

The Societal Cost of Schizophrenia in China from 2010 to 2024—A Literature Review

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Abstract

Background: Schizophrenia is a chronic disease related to long-lasting and tremendous effects on patient's health in China, which is generally considered as a huge economic burden not only for patients but also for their caregivers and the whole society. Therefore, it is necessary to conduct an analysis of cost. Previous cost-of-illness (COI) studies have already provided some useful information on the economic burden that schizophrenia brought to global society, including China. **Objectives:** This systematic review aims to obtain a comprehensive understanding of the economic burden of schizophrenia in China. **Method:** A literature review was performed through CNKI, Wanfang, CQVIP, EMBASE and Medline databases to identify COI studies published between 2010-2024. The primary outcome of this review was societal cost per schizophrenia patient by cost component, including direct medical costs, non-medical costs and indirect medical costs. **Results:** 14 COI studies in schizophrenia were identified, covering 7 municipalities and 8 provinces of China. The annual societal cost per patient ranged from 10,765 CNY in Zhejiang province to 406,382 CNY in Xuancheng city (Anhui province). The ratio of indirect cost ranged from 66.6% to 96.8%. The main cost drivers were the productivity losses. There was an enormous heterogeneity between societal cost estimations that could be interpreted by the difference in economic state and regional healthcare resource allocation. **Conclusions:** This review highlights the large economic burden of schizophrenia in varied areas in China. Substantial cost variation was observed both nationwide and globally, which may be caused by the varied economic situation and healthcare policy. Limitation of this review

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was summarized, which may provide a useful guidance for the future COI studies in China.

Keywords

China, Schizophrenia, Review, Cost-of-Illness, Economic Burden, Indirect Cost

1. Introduction

1.1. Schizophrenia

Schizophrenia is a chronic, severe and long-term mental illness that triggers a person's disorder in perception, thoughts and behavior. Subsequently, it is documented that over 80% of individuals with a schizophrenic family member suffer from tremendous burden in multiple aspects, including economy, social activities, and physical and mental health [1]. According to the World Health Organization (2022), schizophrenia affects 24 million people worldwide, or 1 in 300 people [2]. According to the data provided by the Ministry of Health of China, in 2024, there are about 100 million people with severe mental illness in China, including about 6.4 million people with schizophrenia [3]. People with schizophrenia are at high risk of physical morbidity and premature mortality, including cardiovascular disease and type II diabetes mellitus, compared with the general population. Life expectancy for patients with schizophrenia is reduced by up to 20 years compared with the general population [4].

Furthermore, schizophrenia is also considered as a disease with extremely high economic burden, ranking as No. 1 among all mental illnesses [5]. In terms of disability-adjusted life years (DALYs), mental illness ranks first in the total burden of disease in China [6]. According to the WHO, the burden of mental illness has risen to a quarter of the total burden of disease in China by 2020 [7]. In the 1990s, schizophrenia ranked 10th in the global median burden of non-fatal diseases, accounting for 2.6% of years of life with disability (YLD). In 2000, it rose to 2.8%, ranking as No. 7 [8].

1.2. Schizophrenia Management in the People's Republic of China

A substantial reform of healthcare system in China has occurred during the previous 48 years. Starting from 1978, decreased central government support and key policy changes triggered a decentralized and privatized healthcare system [9] [10]. Since then, to correspond with the rising marketing-based economy, more and more hospitals tend to prioritize profit-making as the most important goal. Meanwhile, government-dependent mental health rehabilitation facilities were closed or changed into small-scale psychiatric hospitals [11]. As a result, the number of community-based and work-rehabilitation centers dramatically declined, especially in less wealthy rural areas, in which mental health services rarely exist.

Specialized psychiatric hospitals became the main medical intervention set for patients with mental health problems, whereas the community-based psychiatry services were extremely rare [12].

In 2002, the first national mental health plan was published, which included central government-announced goals to facilitate an effective healthcare system for mental disease as well as to improve existing mental health services to decrease the burden brought by mental illness. Correspondingly, the relevant projects were swiftly initiated and imposed a tremendous effect on some regions nationwide [11]. To further enlarge the community healthcare services for mental disease, in 2005, the central government set up “686” program (a severe mental illness management treatment program), details of which have been widely reported [13], which led to establish 60 demonstrated sites over 30 provinces and provide active intervention including medical treatment following release and community follow-up, etc. By 2009, the coverage had been expended to 112 cities and 96.9 million people, with the nation-provided funding increased from CNY 700 to CNY 5000 cases per year.

On the other hand, the availability of healthcare insurance has also largely expended in the last 25 years in China since 1998. The major healthcare insurance system is known as the “basic social medical insurance (BSMI)”, driven by the central government’s target to improve the total coverage of healthcare support for Chinese people, and has developed rapidly [14]. The coverage for residents’ population of BMSI gradually increases year by year, including urban employees (since 1998), urban residents (since 2007) and the New Rural Cooperative Medical Insurance for rural residents (since 2003) [14]. Thereafter, majority of people in China could benefit from the healthcare support from nation. However, still not people from all areas could benefit from the above welfare due to the limitation of poor regional economic status. More than 30% of the less developed areas in north-west China have no specific health insurance policies and service, whereas those policies and services are commonly implemented in eastern China [15].

