Original Article

Cost of Illness Trends of Schizophrenia from 2010 to 2022: A Systematic Review

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Abstract

Background: Schizophrenia is a severe and complicated mental disorder that often manifests early and is accompanied by cognitive or behavioural abnormalities. It severely affects the patient's family and the surrounding community.
Objectives: This research aimed to conduct a systematic review of the recently published cost of illness articles on Schizophrenia from 2010 to 2022. Besides, it aimed to compare the direct medical and non-medical costs and indirect costs of Schizophrenia across several countries.
Methods: All costs associated with schizophrenia, including direct medical costs, direct non-medical costs, and indirect costs, are considered in this systematic review. Electronic databases were searched, including PubMed, EMBASE, Web of Science, PsycINFO, OpenSIGLE, Wiley Online, and Science Direct. This research adopted Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) to document systematic reviews. Search tactics are developed concerning schizophrenia using the health economics terms such as cost analysis, direct medical costs, hospital cost, and indirect costs.
Results: Nineteen of the articles were included because they fulfilled the established inclusion criteria. From the articles included, 36.8% (7/19) were from Asia, 31.5 % (6/19) from Europe, 21.1 % (4/19) from America, 5.2 % (1/19) from Africa, and 5.2 % (1/19) from Australia. The direct medical costs were 13.5 to 40.1% of the total community cost. At the same time, the indirect costs ranged from 35.9 to 83.0%.
Conclusion: This review emphasizes the cost of illness articles across countries, mainly from 2010 to 2022. This review might open new horizons in practice for future schizophrenia COI studies.

Keywords: Schizophrenia, Cost of Illness, Health Economic, Direct Medical Costs, Direct Non-Medical Costs, Indirect Cost.

1. INTRODUCTION

Schizophrenia (SCZ) can be marked by acute psychotic conditions such as delusional agitation, abnormal manic or melancholy crisis, and visual hallucinations that look like a dream in a state of mental confusion. The frequency of SCZ cases rose from 13.1 million in 2010 to 20.9 million in 2018 (WHO, 2020). The costs associated with SCZ are complicated to assess due to the wide range of services used and the necessity to ascribe the expenses included in the estimations. According to a comprehensive assessment of several publications, SCZ has an average lifetime incidence of 0.4 % worldwide (Cahoon, et al., 2018; Hairong He, et al., 2020; Crespo-Facorro, et al., 2020; Ayano, et al., 2019)). An analysis of retrospective data from the United States (US) suggests that the average yearly cost of SCZ is between $23,887 and $24,988 (Cahoon et al., 2018). Due to the frequent episodes of relapse that patients have, patients may have higher costs. Furthermore, pilot research based on the medical literature found that indirect medical expenses are linked to productivity loss. Such indirect medical expenditures are approximately four times greater than direct medical expenditures in Malaysia (Teoh et al., 2017), 8.5 times in China (Zhang et al., 2018), and three times in the United Kingdom (UK) (Mangalore & Knapp, 2007). Concerning the community, SCZ patients' life expectancy was shortened by up to 20 years (Pinho et al., 2018).
Additionally, SCZ significantly affects those who provide care for the patients. Patients' and carers' health may be impacted by the disease's socio-cognitive procedures, the experience of seeking aid, and interactions within families (Chen, et al., 2019). Caregivers' burdens can also negatively impact their health and quality of life, socialization, and economic state. Cost of illness analysis might produce data that shows the costs and effects of various uses of finite resources, which can be used as evidence by decision-makers (Huajie Jin, et al., 2020). Despite the wide range of available medications for the treatment of schizophrenia, therapeutic therapies continue to be burdensome and challenging because of unfavorable side effects. To reconcile therapeutic outcomes with resources used, pharmacoeconomic evidence is therefore necessary.
Prior systematic reviews assessed on SCZ costs researches released after 2010 (Buck, et al., 2017; Christensen, et al., 2020; Fasseeh, et al., 2018; Jin, et al., 2020; Praveena, et al., 2020; Wang, et al., 2021; Zhai, et al., 2013). However, none of them went into detail about the treatment plans or the techniques used. Additionally, the majority of them have a broad range of publication years, making it difficult to discern researches done recently. Current study aimed to review the latest framework cost of illness analysis on psychiatric drugs that have been published and to present a concise summary of the statistical approaches, such as model structures, base settings, the integration and interpretation of clinical events, and facility value selection.

2. Cost of Illness Studies

Surveys on SCZ costs are valuable for understanding the amount a disease will cost a community. These details can point out areas for illness and treatment procedures that require development, which can help with planning for health care and identifying research priorities (Jin et al., 2020). Furthermore, research on SCZ costs indices offers crucial data for the cost of illness, cost-feasibility, and cost-benefit analyses, which are used in the economic assessment of health care interventions. The critical methodological considerations while evaluating a study on contingent-owned tools are briefly summarized below.

