity for patients resulting from working days losses or decreased productivity in working places, losses of productivity for care givers and future income forgone due to suicides. Where estimated, the cost of loss of productivity at work, weighs more than the loss of productivity for absence from work. Despite this huge burden, indirect costs are usually overlooked in economic analysis on treatment strategies for major depression and even when computed they are hardly comparable across settings, due to the deep differences across welfare systems.

A recent study estimated the social cost of cognitive impairment in working patients with MD. Using a model the authors estimated the annual productivity losses due to MD-related cognitive impairment, by relating data concerning absenteeism and presentism to patients' cognitive function measured by a 10-point scale then converted into a Sheehan Disability Scale (SDS). Authors found a loss of € 1129 per patient per month attributable only to cognitive impairment. In the sensitivity analysis such a figure ranged between €1104 and 1464 according to the scale utilized to measure cognitive impairment. Compared to an healthy individual, a patient with major experiences a loss of productivity of 42,27% (Coretti et al., 2016).

Among direct health care costs, the most important items are hospitalizations and visits, whereas drugs represent a modest share of total direct cost. To this end, existing literature as well as real world evidence show that in the area of depression and mental disorders in general, a big problem of under-treatment or mistreatment exists. Some authors attribute this phenomenon to the lack of awareness of clinicians in the diagnostic phase and in the definition of the most appropriate pathway for the patient. Another branch of literature attributes such phenomenon to the lack of patient's compliance due to the reluctance to undertake the therapy to avoid social stigma (Lasalvia et al., 2013; Battaglia et al. 2004). Nonetheless, research that aims to design and evaluate comprehensive interventions aimed at minimizing stigma and social exclusion and facilitating access to care is still lacking (Lasalvia et al., 2013; Evans-lacko, Brohan, Mojtabai & Thornicroft, 2012).

Our study carries a few limitations that deserve mention. Firstly, the choice of strict inclusion criteria has limited the scope of the analysis to studies published in English in the last ten years. Such a choice may have determined the omission of potentially relevant pieces of evidence. However, usually studies published in international journals in English language have higher quality. Moreover, the choice of restricting the time span to the last ten years, was done because considering long time spans carries the risk of including cost-of-illness studies very heterogeneous in terms of state of art of clinical and technological practice. Another limitation is that the summary of evidence is only narrative. The great heterogeneity of the included studies prevented us from performing a quantitative synthesis of results.

On the other hand, our study sheds new light on the burden of this condition and the challenges for the management of patients with MD. In the current review, we found that spending for hospital admission is higher in contexts where spending on medical treatments is low. Appropriateness of medical treatments prescribed for MD is another topic that deserves attention in future research. A study conducted in Northern Italy showed that, regardless of the type drug utilized patients receiving medical treatments exhibited a lower hospitalization rate (Deambrosis, Terrazzini, Giusti, Pullia, & Chinellato, 2007). Moreover, a case-control study performed in Sardinia (Italy) showed that patients diagnosed with major depression require a higher health care resource consumption compared to the non-depressed individuals and to healthy ones. In addition, an increase in direct health care cost, such as drugs and hospital admission was found in patients without adequate medical treatment (Carta, Hardoy, Kovess, Dell'Oso and Carpinello, 2003).

5. Conclusions

Despite being one of the major causes of disability in the world, major depression is still largely under-diagnosed and undertreated, also due to the social stigma associated with it. Evidence on epidemiology of the disease as well as on its economic burden is now very fragmentary and poorly generalizable, due to the deep differences across settings. Nonetheless, our analysis allowed to draw some conclusions: i) hospitalization is often the most relevant cost item when looking at direct healthcare costs; the larger this item is the smaller is the expenditure on medical treatments. This relation probably means that complications are more usual when the medical management of disease is poor or inadequate. This aspect deserves a deeper investigation in future research; ii) most of the economic burden of disease is represented by productivity losses resulting in the indirect costs; this is due to the characteristics of the disease which affects individuals in their working age; iii) productivity losses from presentism are usually heavier than those resulting from absenteeism. These aspects should be further investigated in future research and need to be taken into account when performing economic evaluations of treatment strategies for patients with MD.

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