1.3. Cost-of-Illness Studies (COIs)

Cost-of-illness studies aim to estimate the total cost or excess cost of people diagnosed with a disease of interest, which could indicate aspects of the disease and processes of care where amendments are necessary and thus inform the plan of medical treatment and the priority of research [16].

Furthermore, COI studies provide significant information for economic evaluation for varied medical treatment analysis, particularly cost-benefit analysis, cost-effectiveness analysis and cost-utility analysis, to support decision-making and mental health practices. The vital methodological aspects needed to be considered when conducting a COI study are summarized as the following.

1.3.1. Perspective of Cost Analysis

Generally, the choice of perspective would have an enormous effect on the cost estimation [17]. Based on the report recommended by ISPOR [18], the perspectives

are classified into three categories: 1) Healthcare system perspective, including healthcare system, ministry of health, national health, service and government; 2) Payer perspective, including payer, third-party payer, and health insurance; 3) Societal perspective, including societal, modified societal, and broadly societal perspective. The perspective used in COI study defines which type of cost to include [18] [19].

Herein, studies of single-payer health system countries using both the healthcare and payer were classified into the payer perspective. The perspective used in COI study defines which type of cost to include [18] [19]. Direct medical costs, both direct and indirect costs, and costs paid by payers are most relevant to the healthcare system perspective, the societal perspective, and the payer perspective, respectively [19] [20].

In general, a COI study tends to take the perspective considering who is the organization of sponsor [21]. Besides, economists preferred the societal perspectives more than others [22]-[24] mainly because it would reduce the potential bias of narrower views [25].

1.3.2. Cost Component

Generally, all comprehensive COI studies need to consider three types of cost components, including direct medical costs, direct non-medical costs and indirect costs. Direct medical costs are associated with treating the disease and its consequences, normally including hospital inpatient care, physician inpatient care, physician outpatient care, community-based care, nursing home care, rehabilitation care, diagnostic tests and medications. Direct non-medical costs refer to the costs of non-health care resources, such as supported costs, legal costs, transportation and other private expenses. Indirect costs include the losses in productivity of patients (morbidity costs and morality costs) or their carers (informal care). Herein, morbidity costs define the monetary value of productivity due to absenteeism, unemployment, permanent disability as well as early retirement [26]-[30]. Morality costs represent the monetary value of lost productivity due to the early death of patients [30]. On the other hand, intangible costs relating to the deterioration in quality of life for both patients and their families (such as pain or sadness) tend not to be reported in COI studies due to its characteristics of being extremely difficult to quantify [31].

1.3.3. Methods to Estimate Productivity Losses

When indirect cost is quantified in a COI study, generally there are three main categories of productivity losses that could be considered: carer productivity loss (informal care), patient productivity loss due to morbidity, and patient productivity loss due to morality.

To estimate carer productivity losses (informal care), generally the human capital approach (HCA) includes the replacement approach, and the opportunity cost approach is most widely adopted [31]. The former tends to use the national or regional minimum wage, average hourly wage or the actual wage of the caregiver

as the unit cost, and its disadvantage is that it does not consider the time use preference of informal caregivers. On the other hand, the latter generally takes the average salary or market price of formal caregivers (such as nursing home workers, domestic staff, etc.) as the unit cost of informal caregivers when calculating the cost. Its disadvantage is that the market substitutes used may not be able to completely replace informal care [32].

To estimate patient productivity losses, four methods are available: human capital approach (HCA), friction capital approach (FCA), willingness-to-pay (WTP) and conjoint analysis (CA). HCA and FCA are more commonly applied in cost estimation, although other two methods WTP and CA are also sometimes applied due to its reflection of carer's selection preference fulfilling the varied needs of the sponsor.

1.3.4. Progress of Global COI Studies for Schizophrenia

Chaiyakunapruk *et al.* (2016) [33] first summarize the methodologies used in global COI study of schizophrenia, including data source classification between high-income countries and low-income countries, cost components (especially indirect cost) emphasis and cost estimation approach. However, it only presents the aggregated data that does not include cost per patient. Indirect cost accounted for 50% - 85% of the total societal cost.

Then, another more comprehensive published systematic review conducted by Jin *et al.* (2016) [34] was widely concerned by providing a general overview of COI studies for schizophrenia across high-income countries between 1996-2016. In addition, the main components of schizophrenia cost, cost drivers as well as useful recommendations about good practice for future schizophrenia COI studies were also discussed.

