

1 **The Societal Cost of Schizophrenia – an updated systematic review of cost-of-illness studies**

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3 **1. Title of paper**

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7 **3. List of authors**

Name	Preferred degree	Affiliation	Contact details	ORCID ID
Claire Lin	MSc	King's Health Economics (KHE), Institute of Psychiatry, Psychology & Neuroscience at King's College London, London, UK.	Email: linclaire@outlook.com Telephone: +44 (0)20 7848 0878 Address: King's Health Economics Institute of Psychiatry, Psychology & Neuroscience at King's College London Box 024, The David Goldberg Centre, London, UK, SE5 8AF	0000-0001-9073-5905
Xiaoyu Zhang	MSc	King's Health Economics (KHE), Institute of Psychiatry, Psychology & Neuroscience at King's College London, London, UK.	Email: xiaoyu.zhang@ucdconnect.ie Telephone: +44 (0)20 7848 0878 Address: King's Health Economics Institute of Psychiatry, Psychology & Neuroscience at King's College London Box 024, The David Goldberg Centre, London, UK, SE5 8AF	0000-0003-3051-6684
Huajie Jin	PhD	King's Health Economics (KHE), Institute of	Email: huajie.jin@kcl.ac.uk Telephone: +44 (0)20 7848 0878	0000-0002-3872-3998

Name	Preferred degree	Affiliation	Contact details	ORCID ID
<i>(Corresponding author)</i>		Psychiatry, Psychology & Neuroscience at King's College London, London, UK.	Address: King's Health Economics Institute of Psychiatry, Psychology & Neuroscience at King's College London Box 024, The David Goldberg Centre, London, UK, SE5 8AF	

8

9 **Abstract**

10 **Background:** Schizophrenia imposes a substantial economic burden on the society. This updated systematic
 11 review aims to collate the latest societal cost of schizophrenia across countries by reviewing the recent cost-of-
 12 illness (COI) studies.

13 **Methods:** An electronic search was conducted across several databases (MEDLINE, Embase, PsycINFO,
 14 Cochrane Database of Systematic Reviews, Health Management Information Consortium, and System for
 15 Information on Grey Literature) to identify COI studies published from 2016 to 2022. Two independent
 16 reviewers selected studies for inclusion. The cost components and estimates reported by included studies were
 17 descriptively summarised. All costs were converted to US dollars (2022 values). Study quality was assessed
 18 using a checklist adapted from Larg & Moss.

19 **Results:** Twenty-four studies were included (five from the update review and nineteen from the original
 20 review), of which only two were conducted for low- and middle-income countries (LMICs). Widespread
 21 methodological heterogeneity among included studies was observed. The annual societal cost per person varied
 22 from \$US 819 in Nigeria to \$US 94,587 in Norway. Productivity losses accounted for 32% to 83% of the
 23 overall societal cost, whilst direct healthcare cost made up 11% to 87%. The reporting quality of included
 24 studies varied.

25 **Conclusion:** This review highlights the substantial economic burden of schizophrenia and a lack of COI studies
 26 for LMICs. Recommendations on future research, and good practices on improving the methodological and
 27 reporting quality of COI research for schizophrenia are provided.

28 **Key Points for Decision Makers**

- 29 • This update review highlights the substantial economic burden of schizophrenia across countries. The
30 annual societal cost of schizophrenia per person varied from \$US 819 in Nigeria to \$US 94,587 in
31 Norway.
- 32 • Productivity losses accounted for 32% to 83% of the overall societal cost. Substantial savings could
33 potentially be achieved by providing vocational rehabilitation to the schizophrenia patients and support
34 to their caregivers.
- 35 • There is a lack of COI studies of schizophrenia in low- and middle-income countries (LMICs). Since
36 the results of economic studies may not be transferable between different countries, it is recommended
37 that more COI studies need to be conducted for LMICs.
- 38 • Recommendations on future research, and good practices for improving the methodological and
39 reporting quality of future COI studies are provided.

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41

The Societal Cost of Schizophrenia – an updated systematic review of cost-of-illness studies

1. Introduction

Schizophrenia is a long-term illness that obstructs one's capacity to reason rationally, manage emotions, make decisions, and interact with others. Compared to the general population, patients with schizophrenia are at a higher risk of developing weight gain, cardiovascular disease, diabetes and substance use disorders [1,2]. In addition, compared to the general population, people with schizophrenia are more likely to be homeless, jobless, or in poverty [3]. As a result, the economic burden associated with schizophrenia is substantial not only for the patients but also for their families, caregivers, and the larger society [4]. For example, in the US, the societal cost of schizophrenia was reported to be \$62.7 billion in 2002 [5] and \$281.6 billion in 2020 [6].

