Original Research

The Lifetime Burden of Schizophrenia as Estimated by a Government-Centric Fiscal Analytic Framework

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Abstract

Objective: To estimate the fiscal consequences of schizophrenia compared to the general US population using a "government perspective" fiscal analytic modeling framework capturing lost tax revenue and broader government costs in 2021.

Methods: Schizophrenia was modeled from age 23 using a cohort-based Markov chain with 6-week cycles, simulating the effect of antipsychotic treatment sequences on remission and relapse. Markov states were defined using efficacy and safety outcomes from short- and long-term clinical trials. Mortality was based on US lifetables, schizophrenia-related suicide, and cardiovascular risks. A semi-Markov model with annual cycles simulated the likelihood and costs of incarceration and homelessness in community-based individuals. Lifetime fiscal consequences were estimated conditionally to survival, remission/relapse status, and likelihood of socioeconomic outcomes. Costs and life years were discounted at 3.0% annually. Uncertainty was explored in 1-way and scenario analyses.

Results: Unemployment, disability, incarceration, homelessness, health care use, and productivity losses were more common in people living with schizophrenia. Schizophrenia was associated with a $1,540,042 per person lifetime fiscal loss to the government, with $56,707 per life year lived with schizophrenia. Health care costs represented 41.9% of the fiscal losses, 39.4% were due to criminal and homelessness costs, and 17.5% related to foregone tax revenue. Considering a 1.19% prevalence of schizophrenia, the estimated annual fiscal burden in the US was $173.6 billion.

Conclusions: The fiscal framework illustrates how schizophrenia influences taxation and government transfer payments over time. These findings can be used to augment cost-effectiveness analyses and inform stakeholders of the fiscal impact of schizophrenia to inform priority interventions.

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Schizophrenia is a chronic and complex mental illness manifesting through positive symptoms such as hallucinations, negative symptoms like avolition or decreased ability to express emotion, in combination with disorganized thinking or speech.[1,2] Persisting symptoms impact several domains of everyday functioning, including social interactions, academic achievements, vocational activities, and the ability of living independently.[3–6] Despite its relatively low prevalence, schizophrenia accounts for 13.4 million years lived with disability, 1.7% of the annual global disability burden.[7] Due to its early onset and severity, acute schizophrenia has been found to be the disease with the highest disability weight ratio (0.78, uncertainty interval 0.61 to 0.90).[8]

It is thought that 1.19% of the 258 million US adults (2021) have schizophrenia, approximately 3.1 million individuals.[9] The annual societal cost per person living with schizophrenia (PLWS) in the US has been estimated to range from $17,569 to $55,373 in 2015.[10,11] Given these figures, the estimated annual societal cost of schizophrenia ranges from $68 to $214 billion 2021 US dollars,[12] approximately 0.3%–1.0% of the US gross domestic product.

The breakdown of schizophrenia's economic burden varies among published burden of disease studies, but indirect costs, from PLWS and caregivers' productivity losses, are unanimously reported as the largest cost component (48.9%–81.4%), followed by direct medical costs (19.5%–36.8%) and direct nonmedical costs such as legal, social benefits, and sheltering expenses (4.0%–18.2%).[10,13] Cost-effectiveness analyses assessing the value of schizophrenia treatments can rightfully include broader economic consequences of the disease, albeit the large majority of these analyses solely focus on health system or third-party payer costs.[14]

Clinical Points

- Schizophrenia is a serious and lifelong condition linked to substantial costs to the US government that are worth estimating to inform policy and practice.
- Active disease increases the risk of criminal offense, imprisonment, homelessness, and need for health care, all translating into additional public expenses.
- Treatments and programs effectively maintaining stable disease, particularly in early life, can offset government costs and ultimately alleviate public tax burden.

The policy-led reduction of publicly funded mental health beds in the US has increased the pressure on community services and, since the mid-1970s, progressively contributed to mass incarceration[15–17] and homelessness among PLWS.[18] Because schizophrenia is associated with a substantial decrease in labor force participation and record high rates of incarceration and homelessness,[17,19,20] disease externalities are likely to have an important impact on the broader economy and tax-funded resources utilization.

The goal of our research was to update existing estimates of the economic burden of schizophrenia[21] and to quantify lifetime fiscal economic consequences not captured by other studies[22] by utilizing a "government perspective" framework.[23,24] The framework enabled estimating the monetary value of foregone tax contributions, and public expenses associated to justice, law enforcement, health care, and social support services in PLWS compared to the general US population.

METHODS

Modeling Framework

Failure to achieve and maintain schizophrenia symptoms remission (stable disease) has been associated with increased health care utilization and worse functional outcomes.[25,26] Relapse can therefore impact the likelihood of social events and have monetary fiscal consequences for state and federal governments. An analytic model was developed in Microsoft Excel to simulate the lifetime economic burden of schizophrenia focusing on costs incurred by the US Government and Social Security Administration (SSA).[23,24] A Markov trace simulated schizophrenia progression and estimated the annual proportion of individuals in remission or relapse (unstable disease), according to the efficacy of sequential antipsychotic (AP) treatments (Figure 1). An additional, semi-Markov process simulated transitions between the community, homelessness, and incarceration social states, conditionally to individual's remission or relapse status. The annual fiscal costs of schizophrenia were compared to the fiscal costs of a cohort with the same age and gender unaffected by schizophrenia (general population). All calculations used the adult US population in 2021 (258,327,312),[27] a 1.19% schizophrenia prevalence[28] and a 66% proportion of males.[29,30]

Modeling Schizophrenia Progression

Simulating schizophrenia lifetime progression used a Markov model with a 6-week cycle, mimicking the duration of short-term clinical trials of APs. The model structure (Figure 1) departed from that described by Park and Kuntz,[31] being expanded to consider a likely long-term distribution of AP treatments in the US. The model started at age 23,[29,30] with individuals experiencing their first psychotic episode. Psychosis was modeled to remain undiagnosed for 74 weeks.[29] Of the undiagnosed and/or untreated individuals, 74.1% were assumed to present active disease at any given time.[32]

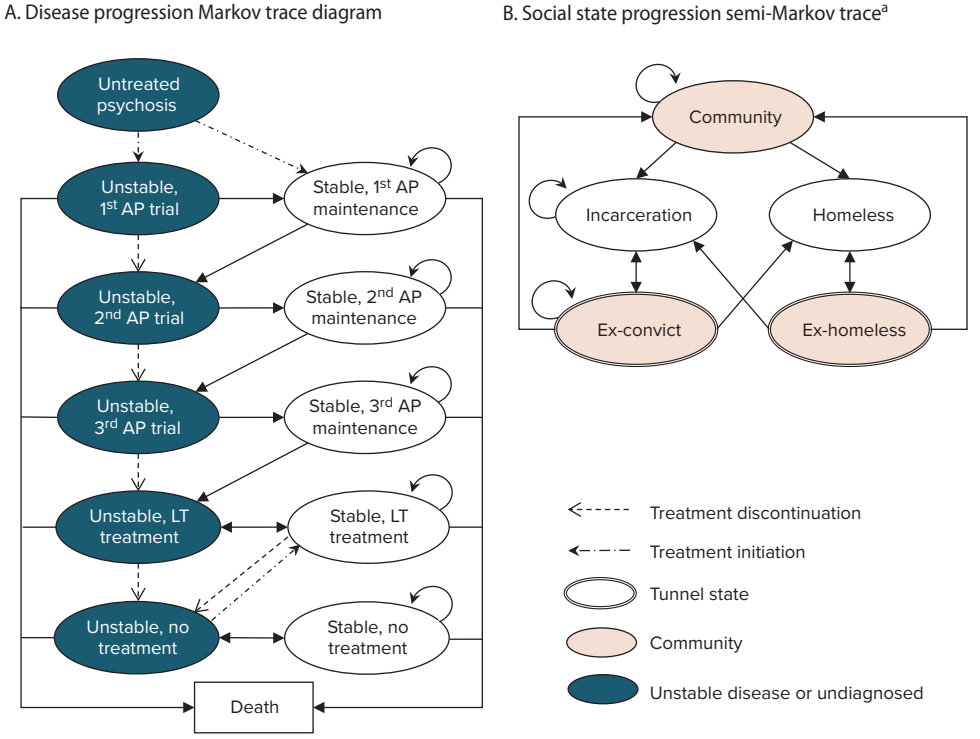
Upon diagnosis, individuals started first-line treatment with a second-generation AP. Subsequently, people could remit and move to a stable/maintenance state, or discontinue treatment, remain unstable, and move to second-line treatment. The AP with the highest market share,[33] not used as first-line treatment, was used as the second-line agent. On the following cycle, individuals could remain on the second-line AP, or discontinue/relapse, starting third-line AP therapy with another oral second-generation drug.[33] Further discontinuation or relapse transitioned individuals to the long-term phase of the model with 40% not to receiving any schizophrenia treatment.[34] Antipsychotic usage for the remaining 60.0% was informed by an analysis of Medicaid data,[35] with 78.0% receiving an oral second-generation AP (same efficacy and safety as third-line oral AP), 16.8% a long-acting injectable AP (LAI), and 5.1% receiving clozapine. Those remaining on any AP treatment were assumed to achieve remission, facing the risk of relapse on the following cycle.[36,37] The long-term phase of the model was assumed to repeat indefinitely until individuals' death. General mortality was implemented using US lifetables.[38] In PLWS, mortality accounted for the increased risk of suicide and AP-related cardiovascular risk.[39,40] A detailed description of the inputs and methods used to model schizophrenia progression can be found in Supplementary Appendix 1.

