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
burden imposed by schizophrenia has been linked to the early onset of the disease and its incurable nature with persisting symptoms.\textsuperscript{4} Societies and communities find it increasingly difficult to offer support to schizophrenia patients through family and social bonds.\textsuperscript{9}

With productivity losses as the largest component of the overall societal cost of schizophrenia,\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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 indices\textsuperscript{15} and exchange rate.\textsuperscript{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 country\textsuperscript{15} 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.\textsuperscript{17} They include medical care costs and morbidity costs of schizophrenia within the study year.\textsuperscript{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.\textsuperscript{18}
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. Generally, this information is collected from national health care statistics, patient registers, and so on. The bottom-up approach calculates the resources utilization and productivity loss at the level of patient or individual. The mean per-person costs are usually then extrapolated to the whole population with relevant epidemiological data.

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. Direct nonmedical costs are the costs of nonhealth care resources, such as transportation, food, and lodging incurred during health care visit, and cost-associated social services.

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. On the other hand, mortality cost
is defined as the monetary value of lost production due to the premature death of the patient.\textsuperscript{26} In addition, costs associated with other consequences such as incarceration are included.\textsuperscript{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.\textsuperscript{21} These costs are extremely difficult to quantify, and therefore are often omitted from economic studies.\textsuperscript{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, censuses, and national health accounts;\textsuperscript{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,\textsuperscript{29–53} 16 in America,\textsuperscript{10,54–68} 13 in Asia Pacific,\textsuperscript{11,69–80} and 2 in Africa\textsuperscript{11,82}). 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\textsuperscript{10,11,31–33,36,39,43,44,52,53,55–57,61,63,65,67,68,73,77} were undertaken at the national level. Over half of the studies (30/56, 54\%) were conducted in selected health care institutions,\textsuperscript{30,38,47,69,71,74–76,78,81,82} one or several provinces/states/counties,\textsuperscript{29,37,45,48,30,54,56,62,64,66,70,72} specific health care program for schizophrenia patients,\textsuperscript{34,35,42,46,49,80} and an insurance scheme,\textsuperscript{51} while it was not reported in two studies.\textsuperscript{50,41}