Cost-of-illness (COI) studies provide a summary of the economic burden of a specific disease to the healthcare system or the society. A COI study can be conducted from different costing perspectives, such as the healthcare system, third-party payer (e.g., insurance company), or the society as a whole. The choice of the costing perspective may have a substantial impact on the cost estimates. COI studies can be prevalence-based or incidence-based. The prevalence-based method calculates the financial impact of an illness over a given time frame, often between six and twelve months; whilst the incidence-based method calculates the lifetime cost from the start of an illness to conclusion. There are several methods to estimate expenses in COI studies. The bottom-up method ("person-based") estimates the average cost per patient and multiplies it by the disease prevalence; whilst the top-down approach ("population-based") uses a population-attributable fraction to assign a percentage of the total expenditures to patients with the disease of interest. The econometric approach compares the cost difference in patients with and without the disease of interest. A COI study can consider three different categories of productivity losses including caregivers' productivity losses, patients' productivity losses due to morbidity, and patients' productivity losses due to premature mortality. Two approaches have been commonly used for estimating carers' productivity losses: replacement method and opportunity cost method. Whilst the replacement method values unpaid labour at the market price that would need to be paid for a substitute to complete the task, the opportunity cost method estimates the paid or unpaid work it disrupts as measured by the salary the individual would make if in paid employment. Three main methods have been commonly used for estimating patient productivity losses due to morbidity or premature mortality: the human capital approach (HCA), the friction cost approach (FCA), and the willingness-to-pay (WTP) method. The HCA assigns a monetary value to the predicted productivity losses of an illness that are avoided as a result of a health

72 intervention. The FCA takes into account the projected productivity losses during the “friction period”, or the
73 time required to replace an employee that is ill. The WTP method measures the amount an individual or the
74 society would pay to reduce the incidence or the mortality of the disease of interest. There is no consensus on
75 which method is superior to the others.

76

77 A previous systematic review of COI studies for schizophrenia conducted by Jin and Mosweu [7] summarised
78 the societal cost of schizophrenia across countries. That review identified 19 COI studies and reported that the
79 societal cost of schizophrenia per patient ranges from \$US 5,818 in Thailand [8] to \$US 94,587 in Norway [9].
80 However, the literature searches of Jin and Mosweu were conducted in 2016 and all cost estimates were
81 reported in 2015 US dollars. Several new COI studies have been published since 2016, thus warranting a new
82 systematic review of the subject and an uplift of the cost estimates to the current year value. In addition, Jin and
83 Mosweu did not assess the quality of identified COI studies.

84

85 To fill this gap, our study aims to conduct an updated systematic review of COI studies for schizpohirena.

86 Specific objectives were as follows:

- 87 (1) To identify new COI studies which reports the societal cost of schizophrenia published from 2016-
88 2022;
- 89 (2) To uplift the cost estimates reported by COI studies included in the original review to the current year
90 value;
- 91 (3) To assess the reporting quality of all COI studies and to provide recommendations for good practices
92 for future COI studies.

93

94 **2. Methods**

95 This review was conducted according to the PRISMA standards for reporting systematic reviews and meta-
96 analyses of studies evaluating healthcare treatments [10]. The protocol for this review was registered on
97 PROSPERO (CRD42022328723).

98

99 **2.1 Inclusion/exclusion criteria**

100 The inclusion and exclusion criteria were reported in detail in the original review [7] and are briefly summarised
101 below. Studies were included if they met both of the following criteria: (i) original COI studies which adopted a

102 societal perspective (include both direct costs and productivity losses); (ii) children/young people/adults with a
103 diagnosis of schizophrenia or psychosis. Studies were excluded if they met any of the following criteria: (i) cost-
104 effectiveness analysis; (ii) the cost of schizophrenia was not reported and could not be derived; (iii) focusing on
105 the cost of just one health state of schizophrenia, such as relapse; (iv) reviews, commentaries, letters, editorials,
106 or abstracts; (v) published before 1996; and (vi) not reported in English. All studies included in the original
107 review [7] were retained in the current review.

108

109 **2.2 Search strategy**

110 A literature search was conducted on 22 June 2022 to identify COI studies of schizophrenia published since
111 2016. Six databases were searched, including MEDLINE, Embase, PsycINFO, the Cochrane Database of
112 Systematic Reviews, the Health Management Information Consortium (HMIC) and OpenGrey. We used the
113 same search strategy as the original review [7], which included medical terms such as schizophrenia, psychosis,
114 delusion, hallucination, catatonia as well as health economic terms such as cost of illness, healthcare cost,
115 hospital cost, productivity loss and burden. The detailed search strategy is reported in Online Resource 1,
116 Appendix 1.

