Societal Costs of Schizophrenia in Denmark: A Nationwide Matched Controlled Study of Patients and Spouses Before and After Initial Diagnosis

Lene Halling Hastrup^{*1}, Erik Simonsen^{1,2}, Rikke Ibsen³, Jacob Kjellberg⁴, and Poul Jennum⁵

¹Psychiatric Research Unit, Psychiatry Region Zealand, Slagelse, Denmark; ²Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark; ³i2minds, Aarhus, Denmark; ⁴VIVE—The Danish Center for Social Science Research, Denmark; ⁵Faculty of Health Sciences, Danish Center for Sleep Medicine, Neurophysiology Clinic, University of Copenhagen, Rigshospitalet, Copenhagen, Denmark

*To whom correspondence should be addressed; Psychiatric Research Unit, Psychiatry Region Zealand, Slagelse, Denmark; e-mail: lhhs@regionsjaelland.dk

Background: Information on welfare cost of patients with schizophrenia and spouses is limited. **Aim:** The main aim of this study to investigate factual societal mean annual costs per individual during 5 years before and after the initial diagnosis of schizophrenia. **Method:** A register-based cohort study of 12 227 patients with incident schizophrenia (*International Classification of Diseases, Tenth Revision* F20–F20.99) with spouses and 48 907 matched controls in Denmark during 2002–2016. **Results:** The total annual costs of health care and lost productivity were Euro 43 561 higher for patients with schizophrenia and health care costs and costs of lost productivity were increased during 5 years before the initial diagnosis. The total annual direct health care and indirect costs of lost productivity were Euro 21 888 higher for spouses to patients with schizophrenia than spouses of individuals with no diagnosis of schizophrenia. Also before initial diagnosis, health care costs and lost productivity were increased among spouses of patients with schizophrenia. **Conclusion:** Patients with schizophrenia differed from the general population with respect to all included costs. The study documented a significant burden on spouses. The excess health care costs of schizophrenia are further increased by psychiatric and somatic comorbidity, and the societal costs are 4–10 times higher than chronic neurological disorders such as epilepsy and multiple sclerosis. Early onset of schizophrenia implies that patients are affected before finishing school and before entrance to labor market. Cost savings could be achieved by investments in preventive interventions reaching young people's needs; in initiatives to reduce hospital admissions caused by medication side effects, substance misuse, and lifestyle factors; and in occupational training.

Key words: schizophrenia/matched controlled study/societal cost/caregiver costs/health care costs/productivity loss

Introduction

Schizophrenia is a severe mental disorder characterized by positive psychotic and negative symptoms, which leads to dysfunctional self-care, impaired social and occupational functioning, and reduced quality of life. Schizophrenia is a highly heterogeneous disorder with variations in long-term course from patient to patient.¹

Most patients have their first diagnosis of schizophrenia in the late teens or early 20s.^{2–4} The early age of onset causes a high risk that patients with schizophrenia drop out of education, which may preclude them from starting to work.⁵

The mortality in schizophrenia is high in all age groups resulting in lower life expectancy of 15–20 years compared to the general population in the Nordic countries.⁶ The lower life expectancy is associated with several factors: psychiatric comorbidity, elevated risk of somatic illnesses, eg, diabetes, hypertension, and endocrine, nutritional and metabolic diseases,⁷ side effects of antipsychotic medicine, lifestyle factors, substance misuse, and suicide.⁸ Indicators of social disadvantage such as experiences of separation or loss of parent in childhood, living alone, unemployment, low long-term labor market attachment, and low income are prevalent in patients with schizophrenia.^{9–11} High prevalence of substance use diagnoses puts them in risk for poorer outcomes and increased use of social and health care services.^{12–14} Compared with the general population, patients with schizophrenia have much higher rates of violence and legal problems,^{15,16} and they are also more in risk of becoming a victim of violence.¹⁷ Informal caregiving puts a large physical, social, and financial burden to the families of people with schizophrenia^{18,19} and has an impact on the relatives' mental health, eg, risk of depression, anxiety, and grief.^{20,21}