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 adopted both prevalence- and incidence-based design. Among three studies estimated the lifetime costs of schizophrenia using incidence-based approach\textsuperscript{31,79} and prevalence-based approach,\textsuperscript{26} 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,\textsuperscript{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.\textsuperscript{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 nonmedical, 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,\textsuperscript{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\textsuperscript{10,11,31,32,33,37,38,42,43,48,51,52,54–64,66–68,73,78} 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                                                                 | Setting details                                                                 | Study period/duration | Sample size (n) |
|-----------------|---------------|-------------|-----------------------|--------------|----------------|-------------------------------|-------------------------------|--------------------------------------------------------------------------------|-------------------------------------------------------------------------------|----------------------|-----------------|
| Amoo and Ogunlesi<sup>81</sup> | Nigeria       | NR          | NGN 2005<sup>a</sup>  | P            | PB             | Bottom-up                     | NR                            | Aro Neuropsychiatric Hospital and the Federal Medical Centre, Abeokuta          |                                                                              | 6 months            | 57              |
| Suleiman et al<sup>82</sup>      | Nigeria       | NR          | NGN 1997<sup>a</sup>USD 1997<sup>a</sup> | P            | PB             | Bottom-up                     | NA                            | Yaba Psychiatric Hospital                                                                 |                                                                              | 6 months            | 50              |
| Carr et al<sup>70</sup>          | Australia     | Payer       | AUD 2000              | P            | PB             | Bottom-up                     | Human capital                 | Four metropolitan Australian Capital Territory, Queensland, Victoria, Western Australia | 1997–1998            | 980             |
| Fitzgerald et al<sup>80</sup>    | Australia     | NR          | AUD 2007<sup>a</sup>  | P            | PB             | Bottom-up                     | Human capital                 | As part of the Australian SCAP                                                                 |                                                                              | 3 years             | 347             |
| Hall et al<sup>72</sup>          | Australia     | NR          | USD 1975              | R            | IB             | Top-down and bottom-up        | Human capital                 | New South Wales                                                                 |                                                                              | 1974–1977           | NR              |
| Langley-Hawthorne<sup>79</sup>   | Australia     | NR          | AUD 1997<sup>a</sup>  | Markov model   | IB             | Bottom-up                     | Human capital                 | National                                                                          |                                                                              | NA                  | NR              |
| Zhai et al<sup>78</sup>          | People’s Republic of China | NR          | USD 2013<sup>a</sup>  | P            | PB             | Bottom-up                     | Human capital                 | Two centers in North and South China                                                 | Departments of psychiatry and endocrinology of a tertiary hospital               | 2010                | 356             |
| Grover et al<sup>71</sup>        | India         | NR          | INR 2005<sup>a</sup>  | P            | PB             | Bottom-up                     | Human capital                 |                                                                                   |                                                                               | NR                  | 50              |
| Pahuja et al<sup>75</sup>        | India         | NR          | INR 2011<sup>a</sup>  | P            | PB             | Bottom-up                     | NA                            | A tertiary care hospital in Kerala, India                                            |                                                                              | 6 months            | 25              |
| Sado et al<sup>77</sup>          | Japan         | Societal    | JPY 2008 USD 2008     | CS           | PB             | Top-down                      | Human capital                 | National                                                                          |                                                                              | 2008                | NR              |
| Chang et al<sup>73</sup>         | South Korea   | Societal    | USD 2005              | R            | PB             | Top-down                      | Human capital                 | National                                                                          | Outpatient psychiatry clinic of the National Hospital of Sri Lanka              | 2005                | 161,058         |
| de Silva et al<sup>79</sup>      | Sri Lanka     | NR          | LKR 2012<sup>a</sup>  | P            | PB             | Bottom-up                     | Human capital                 |                                                                                   |                                                                               | 2 months            | 91              |
| Lang and Su<sup>73</sup>         | Taiwan        | NR          | USD 1999              | R            | PB             | Top-down                      | NA                            | National                                                                          | Psychiatric outpatient clinics in three cities: Tainan, Chiayi, Changhua       | NR                  | 52,432          |
| Lee et al<sup>74</sup>           | Taiwan        | Societal    | USD 1999              | P            | PB             | Bottom-up                     | Human capital                 |                                                                                   |                                                                               | August 1999–May 2000 | 74              |
| Phanthunane et al<sup>76</sup>   | Thailand      | Societal    | THB 2008              | P            | PB             | Bottom-up                     | Human capital                 | Nine hospitals                                                                    |                                                                              | September to November 2008 | 429             |
| De Hert et al<sup>10</sup>       | Belgium       | NR          | USD 1994              | P            | PB             | Bottom-up                     | NA                            | Four psychiatrists’ agendas and six hospital wards                                |                                                                              | 1994                | 108             |

