

Global economic burden of schizophrenia: a systematic review

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Background: Schizophrenia is one of the top 25 leading causes of disability worldwide in 2013. Despite its low prevalence, its health, social, and economic burden has been tremendous, not only for patients but also for families, caregivers, and the wider society. The magnitude of disease burden investigated in an economic burden study is an important source to policymakers in decision making. This study aims to systematically identify studies focusing on the economic burden of schizophrenia, describe the methods and data sources used, and summarize the findings of economic burden of schizophrenia.

Methods: A systematic review was performed for economic burden studies in schizophrenia using four electronic databases (Medline, EMBASE, PsycINFO, and EconLit) from inception to August 31, 2014.

Results: A total of 56 articles were included in this review. More than 80% of the studies were conducted in high-income countries. Most studies had undertaken a retrospective- and prevalence-based study design. The bottom-up approach was commonly employed to determine cost, while human capital method was used for indirect cost estimation. Database and literature were the most commonly used data sources in cost estimation in high-income countries, while chart review and interview were the main data sources in low and middle-income countries. Annual costs for the schizophrenia population in the country ranged from US\$94 million to US\$102 billion. Indirect costs contributed to 50%–85% of the total costs associated with schizophrenia. The economic burden of schizophrenia was estimated to range from 0.02% to 1.65% of the gross domestic product.

Conclusion: The enormous economic burden in schizophrenia is suggestive of the inadequate provision of health care services to these patients. An informed decision is achievable with the increasing recognition among public and policymakers that schizophrenia is burdensome. This results in better resource allocation and the development of policy-oriented research for this highly disabling yet under-recognized mental health disease.

Keywords: schizophrenia, economic burden, cost of illness, systematic review

Introduction

Schizophrenia is ranked among the top 25 leading causes of disability worldwide in 2013.¹ Despite its low lifetime prevalence (median 4.0 per 1,000 persons²) and point prevalence range from 2.6 to 6.7 per 1,000,^{3,4} health, social, and economic burden related to schizophrenia has been tremendous, not only for patients but also for families, other caregivers, and the wider society. The World Health Organization estimated that direct costs of schizophrenia in Western countries range from 1.6% to 2.6% of total health care expenditures, which in turn account for between 7% and 12% of the gross national product (GNP).⁵ In the US, the economic burden of schizophrenia is found to be more than US\$60 billion per year.⁶ Albeit the increasing evidence base, this multifaceted burden of schizophrenia remains underestimated.⁷ The substantial

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burden imposed by schizophrenia has been linked to the early onset of the disease and its incurable nature with persisting symptoms.⁸ Societies and communities find it increasingly difficult to offer support to schizophrenia patients through family and social bonds.⁹

With productivity losses as the largest component of the overall societal cost of schizophrenia,¹⁰ an economic burden study which often incorporates both direct and indirect costs serves as a useful source. Economic burden studies have primarily been employed to advise policymakers on resources allocation.¹¹ Economic burden studies, however, vary due to methodology differences and costs included. These include study settings, data sources, epidemiological approaches taken (eg, prevalence- or incidence-based), cost determination method (eg, top-down, bottom-up, or a combination of both), time frame of costs, and perspective (ie, societal or payer), all of which are important factors having substantial impact on the outcomes.

Previous literature review studies were focused on summarizing direct costs associated with schizophrenia.^{12,13} There has been a lack of emphasis on methodology details and indirect costs estimation, which prompts the need for a more comprehensive and updated review. This study aims to systematically identify studies focusing on the economic burden of schizophrenia, describe methods and data sources, and summarize the findings of the economic burden of schizophrenia.

Methods

Search strategy and data sources

A systematic review was performed for economic burden studies in schizophrenia using four electronic databases – Medline, EMBASE, PsycINFO, and EconLit. The search strategy was based on a broad combined search string “burden OR economic* OR cost* OR “cost of illness” OR resource OR expenditure” AND schizophrenia in abstract or title fields to retrieve potentially relevant publications from inception to August 31, 2014. Search strategies were limited to English and humans only.

Study selection

All identified studies were screened for relevance based on the predefined inclusion criteria. The inclusion criteria were an original research that: 1) reported cost of illness, economic burden, health care expenditure, or resource utilization for schizophrenia and 2) provided information on data sources. Studies on economic evaluation of drug or other treatment, and study population referring to a specific subgroup of schizophrenia patients only were excluded from the analysis.

Two reviewers (HYC, SLT) independently screened the identified studies based on the title and abstract using the aforementioned inclusion criteria. In case of disagreement, this was resolved by discussion between the two reviewers. Thereafter, the full-text of all potentially relevant studies was reviewed. A flow chart that illustrates the selection process is shown in Figure 1.

Quality assessment

Quality assessment is generally a crucial component of a systematic review.¹⁴ However, our review is focused mainly on describing the diversity of the methodology used in economic burden studies. Therefore, quality assessment is not relevant for our review.

Data extraction

A standardized data extraction form was used to extract data of all eligible studies. The data were extracted by HYC or SLT. In case of doubt, there was a consultation process to base the extraction upon consensus. Where possible, country, perspective, currency, pricing year, study design and approach, cost estimation methods, setting, study period/duration, sample size, cost components, data sources, and cost estimates were defined precisely.

For costs comparison across studies, the cost estimates were converted to 2013 US dollars, based on country-specific consumer price indices¹⁵ and exchange rate.¹⁶ If the year of the cost data was not reported, it was assumed to be the publication year of the article. Furthermore, the total cost estimates in term of gross domestic product (GDP) or GNP were extracted as originally published. To facilitate further comparisons across studies in terms of the magnitude of the total estimates relative to the GDP, the total cost as percentage of GDP 2013 of the country¹⁵ was estimated.