Furthermore, Fasseeh *et al.* (2018) [35] led a study that only focused on indirect cost discussion of schizophrenia in European countries, in which the caregiver's informal care lost and patients productivity losses were specifically compared. Moreover, the study also found that gender, age, disease severity, negative symptoms and treatment type are the most relevant factors associated with indirect cost of schizophrenia. It is noted that the average proportion of indirect cost was approximately 44%.

Based on Jin's work, the latest literature review including global studies ranging from 2016 to 2022 was updated by Lin *et al.* (2023) [36]. It assessed the quality of identified COI studies and further suggested practical recommendations on how to improve the methodological and reporting quality of future COI studies. Productivity losses were found to be an enormous proportion of total societal cost, which made up 32% - 83%.

Although the above four systematic reviews have already provided a comprehensive overview of COI studies for schizophrenia worldwide so far, they mainly restrained the discussion within Western countries, whereas the COI study conducted in China was rarely mentioned, which may be caused by the little literature published in English.

1.4. Aims and Objectives

The aim of this study is to systematically review all published COI studies for schizophrenia in China between 2010 and 2024. More specifically, this review aims to answer the following questions: 1) What is the societal cost of schizophrenia per patient in different regions of China? 2) What are the main cost components of schizophrenia in China? Based on the results of this review, we also aim to provide suggestion for the future COI research for schizophrenia in China.

2. Methods

This systematic review was conducted according to the PRSIMA standards (preferred reporting items for systematic reviews and meta-analysis) recommendations for reporting systematic reviews and meta-analyses of studies that evaluate medical treatments.

2.1. Search Methodology

A literature review was performed through Wanfang, CNKI, CQVIP, EMBASE and Medline databases to identify cost studies published between 2010 and 2024. The search keywords included the medical subject heading terms “schizophrenia”, “psychosis”, “mental disorder”, “informed care” accompanied with the following Pharmacoeconomics terms “cost of illness”, “direct cost”, “indirect cost”, “productivity loss”, “China” was used.

2.2. Inclusion and Exclusion Criteria of Studies Selection

Studies were included if the population of interest was children or adults with a clinical diagnosis of schizophrenia and the study adopted both a societal perspective (included direct costs and indirect costs) and payer perspective (included direct costs only). The range was expanded because there were insufficient studies based on societal perspective. The rationale and limitations of choosing the aforementioned perspectives was recorded in Section 1.3.1. The varied cost components were described in sufficient detail. As a minimum, the direct costs are supposed to include at least inpatient costs; the indirect costs (If reported) need to include productivity loss for patient due to morbidity.

The exclusion criteria were adopted as following: 1) studies compared the cost-effectiveness/utility of varied interventions for schizophrenia; 2) the targeted data of costs were not reported or could not be obtained; 3) the study participants were not representative of the general population; 4) the study focus on only one specific disease phase of schizophrenia, such as first episode; 5) studies published before 2000 as they were unlikely to be relevant to current practice; 6) reviews, letters or abstracts; and 7) the study was conducted out of China.

2.3. Presentation of Cost Estimation

The cost estimation of varied cost components was reported separately. Studies included in this review adopted different definition for “direct medical costs” and

“direct non-medical costs” while almost identical definition for “indirect cost”. For example, some studies included rehabilitation care and patient nutrition as direct non-medical cost, whereas other studies regarded it as direct medical cost. In order to maintain the consistency, all cost components reported by included studies according to the following definitions:

1) Direct medical cost: Inpatient cost, outpatient cost, medication cost, other direct medical cost to the medical system.

2) Direct non-medical cost: Transportation cost and private expenditure.

3) Indirect cost: Carer’s productivity losses, patient’s productivity losses due to morbidity or mortality and value of damaged properties.

3. Results

3.1. Study Characteristics

Table 1 provides the basic features of the included studies. 321 titles and abstracts were reviewed, 225 full articles were retrieved after de-duplication. Herein, only 14 studies were satisfactory and were included. 13/14 of the included studies evaluated the cost of schizophrenia after 2010, only 1/14 of the includes studies was published after 2020. 7 municipalities and 8 provinces (the regions from south to north, east to west) of China were covered within these studies. Between 299 and 200,000 people with schizophrenia were included in that research as the sample size used to estimate total societal costs.

Table 1. Characteristics of included studies.

Study	Year of valuation	Region (China)	Patient characteristics			
			Inclusion criteria	Sample size for cost calculation	Age (years)	Male (%)
Zhai <i>et al.</i> [37]	2010	2 hospitals in Shandong province & Hunan province	Schizophrenic patients who met with DSM-IV criteria	299	16 - 65	60.5
Huang <i>et al.</i> [38]	2010-2012	Guangzhou city	All Schizophrenic patients in Guangzhou	NA	All ages	53
Guo <i>et al.</i> [39]	2010-2014	Xuancheng city in Anhui province	Schizophrenic patients who met with CCMD-3 criteria	316	15 - 76	60.4
He <i>et al.</i> [40]	2008-2010	Tianjin city	Patients with schizophrenia with ≥ 1 prescription for antipsychotics after ≥ 90 -day washout and 12-month continuous enrollment after first prescription	1131	≥ 18	45.5
Xu <i>et al.</i> [41]	2012	Rural area in Guangdong & Sichuan & Hebei province	Schizophrenic patients who met with ICD-10 criteria from 2005 to 2012 in the “unlocking and treatment” intervention	264	18 - 60	71
Tang <i>et al.</i> [42]	2016	Yunnan province	Schizophrenic patients	200,000	≥ 18	59.3