117

118 **2.3 Selection of studies**

119 The initial screening of the literature search results was carried out by two independent reviewers (CL and XZ)
120 by comparing the titles and abstracts to the inclusion criteria. Final inclusion of studies in the review was
121 determined by agreement of both reviewers, with any disagreements resolved by discussion with a third
122 reviewer (HJ).

123

124 To confirm that all pertinent COI studies had been found by the search approach employed, the bibliographies
125 of published review/overview articles obtained from the search were also examined.

126

127 **2.4 Data extraction and analysis**

128 Data were extracted by one reviewer (CL) and checked by a second reviewer (XZ), with disagreements resolved
129 by discussion. The following information was extracted from all included studies: author; year; country;
130 patient/disease specification; costing perspective and methods; cost estimates by component; and information on
131 quality criteria set out by the COI checklist (see the next section for details). It was noted that different studies

132 employed different definitions for ‘direct healthcare costs’, ‘direct non-healthcare costs’ and ‘informal
133 care/productivity losses’. For example, informal care (productivity losses for the carer) was considered as direct
134 non-healthcare cost by some studies but was considered as indirect cost by other studies. To keep consistency,
135 the cost components reported by included studies were reclassified by the authors of this review, according to
136 the following definitions:

- 137 • Direct healthcare costs include the cost of inpatient, outpatient, and community service, as well as the
138 medicine costs and any other healthcare system-related costs.
- 139 • Direct non-healthcare costs include the costs of sheltered housing, legal costs, the expense of
140 administering social welfare payments, transportation expenditures, private expenses, and any other
141 direct non-healthcare costs.
- 142 • Productivity losses include productivity losses for the schizophrenia patients due to morbidity or
143 premature mortality, and productivity losses for the caregivers.

144

145 Social welfare benefits were excluded by the authors, as such costs are considered as transfers from one group
146 of people (taxpayers) to another group of people (social welfare beneficiaries), and thus do not impose any cost
147 on the society.

148

149 The cost estimates reported by all included studies were converted to 2022 US dollars using the Campbell and
150 Cochrane Economics Methods Group Evidence for Policy and Practice Information and Coordination
151 (CCMEMG-EPPI) Centre cost converter (<http://epi.ioe.ac.uk/costconversion/default.aspx>)[11].

152

153 **2.5 Quality assessment**

154 The reporting quality of all included studies were assessed using a checklist adapted from the Larg and Moss's
155 guide to critical evaluation of COI studies [12]. Elements explored include the reporting of the costing
156 perspective, epidemiological approach, study question, methods of valuation of different cost components,
157 estimation of intangible cost, description of statistical analyses, inclusion of sensitivity analysis and reporting of
158 the detailed cost components. The quality assessment was conducted by two independent reviewers (CL and
159 XZ), with any disagreements resolved by discussion with a third reviewer (HJ).

160 **3. Results**

161

162 After de-duplication, the updated search identified 1,699 titles and abstracts, of which full texts were obtained
163 for 152 of them. 5 newly identified studies met the requirements for inclusion and were added to the 19 studies
164 which were included in the original review. The Cohen's kappa value for the inter-reviewer agreement was 0.76,
165 which is considered to be a substantial level of agreement [13]. The PRISMA flow chart [14] is shown in Figure
166 1.

167 **3.1 Study Characteristics**

169 The characteristics of all included studies (including five newly identified studies [15–19] and nineteen studies
170 included in the original review) are presented in Table 1. Half of included studies (12/24) originated in Europe,
171 followed by 25% (6/24) in America, 17% (4/24) in Asia, 4% (1/24) in Africa and 4% (1/24) in Australia. All
172 studies were conducted for high-income countries except two: one for Nigeria [18] and one for Malaysia [19];
173 both of which were identified during the update review. A range of data sources were used such as patient
174 registries, including hospital /clinic databases and published literature. All included studies were retrospective,
175 except Hastrup et al. [15], Mangalore and Knapp [20], and Sarlon et al. [21]. 92% (22/24) of the included
176 studies were prevalence-based; the rest are incidence-based (2/24, 8%) [22,23] and activity-costing based (4%)
177 [16]. Among all included studies, 14/24 (58%) used a bottom-up approach, 6/24 (25%) used a mixed approach,
178 2/24 (8%) used an econometric approach [24,25], and 2/24 (8%) used a top-down approach [26,27].

179
180 Nine studies (9/24, 38%) did not include or report caregiver's productivity losses. In the rest 15 studies, the
181 methods used to estimate caregiver's productivity losses varied, including opportunity cost approach (9/15,
182 60%), human capital approach (HCA) (4/15, 27%) [15][17][18][19], the mixed approach (1/15, 7%) [28], and
183 the replacement approach (1/15, 7%) [20].