Methodological and costing approach

The study design was classified as retrospective, prospective, cross-sectional, or modeling-based; subsequently, the approach undertaken either as prevalence- or incidence-based was defined. Prevalence-based studies estimate the costs of all disease cases (new as well as pre-existing) in a given year.¹⁷ They include medical care costs and morbidity costs of schizophrenia within the study year.¹⁸ Incidence-based studies, on the other hand, estimate the lifetime costs of a disease from its onset to its termination, which include the discounted morbidity and mortality costs for the incident cohort, usually calculated based on the year when schizophrenia first appeared.¹⁸

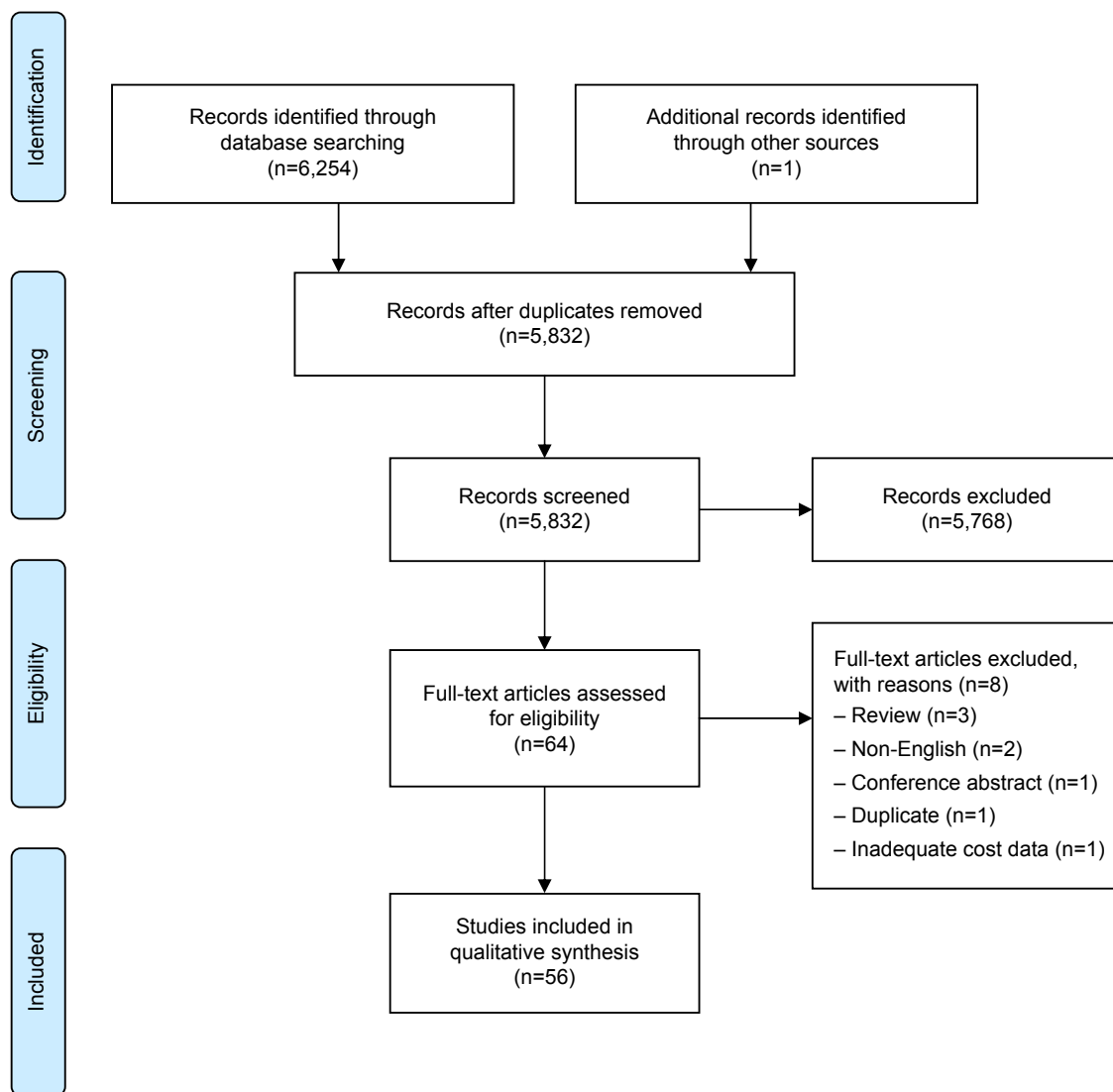


Figure 1 Flow diagram of the selection process to identify studies to be included.

To quantify the resources used, approaches commonly used are the top-down and bottom-up. The top-down approach estimates economic costs by using aggregate data on mortality, morbidity, hospital admissions, general practice consultations, disease-related costs, and other health-related indicators.¹⁸ Generally, this information is collected from national health care statistics, patient registers, and so on.¹⁸ The bottom-up approach calculates the resources utilization and productivity loss at the level of patient or individual.^{18,19} The mean per-person costs are usually then extrapolated to the whole population with relevant epidemiological data.¹⁸

Cost components and data sources

Broadly, the economic burden of schizophrenia can be reported as direct (medical and nonmedical), indirect costs, and intangible costs. Direct medical costs are expenditure for

hospital inpatient care, physician inpatient care, physician outpatient care, emergency department visits, community-based care, nursing home care, long-term institutional care, rehabilitation care, specialists' and other health professionals' care, diagnostic tests, prescription drugs, and medical supplies.²⁰ Direct nonmedical costs are the costs of nonhealth care resources, such as transportation, food, and lodging incurred during health care visit,²¹ and cost-associated social services.²²

Indirect costs are defined as productivity losses related to morbidity and premature mortality. Morbidity costs represent the monetary value of productivity loss due to absenteeism or sick leave (forgone work productivity), presenteeism (decreased work productivity), unemployment, permanent disability, and early retirement for patients, family members, or caregivers.^{20,23–26} On the other hand, mortality cost

is defined as the monetary value of lost production due to the premature death of the patient.²⁶ In addition, costs associated with other consequences such as incarceration are included.²⁷

The third category of costs is referred to as intangible costs. These relate to the deterioration in quality of life to patients, families, and friends due to other factors, such as pain or suffering.²¹ These costs are extremely difficult to quantify, and therefore are often omitted from economic studies.²⁸

Data sources were further classified into four major groups – database, chart, interview, and literature. Database is defined as a collection of health data in the form of: 1) population, household, and health survey; 2) surveillance data, including disease-specific registries, census, and national health accounts;¹⁵ and 3) electronic medical records, administrative, and claims database. Chart includes patient medical record and hospital record. Interview involves patient, caregiver, or health care provider/expert using structured/standardized questionnaire. Literature includes published or unpublished sources and governmental report/document.