Modeling Social States Transition

A semi-Markov model with a 12-month cycle simulated transitions between mutually exclusive social states (community, incarceration, and homelessness) in the general US population and in PLWS (Figure 1). For simplicity, social states were modeled not to impact mortality. For example, incarcerated individuals had the same death rates as community-dwelling individuals.

All individuals started in the community social state where they could remain, transition to incarceration (prison or jail) or homelessness. Incarceration probability, duration, and recidivism were informed by nationwide

Figure 1.
Schizophrenia Fiscal Model Diagram



[a]Separate social state progression traces were created for individuals with stable and unstable schizophrenia to account for the different probabilities of relevant events and costs.
Abbreviations: AP = antipsychotic, LT = long-term.

US data and publications comparing the general population and PLWS. To account for time dependency in the Markov structure, incarcerated individuals were tracked using tunnel states.[41] Tunnel states were also used to define a period of increased risk of reincarceration and homelessness in ex-convicts. We assumed that homelessness would last for 1 year, after which individuals would transition to a year-long ex-homeless state, being at higher risk of repeated homelessness and incarceration or could return to the community. The inputs and calculations used to model social state transitions are detailed in Supplementary Appendix 1.

Fiscal Consequences of Socioeconomic States

The likelihood of being in a social state was linked to fiscal consequences (taxes revenue and government expenses). The focus of this analysis was to estimate the fiscal burden of schizophrenia on the US Government and SSA, therefore the economic impact of the disease on private institutions was disaggregated from public costs. Foregone employment earnings in PLWS and their informal caregivers compared to the general US population do not constitute a loss to the government but were used to calculate disease-related decrements to labor-related tax contributions and consumption tax, as these affect fiscal revenue. Fiscal consequences with a negative economic impact on the US government (financial support, health care costs, legal costs) were represented as negative values. Sources of government revenue (direct and indirect taxation) were shown as positive values. Fiscal cost and cost consequences were sourced from peer reviewed or national US data and inflated to 2021 US dollars using the Consumer Price Index.[12] Fiscal consequences associated to each social state are listed in Table 1. Additional information about the implementation and value of the modeled economic consequences can be found in Supplementary Appendix 1.

Model Results

The results of the model were synthesized as incremental net consequences (INC) calculated as the difference between each cohort's net present value (NPV). The NPVs for the general population and the schizophrenia cohort were derived using the equations below.[23]

$$NPV_i = \sum_{t0}^{t} \frac{Tax_t - Costs_t}{(1+r)^t}$$

$$Tax_t = Direct\ tax_t + Indirect\ tax_t + Social\ security\ contributions_t$$

$$Costs_t = Health_t + Disability_t + Criminal_t + Other\ transfers_t$$

Where i is the cohort under study, r is the discount rate and t is time. Lifetime employment earnings

Table 1.
Fiscal Consequences of Social States

Social state	Fiscal consequences	Economic impact
Community[a]	Direct taxes[b]	Fiscal gain
	Indirect taxes[c]	Fiscal gain
	Legal costs (individuals being arrested but not yet incarcerated)	Fiscal loss
	SSI and SSDI	
	Victimization costs	
	Direct taxes (informal caregiver's earnings)[b]	Fiscal gain
	Indirect taxes (informal caregiver consumption)[c]	Fiscal gain
Incarceration	Incarceration costs	Fiscal loss
	Health care costs	
Homeless	Homelessness costs	Fiscal loss
	Health care costs	

[a]Ex-convicts and ex-homeless individuals were considered to be in the community, incurring the same fiscal consequences as people ever incarcerated or experiencing homelessness.
[b]Direct taxes were calculated by multiplying gross income from employment by the US tax wedge. The tax wedge represents the amount of taxes and social security contributions related to a single worker. Taxes are paid by the employee and social security contributions are paid by the employee and employer.
[c]Consumption tax.
Abbreviations: SSDI = Social Security Disability Insurance, SSI = Supplemental Security Income.

were reported along with the main results of the analysis but were not directly included in the NPV calculations. Earnings were utilized to calculate tax and Social Security contributions per capita.

Since the fiscal burden of disease may also have wider societal implications, we have estimated the societal deadweight loss from schizophrenia. In a perfectly competitive market, without tax-related distortions, transfers from governments to individuals are not counted as societal losses, comprising a redistribution of wealth. Nonetheless, increased public expenditure caused by a burdensome disease, leads to increased taxation which, in turn, affects commodity prices and hence all individuals in a society.[42,43] Depending on how progressive the imposed tax rate is, increased commodity prices implies that consumers demand less quantities, leading to a loss of consumer welfare and utility, ie, the societal deadweight loss of increased taxation.[44] This was estimated by multiplying the INC estimated by this study by the rate of excess burden reported in the guidelines for the cost-benefit analysis of federal programs (25%).[45,46]

Sensitivity Analysis

We implemented 5 scenarios to explore assumptions to base case inputs. In these scenarios we varied the US prevalence of schizophrenia, the prevalence of schizophrenia in prisons, the proportion of PLWS using publicly funded health insurance, the source of criminal justice costs and the time horizon of the analysis. One-way sensitivity analyses (OWSA) were conducted by individually replacing most model inputs by the lower or upper bounds of their 95% confidence intervals, to determine which parameters impacted results the most. The results of the OWSA were synthesized in a tornado diagram.

Ethics Approval

The analysis described here is based on secondary data from public sources. No intervention was directly assessed in this work and no individual patient data have been used in the conduct of this evaluation; therefore, no ethics approval is required.

RESULTS

The reported results are per capita and discounted at a 3.0% annual rate. The model predicted that over a lifetime horizon, the schizophrenia cohort would be associated with 26.54 discounted life years compared to 26.96 in their general population equivalents, a 0.42 life years difference. For caregivers and their equivalents, the model estimated an average of 20.84 life years.

Table 2 depicts the incremental fiscal results using base case assumptions. Since the onset of the disease at age 23, a PLWS was associated with an excess fiscal burden of $1,487,243 to the US government and SSA. The largest share of this value was related to health care costs, 42.4% ($630,962), followed by disability benefits, criminal justice, incarceration, victimization, and homelessness costs (39.9%, $593,495), and the remaining 17.7% ($262,786) being due to lost tax revenue. The model also predicted that 1.2% ($17,799) of the incremental net consequences (INC) related to foregone tax revenue from informal caregivers. Overall, the fiscal loss added to $1,505,042 per person over the time horizon of the analysis, which equates to $56,707 per life year lived with schizophrenia.

Table 2.
Base Case Results

	Fiscal consequences	Affected by schizophrenia	General population	Incremental[a]
Person with schizophrenia or general population equivalent	Direct tax	$93,616	$313,602	–$219,986
	Indirect tax	$17,175	$59,975	–$42,800
	Disability benefits	–$1,617	–$1,818	$201
	Criminal justice	–$26,152	–$3,819	–$22,333
	Incarceration	–$537,216	–$79,131	–$458,085
	Homelessness	–$104,403	–$7,258	–$97,144
	Victimization	–$17,939	–$1,806	–$16,133
	Health care costs	–$734,460	–$103,498	–$630,962
Caregiver or general population analog	Direct tax	$185,330	$200,380	–$15,051
	Indirect tax	$33,835	$36,583	–$2,748
Overall fiscal consequences (INC)		**–$1,091,832**	**$413,210**	**–$1,505,042**

[a]Calculated as the difference between fiscal consequences for people with schizophrenia and those for the general US population. Negative values represent a loss to the US government and Social Security Administration; positive values represent a source of revenue.
Abbreviation: INC = incremental net consequences.