2.1. Analysis and costs assessed Perspective

The illness cost publications may be undertaken from various angles, such as that of society or the healthcare system, based on its goals. The perspective option could significantly affect actual cost estimations (Cabello-Rangel et al., 2020). A study of illness costs will often adopt the perspective of the sponsoring organization (Canady, 2021). However, economists favour the social viewpoint and reduce potential bias in more limited perspectives.

2.2. Epidemiological approach

Prevalence and incidence rate-based approaches are the two most noteworthy methods for studying costs of illness by most researchers. Regardless of when an illness began, the first method may be used to calculate the expenses of the disease over a specific time frame, often one year. An alternative, an incidence-rate-based method, may calculate the total lifetime illness expenses for patients who begin the research period (Evensen et al., 2015).

2.3. Estimating resource consumption

The three primary methods for predicting resource utilization are the top-down, bottom-up, and econometric approaches. The top-down method assigns a part of overall expenditures (attributable costs) to the disease of interest using data aggregated with a causal subset of the population. The bottom-up strategy estimates the typical costs of medical care per patient and multiplies them by the condition's prevalence (Crivera et al., 2011). In the econometric method, the costs incurred in a population group are contrasted with the expenditures predicted for that group in the absence of disease. Cost estimates are occasionally significantly impacted by the strategy picked. As there is no definite agreement, every strategy is viable. The disease or risk factor under examination, the study's question, and the data at hand all play a significant role in determining whether the method for estimating resource consumption is acceptable. The causal subset of the population and aggregate statistics (such as total healthcare spending) are frequently used in the top-down method to determine the allocated costs. Typically, the bottom-up strategy needs information and unit prices from several sources at the patient level. The econometric strategy needs the least amount of data since it frequently just needs one database on how those use resources without the condition.

2.4. Retrospective COI

All events would have occurred at the start of retrospective research on the expenses associated with treating a patient's disease. The cost of the aggregated historical resource consumption data will be set at a price first from the base year. In contrast, the research on the future costs of illness began before any significant events that might later be important. In order to get data, researchers can thus create ways for gathering it and then follow patients over time (Jin et al., 2020).

2.5. Cost components

All costs associated with illness, including direct medical costs, direct non-medical costs, and indirect costs, must be considered in a thorough analysis of the costs of illness. Inpatient, outpatient, community care, nursing home care, rehabilitation care, diagnostic tests, and medications are just a few examples of the direct medical costs that result from treating a disease and its effects. Subsidized living expenditures, transportation, and private expenses are non-medical direct costs. Indirect costs include reductions in patients' or caregivers' (informal care) productivity brought on by illness and treatment, any disabilities brought on by illnesses (illness costs), and any premature deaths like suicide (mortality costs). Indirect costs are frequently employed in accounting for overhead expenses and other patient-level health care service costs.

3. Methods

The systematic review was conducted according to the PRISMA standards (Liberati et al., 2009) to document systematic reviews and meta-analyses of research that assesses medical treatments. review.

3.1. Search Method

Electronic databases include PubMed, EMBASE, Web of Science, PsycINFO, OpenSIGLE, Wiley Online, and Science Direct. The search strategy included the following medical terms: schizophrenia, psychosis, delusion, hallucinations, thought disorder, hebephrenia, catatonia, and paranoia. It also included the following health economics terms: direct medical costs, direct non-medical costs, and indirect costs, that are components of cost of illness analysis. A particular language or nation did not limit the search. However, it is limited to period of time, particularly from 2010 – 2022.

3.2. Quality Assessment

For this review, economic assessment indexes by (Mangalore & Knapp, 2007) and (Crivera et al., 2011) were considered. They differ in terms of the quality assessment's aim and the types of research used for the different econometric assessments. For reference lists to be helpful in the present evaluation, they should concentrate on the studies' methodological quality and offer an in-depth assessment of that quality. This will help the reviewers compare and summarize the included research's methodological standards.

3.3. Data Abstraction

All information on disease status, direct medical components costs, study setting, resource use data sources, sample size, and time frame were all abstracted using a formalized data collection form. All expenses were changed to USD since it is used to compare the values of several currencies using the US dollar as a standard benchmark. The currency conversion rate is based on the year of the study. It uses purchasing power parity conversions to convert local currencies into USD (Shemilt et al., 2010). The average exchange rate cost is considered when comparing summary estimates of inpatient and outpatient expenditures. The comprehensive assessment of the literature search results was carried out by two reviewers (Alotaibi and Ong), who compared the titles and abstracts to the inclusion criteria. Then, all information for research that could be helpful was acquired, and inclusion criteria were evaluated. Studies were ultimately included in the review, as both reviewers agreed.