Continued

Luo <i>et al.</i> [43]	2014	5 hospitals of Wuhan city & Shiyan city of Wuhan province	Schizophrenic patients who met with ICD-10 criteria	289	NR	45
Yang <i>et al.</i> [44]	2010	14 hospitals in Zhejiang province	Schizophrenic patients	3117	NR	40.4
Wu <i>et al.</i> [45]	2008-2009	Tianjin city	Adult patients with ≥ 1 diagnosis of schizophrenia and 12-month continuous enrollment after the first schizophrenia diagnosis	2125	≥ 18	49.3
Zhang <i>et al.</i> [46]	2010-2014	Guangzhou city	Schizophrenic patients who met with ICD-10 criteria (F10)	2971	All ages	60.6
Feng <i>et al.</i> [47]	2013	Shenzhen city	Schizophrenic patients	NR	All ages	NR
Lin <i>et al.</i> [48]	2016-2018	Wuhan city	Schizophrenic patients who met with ICD-10 criteria	11,461	All ages	56
Liu <i>et al.</i> [49]	2005-2014	1 hospital in Chongqing city	Schizophrenic patients who met with CCMD-3 criteria, inpatient	327	All ages	58.1
Yang <i>et al.</i> [50]	1999-2001	Harbin city	Schizophrenic patients	NR	All ages	NR

Table 2. Data source and methods adopted by included study.

Study	Disease specification	Basis of analysis	Prospective or retrospective	Estimating resource consumption	Methods for valuating productivity losses		
					Career lost productivity	Patient's lost productivity (morbidity)	Patient's lost productivity (morality)
Zhai <i>et al.</i>	Schizophrenia (DSM-IV)	Data from survey completed by psychiatrists and main carer of 2 hospitals in Shandong province & Hunan province 2010	Prospective	Bottom-up	Opportunity cost	HCA	NI
Huang <i>et al.</i>	Schizophrenia	Data from Guangzhou medical insurance database of China Bureau of Statistics and published literature	Retrospective	Top-down & Bottom-up	NI	HCA	NI
Guo <i>et al.</i>	Schizophrenia (CCMD-3)	Electronic medical records and Hospital Information Center HIS system from 3 hospitals, survey and phone investigation from main carers, Xuancheng City Statistics Bureau	Retrospective	Bottom-up	NI	HCA	HCA
He <i>et al.</i>	Schizophrenia (ICD-10)	Urban employee basic medical insurance (UEBMI) database of Tianjin from 2008 through 2010, which was obtained from the Tianjin Municipal Human Resources and Social Security Bureau	Retrospective	Econometric	NI	NI	NI

Continued

Xu <i>et al.</i>	Schizophrenia (ICD-10)	Interview data from main carer during home visits	Retrospective	Bottom-up	Opportunity cost	HCA	NI
Tang <i>et al.</i>	Schizophrenia	2016 Statistical Yearbook of Yunnan Province; Mental health epidemiological survey data	Retrospective	Top-down & Bottom-up	NI	HCA	HCA
Luo <i>et al.</i>	Schizophrenia (ICD-10)	Data from on-site survey and patient medical record	Retrospective	Bottom-up	Opportunity cost	HCA	NI
Yang <i>et al.</i>	Schizophrenia	Data from survey completed by attending-level physicians and patients' charts	Prospective	Bottom-up	NI	NI	NI
Wu <i>et al.</i>	Schizophrenia (ICD-10)	Data from the urban employee basic medical insurance (UEBMI) database claims of Tianjin city from 2008 to 2010	Retrospective	Econometric	NI	NI	NI
Zhang <i>et al.</i>	Schizophrenia (ICD-10)	Data from urban health insurance claims databases of Guangzhou city	Retrospective	Econometric	NI	NI	NI
Feng <i>et al.</i>	Schizophrenia	Data from urban health insurance claims databases of Shenzhen city	Retrospective	Econometric	NI	NI	NI
Lin <i>et al.</i>	Schizophrenia (ICD-10)	Data from urban health insurance claims databases of Wuhan city	Retrospective	Econometric	NI	NI	NI
Liu <i>et al.</i>	Schizophrenia (CCMD-3)	Data from patient chart	Retrospective	Bottom-up	NI	NI	NI
Yang <i>et al.</i>	Schizophrenia	Data from patient chart, Harbin Health and Epidemic Prevention Station (Population basic data), National Bureau of Statistics (GDP per capita)	Retrospective	Top-down & Bottom-up	NI	HCA	NI

NA: not applicable; NR: not reported; NI: not included in analysis.