Table 3.
Incremental Fiscal Consequences for Scenario Analyses

		Scenarios				
	Fiscal consequences	100% Public health insurance	Prevalence of schizophrenia 1.62%[a]	Prevalence of schizophrenia in prisons[b]	Source criminal justice costs[c]	Time horizon 35 years
Person with schizophrenia or general population equivalent	Direct tax	–$219,986	–$219,986	–$220,672	–$219,986	–$204,451
	Indirect tax	–$42,800	–$42,811	–$42,926	–$42,800	–$39,207
	Disability benefits	$201	$404	$217	$201	$124
	Criminal justice	–$22,333	–$22,333	–$23,212	–$29,297	–$18,944
	Incarceration	–$458,085	–$458,085	–$477,508	–$458,085	–$386,857
	Homelessness	–$97,144	–$97,144	–$93,453	–$97,144	–$55,948
	Victimization	–$16,133	–$16,133	–$15,910	–$16,133	–$14,585
	Health care costs	–$769,439	–$630,962	–$635,819	–$630,962	–$561,609
Caregiver or general population analog	Direct tax	–$15,051	–$15,051	–$15,051	–$15,051	–$15,051
	Indirect tax	–$2,748	–$2,748	–$2,748	–$2,748	–$2,748
Overall fiscal consequences (INC)		**–$1,643,519**	**–$1,504,849**	**–$1,527,081**	**–$1,512,006**	**–$1,299,276**

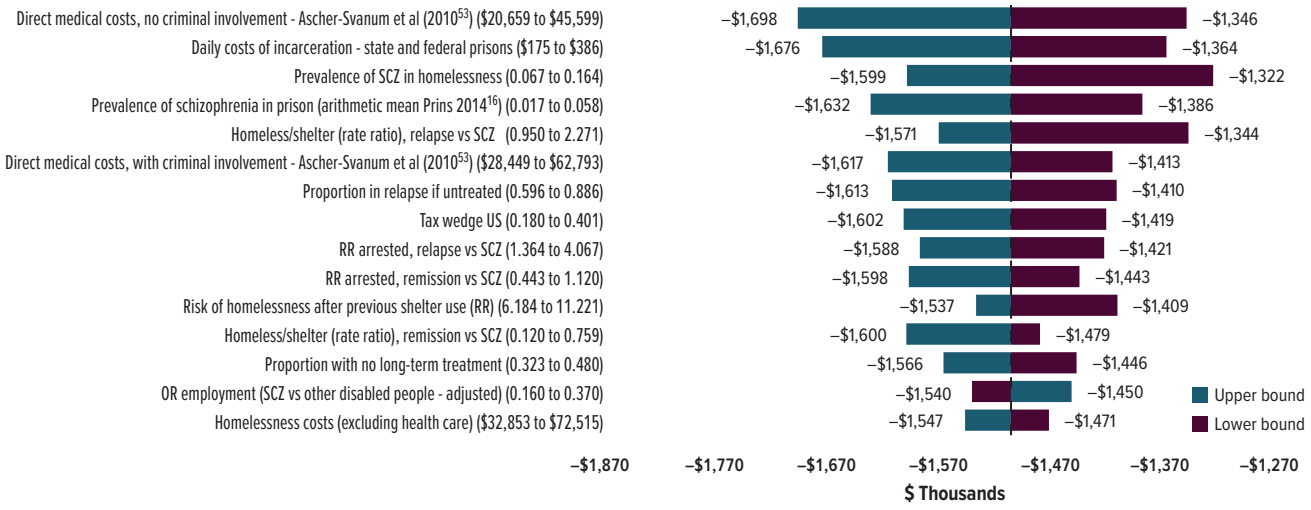
[a]Using evidence from Mojtabai 2021.[48]
[b]Using evidence from Bronson and Berzofsky 2017.[49]
[c]Using evidence from Lin et al 2015.[52]
Abbreviation: INC = incremental net consequences.

From a societal perspective, a PLWS was associated with $825,270 foregone earnings from employment, compared to a similar person without the disease. This value was $52,996 in informal caregivers who had to reduce or stop employment. When combined, the fiscal and productivity losses added to $2,383,308 over a lifetime or $89,798 per life year lived with schizophrenia.

Considering the 2021 adult US population (258,327,312) and a 1.19% schizophrenia prevalence[28] we can infer that there are currently just over 3.07 million individuals living with the condition. Using our predicted value of $56.7 K per life year lived with schizophrenia we estimate that the fiscal cost to the US government and SSA would result in $173.6 billion lost annually. To society, the estimated economic loss, inclusive of productivity losses would correspond to $271.9 billion annually.

The INC of schizophrenia represents the economic burden of the disease to the US government due to loss productivity and increased need for social benefits. Raising taxes to offset this economic loss could result in friction in the supply and demand equilibrium, leading to an inefficient use of resources and loss of consumer utility. Schizophrenia-related societal deadweight loss from taxation was estimated to be up to $376,262 over the lifetime of a person with the condition or $43.4 billion annually if the entire schizophrenia population was considered.

Figure 2.
Tornado Diagram



Abbreviations: OR = odds ratio, RR = relative risk, SCZ = schizophrenia.

Scenario Analyses

The incremental fiscal consequences resulting from scenario analyses are shown in Table 3. According to Khaykin et al,[47] most of the schizophrenia population are likely recipients of publicly funded health insurance. Assuming that this would be true for all PLWS resulted in an INC of –$1,643,519 per person over their lifetime, a 9.2% increase from base case. Due to the uncertainty around schizophrenia prevalence, we have varied the base case prevalence in the general population from 1.19%[28] to 1.62%[48] and in incarcerated people from 3.4% in prisons and jails[16] to 3.8% in prisons and 5.9% in jails.[49,50] The first scenario caused virtually no change to the INC, and the second increased the overall fiscal loss by 1.5% only. We also varied criminal justice cost per arrest (increased from $2,910[51] to $3,817[52]) as there is likely to be variation nationally. The effect of this scenario was negligible, affecting the INC by less than 1%. Finally, we varied the time horizon of the analysis to 35 years since onset of schizophrenia to the age of retirement (rather than death). The INC became $1,299,276, a reduction of 13.7% from baseline.

One-Way Sensitivity Analysis

The effect of the 15 most influential parameters is shown in Figure 2. Direct medical costs in PLWS with no criminal involvement caused the largest change, resulting in a 12.8% increase ($1,698,011) and 10.6% reduction ($1,346,103) of the total fiscal loss. Inputs related to incarceration costs, prevalence of schizophrenia in prisons and among homeless people, and homelessness costs, lead to an approximate 10% increase or decrease of the overall fiscal loss. The remaining parameters led to a less than 7.5% INC variation.

DISCUSSION

We predicted that PLWS would be associated with a lifetime incremental fiscal loss of $1,505,042 compared to an equivalent person unaffected by the disease. Of these costs, 41.9% were related to health care expenses; 39.4% to government transfers in areas such as legal, criminal justice, and social support to homeless or disabled individuals; 17.5% related to forgone tax revenue; and 1.2% to informal care costs. The predicted impact on one's ability to remain in employment resulted in $825,270 in lifetime foregone earnings. Overall, schizophrenia was predicted to impose an annual fiscal burden of $173.6 billion to the US government. From a societal perspective, losses accrued to $271.9 billion annually, and $315.3 billion if considering deadweight losses from taxation.

We have shown that the economic burden of schizophrenia far exceeds direct medical costs, which are often the focus of policy and cost-effectiveness assessments. Schizophrenia's direct nonmedical and indirect costs directly increase public expenses, which impact prices and purchasing power and have a real effect on societal welfare capacity.[54,55] Consequently, investing in programs and interventions mitigating the burden of schizophrenia will ultimately impact the broader economy. Assessing the value of these interventions should consider the full spectrum of economic consequences generated from schizophrenia and other chronic conditions.

We believe this is the first study estimating the burden of schizophrenia falling on the US government, thus filling an important evidence gap. Our approach differs from other burden of schizophrenia studies[21,22] because we modeled the life course of the disease,

accounting for the age-specific likelihood of events such as employment, incarceration and homelessness, and age-specific cost-consequences. Additionally, when estimating the impact of informal care, we attempted to predict the effect of caregiving intensity on decreased labor participation. This approach is substantially different from simply calculating replacement costs given weekly hours of informal care. Comparing our results with those from other publications must be done with caution, being mindful of methodological differences.

An additional finding of this study was that despite the higher proportion of PLWS entitled to disability benefits (6.7% vs 2.9%), the overall value of received benefits was lower than that obtained by the population unaffected by schizophrenia. This may be explained by schizophrenia-related mortality, the lack of a formal diagnosis, challenges in navigating the application system, and subsequent dropout.[56]

Our results were robust to sensitivity analyses, requiring extreme parameter variations to produce meaningful changes to the results. Interestingly, varying the time horizon to 35 years (a more than 50% reduction of the analysis time horizon) led to a 13.8% reduction of the fiscal loss. This finding is important, suggesting that 86.2% of the economic consequences of the disease occur within 35 years of symptom onset.

There are limitations to our analysis. The model uses data from very different sources, involving several assumptions, which consequently increases uncertainty. Inputs such as schizophrenia prevalence in the general population and among the homeless or incarcerated populations are not consensual,[16,19,22,48] also contributing to overall uncertainty. Evidence linking symptom remission and relapse to functional and socioeconomic consequences is scarce, with existing sources having limited generalizability to the entire schizophrenia population. Additionally, we have not modeled the effect of incarceration/homelessness on mortality to avoid double-counting and further assumptions. Due to the increased risk of death in incarcerated/homelessness individuals[17,57,58] and higher propensity for PLWS to be incarcerated/homeless, this approach is likely to be conservative and underestimate the disease burden. Accounting for costs such as those related to housing, provision of various social services by state departments, and the impact of informal care on caregiver's health[59] would likely contribute to augmenting the estimates of the fiscal economic burden of schizophrenia. Finally, informal caregivers' health is likely to be impacted by the caregiving process.