(Continued)
| Author                      | Country                        | Perspective | Cost (currency, year) | Study design | Study approach         | General cost estimation method | Indirect cost estimation method | Setting                                      | Setting                                      | Study period/duration               | Sample size (n) |
|-----------------------------|--------------------------------|-------------|----------------------|--------------|------------------------|-------------------------------|-------------------------------|------------------------------------------|------------------------------------------|-------------------------------|-----------------|
| Mangalore and Knapp         | England                        | Societal    | GBP 2007<sup>a</sup> | R            | PB                     | Bottom-up                     | Human capital                 | As part of UK SCAP                | NR                                        | 600              |
| Rousillon                   | France                         | Payer       | USD 1992             | CS           | PB                     | Bottom-up                     | NA                            | Three integrated areas in northern, central, and southern France | November 1992                     | 477              |
| Sarlon et al<sup>b</sup>    | France                         | NR          | EUR 2007             | P            | PB                     | Top-down and bottom-up        | Human capital                 | Three centers in France, four centers in Germany, and two centers in the UK | 1998–2002                    | 1,208            |
| Heider et al<sup>c</sup>    | France                         | 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<sup>d</sup>            | Germany                        | Societal    | EUR 2008             | R            | PB                     | Bottom-up                     | Friction cost                 | National                         | 2005–2008                     | 8,224            |
| Salize and Rossler<sup>e</sup> | Germany                        | Payer       | USD 1994             | P            | PB                     | Bottom-up                     | NA                            | Two hospitals                    | 1 year                        | 66               |
| Zeidler et al<sup>f</sup>   | Germany                        | Payer       | EUR 2006             | R            | PB                     | Bottom-up                     | NA                            | One insurance scheme             | 2004–2006                     | 9,946            |
| Behan et al<sup>g</sup>     | Ireland                        | NR          | EUR 2006             | R            | PB                     | Top-down and bottom-up        | Human capital                 | National                         | 2006                          | 10,126           |
| Garattini<sup>h</sup>       | Italy                          | Payer       | EUR 1997             | R            | PB                     | Bottom-up                     | NA                            | 14 CMHCs                         | September to December 1998     | 702              |
| Garattini et al<sup>i</sup> | Italy                          | Payer       | USD 1998             | P            | PB                     | Bottom-up                     | NA                            | 14 CMHCs                         | 1 year                        | 643              |
| Tarricone et al<sup>j</sup> | Italy                          | NR          | ITL 1995             | R            | PB                     | Bottom-up                     | Human capital                 | 10 CMHCs                         | 1995                          | 100              |
| Evers and Ament<sup>k</sup> | the Netherlands                | Societal    | ANG 1989             | R            | PB                     | Top-down                      | Human capital                 | National                         | 1989                          | NR               |
| Knapp et al<sup>l</sup>     | Denmark                        | NR          | GBP 2002<sup>2</sup> | R            | PB                     | Bottom-up                     | NA                            | NR                            | 3 months                      | 404              |
| Rund and Ruud<sup>m</sup>   | Norway                         | NR          | NOK 1994             | P            | PB                     | Bottom-up                     | NA                            | All treatment units serving six catchment areas | 4 weeks                       | 412              |
| Saldívia Borquez et al<sup>n</sup> | Spain                        | NR          | USD 1994             | NR           | PB                     | Bottom-up                     | NA                            | Granada Province                  | 1999                          | NR               |
| Haro et al<sup,o</sup>     | Spain                          | NR          | USD 1994             | P            | PB                     | Top-down and bottom-up        | Human capital                 | Three areas: Burlada, Cantabria, the Eixample National | NR                           | 112              |
| Oliva-Moreno et al<sup>p</sup> | Spain                        | Payer       | EUR 2002             | R            | PB                     | Top-down                      | NA                            | National                         | 2002                          | NR               |
| Vazquez-Polo et al<sup>q</sup> | Spain                        | Societal    | EUR 1997             | Markov Chain Monte Carlo simulation | PB                     | Bottom-up                     | NA                            | Four areas: Catalonia, Andalusia, Madrid, Navarre | 3-year follow-up from 1997 (1998–2000) | 356              |
| Study            | Country | Region | Year | Price Year | Study Type | Model | Database | Time Period | Cost (€/US$) |
|------------------|---------|--------|------|------------|-------------|-------|----------|-------------|--------------|
| Salize et al     | Spain   | NR     | EUR 2004 | P | PB | Bottom-up | NA | Community psychiatric services | 12 months | 507 |
| Ekman et al      | Sweden  | Societal | EUR 2009 | R | PB | Top-down and bottom-up | Human capital | National | 2006–2008 | 2,161 |
| Hertzman         | Sweden  | NR     | SEK 1975 | NR | PB | Top-down | Human capital | National | 1975 | NR |
| Lindstrom et al  | Sweden  | NR     | SEK 2005 | P | PB | Bottom-up | Human capital | National | 5 years | 225 |
| Davies and       | UK      | NR     | GBP 1990/1991 | NR | PB/IB | Top-down | Human capital | National | NR | 185,400 |
| Drummond         | UK      | Societal | GBP 1997 | IB | Bottom-up | Human capital | National | 5 years | 7,500 |
| America          | Brazil  | NR     | USD 1998 | Decision tree model | PB | Bottom-up | NA | Sao Paulo | 1998 | 120 |
| Goeree et al     | Canada  | Societal | CAD 2004 | R | PB | Top-down | Friction cost | National | 2004 | 234,305 |
| Rubio-Stipec et al | Puerto Rico | Societal | USD 1994 | CS | PB | Top-down | Human capital | National | January 1–December 31, 1999 | 9,844 |
| Bartels et al    | US      | NR     | USD 1999 | R | PB | Bottom-up | NA | New Hampshire | 1999 | 120 |
| Crown et al      | US      | NR     | USD 2001 | R | PB | Bottom-up | NA | National | 1991–1993 | 665 |
| Cuffel et al     | US      | NR     | USD 1986 | R | PB | Top-down | NA | San Diego | 1986 and 1990 | 15,403; 16,206 |
| Desai et al      | US      | Societal | USD 2008 | R | PB | Bottom-up | Human capital | National | 2005–2008 | 348 |
| Dixon et al      | US      | Payer  | USD 2001 | R | PB | Bottom-up | NA | National | 1991 | 12,440 |
| Feldman et al    | US      | NR     | USD 2010 | R | PB | Bottom-up | NA | National | 2003–2008 | 36,852 |
| Gunderson and    | US      | Societal | USD 1975 | R | PB | Bottom-up | Human capital | National | 1968, 1971, 1973 | NR |
| Mosher et al     | US      | NR     | USD 1993 | R | PB | Bottom-up | NA | National | 1993–1995 | 3,456; 3,759 |
| Leslie and       | US      | NR     | USD 1998 | R | PB | Bottom-up | NA | Georgia | January 1, 1991–December 31, 1993 | 6,443 |
| Martin and Miller| US      | NR     | USD 1998 | R | PB | Bottom-up | NA | Georgia | 1993 | 6,443 |
| McDonald et al   | US      | NR     | USD 2005 | CS | PB | Bottom-up | NA | National | 2001–2002 | 571,000 |
| Miller and Martin| US      | NR     | USD 1995 | R | PB | Bottom-up | NA | Georgia | 1990–1997 | 16,227 |
| Wu et al         | US      | Societal | USD 2002 | R | PB | Bottom-up | Human capital | National | 2000–2003 | NR |
| Wyatt et al      | US      | NR     | USD 1995 | NR | PB | Bottom-up | NA | National | 1991 | NA |