3.4. Selection of Publications

Multifarious strategies have been devised to ensure that pertinent research is not overlooked. First, all articles included in the current analysis had their reference lists verified for any additional studies that an automated search strategy could have overlooked. Second, it was determined if essential health economists' primary papers and publications should be included and whether any new pertinent articles should be developed. Last but not least, research, including all literature reviews found by the search undertaken for the current systematic review, were double-checked for any additional studies that electronic search algorithms could have overlooked.

The assessment checklist by (Allison & Moss 2011) outlines the pre-established inclusion and exclusion criteria. The research was included if:

I. The subjects of interest were children, teens, or adults diagnosed with schizophrenia or psychosis.

II. The research that uses a social viewpoint includes both direct and indirect costs.

At the very least, the direct medical expenses cover inpatient, outpatient, and community charges. Indirect medical costs must take into account patient productivity loss as a result of the disease. On the other hand, articles were excluded if they did any of the following:

I. The researchers evaluate the cost of illness for various schizophrenia therapies or discuss the costs of the interventions.

II. The cost of interest is not disclosed and cannot be recovered.

III. Researchers only include patients who are getting a particular type of intervention and at a specific stage of the disease. For instance, patients who have relapsed or are being treated in a particular setting (for example, outpatient only) are said not to be typical of the entire population with schizophrenia.

IV. Researches only focus on one stage of SCZ disease, such as relapse.

V. Researches conducted over 20 years ago (before 2000) are not likely to apply to contemporary procedures and expenses.

VI. Articles that are not presented in English. Only publications published in English were included in the review, even though there were no language constraints placed on the study.

3.5. Presentation of Cost Estimate

In the prevalence-based research, the annualized medical cost per patient served as the primary outcome. The costs indicated by previous investigations were reported with different time horizons and converted to annual costs. The lifetime cost per patient served as the leading indicator in incidence-based research. The authors estimated the cost per patient when the available data permitted, even if it was not published. The patient's or condition features, the baseline analysis, the costing procedures, and the variables contributing to cost rises were considered secondary outcomes. Separate cost estimates have been provided for each of the cost components. The criteria of "direct medical costs," "direct non-medical costs and "indirect medical costs" utilized in the research included in this review varied. For instance, although some research saw informal care (losses in caregiver productivity) as an indirect cost, some studies included it as a direct non-medical expense. All cost elements given by the included studies were reclassified to ensure consistency using the criteria below:

First, the direct medical costs. Such costs cover inpatient, outpatient, community, medication, diagnosis and other expenditures to the health care system. Second, direct non-medical costs. They are not tied to providing medical treatment. However, they are associated with costs of accommodation, the legal cost, and the costs of administering social welfare benefits, transportation, private expenses, and any other direct costs not related to health care. Third, the indirect costs. They are related to caregivers' lost productivity and patients' lost productivity due to illness or passing away.

The cost of illness analysis was considered in thorough research and welfare benefits. These studies thus did not include the authors' social welfare advantages. The administrative cost of welfare benefits is considered in this study if it is recorded separately, as it is an extra expense associated with schizophrenia. When a caregiver is an employee and qualifies for paid leave to care for sick family members, the indirect medical costs that result from such absence may also be accounted for as transportation expenses. Researchers cannot, however, determine the percentage of caregiver productivity losses that are compensable for social care since the cost of illness analysis studies seldom provides information regarding the work status of caregivers and their eligibility for care allowance.

Utilizing the "Campbell and Cochrane Economics Methods Group" of the Center for Information and Coordination on Policy and Practice (CCEMG-EEPPI) to the cost converter at: https://eppi.ioe.ac.uk/costconversion/, all costings reported by the included research findings were converted into USD (Shemilt et al., 2010). An indicator of GDP contraction is the annual price adjustment while purchasing power parities of GDP are used in currency conversion. The key finding of this review is the cost

of illness analysis of SCZ, a substantial amount of which reflects indirect medical expenses like lost productivity. Hence, the GDP deflator is chosen rather than the health service deflator.

4. Results

A total of 3,176 titles and abstracts were examined after duplicates were removed, 191 articles were obtained. 19 of these criteria were included because they satisfied the established inclusion criteria. As indicated by (McHugh, 2012), the two reviewers' agreement, as determined by Kappa and Cohen's supervision, was 0.52, which denotes a reasonable level of agreement for inclusion of studies. The method of choosing literature is shown in Figure 1.