Results

Study selection

The search strategy yielded 6,255 articles, of which 423 duplicates were removed. Of the remaining 5,832 articles, only 64 met the inclusion criteria and were retrieved to be reviewed in full-text. During the full-text screening, a further eight articles were excluded due to review paper (n=3), non-English publication (n=2), conference abstract (n=1), duplicate (n=1), and inadequate information on data sources (n=1). This resulted in a total of 56 relevant articles that were included in this review.

General methodological characteristics

The methodological characteristics of the included articles are summarized in Table 1. These studies were conducted for 24 countries covering four regions (25 in Europe,^{29–53} 16 in America,^{10,54–68} 13 in Asia Pacific,^{11,69–80} and 2 in Africa^{81,82}). More than two-third of the studies (48/56, 86%) were conducted in high-income countries (HIC), for example, the US (n=13), Spain (n=6), Germany (n=5), the UK (n=5), Sweden (n=4), and Australia (n=4).

Of the included studies, it was found that 24 studies^{10,11,31–33,36,39,43,44,52,53,55,57–61,63,65,67,68,73,77,79} were undertaken at the national level. Over half of the studies (30/56, 54%) were conducted in selected health care institutions,^{30,38,47,69,71,74–76,78,81,82} one or several provinces/states/counties,^{29,37,45,48,50,54,56,62,64,66,70,72} specific health care program for schizophrenia

patients,^{34,35,42,46,49,80} and an insurance scheme,⁵¹ while it was not reported in two studies.^{40,41}

Less than half of studies (23/56, 41%) explicitly stated the perspective undertaken. The societal perspective was the most commonly employed (n=16), followed by payer perspective (n=11).

Furthermore, most studies undertook a retrospective (n=24) and prevalence-based (n=53) study design. Only four studies employed an incidence-based approach where two adapted discrete event modeling³⁶ and Markov modeling,⁷⁹ respectively. It is noted that Davies and Drummond³¹ adopted both prevalence- and incidence-based design. Only three studies estimated the lifetime costs of schizophrenia using incidence-based approach^{31,79} and prevalence-based approach,⁶⁵ while the remaining studies presented the burden measurement as total cost and/or average cost per patient over a specific time period.

Generally, the most commonly used method to determine costs was bottom-up (n=37), followed by top-down (n=12), and a combination of both methods (n=7). Among 19 studies that adapted the top-down method,^{10,11,31,32,36–39,43,48,52,53,56,59,60,65,72,73,77} 16 were conducted using prevalence-based approach at the national level. It is noted that all 16 studies were conducted in HIC – Japan, South Korea, Taiwan, France, Ireland, the Netherlands, Spain, Sweden, UK, Canada, Puerto Rico, and the US.

Overall description of cost components and data sources for cost estimation

Among all included studies, 56 captured direct medical costs, 28 direct nonmedical costs, and 32 indirect costs. Only one study attempted to quantify intangible cost.⁴¹ Over a third of the studies (21/56, 38%) investigated direct medical, direct nonmedical, and indirect costs of schizophrenia.

An overview of the cost components included and data sources used in the estimation of direct medical, direct non-medical, and indirect cost among the studies is presented in Tables 2–4. All cost components and data sources used in each study are summarized in the [Supplementary table](#).

Direct medical costs

For the estimation of direct medical costs, the majority of the studies, besides from two studies,^{65,72} included costs associated with hospitalization (n=45), pharmacy (n=45), outpatient care (n=33), or home- and community-based care (n=31). In general, more than a third of the studies^{10,11,32,33,37,38,42,43,48,51,52,54–64,66–68,73,80} estimated the utilization data of direct medical cost using database (27/56, 48%), interview (n=20), literature (n=17), and chart (n=12) as the data source.

Table 1 Methodological characteristics of the included studies

Author	Country	Perspective	Cost (currency, year)	Study design	Study approach	General cost estimation method	Indirect cost estimation method	Setting	Study period/duration	Sample size (n)
Africa										
Amoo and Ogunlesi ⁸¹	Nigeria	NR	NGN 2005 ⁸¹	P	PB	Bottom-up	NR	Aro Neuropsychiatric Hospital and the Federal Medical Centre, Abeokuta	6 months	57
Suleiman et al ⁸²	Nigeria	NR	NGN 1997 ⁸² USD 1997 ⁸²	P	PB	Bottom-up	NA	Yaba Psychiatric Hospital	6 months	50
Asia Pacific										
Carr et al ⁷⁰	Australia	Payer societal	AUD 2000	P	PB	Bottom-up	Human capital	Four metropolitan Australian Capital Territory, Queensland, Victoria, Western Australia	1997–1998	980
Fitzgerald et al ⁸⁰	Australia	NR	AUD 2007 ⁸⁰	P	PB	Bottom-up	Human capital	As part of the Australian SCAP	3 years	347
Hall et al ⁷²	Australia	NR	USD 1975	R	IB	Top-down and bottom-up	Human capital	New South Wales	1974–1977	NR
Langley-Hawthorne ⁷⁹	Australia	NR	AUD 1997 ⁷⁹	Markov model	IB	Bottom-up	Human capital	National	NA	NR
Zhai et al ⁷⁸	People's Republic of China	NR	USD 2013 ⁷⁸	P	PB	Bottom-up	Human capital	Two centers in North and South China	2010	356
Grover et al ⁷¹	India	NR	INR 2005 ⁷¹	P	PB	Bottom-up	Human capital	Departments of psychiatry and endocrinology of a tertiary hospital	NR	50
Pahuja et al ⁷⁵	India	NR	INR 2011 ⁷⁵	P	PB	Bottom-up	NA	A tertiary care hospital in Kerala, India	6 months	25
Sado et al ⁷⁷	Japan	Societal	JPY 2008 USD 2008	CS	PB	Top-down	Human capital	National	2008	NR
Chang et al ¹¹	South Korea	Societal	USD 2005	R	PB	Top-down	Human capital	National	2005	161,058
de Silva et al ⁶⁹	Sri Lanka	NR	LKR 2012 ⁶⁹	P	PB	Bottom-up	Human capital	Outpatient psychiatry clinic of the National Hospital of Sri Lanka	2 months	91
Lang and Su ⁷³	Taiwan	NR	USD 1999	R	PB	Top-down	NA	National	NR	52,432
Lee et al ⁷⁴	Taiwan	Societal	USD 1999	P	PB	Bottom-up	Human capital	Psychiatric outpatient clinics in three cities: Tainan, Chiayi, Changhua	August 1999–May 2000	74
Phanthunane et al ⁷⁶	Thailand	Societal	THB 2008	P	PB	Bottom-up	Human capital	Nine hospitals	September to November 2008	429
Europe										
De Hert et al ³⁰	Belgium	NR	USD 1994	P	PB	Bottom-up	NA	Four psychiatrists' agendas and six hospital wards	1994	108