Schizophrenia is characterized by insidious mode of onset, and many patients have a long duration of untreated

psychosis (DUP) before getting into adequate psychiatric treatment. In a Danish population of patients below 25 years, one-third patients with first-episode schizophrenia had a DUP longer than 12 months, whereas only one-third of the patients had a DUP less than 6 months.²² Patients with prolonged DUP have lower functional outcome, poorer prognosis, increased risk of relapse, and lower quality of life.^{23,24} Focus on minimizing treatment delay has led to the development of early intervention services in most Western countries.^{25,26} In Denmark, early intervention services (EIS) have become standard treatment for patients with first-episode schizophrenia all over the country during the last decade²⁷ and have proved to be cost-effective.²⁸ Inspired by the Early Treatment and Intervention in Psychosis Study from Norway,^{29,30} an early detection team is implemented in 1 of the 5 Danish regions. Patients with first-episode schizophrenia were subsequently identified in a younger age in the early-detection area compared with regions without early-detection team,³¹ which suggests that early-detection teams in combination with an information campaign as an add-on to existing EIS have potential to earlier detecting of patients with first-episode schizophrenia.

The earlier-mentioned factors document the burden of schizophrenia on patients, their families, the service system, and the wider society,^{32–36} which implies a large economic societal burden.^{33,35,37–40} Studies of cost of illness can provide useful information on the magnitude of the impact of a disorder on the society and highlight aspects or processes of care where improvements are needed to inform planning of health care services.⁴¹ Information, however, on societal costs of schizophrenia in Denmark is limited.

The estimates of cost of illness of schizophrenia so far vary greatly across countries and studies.^{33,39,42,43} Despite the diversity of dataset, including costs and use of methodology in relation to cost calculation, direct health care costs and lost productivity have been documented as the main cost components.^{44–46} Only few cost of illness studies have accounted for the costs for caregivers³⁵ and these studies have mostly assessed productivity losses of caregivers and not focused on potential excess direct costs of caregivers.⁴⁵ The majority of international studies of cost of illness of schizophrenia are based on an adopted prevalence-based approach,³³ which cannot assess how costs vary at different stages of the disease. In a top-down population-based design, Evensen et al⁴⁷ used national register data to assess the costs of mental health care services and lost productivity of individuals with schizophrenia in Norway in 2012. The average cost per individual was Euro 93 000. In a Swedish study, Ekman et al⁴⁸ combined hospital-based registry data with national registry databases to assess the societal costs of schizophrenia in Sweden in 2008. The study included mental health care costs, costs of somatic care and pharmaceuticals related to mental health care, community mental health care, and lost productivity costs.

The total costs amounted to Euro 55 100 per patient. Of these, 60% were costs due to lost productivity. These studies did not take somatic health care costs, which were not directly related to schizophrenia into account because the studies had no control groups.

We are not aware of any national studies of the excess societal costs of schizophrenia. In this nationwide matched controlled register study, we attempted to address this knowledge gap by estimating potential factual societal costs of all patients and their spouses during 5 years before and after the first diagnosis of schizophrenia.

Aims of the Study

The aims were (a) to estimate the total average direct health care costs and indirect costs in terms of productivity loss of patients with schizophrenia and their spouses in comparison with a matched group of people with no diagnosis of schizophrenia and (b) to determine societal costs of patients with schizophrenia and their spouses during 5 years before and after first diagnosis of schizophrenia.

Material and Methods

Patients

We identified all patients with first diagnosis of schizophrenia (*International Classification of Diseases, Tenth Revision [ICD-10]* F20-F20.99) in contact (inpatient or outpatient) with Danish Mental Healthcare Services during 2002–2016. The population was drawn from the Danish National Patient Registry, which holds information on somatic and psychiatric inpatient admissions and outpatient contacts, including contacts to emergency services, and information on all diagnoses, type of referral, place of treatment, and mode of admission.⁴⁹ Because data are available for the entire observation period, we were able to trace patients respectively and prospectively relative to the time of diagnosis of schizophrenia.