Note: If 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; CMHC, 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 care | Emergency care | Professional fees* | Pharmacy | Laboratory | Day unit | Community-based care | Others | Database | Interview | Chart | Literature |
| Africa                      |                  |                  |                |                 |                  |            |           |          |                  |        |          |            |       |            |
| Amoo and Ogunes³⁰           | -                | -                |                | +                | +                | +          | -         | -         | Registration fees, feeding/bedding |        | √         |            |       |            |
| Suleiman et al²            | -                | +                | -              | +                | +                | -          | -         | -         | -                  |        | √         |            |       |            |
| Asia Pacific               |                  |                  |                |                 |                  |            |           |          | Out-of-pocket expenditure |        | √         |            |       |            |
| Carr et al³⁰               | +                | +                | +              | +                | -                | -          | +         | -         | -                  |        | -         |            |       |            |
| Fitzgerald et al³⁰         | +                | +                | +              | -                | +                | -          | -         | +         | -                  |        | -         |            |       |            |
| Hall et al²                | -                | -                | -              | -                | -                | -          | -         | -         | Unspecified |        | √         |            |       |            |
| Langley-Hawthorne⁷⁹         | +                | +                | -              | +                | -                | -          | +         | -         | -                  |        | -         |            |       |            |
| Zhai et al³⁰               | -                | -                | -              | -                | +                | -          | -         | -         | Unspecified |        | √         |            |       |            |
| Grover et al³¹              | -                | -                | -              | +                | +                | -          | -         | -         | Unspecified |        | √         |            |       |            |
| Chang et al³¹              | +                | -                | -              | +                | +                | +          | -         | -         | Infrastructure |        | -         | √         |       |            |
| de Silva et al³⁰           | -                | -                | -              | +                | +                | -          | -         | -         | Out-of-pocket expenditure |        | -         |            |       |            |
| Lang and Su⁷³              | -                | -                | -              | -                | -                | -          | +         | -         | -                  |        | -         |            |       |            |
| Lee et al³⁴                | +                | +                | +              | -                | +                | -          | +         | -         | Alternative treatment |        | -         | √         |       |            |
| Phanthunane et al³⁵         | +                | +                | -              | -                | +                | -          | -         | -         | Alternative treatment |        | -         | √         |       |            |
| Europe                      |                  |                  |                |                 |                  |            |           |          | Nonmedication therapy |        | -         |            |       |            |
| De Hert et al³⁰            | +                | -                | -              | +                | +                | -          | -         | -         | -                  |        | -         | √         |       |            |
| Mangalore and Knapp⁴²      | +                | -                | +              | +                | +                | -          | +         | -         | -                  |        | -         | √         |       |            |
| Rouillon⁴⁴                 | +                | -                | -              | +                | +                | -          | -         | -         | Intermediate facilities |        | -         | √         |       |            |
| Sarlon et al⁴⁸             | +                | -                | -              | +                | +                | -          | +         | -         | -                  |        | -         | √         |       |            |
| Heider et al³⁸             | +                | -                | -              | +                | +                | -          | -         | -         | -                  |        | -         | √         |       |            |
| Frey¹³                      | -                | -                | +              | -                | +                | -          | -         | -         | Out-of-pocket expenditure |        | -         |            |       |            |
| Salize and Rossler⁴⁷       | +                | +                | -              | -                | +                | -          | -         | -         | -                  |        | -         | √         |       |            |
| Zeidler et al³¹             | +                | +                | -              | +                | -                | -          | -         | -         | Unspecified |        | √         |            |       |            |
| Behan et al³²              | +                | +                | +              | +                | -                | +          | +         | -         | -                  |        | -         | √         |       |            |
| Garattini³⁴                 | +                | +                | -              | +                | +                | +          | +         | -         | -                  |        | -         | √         |       |            |
| Garattini et al³⁵           | +                | +                | -              | +                | +                | +          | +         | -         | -                  |        | -         | √         |       |            |
| Study Reference | Dimension | Include Physician | Include Psychiatrist | Include Psychologist | Include Other Health Care Provider | Include Medical Equipment | Include Nursing Home, Long-Term Institutional, and Rehabilitation Care | Include Infrastructure | Include Out-of-Pocket Expenditure | Include Insurance-Related | Include Alternative Treatment | Include Construction | Include Substance Abuse | Notes | Abbreviation |
|-----------------|-----------|-------------------|----------------------|----------------------|-----------------------------------|--------------------------|---------------------------------------------------------------------|----------------------|---------------------------------|---------------------|----------------------------|--------------------------|-----------------|---------|-----------|