(Continued)

Table 1 (Continued)

Author	Country	Perspective	Cost (currency, year)	Study design	Study approach	General cost estimation method	Indirect cost estimation method	Setting	Study period/duration	Sample size (n)
Mangalore and Knapp ²	England	Societal	GBP 2007 ^a EUR 2007 ^b USD 2007 ^a	R	PB	Bottom-up	Human capital	As part of UK SCAP	NR	600
Rouillon ⁴⁴	France	Payer	USD 1992	CS	PB	Bottom-up	NA	National	November 1992	477
Sarlon et al ⁴⁸	France	NR	EUR 2007	P	PB	Top-down and bottom-up	Human capital	Three integrated areas in northern, central, and southern France	2 years	288
Heider et al ³⁸	France Germany UK	Payer	EUR 2000	P	PB	Top-down and bottom-up	NA	Three centers in France, four centers in Germany, and two centers in the UK	1998–2002	1,208
Frey ³³	Germany	Societal payer	EUR 2008	R	PB	Bottom-up	Friction cost	National	2005–2008	8,224
Salize and Rossler ⁴⁷	Germany	NR	USD 1994	P	PB	Bottom-up	NA	Two hospitals	1 year	66
Zeidler et al ⁵¹	Germany	Payer	EUR 2006	R	PB	Bottom-up	NA	One insurance scheme	2004–2006	9,946
Behan et al ⁵²	Ireland	NR	EUR 2006	R	PB	Top-down and bottom-up	Human capital	National	2006	10,126
Garattini ³⁴	Italy	Payer	EUR 1997	R	PB	Bottom-up	NA	14 CMHCs	September to December 1998	702
Garattini et al ³⁵	Italy	Payer	USD 1998	P	PB	Bottom-up	NA	14 CMHCs	1 year	643
Tarricone et al ⁴⁹	Italy	NR	ITL 1995	R	PB	Bottom-up	Human capital	10 CMHCs	1995	100
Evers and Arment ⁵³	the Netherlands	Societal	ANG 1989	R	PB	Top-down	Human capital	National	1989	NR
Knapp et al ⁴⁰	the Netherlands Denmark UK	NR	GBP 2002 ^b	R	PB	Bottom-up	NA	NR	3 months	404
Rund and Ruud ⁴⁵	Italy Spain Norway	NR	NOK 1994 USD 1994	P	PB	Bottom-up	NA	All treatment units serving six catchment areas	4 weeks	412
Saldivia Borquez et al ²⁹	Spain	NR	EUR 1999	NR	PB	Bottom-up	NA	Granada Province	1999	NR
Haro et al ³⁷	Spain	NR	USD 1994	P	PB	Top-down and bottom-up	Human capital	Three areas: Buriada, Cantabria, the Eixample	NR	112
Oliva-Moreno et al ⁴³	Spain	Payer	EUR 2002	R	PB	Top-down	NA	National	2002	NR
Vazquez-Polo et al ⁵⁰	Spain	Societal payer	EUR 1997	Markov Chain Monte Carlo simulation	PB	Bottom-up	NR	Four areas: Catalonia, Andalusia, Madrid, Navarre	3-year follow-up from 1997 (1998–2000)	356

Salize et al ¹⁶	Spain the Netherlands UK	NR	EUR 2004	P	PB	Bottom-up	NA	Community psychiatric services	12 months	507
Ekman et al ³²	Sweden	Societal	EUR 2009	R	PB	Top-down and bottom-up	Human capital	National	2006–2008	2,161
Hertzman ³⁹	Sweden	NR	SEK 1975	NR	PB	Top-down	Human capital	National	1975	NR
Lindstrom et al ⁴¹	Sweden	NR	SEK 2005	P	PB	Bottom-up	Human capital	NR	5 years	225
Davies and Drummond ³¹	UK	NR	GBP 1990/1991	NR	PB/IB	Top-down	Human capital	National	NR	185,400
Guest and Cookson ³⁶	UK	Societal payer	GBP 1997	Discrete event model	IB	Top-down	Human capital	National	5 years	7,500
America										
Leitao et al ⁶⁶	Brazil	NR	USD 1998	Decision tree model	PB	Bottom-up	NA	Sao Paulo	1998	120
Goeree et al ⁶⁰	Canada	Societal	CAD 2004	R	PB	Top-down	Friction cost	National	2004	234,305
Rubio-Stipec et al ⁶⁵	Puerto Rico	Societal	USD 1994 ^a	CS	PB	Top-down	Human capital	National	NR	NR
Bartels et al ⁵⁴	US	NR	USD 1999	R	PB	Bottom-up	NA	New Hampshire	January 1– December 31, 1999	9,844
Crown et al ⁵⁵	US	NR	USD 2001 ^a	R	PB	Bottom-up	NA	National	1991–1993	665
Cuffel et al ⁵⁶	US	NR	USD 1986	R	PB	Top-down	NA	San Diego	1986 and 1990	15,403; 16,206
Desai et al ⁵⁷	US	Societal	USD 2008	R	PB	Bottom-up	Human capital	National	2005–2008	348
Dixon et al ⁵⁸	US	Payer	USD 2001 ^a	R	PB	Bottom-up	NA	National	1991	12,440
Feldman et al ⁵⁹	US	NR	USD 2010	R	PB	Top-down	NA	National	2003–2008	36,852
Gunderson and Moshier ⁶⁸	US	Societal	USD 1975 ^a	R	PB	Bottom-up	Human capital	National	1968, 1971, 1973	NR
Leslie and Rosenheck ⁶¹	US	NR	USD 1993	R	PB	Bottom-up	NA	National	1993–1995	3,456; 3,759
Martin and Miller ⁶²	US	NR	USD 1998 ^a	R	PB	Bottom-up	NA	Georgia	January 1, 1991– December 31, 1993	6,443
McDonald et al ⁶³	US	NR	USD 2005 ^a	CS	PB	Bottom-up	NA	National	2001–2002	571,000
Miller and Martin ⁶⁴	US	NR	USD 1995	R	PB	Bottom-up	NA	Georgia	1990–1997	16,227
Wu et al ¹⁰	US	Societal	USD 2002	R	PB	Top-down and bottom-up	Human capital	National	2000–2003	NR
Wyatt et al ⁶⁷	US	NR	USD 1995 ^a	NR	PB	Bottom-up	NR	National	1991	NA