184
185 All included studies considered patients' lost productivity due to morbidity, and all studies used HCA to
186 estimate patients' lost productivity due to morbidity except one study which used friction cost approach (FCA)
187 (1/24, 4%) [24]. Ten studies (10/24, 42%) did not include or report patients' lost productivity due to premature
188 mortality. In the rest 14 studies, the methods used to estimate patients' lost productivity due to premature
189 mortality include HCA (9/14, 64%), FCA (4/14, 29%) [27,29–31], and willingness to pay method (1/14, 7%)
190 [32]. Only 58% (14/24) of included studies reported results of sensitivity analysis. More details about the
191 included studies, including year of valuation, sample size, and details about patients' diagnosis, age and sex are
192 reported in Online Supplementary Material, Appendix 2.

Table 1 – Characteristics of included studies

Study	Country	Basis of analyses	Year of valuation	Prospective or retrospective	Epidemiological approach	Estimating resource consumption	Methods for valuating productivity losses			Results of sensitivity analysis reported?
							Carer	Patient (morbidity)	Patient (premature mortality)	
Data extracted from the newly identified studies (n=5)										
Hastrup et al.[15]	Denmark	Danish National Patient Registry	2015	Prospective ^a	Prevalence ^b	Mixed	HCA	HCA	NI	No
Latorre et al.[16]	Italy	Medical records	2010-2018	Retrospective	Prevalence	Mixed	NR	HCA	NI	No
Marcellusi et al.[17]	Italy	Literature review	2002-2016	Retrospective	Prevalence	Bottom-up	HCA	HCA	NI	Yes
Oloniniyi et al.[18]	Nigeria	Clinic registry	2011-2012	Retrospective	Prevalence	Bottom-up	HCA	HCA	NI	No
Teoh et al.[19]	Malaysia	Ministry of Health Malaysia psychiatric services report and annual reports of university hospitals	2015	Retrospective	Prevalence	Bottom-up	HCA	HCA	HCA	Yes
Data extracted from studies included in the original review (n=19)										
Behan et al.[32]	Ireland	Multiple sources, including the National Inpatient Reporting System, survey, census, published literature	2006	Retrospective	Prevalence	Mixed	Opportunity cost	HCA	WTP	No
Desai et al.[33]	USA	Medical Expenditure Panel Survey	2005–2008	Retrospective	Prevalence	Bottom-up	Opportunity cost	HCA	HCA	Yes
Ekman et al.[34]	Sweden	Northern Stockholm Psychiatry, the National Board of Health and Welfare, Swedish Social Insurance Agency, and published studies	2008	Retrospective	Prevalence	Bottom-up	NI	HCA	NI	No
Evensen et al.[9]	Norway	Comprehensive and mandatory health and welfare registers in Norway	2012	Retrospective	Prevalence	Top-down	NI	HCA	NI	No
Frey[29]	Germany	Data from Sickness fund (Techniker Krankenkasse, a public health insurance provider) and Federal Statistical Office	2008	Retrospective	Prevalence	Econometric	Opportunity cost	FCA	FCA	Yes

Study	Country	Basis of analyses	Year of valuation	Prospective or retrospective	Epidemiological approach	Estimating resource consumption	Methods for valuating productivity losses			Results of sensitivity analysis reported?
							Carer	Patient (morbidity)	Patient (premature mortality)	
Goeree et al.[35]	Canada	A review of the published literature, secondary analysis of administrative datasets, and information collected directly from various federal and provincial government programmes and services	2004	Retrospective	Prevalence	Mixed	NI	HCA	FCA	Yes
Goeree et al.[36]	Canada	Published literature and direct contact with representatives from various provincial and federal programs	1996	Retrospective	Prevalence	Mixed	NI	HCA	FCA	Yes
Guest and Cookson[22]	UK	A discrete-event model populated by literature review and interviews among a panel of healthcare professionals	1997	Retrospective	Incidence	Bottom-up	Opportunity cost	HCA	HCA	Yes
Langley-Hawthorne[23]	Australia	A Markov model populated by data obtained from published literature and assumptions	1995	Retrospective	Incidence	Bottom-up	Opportunity cost	HCA	NI	Yes
Mangalore and Knapp[20]	UK	UKSCAP survey, psychiatric morbidity surveys, Department of Health, and government publications	2004–2005	Prospective	Prevalence	Bottom-up	Replacement	HCA	HCA	No
Oliva-Moreno et al.[28]	Spain	Data from the Ministry of Health Care and Consumer Affairs, the National Institute of Statistics	2002	Retrospective	Prevalence	Bottom-up	Mixed	HCA	HCA	No
Phanthunane et al.[8]	Thailand	Medical record review and interviews with patients and caregivers	2008	Retrospective	Prevalence	Bottom-up	Opportunity cost	HCA	NI	Yes
Pletscher et al.[37]	Switzerland	Hospital registry, outpatient physician survey and health insurance claim data	2012	Retrospective	Prevalence	Bottom-up	Opportunity cost	HCA	NI	Yes
Rice and Miller[38]	USA	National household interview, provider survey and published literature	1990	Retrospective	Prevalence	Mixed	NR	HCA	HCA	No
Rice and Miller[39]	USA	National surveys and government reports	1985	Retrospective	Prevalence	Bottom-up	NR	HCA	HCA	No