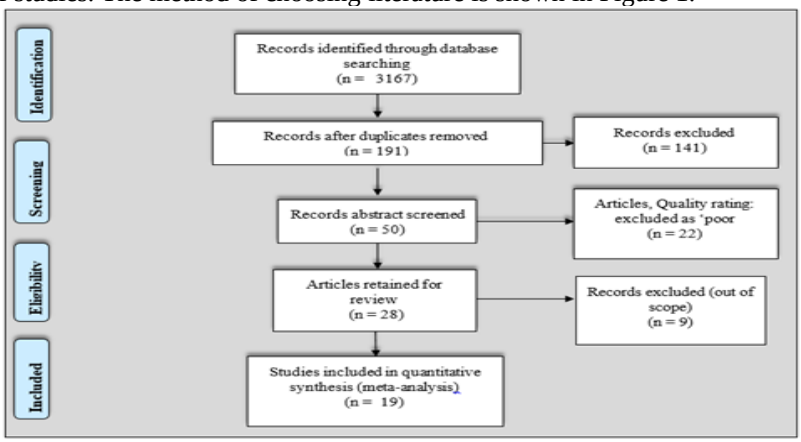

Figure 1: Systematic Review and Articles Exclusion Process for Review

To ensure that all relevant publications were incorporated into this review, the contents of 19 published publications were examined.

4.1. Study Characteristics

Table 1 provides an outline of the features of the included articles. 14/19 of the included articles evaluated the cost of schizophrenia after 2015. In the initial five publications, one research analysed expenses in 2010, while the other four articles examined expenditures between 2011 and 2015. Of the articles included, 36.8% (7/19) were from Asia, 31.5 % (6/19) from Europe, 21.1 % (4/19) from America, 5.2 % (1/19) from Africa, and 5.2 % (1/19) from Australia. Between 100 and 11,682 people with schizophrenia were included in those publications as a sample size used to determine costs.

Table 1. Characteristics of included studies

		Patients' characteristics			
Study	**Country**	**Inclusion criteria**	**Sample size for cost calculation**	**Age (years)**	**Male (%)**
Sado et al, 2013	Japan	Societal burden of SCZ: Direct and indirect medical costs (People with SCZ)	N/A	≥15	Not reported
Teoh et al, 2017	Malaysia	Patients with schizophrenia.	417	All ages	66.0
Zhang et al, 2018	China	Schizophrenic patients in China.	365	≥18	60.5
Phanthunane et al, 2010	Thailand	All Thai patients had a main diagnosis of schizophrenia.	11,682	≥15	49.5
Jo, et al., 2020	South Korea	Schizophrenia patients who enrolled as having a mental disability, or who died from schizo-phrenia/committed suicide from 2006 to 2016.	2,400	≥15	54.3
Abdin et al, 2021	Singapore	Adult SCZ patients in Singapore.	6126	18-64	52.0
Yan et al, 2019	China	All SCZ patients enrolled in an FDP	4,008	Not reported	Not reported

Sarlon et al, 2013	France	French Schizophrenic patients during 2 years of prospective follow-up.	288	≥15	51.4
Evensen et al, 2015	Norway	All patients who are registered in the Norwegian Patient Register.	8,399	All ages	N/A
Hastrup et al, 2019	Denmark	Schizophrenic who have just received a diagnosis.	12,227	All ages	Not reported
Siagian et al, 2015	UK	Individuals diagnosed with SCZ	N/A	Not reported	Not reported
Gouveia et al, 2015	Portugal	Treated patients with SCZ.	4,041	15-60	60.5
Pletscher, et al. 2014	Switzerland	SCZ patients, caregivers and society as a whole	N/A	Not reported	Not reported
Galletly et al, 2016	Australia	SCZ Therapy, schizophreniform disease, or schizoaffective disorder	N/A	Not reported	Not reported
Oloniniyi et al, 2019	Nigeria	Adults with SCZ in Nigeria .	100	35	48.0
Lecomte et al 2022	Canada	Individuals with either primary or secondary SCZ diagnoses.	N/A	Not reported	Not reported
Keepers et al 2020	USA	Individuals with a primary or secondary diagnosis of schizophrenia	N/A	All ages	Not reported
Barbosa et al, 2018	Brazil	SCZ patients (adults).	174,310	≥18	51.7
Cloutier et al, 2016	USA	All individuals diagnosed with SCZ.	2,144	All ages	55.7

4.2. Data Sources and Methods Employed by Included Studies

4.2.1 Cost estimates

Various components are used to depict the cost of illness analysis of SCZ for the research listed in Table 2. The cost of living for a patient with a recent diagnosis of schizophrenia was included in the study (Pletscher et al., 2014). In Australia, the total lifetime cost was $988,264, with lost productivity costs of $595,537 (or 60.3%) and direct medical cost expenditures of $302,812 (or 30.6%) being the other costs (9.1 %). The remaining studies showed how much each patient with schizophrenia costs the community annually. The overall social cost ranged from $5,818 in Thailand to $94,587 in Norway. There were vast divergences in the proportion of societal cost per patient to GDP per capita, ranging from 37% in Switzerland (Pletscher et al., 2014) to 214% in the United Kingdom (Siagian et al., 2015).