Note: ^aIf no price-year was reported in a study, the year of publication was referred as the year of pricing.

Abbreviations: ANG, Dutch guilder; AUD, Australian dollar; CAD, Canadian dollar; CMMHC, community mental health center; CS, cross-sectional; EUR, Euro; GBP, British pound; IB, incidence-based; INR, Indian rupee; ITL, Italian lira; JPY, Japanese yen; LKR, Sri Lankan rupee; NA, not applicable; NGN, Nigerian naira; NOK, Norwegian krone; NR, not reported or insufficient information; P, prospective; PB, prevalence-based; R, retrospective; SCAP, schizophrenia care and assessment program; SEK, Swedish krona; THB, Thai baht; USD, US dollar.

Table 2 Direct medical cost components and data sources used in cost estimation

Author	Cost components							Data source for utilization data					
	Hospital inpatient	Outpatient	Emergency care	Professional fees ^a	Pharmacy ^b	Laboratory	Day unit	Community-based care ^c	Others	Database	Interview	Chart	Literature
Africa													
Amoo and Ogunlesi ⁸¹	-	-	-	+	+	+	-	-	Registration fees, feeding/bedding	✓			
Suleiman et al ⁸²	-	+	-	+	+	-	-	-		✓			
Asia Pacific													
Carr et al ⁷⁰	+	+	+	+	+	-	+	+	Out-of-pocket expenditure				✓
Fitzgerald et al ⁸⁰	+	+	+	-	+	-	+	+		✓			
Hall et al ⁷²	-	-	-	-	-	-	-	-	Unspecified			✓	✓
Langley-Hawthorne ⁷⁹	+	+	-	+	+	-	+	+				✓	
Zhai et al ⁷⁸	-	-	-	-	+	-	-	-	Unspecified Infrastructure	✓	✓		
Grover et al ⁷¹	-	-	-	+	+	-	-	-	Out-of-pocket expenditure	✓	✓		
Pahuja et al ⁷⁵	+	-	-	+	+	+	-	-				✓	
Sado et al ⁷⁷	+	+	-	-	-	-	-	-					✓
Chang et al ¹¹	+	+	-	-	+	-	+	+	Alternative treatment	✓			✓
de Silva et al ⁶⁹	-	-	-	+	+	-	-	-		✓			
Lang and Su ⁷³	-	-	-	-	+	-	+	+	Alternative treatment	✓	✓		
Lee et al ⁷⁴	+	+	+	-	+	-	+	+	Nonmedication therapy	✓	✓		
Phanthunane et al ⁷⁶	+	+	-	-	+	-	-	-				✓	
Europe													
De Hert et al ³⁰	+	-	-	+	+	-	-	-				✓	
Mangalore and Knapp ⁴²	+	-	+	+	+	-	+	+		✓			
Rouillon ⁴⁴	+	-	-	+	+	-	-	-	Intermediate facilities	✓	✓		✓
Sarlon et al ⁴⁸	+	-	-	+	+	-	+	+		✓	✓		
Heider et al ³⁸	+	-	-	+	+	-	-	-		✓	✓		
Frey ³³	-	-	+	-	+	+	+	+	Out-of-pocket expenditure	✓			
Salize and Rossler ⁴⁷	+	+	-	-	+	-	-	-				✓	
Zeidler et al ⁵¹	+	+	-	-	+	-	-	-	Unspecified	✓			✓
Behan et al ⁵²	+	+	+	+	+	-	+	+		✓			
Garattini ³⁴	+	+	-	-	+	+	+	+				✓	
Garattini et al ³⁵	+	+	-	-	+	+	+	+				✓	

Table 3 Direct nonmedical cost components and data sources used in cost estimation