CONCLUSION

We estimated the lifetime economic burden of schizophrenia to the US government. This was achieved using a public economic framework linking schizophrenia's natural history and active disease prevalence to foregone tax contributions in PLWS and informal caregivers, increased government transfers due to disability, criminal justice involvement, homelessness, and public health care insurance utilization, compared to the general US population. The economic impact of schizophrenia far exceeds the costs of health care and should be considered by policymakers defining the level of social support and treatments available to this high-risk population.

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Supplementary Material

Article Title: The Lifetime Burden of Schizophrenia as Estimated by a Government-Centric Fiscal Analytic Framework

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1. Appendix 1

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The Lifetime Burden of Schizophrenia as Estimated by a Government-Centric Fiscal Analytic Framework

Appendix 1

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1. Modelling the clinical progression of schizophrenia

The model compares a cohort unaffected by schizophrenia (general US population) with a cohort with schizophrenia from the age of 23 years, over an 80-year time horizon. The disease progression model simulates individuals' response to six sequences of antipsychotic treatments (Table 1). The average of all sequences of antipsychotics (AP) is finally used to predict the proportion of people with schizophrenia in remission or relapse.

Table 1 – Antipsychotic sequences used in the model

Seq.	First line AP	Second Line AP	Third line AP	Long-term treatment [a]
1	Quetiapine	Aripiprazole	Average oral AP	(40.0%) No treatment (46.8%) Average oral APs (10.1%) Average LAIs (3.1%) Clozapine
2	Aripiprazole	Quetiapine		
3	Risperidone			
4	Olanzapine			
5	Lurasidone			

Acronyms: AP, antipsychotic, LAI, Long-acting injectable antipsychotics

The AP agent with the highest market share utilization, not used as first-line treatment, was selected as second-line agent. The market shares used to establish treatment sequences and calculate the average efficacy and safety for oral APs were: 34.0% quetiapine, 18.0% aripiprazole, 16.0% risperidone, 12.0% olanzapine and 4.0% lurasidone.[1] The market shares used to calculate the average efficacy and safety for LAIs were: 66.0% paliperidone LAI, 29.3% risperidone LAI, 3.3% aripiprazole LAI, and 1.5% olanzapine LAI.[2]

[a] On the long-term 40.0% of people were assumed not to receive any treatment for schizophrenia. [3] The distribution long-term AP treatments was informed by Medicaid data. [2] Bareis and colleagues reported that 85.5% of patients would receive an AP (any), 14.4% LAIs, and 4.4% clozapine. These proportions were rearranged to be expressed as a proportion of the 60% receiving AP treatment (i.e., 60.0%[85.5%-14.4%-4.4%]/85.5%=46.8%).*

1.1. Antipsychotic drugs efficacy and safety

1.1.1 Short-term antipsychotic use

The probabilities of discontinuing during the trial period were calculated from the rates of all cause discontinuation reported by published randomized controlled trials (RCTs) assessing the efficacy of oral APs. The likelihood of stable disease (remission) was calculated as 1 minus the probability of all cause discontinuation. The mean weight gain related to each AP was also obtained from published RCTs. The probabilities of unstable disease and mean weight gain used in the model are shown in Table 2 (trial period).

Table 2 – Probability of unstable disease and mean weight gain during the trial period, adjusted for 6-week cycle length

Antipsychotic agent	Probability of discontinuation [a]	Sources	Mean weight gain (Kg)	Sources
Quetiapine	0.417	4-16	1.644	4-11 15 17
Aripiprazole	0.328	7 8 16 18-30	0.692	8 18-20 23 25-27 29
Risperidone	0.304	8 13 15 16 19 25 27 29 31-45	1.930	8 15 19 25 27 29 30 32 40-42 46 47
Olanzapine	0.266	8 13 21 22 24 32 34 48-66	2.346	8 17 32 34 49 51 53-67
Lurasidone	0.337	11 36 39 59 68-73	0.491	11 39 59 68-73

[a] Defined as treatment inefficacy, occurrence of intolerable adverse effects (AE), or treatment discontinuation due to patient's decision at the end of the trial period. The probability of relapse was defined as one minus the probability of all cause discontinuation. It is likely that several sequences are used in clinical practice so efficacy and safety estimates for an average AP drug were calculated using arithmetic means, weighted according to the market shares for quetiapine, aripiprazole, risperidone, olanzapine, and lurasidone.[1]

The probability of unstable disease (relapse) and mean weight gain in people receiving maintenance therapy was sourced from an US cost-effectiveness analysis evaluating the use of atypical AP in the treatment of schizophrenia.[74] The likelihood of hospitalization was used as a proxy for the probability of unstable disease. The inputs utilized in the model are shown in Table 3.

Table 3 – Probability of unstable disease and mean weight gain during the maintenance period, adjusted for 6-week cycle length

Antipsychotic agent	Probability of relapse	Mean weight gain (Kg)

Quetiapine	0.123	0.315
Aripiprazole	0.118	0.238
Risperidone	0.097	0.252
Olanzapine	0.075	1.259
Lurasidone	0.084	0.081
Clozapine	0.053	0.315

Source: O'Day 2013 [74]

The literature search strategy used to identify RCT evidence of the efficacy and safety of APs and the PICOS strategy detailing the inclusion criteria are presented in subsequent sections.

1.1.2 Long-term antipsychotic use

Individuals presenting with active disease, despite third-line AP therapy, entered the long-term phase of the model. The distribution of individuals across long-term treatments is depicted in Table 1. People receiving AP treatment were assumed to achieve stable disease, being at risk of relapse. On the long-term, the efficacy and safety of oral APs were calculated as the average of individual APs effects during maintenance phase[74] (Table 3), weighted according to their US market shares.[1] Evidence informing the efficacy and safety of clonidine was also sourced from the cost-effectiveness study by O'Day et al.[74]

Evidence of the efficacy and safety of LAIs was sourced from a network meta-analysis (NMA) of APs.[75] The efficacy of LAIs was reported as pooled odds ratios (OR) compared to placebo. It was assumed that placebo would be a proxy for no treatment and that 74.1% [76] of all untreated individuals would present with active disease. Odds ratios were rearranged to relative risks (RR) using Equation 1[77] before being applied to the baseline probability of being in active disease.

$$RR = \frac{OR}{\left(1 - p_0 + (p_0 * OR)\right)}$$ *Equation 1*

Where p_0 is the baseline probability of the event.

Evidence for 4 LAIs was selected for use in the model (paliperidone LAI, risperidone LAI, aripiprazole LAI, and olanzapine LAI) matching the availability of US market shares for LAIs identified in the literature.[78] The odds ratios of unstable disease and mean weight gain associated with LAIs use is shown in Table 4.

Table 4 – Odds ratios of unstable disease and mean weight gain associated to long-term use of LAIs

Antipsychotic agent	OR, relapse vs placebo	Mean weight gain (Kg) [a]
Aripiprazole LAI	0.690	-0.032
Olanzapine LAI	0.160	0.291
Paliperidone LAI	0.300	0.171
Risperidone LAI	0.100	0.279

Source: Schneider-Thoma 2022[75]

Acronyms: LAI, long-acting injectable antipsychotic; OR, odds ratios.

[a] Cycle-adjusted.

1.2. Search Strategy

The OVID platform was used to conduct searches in the following literature databases: EMBASE, MEDLINE, including MEDLINE (R) In process, MEDLINE Epub Ahead of Print, In-Process & Other Non-Indexed Citations, MEDLINE Daily, Medline and Versions, Cochrane Central Register of Controlled Trials (CENTRAL) and PSYcINFO. Searches were conducted from inception to September 4th, 2020. The search strategy was based on the combination of free text words, indexing terms (e.g. Excerpta Medica database [EMBASE] subject heading [EMTREE] or Medical Subject Headings [MESH] terms) and their relationship using Boolean terms (e.g. 'and', 'or', 'not'). Full search strategies are specified in Table 5.