All Danish citizens are assigned a personal identification number (CPR), which we used to merge data of the population with data from other registers on use of health care resources and social data covering the entire observation period.

Control Group

Using data from the Civil Registration System Statistics Denmark database (CPR registry),⁵⁰ we randomly selected individuals of the same age, sex, marital status, and geographic area as the patients but with no diagnosis of schizophrenia. The patient to control ratio was 1:4. Data from individuals that could not be identified in Statistics Denmark using the CPR registry database were excluded from the sample.

Spouses and Control Group

To assess potential excess costs of spouses during the years before and after the patients' diagnoses of schizophrenia, all patients' spouses were identified in the CPR registry. The spouses were identified as being married or cohabiting (irrespective of gender) during the year of the initial diagnosis of schizophrenia. In addition, spouses of patients in the case group were matched with spouses in the matched control group.

Follow-up Period

We followed the population from the year of diagnosis until 2016. Thus, the patients diagnosed with schizophrenia at the beginning of the study period provided follow-up data over 14 years. Those who were diagnosed at the end of the period contributed pre-diagnostic data and those in between provided both pre- and post-diagnostic data. Spouses and controls were followed over the same observation period. If an individual was not present in the CPR registry on January 1 each year, the corresponding patient or control was not included in the dataset for that year. Individuals absent from the CPR registry have typically emigrated, deceased, or are imprisoned.

Costs

Direct Costs. The study measures direct costs associated with somatic and mental health inpatient and outpatient treatment and primary care as well as indirect costs linked to reduced productivity that may arise because of work disability. The study distinguishes costs from monetary transfer payments such as disability and welfare payments, which represent a transfer of purchasing power to the recipients from general taxpayers but do not represent net increases in the use of resources and are, therefore, reported separately and not included in the total cost estimate.⁵¹

Direct costs, including inpatient and outpatient health care costs, were calculated using diagnostic-related groups (DRG) weights and specific outpatient tariffs. These cost estimates were all based on data from the Danish Ministry of Health and reflect the average cost of treating patients with similar conditions in a Danish hospital. In Denmark, hospital treatment is provided free of charge to the patient. National DRG charges are used for reimbursements between regional health care authorities providing hospital treatment if a patient from 1 region is treated at a hospital in another region. For analyses conducted from a societal perspective, resource use should be valued at their opportunity costs, which represent their value in their best alternative use.⁵² The DRG estimates are based on detailed accounts of resource use per patient group in prior years and are, therefore, deemed to represent a good approximation

of the opportunity costs. DRG charges for psychiatric care have only been available since 2007, which allowed us a follow-up of 3 years for psychiatric data. Home care data were obtained from the municipalities' care systems and unit costs were derived from a database administered by the National Board of Social Services, which provides transparency of quality standards and costs of delivering home care services across all Danish municipalities. Data were available from 2009. Hence, we were able to assess cost of home care after diagnosis. Unit costs of General Practitioner services and services from other medical specialists were based on the prevailing National Health Insurance fee schedules.⁵³ Data on all patients' use of prescription drugs were collected from the Register of Medicinal Product Statistics, which is a central registry based on transaction reports including the retail price of each transaction from the dispensing pharmacies.⁵⁴

Indirect Costs. Indirect costs related to reduced productivity are based on figures from Danish Income Statistic.⁵⁵ Income comprised annual earnings before tax. Social transfer payments comprised social security, disability pension, sick payment, early-retirement benefit, unemployment funding, housing benefit, and child benefit. Social transfer payments, which in Denmark are primarily publicly funded, were also included, but because transfer payments do not represent net increases in the use of resources, they are not included in the total cost estimate.⁵⁶ The human capital approach was used to measure productivity loss based on the difference in labor market income between cases and controls.⁵¹ We did not adjust for potential future costs and production effects of people who died. This issue has been debated, and it has been suggested to include the net incremental consumption, which is the change in consumption minus change in production.⁵⁷

All costs were measured on annual basis and calculated in 2016 values of Danish Kroner and converted to Euro (Euro 1 is approximately equal to DDK 7.45).