Author	Cost component					Data sources for utilization data			
	Homeless shelter	Social service/voluntary and NGO sector	Travel, food, and lodging	Suicide-related	Others	Database	Interview	Chart	Literature
Africa									
Amoo and Ogunlesi ⁸¹	-	-	+	-	Pocket money for patients and nurses		√		
Suleiman et al ⁸²	-	-	+	-	-		√		
Asia Pacific									
Carr et al ⁷⁰	+	+	-	-	-				√
Langley-Hawthorne ⁷⁹	+	-	-	-	-				√
Zhai et al ⁷⁸	-	-	-	-	Unspecified		√		
Grover et al ⁷¹	-	-	+	-	-		√		
Sado et al ⁷⁷	-	+	-	-	-				√
Chang et al ¹¹	+	-	+	-	-				√
de Silva et al ⁶⁹	-	-	+	-	-		√		
Lee et al ⁷⁴	+	+	+	-	Community resources		√		
Phanthunane et al ⁷⁶	-	-	+	-	-		√		
Europe									
De Hert et al ³⁰	+	-	-	-	-		√		
Mangalore and Knapp ⁴²	+	+	-	-	-	√			√
Rouillon ⁴⁴	-	+	-	-	-		√		√
Frey ³³	-	-	+	-	Housekeeping, administrative, hospital investments	√			
Salize and Rossler ⁴⁷	+	-	-	-	-			√	
Behan et al ⁵²	+	+	-	-	-				√
Evers and Ament ⁵³	+	-	-	-	-				√
Knapp et al ⁴⁰	+	-	-	-	-		√		
Vazquez-Polo et al ⁵⁰	+	+	-	-	-		√		
Salize et al ⁴⁶	+	-	-	-	-			√	
Lindstrom et al ⁴¹	+	-	-	-	-	NR	NR	NR	NR
Guest and Cookson ³⁶	+	-	-	-	-		√		√
America									
Goeree et al ⁶⁰	+	-	-	+	-				√
Gunderson and Mosher ⁶⁸	-	-	-	-	Research				√
Martin and Miller ⁶²	-	-	+	-	-	√			
Wu et al ¹⁰	+	-	-	-	Research and training				√
Wyatt et al ⁶⁷	+	-	-	+	-		√		√

Notes: + included; - not included; √ data source used.

Abbreviations: NGO, non-governmental organization; NR, not reported or insufficient information.

In 48 studies^{10,11,29-59,60-65,67,68,70,72-74,77,79,80} conducted in HIC, database (n=26) and literature (n=16) were most commonly applied as the data source. Claims database was used as the primary data source in ten studies. In contrast, from the eight studies conducted in low- and middle-income countries (LMIC), interview (n=7) was the most commonly used data source for direct medical cost estimation, followed by chart (n=4).

Direct nonmedical costs

A total of 28 studies^{10,11,30,33,36,40-42,44,46,47,50,52,53,60,62,67-71,74,76-79,81,82} estimated the direct nonmedical cost in which homeless shelter

(n=18), travel, food, and lodging expenses (n=9), social care (n=7), and suicide-related (n=2) costs were measured. Data sources used to estimate utilization data of these costs were interview (n=12), literature (n=11), database (n=4), and chart (n=2).

In 28 studies that estimated direct nonmedical costs, literature (n=12) and interview (n=8) were the main data sources used in HIC, while interview (n=6) was used in LMIC.

Indirect costs

In 32 studies that included indirect cost estimates, the human capital approach was used in 27 studies. Friction cost

Table 4 Indirect cost components and data sources used in cost estimation

Author	Cost component							Data sources for utilization data						
	Absenteeism	Presenteeism	Unemployment	Morbidity ^a	Premature mortality	Income assistance	Legal costs	Law enforcement ^b	Informal care	Others	Database	Interview	Chart	Literature
Africa														
Amoo and Ogunles ⁸¹	-	-	+	-	-	-	-	-	+	-	-	✓	-	-
Suleiman et al ⁸²	-	-	-	-	-	-	-	+	+	Accident and damages, unspecified productivity loss	-	✓	-	-
Asia Pacific														
Carr et al ⁷⁰	-	-	-	+	-	+	+	-	+	Tax foregone, unspecified productivity loss	-	-	-	✓
Fitzgerald et al ⁸⁰	-	-	-	-	-	+	+	-	-	Tax foregone, unspecified productivity loss	✓	-	-	✓
Hall et al ⁷²	-	-	-	-	-	-	-	-	-	Unspecified productivity loss	-	-	-	✓
Langley-Hawthorne ⁷⁹	-	-	+	-	-	+	-	-	-	-	-	-	-	✓
Zhai et al ⁷⁸	+	-	-	+	+	-	-	-	+	Accident and damages	-	✓	-	-
Grover et al ⁷¹	+	-	-	-	-	-	-	-	+	Unspecified productivity loss	-	✓	-	-
Sado et al ⁷⁷	-	-	+	+	+	-	-	-	-	Unspecified productivity loss	-	✓	-	✓
Chang et al ¹¹	-	+	+	-	+	-	+	-	+	-	-	-	-	✓
de Silva et al ⁶⁹	+	-	+	-	-	-	-	-	+	Unspecified productivity loss	-	✓	-	-
Lee et al ⁷⁴	-	-	-	-	-	-	-	-	+	-	-	✓	-	-
Phanthunane et al ⁷⁶	+	+	-	-	-	-	-	-	+	-	-	✓	-	-
Europe														
Mangalore and Knapp ⁴²	+	-	+	-	+	-	-	+	-	-	-	✓	-	✓

(Continued)

Table 4 (Continued)

Author	Cost component				Data sources for utilization data									
	Absenteeism	Presenteeism	Unemployment	Morbidity ^a	Premature mortality	Income assistance	Legal costs	Law enforcement ^b	Informal care	Others	Database	Interview	Chart	Literature
Sarlon et al ⁴⁸	+	-	+	-	-	-	-	-	-	-	✓			✓
Frey ³³	+	-	-	+	+	-	-	-	+	-	✓			✓
Behan et al ⁵²	+	-	+	-	+	-	-	+	+	-	✓			✓
Tarricone et al ⁴⁹	+	-	-	-	-	-	-	-	+	-	✓			✓
Evers and Ament ⁵³	+	-	-	+	-	-	-	-	-	-				✓
Haro et al ³⁷	-	-	-	-	-	-	-	-	+	Unspecified productivity loss	NR	NR	NR	NR
Oliva-Moreno et al ⁴³	-	-	-	-	-	-	-	-	+	-				✓
Ekman et al ³²	+	-	-	+	-	-	-	-	-	-				✓
Hertzman ³⁹	-	-	-	+	+	-	-	-	-	Short-term illness				✓
Lindstrom et al ⁴¹	-	-	-	-	-	-	-	-	-	Unspecified productivity loss	NR	NR	NR	NR
Davies and Drummond ³¹	-	-	+	-	-	-	-	-	-	Unspecified productivity loss	NR	NR	NR	NR
Guest and Cookson ³⁶	+	-	+	-	+	-	-	+	+	-	✓			✓
America														
Goeree et al ⁶⁰	-	-	-	+	+	+	-	+	-	-				✓
Rubio-Stipec et al ⁶⁵	-	-	-	-	-	-	-	-	-	Unspecified productivity loss				✓
Desai et al ⁵⁷	+	+	-	-	+	-	-	-	+	-	✓			✓
Gunderson and Mosher ⁴⁸	-	-	-	-	-	+	-	-	-	Unspecified productivity loss				✓
Wu et al ¹⁰	+	+	+	-	+	-	-	+	+	-				✓
Wyatt et al ⁶⁷	-	-	-	-	+	+	+	-	+	Unspecified productivity loss		✓		