Direct medical costs were 19.5% of the total community cost (Teoh et al., 2017), whereas indirect costs were 80.5%. The lowest percentage ranging from 0.3 to 18.2 (Zhang et al., 2018), is for direct non-medical costs. The annual direct medical costs, measured in absolute terms, varied from $1,445 in Thailand (Phanthunane et al., 2010) to $60,630 in Norway (Evensen et al., 2015). Twelve authors showed that the annual direct non-medical costs ranged from $113 in Thailand (Phanthunane et al., 2010) to $8,237 in the US (Cloutier et al., 2016), with the former being the highest. Between Thailand (Phanthunane et al., 2010) and the United Kingdom (Hastrup et al., 2019), annual indirect medical costs varied from $4,260 to $62,431.

Tables 2, 3, 4, and 5 provide details on the expenditures associated with direct medical costs, direct non-medical, and indirect costs correspondingly.

Table 2. Summary of cost per schizophrenic, by each cost component

Study	**Country**	**Annual cost per patient** (in 2022 USD)				**Total costs cost/ GDP per capita**
		Direct medical cost (percentage)	**Direct non-medical cost** (percentage)	**Indirect cost** (percentage)	**Total costs cost**	
Sado et al, 2013	Japan	$ 13,166 (25.5%)	$ 2,518 (4.9%)	$ 35,950 (69.6%)	$ 51,634	106%

Teoh et al, 2017	Malaysia	$ 6,657 (19.5%)	×	$ 27,426 (80.5%)	$ 34,083	61%
Zhang et al, 2018	China	$ 10,572 (22.8%)	×	$ 35,886 (77.2%)	$ 46,458	95%
Jo et al, 2020	South Korea	$ 15,928 (52.8%)	$ 760 (2.5%)	$ 13,451 (44.6%)	$ 30,140	73%
Phanthunane et al, 2010	Thailand	$ 1,445 (24.8%)	$ 113 (1.9%)	$ 4,260 (73.2%)	$ 5,818	107%
Abdin et al, 2021	Singapore	$ 3,204 (13.5%)	$ 817 (3.5%)	$ 19,635 (83.0%)	$ 23,657	86%
Yan et al, 2019	China	$ 302,812 (30.6%)	$ 89,915 (9.1%)	$ 595,537 (60.3%)	$ 988,264	1,914%
Evensen et al, 2015	Norway	$ 60,630 (64.1%)	×	$ 33,958 (35.9%)	$ 94,587	169%
Sarlon et al, 2013	France	$ 6,950 (23.3%)	$ 1,862 (6.2%)	$ 21,052 (70.5%)	$ 29,864	68%
Hastrup et al, 2019	Denmark	$ 19,121 (38.3%)	$ 6,418 (12.9%)	$ 24,380 (48.8%)	$ 49,919	113%
(Siagian et al, 2015)	UK	$ 31,560 (33.5%)	$ 238 (0.3%)	$ 62,431 (66.3%)	$ 94,229	214%
Gouveia et al, 2015	Portugal	$ 7,334 (24.1%)	$ 2,672 (8.8%)	$ 20,399 (67.1%)	$ 30,405	37%
Pletscher et al, 2014	Switzerland	$ 5,946 (33.8%)	$ 3,034 (17.3%)	$ 8,589 (48.9%)	$ 17,569	54%
Galletly et al, 2016	Australia	$ 6,302 (49.8%)	×	$ 6,358 (50.2%)	$ 12,660	48%
Oloniniyi et al, 2019	Nigeria	$ 8,770 (32.7%)	×	$ 18,061 (67.3%)	$ 26,831	71%
Keepers et al, 2020	USA	$ 6,823 (36.8%)	$ 3,369 (18.2%)	$ 8,339 (45.0%)	$ 18,531	57%
Lecomte et al, 2022	Canada	$ 4,123 (19.6%)	$ 1,975 (9.4%)	$ 14,987 (71.1%)	$ 21,085	48%
Barbosa et al, 2018	Brazil	$ 9,365 (27.7%)	×	$ 24,486 (72.3%)	$ 33,851	104%
Cloutier et al, 2016	USA	$ 20,073 (36.3%)	$ 8,237 (14.9%)	$ 28,600 (51.6%)	$ 55,373	99%

4.2.2 Direct Medical Costs

Table 3 displays specifics on direct medical costs. Thailand had the lowest yearly inpatient cost at USD 732 (Phanthunane et al., 2010), while Norway had the highest at USD 36,577 (Evensen et al., 2015). Nigeria had the lowest annual outpatient/community costs, with USD 905 (Oloniniyi et al., 2019), and Norway had the highest, with USD 21 569. Table 3. Outline of direct medical costs for each schizophrenic