Statistical Analysis

As the distribution of health care costs and social transfer payments do not follow a normal distribution and data are left skewed with a large proportion of data equal to zero, we used nonparametric bootstrap analysis to estimate the statistical significance of the costs estimates.⁵⁸

Survival analysis was analyzed using the Kaplan–Meier method. The survival curves are stratified into case and control group and show the estimates of the survival distribution function. The survival curves take into account the censoring of data that arises when all individuals did not die before the end of the analysis period.

All statistical analyses were performed using SAS, version 9.1.3 (SAS, Inc.).

Results

We identified 12 227 patients with schizophrenia (ICD-10 F20-F20.99) and 48 907 matched controls. The age distribution of the patients and matched controls is shown in [table 1](#). Nearly 53% patients and controls were males, and 15% of both were married or cohabiting. Mean age was 46.9 (SD: 17.7).

Mortality in Patients With Schizophrenia

The survival over 14 years was statistically significantly lower in schizophrenia compared with the controls ($P < .001$): 0.629 (95% CI: 0.618–0.641) vs 0.851 (95% CI: 0.846–0.855; see [supplementary figure 1](#)).

Direct and Indirect Costs

Patients. Total direct and indirect costs amounted Euro 47 059 for patients with schizophrenia and Euro 3498 for controls ([table 2](#)). Total health care costs amounted Euro 19 773 per patient per year for people with schizophrenia and Euro 2782 for the controls.

Spouses. Direct and indirect costs of spouses to patients with schizophrenia are Euro 24 442 per year as compared to Euro 2554 among the controls ([table 2](#)). The costs of health care were twice as high among spouses to patients with schizophrenia in comparison with the controls, and they also received significantly more home care. Indirect costs represented more than 75% of the sum of direct and indirect costs among spouses of patients with schizophrenia. The spouses of the controls had twice the earned income and received half the sum of public transfer income compared with spouses to patients with schizophrenia.

Table 1. Characteristics of Patients With Schizophrenia and Controls

	Patients		Controls	
	N	%	N	%
Total	12 227		48 907	
Age				
0–10	7	0.1	28	0.1
11–20	566	4.6	2264	4.6
21–30	2159	17.7	8636	17.7
31–40	2069	16.9	8276	16.9
41–50	2237	18.3	8948	18.3
51–60	2210	18.1	8840	18.1
61–70	1688	13.8	6752	13.8
71–80	884	7.2	3536	7.2
>80	407	3.3	1627	3.3
Gender				
Male	6441	52.7	25 763	52.7
Female	5786	47.3	23 144	47.3
Marital status				
Married	1855	15.2	7419	15.2
Not married	10 372	84.8	41 488	84.8

Costs Before and After Diagnosis

Patients. [Figure 1](#) presents the annual health care costs, income, and social transfers of patients with schizophrenia and their spouses stratified by age and sex during 3 years before and after diagnosis compared with the controls. Both somatic and psychiatric health care costs were statistically higher in patients with schizophrenia than the control group before initial diagnosis. At the time of diagnosis, the health care costs increased and then steadily decreased afterward. Among patients with schizophrenia, the average earned income per year decreased from approximately Euro 3000 during the years before time of diagnosis and continued to decrease to below Euro 1000 during the first 5 years after diagnosis, whereas the average earned income per year amounted Euro 26 000–28 000 in the control group within the same observational period.

Spouses. Total health care costs differed among spouses of patients with schizophrenia and the spouses of the controls. Costs of prescription medication, primary health care, and psychiatric treatment were statistically significantly higher among spouses of patients with schizophrenia both 3 years before and after diagnosis. Earned income decreased before diagnosis to 4 years after the time of diagnosis among spouses to patients with schizophrenia, whereas it increased for other spouses during the same period.