Notes: ^aIncludes permanent disability and early retirement. ^bIncludes incarceration, crime, and police contact. + included; - not included; ✓ data source used. Abbreviation: NR, not reported or insufficient information.

approach was used in two studies in Germany and Canada.^{33,60}

To estimate indirect costs, more than half (19/32, 59%) took into account informal care cost. Furthermore, other main components calculated were productivity loss associated with absenteeism (n=14), premature mortality (n=12), and unemployment (n=11). These indirect costs were estimated mainly based on literature (n=19), interview (n=15), and database (n=5) as their data sources.

Literature (n=19) was used as the main data source in studies from HIC, while it was interview (n=6) in studies from LMIC. In addition, it is found that published mean wage was used as the unit cost in the estimation of productivity loss in all studies from HIC, while reported individual wage obtained from the interview performed was used in three studies from LMIC.^{69,71,76}

Cost estimates of schizophrenia

Cost estimates from 15 national studies that investigated both direct and indirect costs are presented in Table 5 in terms of cost in US dollars in 2013, and the share of the direct medical cost, direct nonmedical cost, and indirect cost. The total cost estimates reported varied significantly where annual costs for the schizophrenia population in the country reported ranged from US\$94 million in Puerto Rico⁶⁵ to US\$102,396 million in the US.⁶⁷ Furthermore, there was a substantial difference

in annual cost estimates in studies conducted in the same country where US\$123 million³² to US\$9,134 million³⁹ in Sweden and US\$25,452 million⁵⁷ to US\$102,396 million⁶⁷ in the US was found.

Notably, indirect costs contributed to 50%–85% of the overall costs associated with schizophrenia in 12 national studies;^{10,11,32,36,39,52,57,60,65,67,68,77} only three studies reported otherwise.^{33,43,53} Similar findings were noted in six studies from LMIC with direct and indirect cost estimates; the contribution of indirect costs to total annual costs is demonstrated to range from 63% to 82% as compared to direct costs,^{69,71,76,78} except for two studies from Nigeria.^{81,82} The cost estimates in LMIC are shown in Table 6.

Only three studies reported the total annual costs incurred by schizophrenia as percentage of GDP^{70,74} or GNP⁶⁸ in the country. However, results varied significantly where it was 0.23%–0.36% GDP in Australia, 5.46% GDP in Taiwan, and 2% GNP in the US. In the 15 national studies,^{10,11,32,33,36,39,43,52,53,57,60,65,67,68,77} the total cost as % GDP in the country estimated was found to range from 0.02% in UK³⁶ to 1.65% in Sweden.³⁹

Discussion

This is the first systematic review summarizing the methodologies used in estimating economic burden of schizophrenia globally. We focused on describing the methodology adopted and its practice. Trends in adopting certain methodological

Table 5 Annual cost estimate of direct and indirect costs and total cost as % of GDP (USD 2013) in national studies

Author	Country	Cost estimates (USD 2013, millions)				Cost contribution to total cost (%)			Total cost as % GDP (USD 2013)
		Direct medical cost	Direct nonmedical cost	Indirect cost	Total	Direct medical cost	Direct nonmedical cost	Indirect cost	
Asia Pacific									
Sado et al ⁷⁷	Japan	7,247	33	18,950	26,230	28	<0.1	72	0.52
Chang et al ¹¹	South Korea	519	36	3,204	3,759	14	1	85	0.31
Europe									
Behan et al ⁵²	Ireland	172	13	488	673	25	2	73	0.30
Frey ³³	Germany	10,635	354	8,978	19,967	53	2	45	0.56
Evers and Ament ⁵³	the Netherlands	774	50	70	894	87	6	8	0.11
Olivia-Moreno et al ⁴³	Spain	1,882	NA	1,669	3,552	53	NA	47	0.26
Ekman et al ³²	Sweden	29	NA	94	123	24	NA	76	0.02
Hertzman ³⁹	Sweden	3,712	NA	5,422	9,134	41	NA	59	1.65
Guest and Cookson ³⁶	UK	154	49	199	403	38	12	50	0.02
America									
Goeree et al ⁶⁰	Canada	2,111	102	5,287	7,500	28	<0.1	72	0.41
Rubio-Stipeck et al ⁶⁵	Puerto Rico	31	NA	63	94	33	NA	67	0.09
Desai et al ⁵⁷	US	4,742	NA	20,710	25,452	19	NA	81	0.15
Wu et al ¹⁰	US	29,279	12,014	41,714	83,007	35	14	50	0.50
Wyatt et al ⁶⁷	US	27,745	4,054	70,597	102,396	27	4	69	0.61
Gunderson and Mosher ⁶⁸	US	12,078	57	48,200	60,335	20	<0.1	80	0.36

Abbreviations: GDP, gross domestic product; NA, not applicable; USD, US dollar.

Table 6 Annual cost estimate of direct and indirect costs in LMIC

Author	Country	Cost estimates (USD 2013)				Cost contribution to total cost (%)		
		Direct medical cost	Direct nonmedical cost	Indirect cost	Total	Direct medical cost	Direct nonmedical cost	Indirect cost
Amoo and Ogunlesi ⁸¹	Nigeria	9,882 ^a	NR	3,604	13,486	73 ^a	NR	27
Suleiman et al ⁸²	Nigeria	2,951	80	430	3,461	85	2	12
Zhai et al ⁷⁸	People's Republic of China	257,980	44,237	515,297	817,514	32	5	63
Grover et al ⁷¹	India	1,814	718	4,310	6,842	27	10	63
de Silva et al ⁶⁹	Sri Lanka	25,075	186	111,574	136,834	18	0.1	82
Phanthunane et al ⁷⁶	Thailand	6,661,900	521,900	17,613,000	24,796,800	27	2	71

Note: ^aIncludes direct nonmedical cost.