3.2. Data Source and Methods Adopted by Included Study

Table 2 indicates the data sources and methods adopted by included studies. A total of 9 studies used international classification of disease (ICD) and related health problems codes or diagnostic and statistical manual (DSM) of mental disorders or Chinese classification and diagnostic criteria of mental disorders (CCMD-3) as diagnostic criteria for schizophrenia, while 5 studies did not specify the diagnostic criteria used.

The data sources mostly included survey or interview results (6), regional health insurance database (6), patient chart (3) and published literature (1). This corresponds with Chaiyakunapruk *et al.* (2016) [33] finding that middle income countries

tend to adopt chart and interview results generally because the data is rarely available from public database and published literature.

12/14 of included studies were retrospective, except one by Zhai *et al.* (2013) [37] and one by Yang *et al.* (2003) [50]. All included studies were prevalence-based studies. To estimate resource consumption, 6/14 of included studies used bottom-up approach, while 3/14 used both top-down and bottom-up approaches, 5/14 used econometric approach.

3/15 of included studies included carer productivity losses, all of which adopted the opportunity cost approach while no study adopted the replacement approach. 7/15 of studies considered patient lost productivity due to morbidity whereas 2/15 of studies considered patient lost productivity due to morality, all of which adopted HCA, no study used neither FCA nor WTP approach.

Only 1/15 study conducted sensitivity analysis and reported the result within the study.

Table 3. Summary of societal cost per schizophrenia patient, by each cost component.

Study	Region	Annual societal cost per patient						
		Direct medical cost		Direct non-medical cost		Indirect cost		Total societal cost
Zhai <i>et al.</i>	Shandong province & Hunan province 2010	3308	(27.6%)	688	(5.8%)	10,081	(66.6%)	
Huang <i>et al.</i>	Guangzhou city 2010	2212	(8.0%)	NI		25,356	(92.0%)	27,568
	Guangzhou city 2011	2241	(12.3%)	NI		15,970	(87.7%)	18,212
	Guangzhou city 2012	2208	(12.6%)	NI		15,356	(87.4%)	17,564
Guo <i>et al.</i>	Xuancheng city 2010	12,023	(5.8%)	656	(0.3%)	194,962	(93.9%)	207,641
	Xuancheng city 2011	12,357	(4.7%)	679	(0.3%)	251,246	(95.1%)	264,282
	Xuancheng city 2012	13,000	(4.1%)	703	(0.2%)	300,353	(95.6%)	314,056
	Xuancheng city 2013	12,919	(3.6%)	694	(0.2%)	340,974	(96.2%)	354,587
	Xuancheng city 2014	13,806	(3.4%)	745	(0.2%)	391,831	(96.4%)	406,382
He <i>et al.</i>	Tianjin city 2008-2010	12,029		NI		NI		12,029
Xu <i>et al.</i>	Rural area in Guangdong & Sichuan & Hebei province	963	(7.6%)	NR		11,724	(92.4%)	12,687
Tang <i>et al.</i>	Yunnan province	NI		NI		23,255		23,255
Luo <i>et al.</i>	Hubei province (urban)	12,231	(68.4%)	704	(3.9%)	4950	(27.7%)	17,885
Yang <i>et al.</i>	Zhejiang province	10,765		NI		NI		10,765
Wu <i>et al.</i>	Tianjin city 2008-2019	13,300		NI		NI		13,300
Zhang <i>et al.</i>	Guangzhou city	41,972		NI		NI		41,972
Feng <i>et al.</i>	Shenzhen city	11,763		NI		NI		11,763
Lin <i>et al.</i>	Wuhan city 2016	39,696		NI		NI		39,696
	Wuhan city 2017	47,556		NI		NI		47,556
	Wuhan city 2018	43,146		NI		NI		43,146
Liu <i>et al.</i>	Chongqing city 2005-2014	9181		NI		NI		13,694
Yang <i>et al.</i>	Harbin city 1999-2001	3437	(3.2%)	NI		104,932	(96.8%)	108,369

All costs are CNY.

3.3. Cost Estimation

Table 3 presents the total societal costs of included studies consisting of varied cost components. The cost details for direct medical costs, direct non-medical costs and indirect costs are reported in **Tables 4-6**, respectively.

No included study reported the lifetime cost for a diagnosed schizophrenia patient. All the studies reported the annual societal cost per schizophrenia patient.

The total societal cost varied from 10,765 CNY in Zhejiang province to 406,382 CNY in Xuancheng city, Anhui province. Direct medical costs contributed 3.2% to 68.4% of the total cost, while the indirect cost (productivity losses) made up 27.7% to 96.8%. The ratio of direct non-medical cost is the lowest, varying from 0.2% to 3.9%.