Discussion

Main Findings

Our study found that individuals with schizophrenia differ markedly from the general population with respect to all included cost items. The average annual direct and indirect costs were more than 13 times higher among patients with schizophrenia (Euro 47 059) compared with the matched controls (Euro 3498).

Earned annual income was more than 20 times lower among patients with schizophrenia, whereas the annual public transfers were more than twice as much in schizophrenia compared with the matched controls.

Our result also showed that higher costs of health care services could be observed during 5 years before the first diagnosis of schizophrenia and that psychiatric inpatient care represented the largest single cost item among patients who were later diagnosed with schizophrenia. Moreover, lower labor market attachment was observed before the first diagnosis of schizophrenia.

The costs of lost productivity increased during the years before index diagnosis. After diagnosis, the patients were transferred from temporary transfer payments, eg, sick or unemployment payment to disability pension, which is in accordance with other studies of vocational status in schizophrenia and other mental illnesses.⁹

Table 2. Total Average Health Care Costs, Earned Income and Public Transfer of Patients With Schizophrenia and Their Spouses After Diagnosis

	Patient	Control	P value	Spouse to patient	Spouse to control	P value
Number of persons (N)	11 320	45 281		1514	5979	
Somatic						
Outpatient services	€ 1088	805	.001	780	724	.851
Inpatient admissions	€ 4299	1268	.001	1497	945	.001
Prescription drugs	€ 2900	369	.001	768	273	.001
Primary health sector	€ 549	341	.001	394	308	.001
Somatic health costs total	€ 8836	2782	.001	3439	2249	.001
Psychiatric outpatient services	€ 2276	64	.001	374	24	.001
Psychiatric inpatient admissions	€ 8661	134	.001	902	59	.001
Health costs total incl. psychiatric cost	€ 19 773	2980	.001	4714	2332	.001
Home care						
Home care—care	€ 1664	419	.001	689	198	.001
Home care—practical help	€ 375	98	.001	147	24	.001
Home care total	€ 2039	518	.001	836	222	.001
Earned income (wage, self-employed)	€ 989	26 236	.001	17 522	36 414	.001
Public transfer						
Unemployment benefit	€ 40	807	.001	742	645	.073
Unemployment benefit	€ 1584	1276	.001	2411	615	.001
Age pension	€ 2809	3283	.001	2841	2438	.001
Early retirement	€ 24	551	.001	521	661	.015
Disability pension	€ 19 179	2682	.001	5565	803	.001
Sick pay (public funded)	€ 154	463	.001	490	450	.958
Housing benefits	€ 2013	773	.001	793	190	.001
Childs benefits	€ 140	462	.001	520	533	1.001
Public transfer income total	€ 25 944	10 297	.001	13 884	6335	.001
Indirect costs, foregone earnings	€ 25 247			18 892		
Sum of direct and indirect costs	€ 47 059	3498		24 442	2554	
Net social cost of schizophrenia	€ 43 561			21 888		

Note: Home care cost data is only available from 2009; Psychiatric costs available from 2007. Statistical significance can be represented in bold. Please use a threshold of $P < .001$ of statistical significance.

* P value from t -test.

Fig. 1. Direct and indirect costs of patients and spouses before and after initial diagnosis of schizophrenia compared with controls. All differences are statistically significant; $P < .05$. For color, see the figure online.

Our study revealed that spouses of patients with schizophrenia have excess direct health care costs and productivity loss compared with a matched control group of people with spouses who do not have schizophrenia. The total costs including productivity loss are higher during the entire observational period. After diagnosis, the health care costs and transfer income of spouses of patients with schizophrenia are twice as high as the control group, whereas the earned income is half the income of the control group of spouses.