Table 5 – Literature search strategy

#	Searches
1	((exp *schizophrenia spectrum disorder/ or schizophreni*.ti. or exp *Schizophrenia Spectrum/) and Other Psychotic Disorders/) or exp *Schizophrenia/
2	randomi*.mp. or exp Randomized Controlled Trial/
3	1 and 2
4	3 not ('case report' or 'case reports' or editorial or comment).ti,pt,xs,sh.
5	limit 4 to English language
6	De-duplicate

In addition, the following relevant conference websites were searched to identify relevant abstracts accepted at the most recent meeting only (abstracts from prior meetings were indexed in Ovid):

1. International College of Neuropsychopharmacology
2. American Psychiatric Association
3. U.S. Psychiatric & Mental Health
4. American Society of Clinical Psychopharmacology
5. American College of Neuropsychopharmacology
6. European College of Neuropsychopharmacology
7. European Congress of Psychiatry
8. European Psychiatric Association
9. Neuroscience Education Institute
10. Schizophrenia International Research Society (SIRS)

Bibliographies of up to three recent reviews on the efficacy and safety of atypical antipsychotics and LAIs in schizophrenic patients were cross-checked to identify additional studies.

Clinicaltrials.gov was consulted to search for any information that could be missing from the primary publication. No search was performed on clinicaltrials.gov for trial identification.

1.3. Eligibility criteria and study selection

The publications identified by the literature search were sifted by 2 researchers based on titles and abstracts according to pre-established criteria (Table 1). Full papers were then inspected and considered for inclusion. Data extraction was conducted by a single reviewer.

Table 6 – PICOS strategy

PICOS	Inclusion Criteria	Exclusion Criteria
Population	Adults (>= 18 years) and adolescents with schizophrenia	• Studies with patients who do not have schizophrenia • Pregnant
Intervention	SGAs[a] approved in the US or Europe and new experimental treatments as monotherapy or their combination • Oral treatment • Long-acting injectables	• Interventions that are not SGAs • Studies with no pharmacological therapy
Comparison	Any of the above listed interventions and placebo	Not applicable
Outcomes	Baseline, change from baseline Primary timepoints include 6 +/- 2 weeks and potential to include 12 +/- 3 weeks Primary outcome: Efficacy • Positive and Negative Syndrome Scale (PANSS) Secondary Outcome: Efficacy • Brief negative symptom scale • The Montgomery–Åsberg Depression Rating Scale (MADRS)	Studies with other outcomes only

	• Clinical Global Impression – Severity scale (CGI-S) • Response Metabolic • Weight gain • ≥7% weight gain Discontinuation • All-cause discontinuation • Discontinuation due to lack of efficacy • Discontinuation due to adverse events	
Study Design	• Randomized controlled trials (RCTs)	• Other study designs
Filters	• English language • Search: no date limit	• Historically assessed experimental therapies: studies published before 2015 for experimental SGAs that are not approved in the US or Europe • Publication types: editorials, letters, notes, commentaries, reviews

Acronyms: RCTs, randomized controlled trials; SGAs, second-generation antipsychotics; US, United States

[a] SGAs approved in the United States and Europe only at the approved doses will be included. For newer experimental treatments not yet approved, all doses will be included.

Antipsychotic-specific outcomes for the probability of unstable disease and weight gain were calculated using arithmetic averages weighted by study sample size. The resulting estimates were used as absolute probabilities in the model. This simplified approach was preferred (to indirect treatment comparison) because the main goal of the evidence review was to calculate the efficacy and safety of an AP therapy (representative of AP with largest market share), rather than comparing one AP or sequence of APs to another.

1.4. Mortality

Mortality was modelled using a lifetable method based on annual mortality rates published by Arias and Xu.[79] The annual mortality rates due to suicide or due to cardiovascular disease in the general population were disaggregated from overall mortality using age and gender specific US prevalence figures for suicide and CVD-related mortality.[80] The resulting risk of suicide was multiplied by published standardized mortality ratios (SMR) in males (SMR 3.39 standard error [SE] 0.03) and females (SMR 8.16, SE 0.04) to derive the increased risk of suicide in the schizophrenia population.[81]

The baseline risk of a cardiovascular event was estimated using the Framingham risk equations featuring body mass index (BMI) predictors.[82 83] The likelihood of death after a cardiovascular event was sourced from a US publication reporting the case fatality rate in individuals having cardiovascular events.[84] The input used in the model (9.5%) was calculated as the weighted average of the case fatality rate amongst people having a myocardial infarction, cardiac arrest, and ischemic or hemorrhagic stroke.

Cardiovascular risk covariates

Gender, age, BMI, systolic blood pressure (SBP) in treated or untreated, diabetes and smoking status covariates were required to inform the Framingham equations. Age and sex were obtained from the progressing model cohort. The remaining inputs were sourced from the literature and are shown in Table 7.

BMI was calculated as the weight in kilos divided by the squared height in centimeters. The height and weight for males and females at the start of the model (30 years) was sourced from average age-specific values from the general US population.[85] The same values were used for the population with schizophrenia. Weight gain due to AP use was modelled in the schizophrenia cohort using efficacy and safety data from trial and maintenance periods APs (Table 2 and Table 3). To avoid indefinite weight increase in people receiving AP therapy, a cutoff point of 7% increase from baseline weight was implemented in the model. It was assumed that people would not return to baseline body weight.

The distribution and SBP values for individuals with normal blood pressure or with hypertension on/off treatment were sourced from US health statistics.[86] The age specific prevalence of diabetes in the group unaffected by schizophrenia was informed by general US population data.[87] The likelihood of diabetes in the schizophrenia population was estimated by adjusting the US population prevalence values using an odds ratio (OR 1.83, 95% CI 1.29 to 2.60) sourced from an US study comparing 326 individuals with schizophrenia or schizoaffective disorder to 1,899 controls.[88] The prevalence of smoking in the general population used US age and gender specific data.[89] The excess likelihood of smoking in people with schizophrenia was informed by a meta-analysis studying the association between schizophrenia and tobacco use (OR 5.30, 95% CI 4.90 to 5.70).[90] Before being applied to the general population values, the ORs were converted to relative risks (RR) using Equation 1.[77]

Table 7 – Mean inputs informing cardiovascular risk factors in the model

Description	Males	Females	SE	Source
Risk of death from a cardiovascular event	9.5% [a]		20% of mean	84
Body mass Index				
Weight (Kg)	94.40	79.30	[1.21], [0.99]	85
Height (cm)	176.30	162.70	[0.40], [0.37]	
Diabetes				
Prevalence of diabetes in US general population	17.9%	16.2%	[0.8%], [0.7%]	87
Prevalence of diabetes by age				
18 to 44 years	4.9%		0.8%	
45 to 64 years	14.8%		0.7%	
65+ years	14.3%		0.5%	
OR diabetes (schizophrenia vs US population)	1.83		0.18	88
Hypertension				
Prevalence of hypertension in US population	33.1%	35.2%	[0.5%], [0.5%]	
Treated hypertension	63.4%	71.3%	[0.8%], [0.8%]	
Untreated hypertension	36.6%	28.7%	[0.8%], [0.8%]	
SBP, no hypertension (mmHg)				
18 to 39 years	117	109	[0.4], [0.6]	
40 to 59 years	119	115	[0.3], [0.4]	
60+ years	121	122	[0.3], [0.2]	
SBP, hypertensive, treated (mmHg)				86
18 to 39 years	127	123	[0.7], [0.6]	
40 to 59 years	129	129	[0.7], [0.9]	
60+ years	135	141	[1.2], [1.5]	
SBP, hypertensive, untreated (mmHg)				
18 to 39 years	140	140	[0.7], [0.8]	
40 to 59 years	145	149	[0.9], [0.8]	
60+ years	154	159	[0.7], [1.8]	
Smoking				
Prevalence of smoking by age				89
18 to 24 years	18.2%		1.0%	
25 to 44 years	25.3%		0.6%	
45 to 64 years	23.0%		0.6%	
65+ years	11.4%		0.4%	
Prevalence of smoking by gender	62.5%	37.5%	[0.5%], [0.4%]	
OR smoking (schizophrenia vs US population)	5.30 [b]		0.17	90

Acronyms: OR, odds ratio; SE, standard error; SBP, systolic blood pressure; US, United States.

[a] Weighted average of the case fatality rates for myocardial infarction, cardiac arrest, and ischemic or hemorrhagic stroke.

[b] Applied to the prevalence of smoking in the general population to derive the likelihood of smoking in people with schizophrenia.