To compare the absolute cost, the annual direct medical cost varied from 2208 CNY in Guangzhou city to 47,556 CNY in Wuhan city. Two studies reported annual direct non-medical costs, which varied from 656 CNY in Xuancheng city (2010) to 745 CNY (2014) in Xuancheng city. The annual indirect costs were different from 4950 CNY in Hubei province to 391,831 CNY in Xuancheng city (2014).

Table 4. Summary of direct medical costs per schizophrenia patient.

Study	Region	Direct medical cost per schizophrenia patient							Total direct medical cost
		Inpatient cost		Outpatient cost		Medication cost		Other direct medical cost	
Zhai <i>et al.</i>	Shandong province & Hunan province 2010	2716	(82.1%)	592	(17.9%)	NR		NR	3308
Huang <i>et al.</i>	Guangzhou city 2010	1833	(82.9%)	15	(0.7%)	364	(16.5%)	NR	2212
	Guangzhou city 2011	1906	(85.1%)	11	(0.5%)	324	(14.5%)	NR	2241
	Guangzhou city 2012	1852	(83.9%)	10	(0.5%)	346	(15.7%)	NR	2208
Guo <i>et al.</i>	Xuancheng city 2010	7311	(60.8%)	2214	(18.4%)	479	(4.0%)	2019 (16.8%)	12,023
	Xuancheng city 2011	7860	(63.6%)	2418	(19.6%)	603	(4.9%)	1476 (11.9%)	12,357
	Xuancheng city 2012	8644	(66.5%)	1693	(13.0%)	486	(3.7%)	2177 (16.7%)	13,000
	Xuancheng city 2013	8871	(68.7%)	1452	(11.2%)	500	(3.9%)	2096 (16.2%)	12,919
	Xuancheng city 2014	9272	(67.2%)	1521	(11.0%)	643	(4.7%)	2370 (17.2%)	13,806
He <i>et al.</i>	Tianjin city 2008-2010	9712	(80.7%)	55	(0.5%)	2262	(18.8%)	NR	12,029
Xu <i>et al.</i>	Rural area in Guangdong & Sichuan & Hebei province	NR		NR		NR		NR	963
Luo <i>et al.</i>	5 hospitals of Wuhan city & Shiyan city of Wuhan province	10452	(85.5%)	NI		1779	(14.5%)	NR	12,231
Yang <i>et al.</i>	Zhejiang province	8952	(83.2%)	NI		1813	(16.8%)	NR	10,765
Wu <i>et al.</i>	Tianjin city 2008-2009	11,995	(90.2%)	13.67	(0.1%)	1292	(9.7%)	NR	13,300
Zhang <i>et al.</i>	Guangzhou city	37,819	(90.1%)	192	(0.5%)	3962	(9.4%)	NR	41,972

Continued

Feng <i>et al.</i>	Shenzhen city	10,528	(89.5%)	NI	1212	(10.3%)	24	(0.2%)	11,763
Lin <i>et al.</i>	Wuhan city 2016	36,680	(92.4%)	NI	2858	(7.2%)	159	(0.4%)	39,696
	Wuhan city 2017	44,465	(93.5%)	NI	2949	(6.2%)	143	(0.3%)	47,556
	Wuhan city 2018	39,392	(91.3%)	NI	3581	(8.3%)	173	(0.4%)	43,146
Liu <i>et al.</i>	Chongqing city 2005-2014	8488	(92.5%)	NI	684	(7.4%)	4.55	(0.1%)	9181
Yang <i>et al.</i>	Harbin city 1999-2001	3437		NI	NR		NR		3437

3.3.1. Direct Medical Costs

Table 4 reports the cost detail information of direct medical costs. The annual in-patient cost was lowest in Guangzhou city (1833 CNY) and highest in Wuhan city (44,465 CNY). The annual outpatient cost was lowest in Guangzhou city (10 CNY) and highest in Xuancheng city (2418 CNY), and the medication cost was lowest in Guangzhou city (324 CNY) and highest in Guangzhou city (3962 CNY).

Table 5. Summary of direct non-medical costs per schizophrenia patient.

Study	Region	Direct non-medical cost per schizophrenia patient		
		Transportation costs	Private expenditure	Total direct non-medical cost
Zhai <i>et al.</i>	Shandong province & Hunan province	NR	NR	688
Guo <i>et al.</i>	Xuancheng city 2010	NR	NR	656
	Xuancheng city 2011	NR	NR	679
	Xuancheng city 2012	NR	NR	703
	Xuancheng city 2013	NR	NR	694
	Xuancheng city 2014	NR	NR	745
Luo <i>et al.</i>	Hubei province (urban)	178	526	704

3.3.2. Direct Non-Medical Costs

Table 5 shows the cost detail information of non-medical costs. Three included studies reported direct non-medical costs. Only Luo *et al.* reported the details including transportation costs and private expenditure. The annual costs varied from 656 CNY in Xuancheng city (2010) to 745 CNY in Xuancheng city (2014).

Table 6. Summary of indirect cost per schizophrenia patient.