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Study	**Country**	**Direct medical costs per schizophrenia patient** (in 2022 USD)				
		Inpatient cost	Outpatient /community cost	Medication	Other direct medical cost	**Total direct medical cost per patient**
Sado et al, 2013	Japan	$ 3,601 (27.4%)	$ 8,903 (67.6%)	$ 662 (5.0%)	×	$ 13,166
Teoh et al, 2017	Malaysia	$ 1,452 (21.8%)	$ 2,678 (40.2%)	$ 2,473 (37.2%)	$ 53 (0.8%)	$ 6,657
Zhang et al, 2018	China	$ 4,849 (45.9%)	$ 3,946 (37.3%)	$ 1,777 (16.8%)	×	$ 10,572
Jo et al, 2020	South Korea	$ 7,882 (49.5%)	$ 5,221 (32.8%)	$ 2,033 (12.8%)	$ 792 (5.0%)	$ 15,928
Phanthunane et al, 2010	Thailand	$ 732 (50.7%)	$ 260 (18.0%)	$ 240 (16.6%)	$ 213 (14.7%)	$ 1,445

Abdin et al, 2021	Singapore	$ 2,442 (76.2%)	$ 2,664 (20.7%)	$ 100 (3.1%)	×	$ 3,204
Yan et al, 2019	China	$ 242,275 (80.0%)	$ 6,852 (12.2%)	$ 7,233 (2.4%)	$ 16,451 (5.4%)	$ 302,812
Evensen et al, 2015	Norway	$ 36,577 (60.3%)	$ 21,569 (35.6%)	$ 2,484 (4.1%)	$0 (0.0%)	$ 60,630
Sarlon et al, 2013	France	$ 5,382 (77.4%)	$ 1,621 (8.9%)	$ 653 (9.4%)	$ 294 (4.2%)	$ 6,950
Hastrup et al, 2019	Denmark	$ 13,099 (68.5%)	$ 5,522 (28.9%)	$ 499 (2.6%)	×	$ 19,121
Siagian et al, 2015	UK	$ 17,668 (56.0%)	No separate results	No separate results	×	$ 31,560
Gouveia et al, 2015	Portugal	$ 4,816 (65.7%)	$ 1,474 (20.1%)	$ 1,016 (13.9%)	$ 28 (0.4%)	$ 7,334
Pletscher et al, 2014	Switzerland	$ 1,314 (22.1%)	No separate results	$ 202 (3.4%)	$ 4,429 (74.5%)	$ 5,946
Galletly et al, 2016	Australia	$ 4,319 (68.5%)	$ 1,200 (3.2%)	$ 1,525 (24.2%)	$ 256 (4.1%)	$ 6,302
Oloniniyi et al, 2019	Nigeria	$ 3,450 (39.3%)	$ 905 (44.5%)	$ 1,415 (16.1%)	×	$ 8,770
Lecomte et al, 2022	Canada	$ 3,002 (72.8%)	$ 1,401 (9.7%)	$ 262 (6.3%)	$ 458 (11.1%)	$ 4,123
Keepers, et al, 2020	USA	$ 1,478 (21.7%)	$ 1636 (9.3%)	$ 226 (3.3%)	$ 4,482 (65.7%)	$ 6,823
Barbosa et al, 2018	Brazil	$ 7,364 (78.6%)	$ 1,809 (19.3%)	No separate results	$ 192 (2.1%)	$ 9,365
Cloutier et al, 2016	USA	$ 2,442 (12.2%)	$ 6,139 (30.6%)	$ 4,455 (22.2%)	$ 7,038 (35.1%)	$ 20,073

4.2.3 Direct Non-Medical Costs

Table 4 presents the costing data for immediate non-medical expenditures. 13/19 publications provided direct non-medical costs. Administrative and sheltered home expenditures were the most often mentioned direct non-medical costs. The yearly administrative costs ranged from USD 21 in China (Zhang et al., 2018) to USD 365 in Japan (Sado et al., 2013). However, the cost of sheltered accommodation differed from USD 173 in Thailand to $6,056 in South Korea (Jo et al., 2020).

Table 4. Outline of direct non-medical costs for each schizophrenic

Study	**Country**	**Direct non-medical cost per schizophrenia patient** (in 2022 U.S dollar)						
		Sheltered home	Legal cost	Administration of benefits	Transport costs	Private expenditure	Other direct non-medical cost	**Total direct non-medical cost**
Sado et al, 2013	Japan	$ 1,022 (40.6%)	$ 1,131 (44.9%)	$ 365 (14.5%)	×	×	×	$ 2,518
Teoh et al, 2017	Malaysia	×	×	$ 100 (33.0%)	$ 144 (18.9%)	×	$ 365 (48.0%)	$ 760
Zhang et al, 2018	China	$ 1,483 (79.7%)	$ 357 (19.2%)	$ 21 (1.2%)	×	×	×	$ 1,862
Jo et al, 2020	South Korea	$ 6,056 (94.4%)	$ 362 (5.6%)	×	×	×	×	$ 6,418
Phanthunane et al, 2010	Thailand	$ 173 (21.1%)	$ 64 (7.7%)	×	$ 55 (6.7%)	×	$ 526 (64.4%)	$ 817
Evensen et al, 2015	Norway	$ 1,407 (71.2%)	$ 380 (19.2%)	$ 189 (9.5%)	×	×	×	$ 1,975
Sarlon et al, 2013	France	No separate results	$ 17 (7.4%)	$ 219 (92.5%)	No separate results	×	×	$ 238