Study	Country	Basis of analyses	Year of valuation	Prospective or retrospective	Epidemiological approach	Estimating resource consumption	Methods for valuating productivity losses			Results of sensitivity analysis reported?
							Carer	Patient (morbidity)	Patient (premature mortality)	
Sado et al.[40]	Japan	Publicly available statistics and reports	2008	Retrospective	Prevalence	Bottom-up	NI	HCA	HCA	Yes
Sarlon et al.[21]	France	Malin System, which covered hospital-based services, day clinic activities, outpatient physician and psychological services, and medications used by the patient	1998–2002	Prospective	Prevalence	Bottom-up	NI	HCA	NI	Yes
Sung et al.[41]	South Korea	Published scientific literature and government reports and documents	2005	Retrospective	Prevalence	Top-down	Opportunity cost	HCA	FCA	Yes
Wu et al.[5]	USA	Administrative claims data, including a large private claims database and the California Medicaid program (MediCal) database	2002	Retrospective	Prevalence	Econometric	Opportunity cost	HCA	HCA	Yes

195

196

Abbreviation

197 *DSM-IV* = Diagnostic and Statistical Manual of Mental Disorders, 4th edition

198 *FCA* = Friction cost approach

199 *HCA* = Human capital approach

200 *ICD-10-CM/GM* = International Classification of Diseases and Related Health Problems, 10th revision, clinical modification/German modification

201 *NI* = not included in analysis

202 *NR* = not reported

203 *UKSCAP* = UK Schizophrenia Care and Assessment Program

204 *WTP* = Willingness to pay

205

206

Notes

208 ^a A retrospective technique is less expensive and takes less time since all pertinent cost components are tracked down from prior data. A prospective method requires gathering data from patients over time meaning all relevant cost components must be followed up for the upcoming year, which can be costly in time and resources.

209

210 ^b There are two main types of COI studies: prevalence-based and incidence-based. The most often used prevalence technique calculates the financial impact of an illness over a given time frame, often between six and twelve months. The incidence-based method calculates the lifetime cost from the start of an illness until its treatment or death.

211

212

213

214 3.2 Cost Estimates

215 The annual healthcare cost and societal cost of schizophrenia per patient by country are shown in Figure 2 and
216 3, respectively. The annual healthcare cost of schizophrenia per patient varied from \$US 350 in Nigeria [18] to
217 \$US 76,019 in Norway [9]. The annual societal cost of schizophrenia per patient varied from \$US 819 in
218 Nigeria [18] to \$US 118,595 in Norway [9]. Generally speaking, north Europe incurred the highest societal cost,
219 followed by the UK, the US, Japan, central Europe, and Canada. The ratio of societal cost per patient to 2022
220 GDP per capita varied from 35% in Nigeria [18] to 237% in the UK [20]. The healthcare and societal costs
221 reported by individual studies are presented in Online Supplementary Material, Appendix 3, Table 2.

222

223 Figure 4 shows the societal cost of schizophrenia by cost component. Productivity losses accounted for 32%
224 [16] to 83% [41] of the overall societal cost, whilst direct healthcare cost made up 11% [16] to 87% [15]. The
225 proportion of direct non-healthcare ranges from 0.3% [20] to 57% [16]. The cost estimates of each cost
226 component are briefly summarised below and presented in detail in Online Supplementary Material, Appendix
227 3, Table 3-5.

228

229 3.3.1 Direct Healthcare Costs

230 The annual direct healthcare ranged from \$US 350 in Nigeria [18] to \$US 76,019 in Norway [9]. The cost of
231 inpatient service is higher than the cost of outpatient/ community service in all countries assessed except the US
232 [25,33], Ireland [32], and France [21]. The medication cost takes up less than 30% of direct healthcare cost in all
233 countries except Italy (35%) [16], US (37%) [33], and Nigeria (51%) [18]. The annual medication cost was
234 lowest in Nigeria [18] (\$US 179) and highest in the US [5] (\$US 4,455).