| Tarricone et al. | +         | −                 | −                    | +                    | +                                 | +                        | −                                                                  | +                   | −                               | √                   | −                           | −                        | −               | +       | −         |
| Evers and Ament | +         | +                 | −                    | +                    | +                                 | +                        | −                                                                  | −                   | √                               | −                   | √                           | √                        | √               | √       | √         |
| Knapp et al.    | +         | +                 | −                    | −                    | −                                 | +                        | +                                                                  | −                   | √                               | −                   | √                           | √                        | √               | √       | √         |
| Rund and Ruud   | +         | +                 | −                    | −                    | −                                 | +                        | +                                                                  | −                   | √                               | −                   | √                           | √                        | √               | √       | √         |
| Saldivia Borquez et al. | + | +                 | −                    | +                    | +                                 | −                        | −                                                                  | −                   | −                               | √                   | √                           | √                        | √               | √       | √         |
| Haro et al.     | +         | +                 | −                    | −                    | −                                 | +                        | −                                                                  | −                   | √                               | −                   | √                           | √                        | √               | √       | √         |
| Oliva-Moreno et al. | + | +                 | +                    | +                    | +                                 | +                        | −                                                                  | −                   | √                               | −                   | √                           | √                        | √               | √       | √         |
| Vazquez-Polo et al. | + | −                 | +                    | +                    | +                                 | −                        | −                                                                  | −                   | −                               | −                   | −                           | −                        | −               | −       | −         |
| Salize et al.   | +         | +                 | −                    | −                    | −                                 | −                        | +                                                                  | −                   | √                               | −                   | √                           | √                        | √               | √       | √         |
| Ekman et al.    | +         | +                 | −                    | −                    | −                                 | −                        | +                                                                  | −                   | √                               | −                   | √                           | √                        | √               | √       | √         |
| Hertzman et al. | +         | +                 | −                    | −                    | −                                 | −                        | −                                                                  | −                   | −                               | −                   | −                           | −                        | −               | −       | −         |
| Lindstrom et al. | + | −                 | −                    | −                    | −                                 | −                        | −                                                                  | −                   | −                               | −                   | −                           | −                        | −               | −       | −         |
| Davies and     | −         | +                 | −                    | −                    | −                                 | −                        | −                                                                  | −                   | −                               | −                   | −                           | −                        | −               | −       | −         |
| Drummond et al. | +         | −                 | +                    | +                    | +                                 | −                        | −                                                                  | −                   | √                               | −                   | √                           | √                        | √               | √       | √         |
| America Leitao et al. | + | +                 | −                    | −                    | −                                 | −                        | +                                                                  | −                   | √                               | −                   | √                           | √                        | √               | √       | √         |
| Goeree et al.  | +         | −                 | +                    | +                    | +                                 | −                        | −                                                                  | −                   | √                               | −                   | √                           | √                        | √               | √       | √         |
| Rubio-Sipiec et al. | + | +                 | +                    | +                    | −                                 | −                        | −                                                                  | −                   | −                               | −                   | √                           | √                        | √               | √       | √         |
| Bartels et al. | +         | +                 | −                    | +                    | +                                 | −                        | −                                                                  | −                   | −                               | −                   | √                           | √                        | √               | √       | √         |