2. Modelling transitions between social states

2.1. Incarceration

Age and gender adjusted lifetime probabilities of incarceration in prisons for the adult US general population were sourced from a publication by the Bureau of Justice Statistics.[91] These probabilities were annualized using Equation 2.

$$p = 1 - exp\left(\frac{ln(1 - p_i)}{t_i} * t\right) \qquad \textit{Equation 2}$$

where p_i is the age and gender specific index probability, t_i the index time calculated as the maximum for the age category minus the minimum age of incarceration (18 years), and t is the cycle length. The maximum age at which individuals would be incarcerated was implemented as 70 years as based on a publication by US Department of Justice.[92] The number of incarcerations in jails were estimated by multiplying these probabilities by a ratio of jail to prison incarceration. The ratio (0.540) was obtained by dividing the proportion of individuals sentenced to jails (33.5% [738,400/2,203,600]) by the proportion of individuals sentenced to prisons (66.5% [1,465,200/2,203,600]) in 2019.[93]

The probability of incarceration in people with schizophrenia was obtained by multiplying the probability of incarceration in the general population by the relative risk (RR) of incarceration in people with schizophrenia. Different RR were calculated to translate the likelihood of incarceration in prisons (3.99) or jails (5.93). These RRs were calculated by dividing the prevalence of incarceration in the US general adult population (0.9% [2,123,100/255,200,373]) by the prevalence of schizophrenia in US prisons. The prevalence of schizophrenia in US prisons was calculated by averaging the values reported by a systematic review of US studies.[94] Due to heterogeneity in the values reported by Prins and colleagues, we ran a scenario using calculated values for the prevalence of schizophrenia in US prisons (8.7% [125,437/1,441,800]) [95] or US jails (11.70% [84,263/720,200]).[95] The prevalence estimates reported by Bronson and Berzofsky [95] considered inmates with schizophrenia and other psychotic disorders in prison and jail. These estimates were adjusted using the proportion of people with schizophrenia amongst the population with schizophrenia and other psychotic disorders (46.1%).[96]

The time dependence associated to varying durations of incarceration reported in the literature were accounted for by implementing a series of tunnel states (20 for prisons and 6 for jails).[97 98] After being released, individuals entered a sequence of 5 ex-convict tunnel states to account for the increased likelihood of reincarceration in this population.[99] When ex-convicts returned to the community state, the model was no longer able to determine if they were ever incarcerated.

The higher probability of incarceration in homeless people was implemented by multiplying the probability of incarceration for community dwelling individuals by the relative risk of incarceration in the homeless (9.03). This ratio was calculated by dividing the proportion of individuals in jail who were homeless (15.3%) by the annual rate of homelessness in the general population (1.7%), both sourced from a survey of 6,953 US jail inmates.[100]

Incarceration rate ratios for individuals in remission or relapse versus the general schizophrenia population were calculated by dividing the cumulative incidence of arrests in people with remission or relapse by the cumulative incidence of arrests in the entire sample of people with schizophrenia, as reported in the US longitudinal study conducted by Haynes and colleagues.[101] Arrest does not mandate incarceration, nonetheless the likelihood of arrest was perceived as a reasonable proxy for incarceration, as it implies a level of offense punishable by law. All inputs related to the likelihood and duration of (re)incarceration are available in Table 8.

Table 8 - Inputs informing the likelihood and duration of (re)incarceration

Description	Input		SE	Source
Total US population 2021	258,327,312		Not varied	[102]
Likelihood and duration of incarceration				
Lifetime probability of incarceration in the US population [a]				
Age groups	Males	Females	0.001%	[91]
65+	3.1%	0.2%		
55 to 64	4.0%	0.3%		
45 to 54	5.3%	0.6%		
35 to 44	6.5%	0.9%		
25 to 34	6.0%	0.7%		
18 to 24	2.7%	0.2%		
Total individuals incarcerated in the US	2,123,100 (100%)		Not varied	[93]
Prison	1,465,200 (66.5%)		Not varied	
Jail	738,400 (33.5%)		Not varied	
% US population incarcerated	0.9%		Not varied	Calculated
Duration of incarceration in prison [b]				
21 years	100.0%		Not varied	[98]
20 years	99.0%			
10 years	95.8%			
5 years	87.7%			
3 years	77.1%			
2 years	66.1%			
1 year	41.9%			
Duration of incarceration in jail [b]				
6 years	100.0%		Not varied	[97]
5 years	93.6%			
3 years	88.6%			
2 years	85.2%			
1 year	76.5%			
Recidivism in the general US population				
Cumulative percentage of rearrests in the general US population				
5 years	70.8%		0.2%	[99]
4 years	67.0%		0.2%	
3 years	61.5%		0.2%	
2 years	52.9%		0.2%	
1 years	36.8%		0.2%	
Cumulative percentage of rearrests leading to conviction in the general US population				
5 years	54.4%		0.2%	[99]
4 years	50.6%		0.2%	
3 years	45.0%		0.2%	
2 years	36.5%		0.2%	
1 years	22.9%		0.2%	
Incarceration in people with schizophrenia				
Prevalence of schizophrenia in US prisons	3.44%		1.04%	[94]
Prevalence of schizophrenia and other psychotic disorders in prison	8.7% [c]		0.02%	[95]
Prevalence of schizophrenia and other psychotic disorders in jail	11.7% [c]		0.04%	
RR of going to prison (schizophrenia vs US population)	3.99		Not varied	Calculated
RR of going to jail (schizophrenia vs US population)	5.93		Not varied	Calculated
Incarceration in the homeless population				
Proportion of individuals in jail who were homeless	15.3%		20% of mean	[100]
Annual rate of homelessness in general population	1.7%			
RR incarceration in homeless vs general US population	9.03			Calculated

Acronyms: RR, relative risk; SE; standard error; US, United States

[a] The lifetime probabilities of incarceration were annualized based on the published probabilities using Equation 2. The period for the rate was calculated by subtracting the minimum age of incarceration (18 years) by the upper age in the age category i.e., 35 to 44 years category, 45-18=27 years; 25 to 34 years category, 35-18=17 years.

[b] Considered to be the same in the general population and in people with schizophrenia.

[c] Used in scenario analysis.

2.2. Homelessness

The inputs utilized to inform transitions to the homeless social state and homelessness recurrence are shown in Table 9. The age adjusted annual probabilities of homelessness were calculated by multiplying the prevalence of homelessness in the general population by the age distribution of sheltered individuals in one year (October 2009 to September 2010).[103] The prevalence of homelessness in the general population (0.7%) was calculated by dividing the number of individuals experiencing homelessness in one year in 2010 (1,593,150) [103] by the total US population in 2010 (234,564,071).[104]

The probability of homelessness in people with schizophrenia was implemented by multiplying the probability of becoming homeless in the general US population by the relative risk of homelessness in the schizophrenia populations. The relative risk of homelessness in the population with schizophrenia (15.55) was calculated by dividing the prevalence of schizophrenia in the homeless population (10.6%) [105] by the prevalence of homelessness in the general population (0.7%).

Table 9 – Inputs informing the likelihood of (repeated) homelessness

Description	Input	SE	Source
Homelessness in the general US population			
Total US population in 2010	234,564,071	Not varied	104
Individuals experiencing homelessness in 1 year (2010)	1,593,150	Not varied	103
% Homelessness in US population (1 year)	0.7%	Not varied	Calculated
Age distribution for homeless population (one single night)			
<18 years	21.8%	0.05%	103
18 to 30 years	23.5%	0.05%	
31 to 50 years	37.0%	0.06%	
51 to 61 years	14.9%	0.05%	
62+ years	2.8%	0.02%	
Probability of being sheltered			
% Sheltered	61.1%	0.1%	106
% Unsheltered	38.9%	0.1%	
Homelessness in people with schizophrenia			
Prevalence of schizophrenia in homeless population	10.6%	2.5%	105
RR of homelessness vs general population	15.55		Calculated
RR of homelessness after previous shelter use	8.33	0.152	107
RR of homelessness in ex-convicts with mental illness	2.47	0.18	

Acronyms: RR, relative risk; SE, standard error; US, United States.

The rate ratios of the likelihood of homelessness for those in remission or relapse were calculated using Adelphi real-world data [108] (Table 11). These ratios were multiplied by the cycle probability of homelessness in the general schizophrenia population, so that the estimates were adjusted to individuals' remission or relapse status.

There is evidence suggesting that ex-convicts have a higher risk of homelessness, compared to the general population. In the general population, the probability of homelessness after release from incarceration used annualized age specific values published by Metraux.[109] Remster and colleagues [107] suggested that ex-convicts with mental illness were approximately 2.47 times more likely to become homeless, compared to the ex-convicts without mental illness. Therefore, this estimate was multiplied by the general population probabilities to obtain the probabilities in the cohort with schizophrenia.

The probability of returning to homelessness was informed by an US publication suggesting that individuals who had been sheltered before had 8.3 higher risk of experiencing homelessness again versus the general population.[107] This estimate was multiplied by the probability of homelessness in the general population or in the schizophrenia cohort to obtain the annual probability in ex-homeless individuals.

3. Likelihood of fiscal consequences

Costs were linked to fiscal consequences to generate total costs for people with and without schizophrenia. Due to the lack of schizophrenia-specific data we assumed that the annual healthcare costs per capita for homeless people with or without schizophrenia would be the same.

3.1. Fiscal consequences for people living in the community

Employment

The level of employment in the general population was implemented using age and gender-specific prevalence figures from the US Bureau of Labor Statistics[110] Following these distributions most individuals stop working around the age of retirement (65 to 67 years) although some do stay employed. Because there is no age at which individuals must stop working, we assumed 70 as the age after which individuals would no longer be employed.