235

236 3.3.2 Direct Non-Healthcare Costs

237 Direct non-healthcare costs varied from \$US 113 in Malaysia [19] to \$US 23,857 in Italy [16]. The types of
238 direct non-healthcare costs of schizophrenia considered by COI studies include legal cost, sheltered home,
239 programme monitoring and evaluation, data analysis, and repair to property. Legal cost has been more
240 commonly reported in COI studies conducted for western countries (e.g., U.S, U.K, and Canada) compared to
241 those COI studies conducted for Asian countries (e.g., Japan and Malaysia).

242

243 3.3.3 Productivity Losses

244 The annual productivity losses due to schizophrenia ranged from \$US 346 in Nigeria [18] to \$US 62,431 in the
245 UK [20]. For those 15 studies which considered carer's lost productivity, the ratio of carer's lost productivity to

246 the total productivity loss ranged from 2% in the UK [20] to 95% in Italy [16]. The annual productivity losses
247 for carers varied from \$US 120 in Nigeria [18] to \$US 12,542 in Italy [16]. Patient's productivity losses varied
248 from \$US 226 in Nigeria [18] to \$US 48,648 in the UK [20]. Of those 14 studies which considered patient's lost
249 productivity to premature mortality, the estimated productivity losses due to premature mortality ranged from
250 \$US 1 in Canada [35] to \$US 17,333 in the UK [20].

251

252 **3.3 Quality assessment**

253 The performance of included studies on all items of the checklist is shown in Figure 5. Items where all studies
254 performed well (24/24, 100%) included reporting of the costing perspective, study question, and valuation
255 methods of healthcare resource. Items where studies performed particularly badly included reporting of included
256 intangible cost (only one study reported it, 1/24, 4%), results of sensitivity analysis (14/24, 58%), and valuation
257 methods of productivity losses (17/24, 71%). The quality assessment results of each individual study are
258 reported in Online Supplementary 1, Appendix 4.

259

260 **4. Discussion**

261 **4.1 Interpretation of results**

262 This review provides an update on the societal cost of schizophrenia per person, ranging from \$US 819 in
263 Nigeria to \$US 94,587 in Norway (the range reported by the original review is \$US 5,818 in Thailand to \$US
264 94,587 in Norway). Of the 19 COI studies included in the original review, all of them were conducted for high-
265 income countries. Of the five newly identified COI studies, two of them were conducted for low- and middle-
266 income countries (LMICs). As expected, the societal cost of schizophrenia in high-income countries is much
267 higher than the cost in LMICs: the annual societal cost of schizophrenia in Norway [9] is 144 times higher than
268 the cost of Nigeria [18]. However, even in LMICs, the economic burden of schizophrenia is still substantial: in
269 Nigeria and Malaysia, the ratio of societal cost per schizophrenia patient to 2022 local GDP per capita is 35%
270 [18] and 50% [19], respectively.

271

272 Generally speaking, productivity losses are the driver of the societal cost of schizophrenia, followed by direct
273 healthcare cost, and direct non-healthcare cost. Whilst all included studies considered patients' productivity
274 losses due to morbidity, only about 40% of them also considered patients' productivity losses due to premature
275 mortality and productivity losses for the caregivers. If all relevant productivity losses were included in the
276 analysis, productivity losses could take up an even higher proportion in the societal cost of schizophrenia.

277

278 Within direct healthcare cost, inpatient care remains the single most expensive component in most countries.

279 However, in some western countries where deinstitutionalisation (i.e. releasing institutionalised individuals with
280 mental health disorders from institutional care, such as a psychiatric hospital to care in the community) was
281 introduced since 1950s, such as the US [25,33], Ireland [32], and France [21], the cost of outpatient/ community
282 service started to exceed the cost of inpatient care.

283

284 A quarter of the included studies did not include any direct non-healthcare cost, despite the fact that all of them
285 claimed to use a societal costing perspective. Of those studies which did consider direct non-healthcare cost,
286 there is great variation in terms of what cost components were included. This might be caused by the diversity
287 of cultures, social structures and health-care systems across countries. For example, it was noticed that legal cost
288 has been more commonly reported in COI studies conducted in western countries (such as U.S, U.K, and
289 Canada) where deinstitutionalisation has been widely implemented, compared to those countries where few
290 attempts have been made, such as Japan and Malaysia. This might be because, compared with those
291 institutionalised patients, patients who reside in the community may at an increased risk of both committing and
292 being the victim of a violent crime, such as rape/sexual assault, personal and property theft, and other violent
293 attacks, all of which would increase the cost to the criminal justice system. In the US, it was estimated that
294 deinstitutionalisation resulted in 3.2 million people with untreated serious mental illness living in the
295 community, who are responsible for 10% of all homicides and 50% of all mass killings [42]. Another study
296 from the US reported that for those people with severe mental illness using community mental health services in
297 an inner-city area, over 25% of them were victims of at least one violent crime per year, a proportion which was
298 eleven times higher than the inner-city average [43].