Study	Region	Indirect cost per schizophrenia patient								
		Carer's lost productivity	Patient's lost productivity due to morbidity	Patient's lost productivity due to morality	Value of damaged properties	Total indirect cost				
Zhai <i>et al.</i>	Shandong province & Hunan province (Urban)	3884	(38.5%)	5907	(58.6%)	0	0	290	(2.9%)	10,081

Continued

Huang <i>et al.</i>	Guangzhou city 2010	NI		25,356		NI		NI		25,356
	Guangzhou city 2011	NI		15,970		NI		NI		15,970
	Guangzhou city 2012	NI		15,356		NI		NI		15,356
Guo <i>et al.</i>	Xuancheng city 2010	NI		190,443	(97.7%)	4519	(2.3%)			194,962
	Xuancheng city 2011	NI		244,734	(97.4%)	6512	(2.6%)			251,246
	Xuancheng city 2012	NI		293,012	(97.6%)	7341	(2.4%)			300,353
	Xuancheng city 2013	NI		332,479	(97.5%)	8495	(2.5%)			340,974
	Xuancheng city 2014	NI		382,616	(97.6%)	9214	(2.4%)			391,831
Xu <i>et al.</i>	Rural area in Guangdong & Sichuan & Hebei province	4710	(40.2%)	6806	(58.1%)	NI		207	(1.8%)	11,724
Tang <i>et al.</i>	Yunnan province	NI		21,761	(93.6%)	1494	(6.4%)	NI		23,255
Luo <i>et al.</i>	Hubei province (urban)	1251	(25.3%)	3557	(71.9%)	NI		142	(2.9%)	4950
Yang <i>et al.</i>	Harbin city	NI		104,932		NI				104,932

3.3.3. Indirect Costs (Productivity Losses)

Table 6 reports the cost detail information of productivity losses. Of the 15 studies, 3 studies considered carer's lost productivity, all of which employed opportunity costs, and no study used replacement cost. The proportion of carer's lost productivity to total productivity loss varied from 25.3% in Hubei province to 40.2% in rural area of three provinces, and the annual absolute cost varied from 1251 CNY in Hubei province to 4710 CNY in rural area of three provinces. 5 studies reported patient's lost productivity due to morbidity, all of which adopted HCA. Productivity losses due to morbidity ranged from 3557 CNY in rural areas of three provinces to 382,616 CNY in Xuancheng city of Anhui province, ration varied from 58.1% in rural areas of three provinces to 97.6% in Xuancheng city. Of these included studies, three studies reported the patient's lost productivity due to morality, both of which used HCA; Productivity losses due to morality varied from 0 in Shandong and Hunan province to 9214 CNY in Xuancheng city, ratio ranged from 2.3% in Xuancheng city to 6.4% in Yunnan province. Besides, the value of damaged properties was also reported in 3 studies. The annual absolute cost varied from 142 CNY in Hubei province to 290 CNY in Shandong and Hunan province, the ratio ranged from 1.8% in rural area of three provinces to 2.9% in Hubei, Shandong and Hunan province.

4. Discussion

This review indicated a tremendous economic burden of schizophrenia in China nationwide. Besides, it identified the key cost components of schizophrenia as well as factors related to higher societal costs. Furthermore, this review shows some extent of discrepancy in the societal costs among different regions in China. For example, as in 2010, the annual societal cost of schizophrenia per patient in Xuancheng city of Anhui province is 13.3 times as high as in Shandong and Hunan province.

One reason for this discrepancy might be the differences in the state of local economy and differences in healthcare systems across regions, especially the available range of healthcare services. The second reason possibly is the methodological heterogeneity in COI studies among varied regions, especially for direct non-medical costs and indirect costs, which would be discussed as following.

Although seven included studies demonstrated to adopt a societal perspective, four studies did not estimate the direct non-medical costs. For the three studies that did include direct non-medical costs, the costs range indicated an extent of consistency. Although the component of direct non-medical costs might be varied from studies, most studies tend to consider the following type of costs in common: Patients' nutrition costs, caregiver's attendant costs, caregiver's employment costs and transportation costs, which is considerably different with the cases in COI studies of Western countries [34]. The variation may attribute to the diversity of cultures, social structures and healthcare systems between China and Western countries. For example, under the background of "deinstitutionalization" in past decades, many Western countries gradually transferred mental health treatment from hospitals to the community, which may subsequently elevate the costs of sheltered accommodation and legal costs [51]-[53]. However, legal costs are still suggested to be considered into the total cost due to the harmful behaviors including homicides, fire prevention, self-harm that endanger social security triggered by schizophrenic patients who are affected by the mental disorders [53].