An US publication estimated the likelihood of employment in people with schizophrenia (OR 0.24, 95% CI 0.16 to 0.37) compared to individuals unaffected by schizophrenia, using data from the National Health Interview Survey.[111] This value was applied to the rates of employment in the general US population to estimate employment in the schizophrenia cohort. The likelihood of employment in people with remission or relapse was adjusted using rate ratios estimated from an analysis of US Adelphi data [108] (Table 11).

Caregiver consequences on employment

Informal caregivers were modelled uniquely to estimate the impact of weekly hours of informal care on labor participation. We assumed that caregivers would be mostly females (59.2%) have a mean age of 48.3 years.[112] Annual mortality used general US lifetables.[79] Informal caregivers' employment was conditional to age-specific probabilities of employment[110] In those predicted to work, the proportion of a full-time equivalent (FTE) in males and females was calculated using the equations below publication sourced from a Canadian publication.[113]

$$Proportion_{FTE\,Males} = exp(-0.045Primary_{CG} - 0.032Care_{10} - 0.089Care_{15} - 0.156Care_{20}) \quad \textit{Equation 3}$$

$$Proportion_{FTE\,Females} = exp(-0.037Primary_{CG} + 0.023Care_{10} - 0.022Care_{15} - 0.018Care_{20}) \quad \textit{Equation 4}$$

Where $Primary_{CG}$ took the value of 1 for primary caregivers (assumed all were primary caregivers), and $Care_{10}$, $Care_{15}$ and $Care_{20}$ took the value of 1 if informal care was provided for more than 10, 15 or 20 hours weekly, respectively, and took the value of 0 otherwise.

The proportion of individuals in the general US population having informal caregivers (15.6%) and the weekly average provision of informal care (10.0 hours) were informed by national US data.[114] Weekly hours of care in people with schizophrenia in remission and relapse was sourced from an analysis of US Adelphi data.[108]

Taxation

Direct taxes were calculated by multiplying gross income from employment (in people with schizophrenia, caregivers, and general population equivalents) by the US tax wedge (28.4%).[115] The tax wedge represents the amount of taxes and social security contributions related to a single worker. Taxes are paid by the employee and social security contributions are paid by the employee and employer. Indirect taxes were calculated by multiplying the consumption tax rate (10.1%) [116] by the disposable income of all individuals in the model. The rate of disposable income was calculated by dividing the average annual disposable income values by the average annual earnings from employment.[117] The resulting figure was used to estimate the share of individual's earnings or fiscal benefits spent on consumption and paid consumption taxes.

Legal involvement

Only a proportion of arrests result in individuals being incarcerated (66.0%).[118] We therefore implemented the number of people being arrested as 34.0% more than the individuals predicted by the model to be incarcerated.

Disability benefits

The proportion of people receiving Social Security Disability Insurance (SSDI), Supplemental Security Income (SSI) or both was informed by the Social Security administration (SSA) 2019 report.[119] We estimated that 6.6% of the entire schizophrenia population is a recipient of disability benefits, compared to 3.7% of the general US population. The age distribution of these recipients was also informed by SSA data.[119] In the absence of specific data we have assumed that people able to maintain a job would not be a recipient of SSA benefits. This is a simplification of reality as work incentives by the SSA enable employed individuals to still receive monthly financial support as well as Medicaid and Medicare services during a trial work period.[120]

Victimization

The likelihood of being victim of a crime in the general US population was modelled using data published by the US Department of Justice.[121] The relative risk of violent victimization in people with schizophrenia was obtained by dividing the annualized probability of violent victimization in people with schizophrenia [122] by the probability of violent victimization in the general population.[121]

Healthcare Insurance

Healthcare costs incurred by the US government were considered part of the fiscal expenses. In the general US population the proportion of individuals using publicly funded healthcare insurance was informed by US Census Bureau data.[123] In the schizophrenia population these parameters were sourced from an analysis of Medical Expenditures Panel Survey [124] suggesting most individuals with schizophrenia would use publicly funded healthcare insurances.[125]

3.2. Fiscal consequences in incarcerated and homeless individuals

All individuals who were in prisons or jails incurred the costs of incarceration and were also assigned different healthcare costs than same age individuals living in the community. A similar approach was used for individuals who became homeless. An assumption was made that people who were homeless or incarcerated would use 100% publicly funded healthcare insurance. Ex-convicts and ex-homeless people were assumed to have the same rates of public healthcare financing than the remaining individuals living in the community.

Table 10 – Inputs used to model the likelihood of fiscal consequences

Description	Input		SE	Source
Employment general US population				
Age category	Males	Females		
75+ years	11.1%	11.1%	[0.01%], [0.01%]	
70 to 74 years	21.1%	21.1%	[0.02%], [0.02%]	
65 to 69 years	35.9%	35.9%	[0.02%], [0.02%]	
60 to 64 years	59.0%	59.0%	[0.02%], [0.02%]	
55 to 59 years	73.3%	73.3%	[0.01%], [0.01%]	
50 to 54 years	80.1%	80.1%	[0.01%], [0.01%]	
45 to 49 years	83.4%	83.4%	[0.01%], [0.01%]	110
40 to 44 years	83.1%	83.1%	[0.01%], [0.01%]	
35 to 39 years	85.1%	85.1%	[0.01%], [0.01%]	
30 to 34 years	82.4%	82.4%	[0.01%], [0.01%]	
25 to 29 years	77.1%	77.1%	[0.01%], [0.01%]	
20 to 24 years	61.3%	61.3%	[0.02%], [0.02%]	
18 to 19 years	38.5%	38.5%	[0.02%], [0.02%]	
Employment in people with schizophrenia				
OR employment (schizophrenia vs US population)	0.24		0.21	111
Disability - US population not affected by schizophrenia				

All disabled beneficiaries (2019)	9,562,282	Not varied	[119]
All US population (2019)	328,239,523	Not varied	[126]
Disabled beneficiaries excluding schizophrenia population as proportion of total US population (2019)	2.9% [a]	Not varied	Calculated
Distribution of disabled beneficiaries (all beneficiaries)			
60+	39.0%	0.02%	
50–59	38.2%	0.02%	
40–49	14.6%	0.01%	[119]
30–39	6.7%	0.01%	
Under 30	1.5%	0.00%	
Disabled beneficiaries receiving Social Security benefits			
SSDI only	62.2%	0.01%	
SSI only	28.0%	0.01%	[119]
Both SSDI and SSI	9.8%	0.01%	
Disability - Schizophrenia population			
All beneficiaries with schizophrenia or other psychotic disorders	463,142	Not varied	[119]
Beneficiaries with schizophrenia	202,814 [b]	Not varied	Calculated
Total population with schizophrenia (>18 years, 2019	3,036,884	Not varied	[126]
Disabled beneficiaries with schizophrenia as proportion of total schizophrenia population	6.7% [c]		Calculated
Distribution of disabled beneficiaries (people with schizophrenia and other psychotic disorders)			
60+	23.6%	0.07%	
50–59	33.6%	0.08%	
40–49	22.7%	0.07%	[119]
30–39	15.7%	0.06%	
Under 30	4.3%	0.03%	
Disable beneficiaries receiving SSA benefits			
SSDI only	43.9%	0.06%	
SSI only	40.7%	0.06%	[119]
Both SSDI and SSI	15.4%	0.04%	
Probability of victimization in the general US population			
Probability of violent victimization 2019 (all types)	2.1%	0.001%	[121]
Distribution of violent victimization by age (excluding simple assault)			
65+ years	0.4%	0.001%	
50 to 64 years	1.0%	0.001%	
35 to 49 years	1.1%	0.001%	[121]
25 to 34 years	1.5%	0.002%	
18 to 24 years	1.7%	0.002%	
12 to 17 years	1.6%	0.003%	
Victimization in the schizophrenia population			
People with schizophrenia who were victims of a violent crime over 3 years	34.3%	3.6%	[122]
Annualized probability of violent victimization in people with schizophrenia	13.1%	Not varied	Calculated
RR violent victimization (schizophrenia vs general population)	6.22 [d]	Not varied	Calculated
Criminal justice			
Conviction rates for felony defendants	66.0%	20% of mean	[118]
Public healthcare financing in the general US population			
General US population			
65+ years	93.6%	0.003%	
55-64 years	20.5%	0.006%	
45-54 years	15.4%	0.006%	
35-44 years	16.3%	0.006%	[102]
26-34 years	18.2%	0.006%	
19-25 years	18.2%	0.007%	
06-18 years	35.1%	0.005%	
People with schizophrenia			
65+ years	96.7%	0.10%	
40-64 years	75.1%	0.08%	[125]
18-39 years	73.1%	0.11%	

Acronyms: OR, odds ratio; RR, relative risk; SE, standard error; SSDI, Social Security Disability Insurance; SSI, Supplemental Security Income; US, United States.

[a] Calculated by dividing the total number of beneficiaries excluding beneficiaries with schizophrenia by the total US population in 2019.

[b] Calculated by multiplying the total number of beneficiaries with schizophrenia or other psychotic disorder by 43.7% [96], the share of schizophrenia as a proportion of other psychotic diseases.