299

300 Great variance in cost estimates were also observed in COI studies conducted for the same country. For
301 example, both Latorre et al. [16] and Marcellusi et al. [17] used modelling methods to assess the societal cost of
302 schizophrenia in Italy during overlapping years (2010-2018 v.s. 2002-2016). However, the annual societal cost
303 reported by Latorre et al. [16] is about three times as high as the cost reported by Marcellusi et al. [17] (\$US
304 41,827 v.s. \$US 13,022). This was mainly because the cost of sheltered home (\$US 23,109) and carer's lost
305 productivity (\$US 12,542) reported by Latorre et al. [16] were much higher than the costs of sheltered home
306 (\$US 4,184) and carer's lost productivity (\$US 700) reported by Marcellusi et al. [17]. Latorre et al. [16] did not

307 report the details of the data sources used to estimate the cost of sheltered home or carer's lost productivity; it
308 only reported that 'Goods and services use was assessed from medical records (e.g., patient's usage of a specific
309 drug) or focus group (i.e., a team of five experts including the director of the practice and psychiatrists)
310 indication when objective data were not available.' The medical records used in Latorre et al. [16] were
311 obtained from 523 schizophrenia patients in south Italy, with a mean age of 51.5 years (± 13.3 years) and a mean
312 duration of illness of 19.7 years (± 13.3 years). Marcellusi et al. [17] reported that their cost of sheltered home
313 and carer's lost productivity were estimated based on the results of a longitudinal study [44]. It was noticed that
314 the patients recruited in the longitudinal study [44] were on average 20 years younger and with 16 years shorter
315 duration of illness compared with the patients recruited by Latorre et al. [16]. This might explain why the cost of
316 sheltered home and carer's lost productivity reported by Latorre et al. [16] were much higher than the costs
317 reported by Marcellusi et al. [17]. In addition, methodological heterogeneity might also contribute to the great
318 variation in cost estimate. For example, Latorre et al. [16] used a mix of top-down and bottom-up approach for
319 estimating resource use, whilst Marcellusi et al. [17] used the bottom-up approach. Whilst there is no consensus
320 on which method is superior to the others, there is evidence showing that use of different approaches could
321 result in very different cost estimates [45]. Therefore, it is important for COI studies to clearly report their
322 costing methods, data sources, and patient characteristics to help with interpretation of their results.

323

324 **4.2 Implications for policy making and future research**

325 This review found that in most countries, productivity losses started to overtake direct healthcare cost to become
326 the single most expensive component of societal cost of schizophrenia. It was reported that up to 97.5% of
327 schizophrenia patients may want some type of work role (e.g. volunteering or paid employment) [46].

328 However, the employment rate of schizophrenia in most western countries is only around 10-20% [47]; and
329 53% of schizophrenia patients stated they had not received any support in obtaining work [46]. Caregivers'
330 productivity is also affected as they often have to reduce their working hours, take a leave of absence to look
331 after the patients. In some of the included studies, the productivity losses for caregivers have been shown to be
332 higher than the cost of productivity loss borne by schizophrenic patients themselves. Substantial savings could
333 potentially be achieved by providing vocational rehabilitation to the schizophrenia patients and support to their
334 caregivers.

335

336 It should be noted that whilst COI studies are helpful in highlighting the magnitude of economic burden of an
 337 illness and identifying the cost drivers, they do not consider the health outcomes of an intervention and therefore
 338 cannot be used directly to inform resource allocation decisions for a particular intervention – i.e., which
 339 vocational rehabilitation is most cost-effective for schizophrenia patients and thus should be funded [48]. Such
 340 decisions need to be informed by cost-effectiveness analysis (CEA) which examine both the cost and health
 341 outcomes of one or more interventions. It is recommended that more CEAs need to be conducted to assess the
 342 cost-effectiveness of interventions which can improve the employment status for schizophrenia patients and
 343 their caregivers. The cost estimates reported by the COI studies identified in this review can be used to
 344 parametrise such CEAs.

345
 346 This review also highlights a lack of COI studies of schizophrenia in LMICs. Due to the differences in local
 347 economic situations and healthcare systems, it is generally agreed among economists that the results of
 348 economic studies may not be transferable between different countries [49]. Therefore, the societal cost reported
 349 by high-income countries cannot be used to directly inform policy making or parametrise CEAs in LMICs. It is
 350 recommended that more COI and CEA studies of schizophrenia needed to be conducted for LMICs.