| Crown et al.    | +         | +                 | −                    | +                    | −                                 | +                        | −                                                                  | −                   | √                               | −                   | √                           | √                        | √               | √       | √         |
| Cuffel et al.   | +         | +                 | −                    | −                    | −                                 | −                        | −                                                                  | −                   | √                               | −                   | √                           | √                        | √               | √       | √         |
| Desai et al.    | +         | +                 | −                    | +                    | −                                 | −                        | +                                                                  | −                   | √                               | −                   | √                           | √                        | √               | √       | √         |
| Dixon et al.    | +         | +                 | −                    | −                    | −                                 | −                        | −                                                                  | −                   | √                               | −                   | √                           | √                        | √               | √       | √         |
| Feldman et al.  | +         | +                 | −                    | −                    | −                                 | −                        | −                                                                  | −                   | √                               | −                   | √                           | √                        | √               | √       | √         |
| Gunderson and Moshier et al. | + | +                 | −                    | +                    | −                                 | −                        | +                                                                  | −                   | √                               | −                   | √                           | √                        | √               | √       | √         |
| Leslie and Rosenheck et al. | + | +                 | −                    | −                    | −                                 | −                        | −                                                                  | −                   | √                               | −                   | √                           | √                        | √               | √       | √         |
| Martin et al.   | +         | +                 | −                    | +                    | +                                 | +                        | +                                                                  | −                   | √                               | −                   | √                           | √                        | √               | √       | √         |
| Miller et al.   | +         | −                 | +                    | −                    | −                                 | +                        | −                                                                  | −                   | √                               | −                   | √                           | √                        | √               | √       | √         |
| Miller and Martin | + | +                 | −                    | +                    | +                                 | +                        | −                                                                  | −                   | −                               | −                   | √                           | √                        | √               | √       | √         |
| Wu et al.       | +         | +                 | −                    | +                    | −                                 | −                        | −                                                                  | −                   | √                               | −                   | √                           | √                        | √               | √       | √         |
| Wyatt et al.    | +         | +                 | −                    | −                    | −                                 | −                        | +                                                                  | −                   | −                               | −                   | √                           | √                        | √               | √       | √         |
| Notes: Includes physician, psychiatrist, psychologist, and other health care provider fee. Includes medical equipment. Includes nursing home, long-term institutional, and rehabilitation care. + included; − not included; √ data source used. Abbreviation: NR, not reported or insufficient information.
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<sup>81</sup> | − | − | + | − | Pocket money for patients and nurses |
| Suleiman et al<sup>82</sup>     | − | − | + | − | − | √ |
| Asia Pacific    |                |                                  |                            |                  |        |          |           |       |            |
| Carr et al<sup>70</sup>          | + | + | − | − | − | √ |
| Langley-Hawthorne<sup>79</sup>   | + | − | − | − | − | √ |
| Zhai et al<sup>78</sup>                  | − | − | − | − | − | − |
| Grover et al<sup>81</sup>             | − | − | + | − | − | √ |
| Sado et al<sup>86</sup>               | − | + | − | − | − | − |
| Chang et al<sup>77</sup>               | + | − | + | − | − | √ |
| de Silva et al<sup>79</sup>             | − | − | + | − | − | √ |
| Lee et al<sup>74</sup>                | + | + | + | − | − | √ |
| Phanthunane et al<sup>82</sup>       | − | − | + | − | − | √ |
| Europe          |                |                                  |                            |                  |        |          |           |       |            |
| De Hert et al<sup>30</sup>            | + | − | − | − | − | √ |
| Mangalore and Knapp<sup>42</sup>      | + | + | − | − | − | √ |
| Rouillon<sup>11</sup>                 | − | + | − | − | − | − |
| Frey<sup>13</sup>                    | − | − | + | − | − | √ |
| Salize and Rossler<sup>47</sup>       | + | − | − | − | − | − |
| Behan et al<sup>32</sup>              | + | + | − | − | − | √ |
| Evers and Ament<sup>33</sup>          | + | − | − | − | − | √ |
| Knapp et al<sup>40</sup>              | + | − | − | − | − | √ |
| Vazquez-Polo et al<sup>39</sup>       | + | + | − | − | − | √ |
| Salize et al<sup>46</sup>             | + | − | − | − | − | √ |
| Lindsrom et al<sup>81</sup>           | + | − | − | − | − | − |
| Guest and Cookson<sup>46</sup>        | + | − | − | − | − | − |
| America         |                |                                  |                            |                  |        |          |           |       |            |
| Goeree et al<sup>60</sup>             | + | − | − | + | − | √ |
| Gunderson and Mosher<sup>38</sup>     | − | − | − | − | − | − |
| Martin and Miller<sup>42</sup>         | − | − | + | − | − | √ |
| Wu et al<sup>12</sup>                 | + | − | − | − | − | √ |
| Wyatt et al<sup>67</sup>              | − | − | − | + | − | √ |