Comparisons With Other Studies

To the best of our knowledge, this is the first study using national register data to compare societal costs of patients with schizophrenia with a matched control group of people with no diagnosis of schizophrenia before and after diagnosis. Neither have we seen any other matched controlled study assessing the excess costs of spouses to patients with schizophrenia during the years before and after first diagnosis.

A major strength of this study was the nationwide selection of patients with professionally evaluated diagnoses and identification of spouses. Furthermore, data were drawn from continuously updated comprehensive Danish registers, which are independent of memory errors and free of recall bias. Although there are no systematic validation studies of clinical diagnoses in the Danish case register against research diagnoses, validation of the schizophrenia diagnosis has been carried out with good results.⁵⁹ Moreover, the nationwide registration of the severe mental disorders in Denmark is almost complete as no private psychiatric hospitals exist.

In general, it is complicated to compare cost estimates across countries due to differences in organization of health care systems and methodological heterogeneity. Using a common methodology, the European EPSILON study found variations of total service costs of schizophrenia between Euro 4257 in the Netherlands and Euro 11 193 in Denmark (in 1998-prices).⁴³ In present values, the Danish finding is comparable with our study. One explanation of the differences across countries in the

EPSILON study was that the Dutch study used average tariffs to measure charges, which do not fully measure capital and overhead elements instead of opportunity costs and thus underestimate the total costs.

Overall, our results converge with earlier studies, which report poorer higher level of unemployment or other social benefits compared with matched controls up to 19 years before first diagnosis of schizophrenia.⁶⁰ The estimated annual productivity loss per patient was Euro 25 247 in our study, whereas international studies found lower estimates varying between Euro 7375 in the United Kingdom and Euro 8000 in Germany.³³

Evidence from other Nordic countries found average societal costs between Euro 55 100 to Euro 93 000 per patient per year.^{47,48} These estimates were based on studies of the prevalence of schizophrenia for a given year, whereas our study calculated average costs during 5 years after initial diagnosis. Our analyses showed that the total cost per patient peaked during the year of the initial diagnosis and then decreased steadily to a certain level. This could indicate that our estimate over a time frame of 5 years after initial diagnosis would be higher than estimates based on prevalence or incidence studies.

The total annual societal costs of Euro 43 561 per patient greatly exceed costs identified in Danish register studies of chronic neurological diseases, which used the same methodology to identify patients and assessed excess societal costs. Likewise, these studies estimated total average annual societal costs over 5 years after initial diagnosis to be Euro 4544 in dementia,⁶¹ Euro 9572 in narcolepsy,⁶² Euro 11 223 in epilepsy,⁶³ and Euro 14 595 in multiple sclerosis.⁶⁴ The excess costs of schizophrenia can both be explained by higher health care costs, but specifically by lost productivity costs as the patients with schizophrenia are affected by the disorder early in life and before they enter the labor market.

We found no studies reporting both direct health care and indirect costs of spouses with schizophrenia. A recent study reported considerably higher rates of psychiatric health care and social welfare benefits among parents of offspring with schizophrenia compared with other disorders such as rheumatic arthritis, multiple sclerosis, and epilepsy.³⁶ A German study found lost productivity among caregivers to be Euro 8002⁶⁵ and British studies reported productivity losses of caregivers to be Euro 7375–8459.^{66,67} Earlier studies have observed that nonrandom mating of individuals in psychiatric populations is widespread both within and across the spectrum of psychiatric disorders.⁶⁸ This phenomena may contribute to explain that spouses in our study have increased costs both before and after initial diagnosis.

Taken together, our study documents elevated societal costs after initial diagnosis of schizophrenia that are

significantly higher than chronic neurological disorders. The pathways to mental health care tend to have multiple help-seeking contacts and delay before first diagnosis of schizophrenia. This was underpinned by our results, which showed increased use of mental health care services before index date of schizophrenia. The costs of mental health services accounted for at large proportion of the total health care costs. Our findings support earlier reports of a long diagnostic pathway to schizophrenia with depressive and negative symptoms and cognitive deficits before the emergence of psychotic symptoms.^{69–72}

We also found increased use of somatic health care services at least 5 years before index date, which is in line with earlier Danish studies of increased use of primary care⁷³ and somatic diseases before first diagnosis of schizophrenia.⁷⁴ The same pattern of increased societal costs was identified among spouses of patients with schizophrenia, which highlight the need for identification and support of spouses and other family members of patients with schizophrenia.