351

352 **4.3 Recommendations for good practice for COI studies of schizophrenia**

353 Based on the results of quality assessment conducted as part of this updated review, as well as the guide of COI
 354 studies suggested by Larg and Moss [12], good practices for conducting and reporting COI studies of
 355 schizophrenia are derived and summarised in Table 2. The suggested good practices cover both costing methods
 356 and reporting of COI studies. It is recommended that the suggested good practices should be used by health
 357 economists in conjunction with their own judgement, taking into consideration of the local context and practical
 358 resource constrains.

359 **Table 2 - Good practices for conducting and reporting COI studies for schizophrenia**

Element	Recommendations
<i>General costing methods</i>	
Productivity losses	Include patient productivity loss due to morbidity, patient productivity loss due to premature mortality and caregivers' productivity loss.
Direct non-healthcare costs	Include all non-trivial direct non-healthcare costs relevant to the local context. A non-exhaustive list includes sheltered home, legal costs, administration fee of social welfare benefits, transport costs, and private expenditure.

Element	Recommendations
Sensitivity analyses	Sensitivity analyses should be conducted to test the uncertainty of all important parameters and key assumptions.
<i>Reporting of COI studies</i>	
Patient characteristics	Patients' demographic characteristics, such as age, sex, duration of illness, should be clearly reported. In addition, patients' diagnosis should be clearly reported with relevant ICD or DSM codes.
Costing method	The data sources, methods and procedures used to calculate each cost component should be clearly reported.
Presentation of cost outcomes	The cost outcomes should be presented in sufficient details to allow replication of the calculation and various degrees of disaggregation.
Results of sensitivity analysis	The range of value tested for each parameter and their impact on the final cost estimate should be clearly reported.

360

361 **4.4 Strengths and Limitations**

362 This updated review has several strengths. Firstly, it identifies the latest COI studies published since 2016.
363 Secondly, the cost estimate reported by all included studies were uplifted and converted to 2022 US dollar and
364 presented graphically on maps. Thirdly, the original review did not assess the quality of identified COI studies.
365 In this updated review, the reporting quality all of twenty-four included studies was assessed using a checklist
366 adapted from Larg and Moss [45]. Finally, based on the findings of this review and results of quality
367 assessment, recommendations on future research, and good practice for improving the methodological and
368 reporting quality of future COI studies are provided.

369

370 This review is subject to two main limitations. Firstly, as an updated review, we used the same
371 inclusion/exclusion criteria as the original review and therefore only included studies that undertook a societal
372 costing perspective. A societal perspective is often favoured by economists as it is most comprehensive and can
373 provide useful information to decision-makers from different sectors. However, COI studies which are
374 conducted for a narrower perspective (e.g., healthcare system) could also provide valuable information to
375 decision-makers from a particular sector. Secondly, where there is more than one study reporting the cost of
376 schizophrenia for the same country, we used the cost estimate reported by the most recent study when plotting
377 the cost of schizophrenia across different countries on a map. It was acknowledged that the cost reported by the
378 most recent study might not be more accurate than the cost reported by older studies. However, considering the

379 rapid changes in treatment options, care pathways and health policies for schizophrenia across the world, we
380 believe the costs reported by the most recent studies are more likely to reflect the economic burden of
381 schizophrenia in current practice. In addition, our result of quality assessment indicate that the reporting quality
382 of more recent studies is generally better than older studies.

383

384 **5. Conclusion**

385 This review highlights the substantial economic burden of schizophrenia across countries and a lack of COI
386 studies for LMICs. Productivity losses accounted for 32% to 83% of the overall societal cost of schizophrenia.
387 Great cost variation has been observed both across and within countries, which might be caused by differences
388 in local economic state and healthcare systems, and widespread methodological heterogeneity among COI
389 studies. Recommendations on future research, and good practices for improving the methodological and
390 reporting quality of future COI studies are provided.

391

392 **Author Contributions**

393 HJ conceived the idea of this review. CL and XZ performed 1st round (title and abstract) screening and 2nd
394 round (full-text) sifting, data extraction and quality assessment. HJ advised on the overall plan and
395 implementation of the systematic review. CL and HJ wrote the first draft of the paper, which was subsequently
396 been edited by all authors who have approved the final version. CL will serve as a guarantor for the overall
397 content of the manuscript.

398

399 **Compliance with Ethical Standards**

400 **Ethics Approval:** Not Applicable

401 **Informed Consent:** Not Applicable

402 **Data Availability Statement:** All data generated or analysed during this study are included in this published
403 article.

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405 **Conflict of interest:** CL, XZ and HJ declare no conflicts of interest.

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