[c] Calculated by dividing the estimated number of beneficiaries with schizophrenia by the total schizophrenia population in 2019.

[d] Ratio of the annualized probability of violent victimization in people with schizophrenia and the probability of violent victimization in the general US population.

Remission versus relapse

Table 11 depicts the inputs utilized to distinguish between individuals with symptoms of schizophrenia relapse versus remission.

Table 11 – Likelihood of social state transitions and fiscal consequences in people in remission and relapse

Description	Remission	Relapse	SE	Source
Social states				
Homeless/sheltered (rate ratio) [a]	0.30	1.47	[0.47], [0.22]	108
Arrests	0.70	2.36	[0.24], [0.28]	101
Fiscal consequences				
Any employment (rate ratio) [a]	1.66	0.55	[0.07], [0.10]	108
Has a caregiver (rate ratio)	0.42	1.40	[0.16], [0.13]	
Weekly hours of informal care	26.03	39.26	[3.64], [4.50]	
Victimization	0.87	1.33	[0.16], [0.24]	101

Acronyms: SE, standard error

[a] Rate ratios compare the likelihood of an event in people with schizophrenia in remission or relapse versus the general population of people with schizophrenia.

4. Fiscal costs and economic consequences

Membership to different social states determined the likelihood of economic consequences, as explained in the section above. The economic value of these consequences was sourced from peer reviewed or nationally US data and inflated to 2021 US dollars using the Consumer Price Index.[127] Table 12 summarizes the main inputs informing the monetary value of fiscal consequences and respective sources. Measures of variance for cost data were frequently not reported. We have therefore assumed that standard errors for these inputs would be 20% of the mean. This allowed estimating confidence intervals to be used in one-way sensitivity analysis.

Table 12 – Monetary value of fiscal and economic consequences

Description	Input [a]		Source
Average gross income from employment			
Age groups	Males	Females	128
75+ Years	$51,844	$31,950	
65 to 74 years	$67,958	$41,096	
55 to 64 years	$86,013	$51,779	
45 to 54 years	$91,329	$60,186	
35 to 44 years	$83,334	$56,341	
25 to 34 years	$57,014	$44,767	
15 to 24 years	$21,859	$19,971	
Direct and indirect tax inputs			
Tax Wedge US	28.4%		115
Disposable income	51.5%		117
Average tax in the US	10.1%		116
Disability transfers			
Monthly SSDI	All beneficiaries	With schizophrenia [b]	
65+	$1,389	$1,089	119

60–64	$1,410	$1,105	
55–59	$1,311	$1,027	
50–54	$1,233	$966	
45–49	$1,161	$909	
40–44	$1,076	$843	
35–39	$989	$775	
30–34	$895	$702	
25–29	$813	$637	
Under 25	$751	$589	
Average monthly benefit, by sex and diagnostic group (USD 2019)			
Total (all disabled beneficiaries)		$1,258	119
People with schizophrenia and other psychotic disorders		$986	
Weight benefits in people with schizophrenia vs other disabilities		78.4% [c]	Calculated
Average SSI income (monthly)		$748	119
Criminal justice and incarceration			
Costs per arrest		$2,910	129
Daily costs of incarceration - State and federal prisons		$269	130
Daily costs of incarceration - Jails		$161	
Direct medical costs			
Total personal healthcare per capita in the general US population			
85+		$37,083	131
65-84		$19,134	
45-64		$11,509	
19-44		$5,473	
0-18		$4,225	
19 to 24 years		$23,518	
Annual healthcare costs for incarcerated individuals without schizophrenia		$7,113	132
Annual healthcare costs for people with schizophrenia with justice involvement		$31,862	133
Annual healthcare costs in people with schizophrenia without justice involvement		$43,876	
Annual healthcare costs if homeless		$11,520	134
Victimization			
Violent victimization - Police costs per crime		$6,081	130
Homelessness			
Homelessness costs (excluding healthcare)		$50,669	134

Acronyms: SE, standard error; SSDI, Social Security Disability Insurance; SSI, Supplemental Security Income; USD, United States dollars.

[a] Costs are shown in 2021 US dollars. When required, costs were inflated using the US consumer price index.[127]

[b] Estimated from the values for all disabled beneficiaries using a calculated ratio between the average amounts received by all beneficiaries and the cohort with schizophrenia and other psychotic disorders (78.4%).

[c] Ratio of average monthly benefit for people with schizophrenia and other psychotic disorders and all disabled beneficiaries.

5. Additional results

Figure 1 – Social state occupancy, model trace – General population

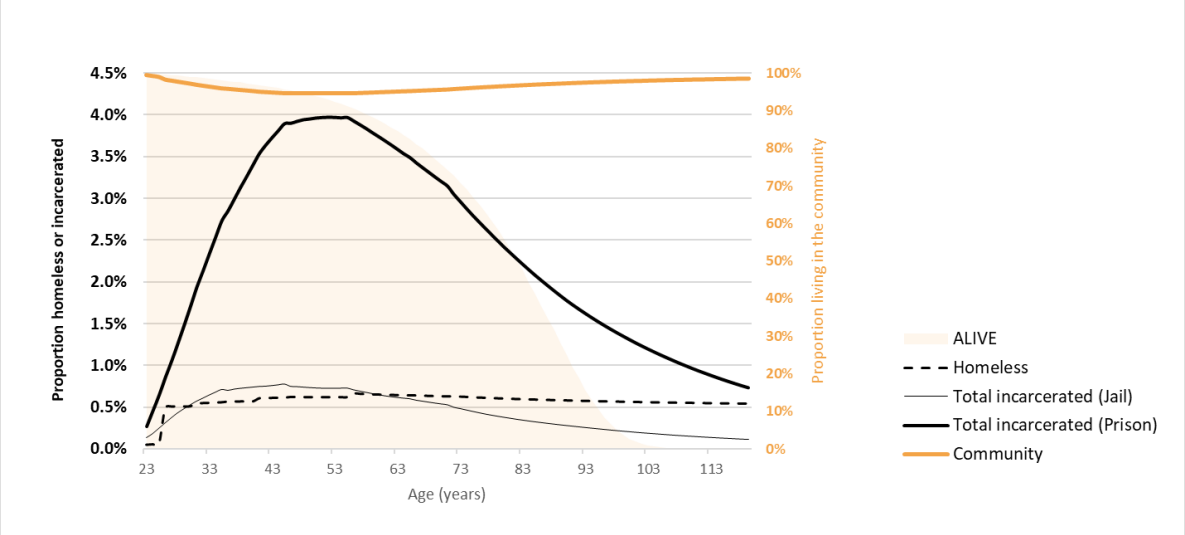
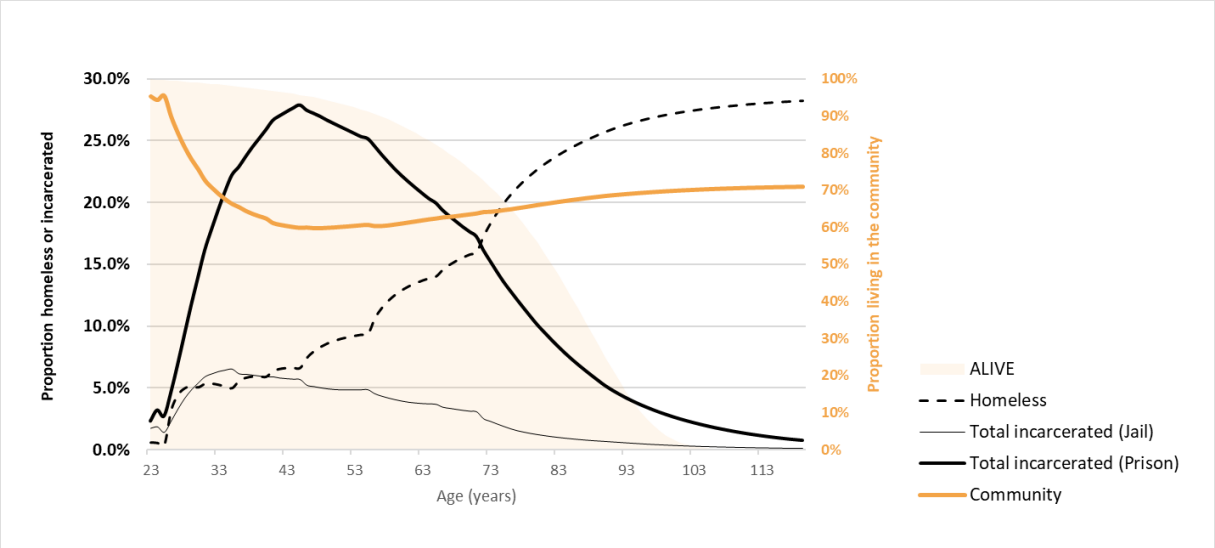


Figure 2 – Social state occupancy, model trace – Cohort affected by schizophrenia



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