Notes: + included; − not included; \(\equiv\) data source used.

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

In 48 studies<sup>10,11,29–59,60–65,67,68,70,72–74,77,79,80</sup> 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<sup>10,11,30,33,36,40–42,44,46,47,50,52,53,60,62,67–71,74,76–79,81,82</sup> 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* | Premature mortality | Income assistance | Legal costs | Law enforcement | Informal care | Others      | Database | Interview | Chart | Literature |
| **Africa**              |                |              |              |            |                |                    |              |                |              |             |           |           |       |            |
| Amoo and Ogunlesi       | −              | −            | +            | −          | −              | −                   | −            | −              | +            | −            | −          | √         |       |            |
| Suleiman et al          | −              | −            | −            | −          | −              | −                   | −            | +              | +            | −            | −          | −          | √     | −          |
| **Asia Pacific**        |                |              |              |            |                |                    |              |                |              |             |           |           |       |            |
| Carr et al              | −              | −            | −            | +          | +              | −                   | +            | −              | +            | −            | −          | −          |       |            |
| Fitzgerald et al        | −              | −            | −            | −          | −              | −                   | +            | +              | −            | −            | +          | −          |       |            |
| Hall et al              | −              | −            | −            | −          | −              | −                   | −            | −              | −            | −            | −          | −          |       |            |
| Langley-Hawthorne       | −              | −            | +            | −          | −              | +                   | −            | −              | −            | −            | −          | −          |       |            |
| Zhai et al              | +              | −            | −            | +          | +              | −                   | −            | −              | +            | −            | −          | −          |       |            |
| Grover et al            | +              | −            | −            | −          | −              | −                   | −            | −              | −            | −            | −          | −          |       |            |
| Sado et al              | −              | −            | +            | +          | +              | −                   | −            | −              | −            | −            | −          | −          |       |            |
| Chang et al             | −              | +            | −            | −          | +              | −                   | −            | −              | +            | +            | +          | −          |       |            |
| de Silva et al          | +              | −            | +            | −          | −              | −                   | −            | −              | +            | −            | −          | −          |       |            |
| Lee et al               | −              | −            | −            | −          | −              | −                   | −            | −              | +            | −            | −          | −          |       |            |
| Phanthunane et al       | +              | +            | −            | −          | −              | −                   | −            | −              | +            | −            | −          | −          |       |            |
| **Europe**              |                |              |              |            |                |                    |              |                |              |             |           |           |       |            |
| Mangalore and Knapp     | +              | −            | +            | −          | +              | −                   | −            | −              | +            | +            | +          | −          |       |            |

(Continued)
Table 4 (Continued)

| Author               | Cost component | Data sources for utilization data |
|----------------------|----------------|----------------------------------|
|                      | Absenteeism    | Presenteeism | Unemployment | Morbidity* | Premature mortality | Income assistance | Legal costs | Law enforcement* | Informal care | Others | Database | Interview | Chart | Literature |
| Sarlon et al48       | +              | −            | +            | −          | −                | −                | −            | −                | −              | −             | √         | √         |         |         |
| Frey95               | +              | −            | −            | +          | −                | −                | +            | −                | −              | −              | √         | √         |         |         |
| Behan et al52        | +              | −            | +            | −          | −                | −                | −            | −                | −              | +              | −         | √         |         |         |
| Tarricone et al59    | +              | −            | −            | −          | −                | −                | −            | −                | +              | −              | √         |         |         |         |
| Evers and Ament53    | +              | −            | −            | −          | −                | −                | −            | −                | −              | −              | √         |         |         |         |
| Haro et al57         | −              | −            | −            | −          | −                | −                | −            | −                | −              | +              | Unspecified productivity loss | NR | NR | NR | NR |
| Oliva-Moreno et al53 | −              | −            | −            | −          | −                | −                | −            | −                | −              | +              | −         | √         |         |         |
| Ekman et al52        | +              | −            | −            | +          | −                | −                | −            | −                | −              | −              | −         | √         |         |         |
| Hertzman79           | −              | −            | −            | +          | +                | −                | −            | −                | −              | −              | Short-term illness | √         |         |         |         |
| Lindstrom et al61    | −              | −            | −            | −          | −                | −                | −            | −                | −              | −              | Unspecified productivity loss | NR | NR | NR | NR |
| Davies and Drummond21| −              | −            | +            | −          | −                | −                | −            | −                | −              | −              | Unspecified productivity loss | NR | NR | NR | NR |
| Guest and Cookson36  | +              | −            | +            | −          | +                | −                | −            | +                | +              | −              | −         | √         | √         |         |
| America              | Goeree et al50 | −              | −            | −          | +                | +                | −            | +                | −              | −              | −         | √         |         |         |
| Rubio-Stúépic et al55| −              | −            | −            | −          | −                | −                | −            | −                | −              | −              | −         | √         | √         |         |
| Desai et al57        | +              | +            | −            | −          | +                | −                | −            | −                | −              | +              | −         | √         | √         |         |
| Gunderson and Mosher68| −              | −            | −            | −          | −                | +                | −            | −                | −              | −              | −         | √         | √         |         |
| Wu et al10           | +              | +            | −            | −          | −                | −                | +            | −                | +              | −              | −         | √         |         |         |
| Wyatt et al67        | −              | −            | −            | −          | −                | −                | +            | +                | +              | −              | −         | √         |         |         |