Abbreviations: USD, US dollar; NR, not reported or insufficient information; LMIC, low- and middle-income countries.

aspects were observed, attributed to data availability and accessibility, methodological feasibility, and practicality.

Our study revealed that the data sources used for estimating economic burden of schizophrenia were distinctively different between HIC and LMIC. We found that electronic database was the most common data source for HIC as it provided more representative cost estimates given its large sample size. This was not the case for LMIC where electronic database was less available and accessible, leading to the use of interview and chart review for data collection. Even though interview is resource-intensive, it can capture out-of-pocket expenditures. We believe that the use of multiple data sources is needed to enhance comprehensiveness of cost findings since one single data source will not be able to capture all relevant costs.

Of all studies reviewed, prevalence-based approach was the most frequently used. However, for chronic illnesses such as schizophrenia, incidence-based approach is more relevant,⁸³ by informing the lifetime costs potentially saved by averting a case of schizophrenia. Prevalence-based studies, however, could be interpreted as a snapshot of the costs incurred by schizophrenia in a year.⁸³ Nevertheless, less data and fewer assumptions required for a prevalence-based approach enhanced its practicality.⁸³ It is recommended for future economic burden studies to implement both study designs alongside to obtain complementary findings.

Our findings revealed indirect costs contributed most to the overall costs in economic burden studies conducted from societal perspective. Economic burden studies conducted from a narrower perspective, excluding indirect costs, consequently underestimated costs incurred by schizophrenia substantially. Unless the purpose of economic burden study is to serve as evidence for payers only, the inclusion of indirect costs is warranted to measure economic burden impacted by schizophrenia on the society. Nevertheless, the accuracy of indirect costs is subjected to the cost estimation method applied.

In estimating indirect costs, human capital method was found to be more prevalent than friction cost method in our review. In view of the theory behind both methods, friction cost method appears to yield more realistic estimates than human capital method in chronic diseases, such as schizophrenia.⁸⁴ This is because long-term absences due to schizophrenia or associated mortality will be covered by a person drawn from the pool of unemployed.⁸⁵ Therefore, there is a little loss to society overall.⁸⁵ Often, due to its practicality and broad scope, human capital method might have been chosen. Considering the strengths and limitations of both methods,⁸⁶ it is highly recommended to use both methods when conducting economic burden analysis to provide comprehensive indirect cost estimates, and thus its comparability can be enhanced.

In addition to the cost components typically captured, special cost components were captured in some studies in our review,^{10,11,30,36,40–42,46,47,49,50,52,53,60,67,70,74,78,79,82} namely, homeless shelter, law enforcement, and accident and damage. In a broader perspective, the prevalence of homelessness is potentially linked to social isolation, stigmatization, and caregiver burden; violent behavior associated with schizophrenia could have contributed to the costs of law enforcement and accident and damage. These special cost components were somewhat specific to schizophrenia which can have a substantial impact on the society in terms of economic and humanistic burden.⁸⁷ While not all studies in our analysis valued these cost components, we highlight its existence of this kind of special cost component and its contribution to overall economic burden of schizophrenia.

Our systematic review showed that all included studies revealed substantial economic impact associated with schizophrenia. The annual costs were estimated to be in the range of US\$94 million to US\$102 billion, which translated into 0.02%–5.46% of GDP. In addition, the economic burden reported in slightly less than half of the

national studies (7/15, 47%) ranged between 0.30% and 0.60% GDP, consistent with those reported in Asia Pacific region. However, there were some extremely low estimates particularly in countries with tax-funded health care during the study period, namely, Sweden, the UK, and Puerto Rico. Therefore, this discrepancy was likely due to the differences in health care system, pattern of resource utilization, scope of cost components, diversity of the sampled populations, and data sources used.^{20,88} Nevertheless, this magnitude of economic burden demonstrated that schizophrenia has been inadequately treated which underscores the need for a comprehensive approach to controlling its impact.

This review is useful to inform health policymakers on the current status of economic burden studies in schizophrenia. In addition, this review advocates increasing the awareness of public and policymakers to recognize schizophrenia as a burdensome illness. In turn, more resources need to be allocated in treating the illness and develop new lines of policy-oriented research targeted on schizophrenia.

Our systematic review is different from previous review studies in a number of aspects. Previous review studies focused only on quantitative findings on the economic burden of schizophrenia.^{12,13} They did not provide a summary of the methodologies undertaken and discuss the implications of methodology on the findings. This present review provides an overall comprehensive comparison of methodologies used in economic burden studies, which could generate insightful information for future economic studies in adopting the relevant methodological approach. In addition, we performed a review using a systematic approach following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement, which led to a better and more comprehensive summary of the overall economic burden studies in current literature.

A limitation of this systematic review is the inclusion of only English literature. It was clear that a number of literatures have been published in local languages, which are evident to be more prevalent among LMIC.⁸⁹ We intentionally excluded non-English literature because of our limited capacity to understand non-English language. During our exhaustive search, we identified two non-English articles which might have provided more information if we had broadened our inclusion criteria.

Our study highlighted the variety of methodological approaches in estimating the economic burden of schizophrenia. On a similar note, it is also crucial to report explicitly on cost components incorporated and their calculations. In order to improve the comparison and interpretation of the

economic burden findings, we recognize and recommend the need to develop a guidance document in both the conduct and reporting of future studies for estimating the economic burden of schizophrenia.

Conclusion

Despite the wide variation in methodologies and cost components in studies reviewed, there is a general consensus which can be drawn that schizophrenia imposes a substantial economic burden on society mainly driven by high indirect costs. Understanding the magnitude of the wide-ranging economic and social burden of schizophrenia among policymakers enables informed decisions to be made by establishing health care priorities and allocating scarce resources for this highly disabling yet under-recognized mental health disease.

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