Hastrup et al, 2019	Denmark	$ 2,672 (100.0%)	×	×	×	×	×	$ 2,672
Siagian et al, 2015	UK	$ 3,027 (89.9%)	$ 264 (7.8%)	$ 78 (2.3%)	×	×	×	$ 3,369
Gouveia et al, 2015	Portugal	$ 5,650 (68.6%)	$ 2,330 (28.3%)	×	×	×	$ 257 (3.1%)	$ 8,237
Galletly et al, 2016	Australia	$ 2,632 (86.7%)	$ 328 (10.8%)	$ 77 (2.5%)	×	×	×	$ 3,034
Lecomte et al, 2022	Canada	×	×	×	$ 113 (100.0 %)	×	×	$ 113
Keepers et al, 2020	USA	*$1 89,915 (100.0%)*	×	×	×	×	×	*$ 89,915*

4.2.4 Indirect Costs

Table 5 presents the publications concerning indirect costs of SCZ. The indirect costs are expressed in terms of "productivity loss". Caregiver lost productivity was considered in 14 out of the 19 included studies. In Switzerland (Pletscher et al., 2014), and Nigeria (Oloniniyi et al., 2019) the caregiver lost productivity to overall production loss, ranging from 2.2 % to 87.9 %, respectively. There was nine research that used opportunity cost. These nine studies assessed yearly productivity losses for caregivers ranging from $538 in Switzerland (Pletscher et al., 2014) to $28,600 in Canada (Lecomte et al., 2022), while the lifetime cost was estimated to be $21052 in Portugal (Gouveia et al., 2015). One research from Brazil employed replacement costs and found that caregiver productivity losses totaled $9,805 (Barbosa et al., 2018). Two American investigations mentioned no technique, which found those caregiver productivity losses varied from $1,552 (Keepers et al., 2020) to $1,025 (Cloutier et al., 2016).

Patient productivity losses as a result of morbidity were observed in all reviewed papers. The productivity loss for combined illness and death was $4,188 in just one research that used the friction cost approach (Lecomte et al., 2022). The remaining publications, which also utilized the human capital approach, found that productivity losses resulting from morbidity ranged from $228 in Switzerland (Pletscher et al., 2014) to $38,800 in Brazil (Barbosa et al., 2018).

Fourteen articles indicated reductions in patient productivity due to mortality among the representative surveys taken into account. The productivity losses caused by mortality varied from $541 in Niagara (Oloniniyi et al., 2019) to $13,824 in Brazil (Barbosa et al., 2018). The friction cost method studies determined that the production losses linked to mortality ranged from $1 in Portugal (Gouveia et al., 2015) to $7,656 in France (Yan et al., 2019). Production losses owing to mortality in France totaled $7,656 adopted willing to pay analysis (Sarlon et al., 2013).

Table 5. Outline of indirect costs for each schizophrenic

Study	**Country**	**Indirect costs per schizophrenia patient** (in 2022 U.S dollar)			
		Carer's lost productivity (percentage)	Patient's lost productivity due to morbidity (percentage)	Patient's lost productivity due to mortality (percentage)	**Total indirect medical cost**
Jo et al, 2020	South Korea	×	$ 18,061 (100.0%)	×	$ 18,061
Yan et al, 2019	China	$ 1,422 (17.1%)	$ 6,175 (74.1%)	$ 742 (8.9%)	$ 8,339
Abdin et al, 2021	Singapore	$ 732 (17.2%)	$ 3,528 (82.8%)	×	$ 4,260
Sarlon et al, 2013	France	$ 4,919 (13.7%)	$ 23,375 (65.0%)	$ 7,656 (21.3%)	$ 35,950
Hastrup et al, 2019	Denmark	$ 8,705 (31.7%)	$ 17,429 (63.6%)	$ 1,290 (4.7%)	$ 27,426
Siagian et al, 2015	UK	×	$ 35,886 (100.0%)	×	$ 35,886
Evensen et al, 2015	Norway	$ 1,555 (18.1%)	$ 6,246 (72.7%)	$ 788 (9.2%)	$ 8,589
Gouveia et al, 2015	Portugal	×	$ 21,051 (100.0%)	$ 1 (0.0%)	$ 21,052
Pletscher et al, 2014	Switzerland	$ 538 (2.2%)	$ 22,795 (93.5%)	$ 1,046 (4.3%)	$ 24,380