Notes: *Includes permanent disability and early retirement. †Includes 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 million59 in Sweden and US$25,452 million57 to US$102,396 million52 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 GDP10,74 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 UK66 to 1.65% in Sweden.59

### 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

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**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 |         |                      |                           |                  | 28     |        |                           |                |                  |
| Sado et al57 | Japan     | 7,247                | 33                        | 18,950           | 26,230 | 72    | 0.52                       |                  |
| Chang et al11 | South Korea | 519                  | 36                        | 3,204            | 3,759  | 85    | 0.31                       |                  |
| Europe     |         |                      |                           |                  | 28     |        |                           |                |                  |
| Behan et al52 | Ireland   | 172                  | 13                        | 488              | 673    | 73    | 0.30                       |                  |
| Frey53 | Germany | 10,635               | 354                       | 8,978            | 19,967 | 45    | 0.56                       |                  |
| Evers and Ament53 | the Netherlands | 774                | 50                        | 70              | 894    | 8     | 0.11                       |                  |
| Olivia-Moreno et al52 | Spain | 1,882                | NA                        | 1,669           | 3,552  | 47    | 0.26                       |                  |
| Ekman et al52 | Sweden | 29                   | NA                        | 94              | 123    | 76    | 0.02                       |                  |
| Hertzman53 | Sweden | 3,712                | NA                        | 5,422           | 9,134  | 59    | 1.65                       |                  |
| Guest and Cookson56 | UK | 154                  | 49                        | 199             | 403    | 50    | 0.02                       |                  |
| America    |         |                      |                           |                  | 28     |        |                           |                |                  |
| Goeree et al60 | Canada  | 2,111                | 102                      | 5,287           | 7,500  | 72    | 0.41                       |                  |
| Rubio-Stipec et al43 | Puerto Rico | 31                        | NA                        | 63              | 94    | 67    | 0.09                       |                  |
| Desai et al53 | US       | 4,742                | NA                        | 20,710          | 25,452 | 81    | 0.15                       |                  |
| Wu et al50 | US      | 29,279               | 12,014                    | 41,714          | 83,007 | 50    | 0.50                       |                  |
| Wyatt et al57 | US | 27,745               | 4,054                     | 70,597          | 102,396 | 69    | 0.61                       |                  |
| Gunderson and Mosher59 | US | 12,078               | 57                        | 48,200          | 60,335 | 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 (%) |
|-------------------------------|---------------------|---------------------------|-----------------------------------|
| Amoo and Ogunlesi⁹⁷           | Nigeria             | 9,882<sup>a</sup>        | 73<sup>a</sup>                     |
| Suleiman et al⁹²              | Nigeria             | 2,951                     | 85                                |
| Zhai et al⁸⁸                  | People’s Republic of China | 257,980                 | 32                                |
| Grover et al⁷⁷                | India               | 1,814                     | 27                                |
| de Silva et al⁸⁹             | Sri Lanka           | 25,075                    | 18                                |
| Phanthunane et al⁷⁶          | Thailand            | 6,661,900                 | 27                                |

Note: <sup>a</sup>Includes 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,a 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, 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. 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. 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 LMICs. 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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