This review also indicated that indirect costs make up a large proportion of the total societal costs. Compared to the range of 32% - 83% shown in Lin *et al.* (2023)'s review [36], the ratio of indirect range reached up to 66.6% - 96.8%, which was much higher than the former. This variation might be due to the limitations of medical resources and healthcare system availability accompanying with less developed economic status in less developed area, which triggered relatively heavier economic burden to the patients' families who take the main responsibility as the caregivers. This result is consistent with Montgomery *et al.* (2013) [54], whose study also indicates the larger proportion of indirect costs in other Asian countries than those in Western countries.

As for indirect costs (productivity losses) estimation, only three included studies considered caregiver's productivity losses and three studies included patients' productivity loss due to morality, both of which only account for less than half of all included studies estimating indirect costs. However, it is highly recommended not to omit these two cost components with the following reasons. As for the data of caregiver's productivity loss (cost of informal care) reported in this review, it made up 25.3% - 40.2% of the total indirect costs, which played a significant role in indirect costs. Besides, Tajima-Pozo *et al.* (2015) [55] indicated that the actual number of people who are affected by schizophrenia were far more than only the number of patients. According to the investigation results from some developed countries [56], it took each caregiver more than 10 extra hours weekly to look after schizophrenic patients, which means it is necessary to count in the "hidden work

hours” in COI studies. Furthermore, Barnes *et al.* (2016) [57] even found that the cost of families’ informal care is higher than the productivity losses of patient. To illustrate why the productivity losses due to morality should not be ignored, the characteristics of schizophrenia could be re-considered. Schizophrenia is chronically and severely disabling, sometimes incur lifelong productivity loss. Worse still, the life expectancy for schizophrenic people decreased by up to 20 years comparing with normal people [4]. Therefore, omitting patient lost productivity due to morality probably incur to an underestimation of the total indirect costs.

In all seven studies considered indirect costs, HCA appeared to be the only method to estimate the productivity losses, which shows a consistency in COI studies of China. However, compared to HCA, FCA was found to yield more realistic estimates in chronic diseases such as schizophrenia [58]. Thus, to provide more comprehensive indirect costs result, it was suggested to adopt both HCA and FCA in economic burden estimation [23]. In addition, the combination of WTP and HCA are also sometimes expected to enhance the sensitivity and accuracy of cost results although WTP only is supposed to be highly subjective and costs overestimated [6].

Two quantitative methods appeared to be employed in selected studies reported patient’s productivity losses. One method was by directly calculating the cost due to patient absenteeism or reduced productivity according to the following formula: Cost of lost labor per patient = Days of missed work per patient per year × Average daily wage per employee of the specific region [43]. The characteristic of this method is that the value of time is assigned by using the local average annual/monthly/daily/hourly wage or the average wage adjusted for age/gender/disability [53]. The other method used the disability-adjusted life year (DALYs = YLLs + YLDs) index to calculate the cost of time lost due to disability and death, which provided the information of social value orientation and subsequently could show the impact of schizophrenia on population more comprehensively and reasonably than the former.

To identify the factors related to higher societal costs, only one sensitivity analysis (SA) was conducted [45] among all fifteen included studies, which means that many important cost drivers(parameters/assumptions) have been missed by this review, as they have not been tested by SA in included studies [59]. Furthermore, eight studies used multivariate regression analysis to determine the key factors associated with societal costs.

5. Limitations

As the COI studies for schizophrenia in China started relatively late comparing to some developed countries during the past decades, the varied costs details and related published literature could be identified were greatly restricted, the main limitations of this review are as follows:

- 1) The data referred in this review was all derived from published literature. We did not perform the database search to specify more accurate prevalence data.

2) Only 3 included studies reported non-medical costs while only 1 study specified the costs elements.

3) Only 5 included studies reported indirect costs. Furthermore, the number of studies reported either costs of informal care or productivity losses due to morality are both only 3, although the significance of these two costs components were used to be highlighted in the previous studies. Only human capital approach was found to adopted in these included COI studies.

4) All 14 studies in this review were prevalence-based studies, probably because it only needs to cover one year stage of disease. Although prevalence-based approach is appropriate for policymakers who are likely concerned more with current health expenditures and societal costs, the future cost of a disease needs to be calculated by discounting the cost in cash flow to the cost at the time point of disease onset and taking the disease progress into account. This is mainly due to the different severity of the disease at varied stages and different levels of resource consumption. Since schizophrenia is a chronic disease, it is suggested that the study focuses on the lifetime cost of the schizophrenia patients, that is, using the incidence-based approach as the basis for policy decision-making [53].

5) Only 1 included study conducted sensitivity analysis.

6) The huge variation of economic burden across varied regions in China was highly associated with the varied policies of medical insurance system released by local governments. The differences in local medical-related policy were not discussed in this review.

6. Conclusion

This review highlighted the tremendous economic burden of schizophrenia in varied regions in China. Indirect costs accounted for 66.6% - 96.8% of the overall societal cost of schizophrenia. Substantial cost variation was observed both nationwide and globally, which may be caused by the varied economic situation and healthcare policy. Limitation of this review was summarized, which may provide a useful guidance for the future COI studies in China.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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