Galletly et al, 2016	Australia	×	$ 33,958 (100.0%)	×	$ 33,958
Oloniniyi et al, 2019	Nigeria	$ 5,590 (87.9%)	$ 228 (3.6%)	$ 541 (8.5%)	$ 6,358
Barbosa et al, 2018	Brazil	$ 9,805 (15.7%)	$ 38,800 (62.2%)	$ 13,824 (22.1%)	$ 62,431
Cloutier et al, 2016	USA	$ 1,025 (5.0%)	$ 19,373 (95.0%)	×	$ 20,399
Lecomte et al, 2022	Canada	$ 6,978 (24.4%)	$ 20,651 (72.2%)	$ 972 (3.4%)	$ 28,600

5. Discussion

This systematic review demonstrated the substantial financial cost of SCZ. For the direct medical costs, the direct medical costs ranged from 19.5% ($6, 6657) in Malaysia (Teoh et al., 2017), to 64.1% ($ 69,630) in Norway (Evensen et al., 2015). It also highlighted the prime expenditures connected with SCZ and contributing variables to the escalating costs. The cost per patient with SCZ to GDP per capita for 2020 was different as there were considerable divergences in the expenditure of SCZ among various nations. The annual cost of SCZ per patient is higher in Europe compared to Asia or Africa. One cause for this deviation could be due to the difference in the economic status and the discrepancy in the healthcare system across nations, particularly the availability of healthcare capacity—besides, the method in COI analyses mainly for productivity losses and direct non-medical expenditures.

This article looked at the annual cost of schizophrenics across the countries. In five of the 19 included papers, subgroup analysis was used. The SCZ costs to society were highest for people with schizophrenia aged 40-65 ($ 24,112), followed by the ones aged 25 to 39 ($ 21,304). While people with schizophrenia under the age of 25 were the lowest with $ 19,930. According to a modelling study, the three most costly treatment cycles are long-term high dependency cycles ($249,756), high dependency followed by a stable cycle ($222,679), and high dependency cycle followed by transverse cycle ($207.024). The initial recovery period was the least expensive ($5 596) to treat.

Sensitivity analysis findings were presented in nine out of the 19 included publications. Research stated that all of their cost estimates were reliable. Nevertheless, another paper reported that all of their cost projections were reliable, except for the incidence of SCZ.

Due to the variousness of healthcare systems among nations, the form of direct non-medical expenditures is feasible to differ extensively. Though mod of incorporated publications contended to use a viewpoint, six journals did not have any direct non-medical costs. For the 13 journals that did assume direct non-medical costs, there is an interpretation concerning the type of non-medical costs included. Patient satisfaction with social relationships, patient contentment with financial circumstances, and recurrence of symptoms during the follow-up period were shown to be substantially linked to more significant direct medical expenses.

6. Limitation

These findings, however, need to be interpreted with care for some reasons. First, comorbidity was not considered. Second, factors that are linked to more significant expenses are not always linked to factors that are linked to higher direct medical expenditures of SCZ. Third, analysis model pinpoints numerous characteristics, including a decline in gender and work status, that were linked to increased SCZ's direct medical costs.

Even though the included publications help draw attention to the economic burden of SCZ and raise awareness, they do not reveal information on how well resources are used. As a result, decision-makers who want to lessen the cost of SCZ must consult various types of data, such as cost-effectiveness, cost-utility, and cost-benefit analysis.

Since 2010, most publications on SCZ have covered all aspects, such as medical decisions and settings, mental health management, and the economic burden. Each variable will influence the magnitude and cost structure of SCZ. Therefore, the discoveries of the included publications should be carefully deciphered.

7. Conclusion and Recommendation

This paper emphasizes the significant financial burden and cost-related factors of schizophrenia. The vast methodological interpretation of the cost of illness studies for SCZ is further shown in this work. Seventeen included publications employed the prevalence-based model. While the other 2 used an incidence-based model. This could be attributed to the fact that prevalence-based models require only gathering data for a specified period and that no assumptions about the upcoming session of schizophrenia are required. The prevalence-based models might be adequate if judgments are merely interested in getting a quick picture of the present burden of SCZ. The incidence method, nonetheless, is more suitable for decision-makers curious about how expenditures vary across various phases as well as the possible advantages achieved by averting SCZ. Thus, to better

understand the incidence of SCZ, future incidence-based COI analysis that employs the most recent empirical evidence and incorporates distinct illness trajectories could be carried out.

Conflict of interest

The authors declared no conflict of interest

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