Limitations

Only spouses were considered as relatives in this study, which probably underestimate the costs of caregivers. Other studies have found a high rate of break-ups/divorces in schizophrenia.⁷⁵ As we defined spouses as being married/cohabiting during the year of the initial diagnosis of schizophrenia no matter if they keep being spouses during follow-up, we did not take this into account. As only 15% patients were married/cohabiting, other important caregivers such as parents or children could have been identified as important caregivers. But, at the same time, living together with the care recipient has been associated with a higher subjective caregiver burden⁷⁶ and potential higher societal costs. By including spouses, we may have identified an important group of caregivers who may be burdened as caregivers but also due to their own mental health problems.

We used the human capital method to estimate indirect cost of schizophrenia. Lost productivity is monetarily valued according to the gross wage of the employee. Despite some shortcomings, eg, using the wage rate as an approximation of the true opportunity cost of labor, difficulties in including productivity loss resulting from health problems (presenteeism) in the calculation of the loss of labor,⁵¹ the human capital method is the most common method to estimate lost productivity.

A limitation was that cost of social services supplied by the municipalities was not included due to low completeness reported to the Danish registers, which probably underestimates the total costs. A Swedish study found that approximately 20% of total costs were due to municipality social services.⁴⁴ Whether this is comparable in a

Danish context is not possible to say. Also, direct costs of policing, investigations, legal defense, prosecution, incarceration, and victim costs could have been included in the total costs. Our study, however, did not assess these costs. Estimated costs from other studies found that contacts with criminal justice represented between 1% and 3% of total costs and between 2% and 6% of direct costs.⁷⁷

In conclusion, our study documents excess annual societal costs of patients with schizophrenia of Euro 43 561 per patient compared with a matched group of individuals with no diagnosis of schizophrenia. Likewise, the societal costs of spouses were Euro 21 888 higher than the matched group of spouses without a diagnosis of schizophrenia. Furthermore, we identified increased societal costs both for patients and their spouses at least 5 years before initial diagnosis of schizophrenia. Consequently, we think that these findings emphasize the need of awareness on early signs of schizophrenia among health care professionals but also professionals working in other sectors. This is important because patients with long DUP have poorer prognosis leading to higher societal costs. Young people constitute the age group with the lowest service access, and it is specifically important with continuing focus on how to design stigma-free interventions reaching their needs.⁷⁸ Potential savings could be achieved by increasing investments investing in initiatives to reducing admissions to somatic and psychiatric hospital and in occupational therapy. Moreover, incorporating mental health care interventions with programs such as Individual Placement and Support appear to be effective in obtaining competitive employment for people with severe mental illness.^{79,80}

Ethics

The study was approved by the Danish Data Protection Agency. Data were handled in a manner that did not reveal the identity of any patients or controls, so neither individual nor ethical approval was required.

Supplementary Material

Supplementary data are available at *Schizophrenia Bulletin* online.

Acknowledgments

The authors have declared that there are no conflicts of interest in relation to the subject of this study.

References

1. Kanahara N, Yoshida T, Oda Y, et al. Onset pattern and long-term prognosis in schizophrenia: 10-year longitudinal follow-up study. *PLoS One*. 2013;8(6):e67273.
2. Pedersen CB, Mors O, Bertelsen A, et al. A comprehensive nationwide study of the incidence rate and lifetime risk for treated mental disorders. *JAMA Psychiatry*. 2014;71(5):573–581.
3. Thorup A, Waltoft BL, Pedersen CB, Mortensen PB, Nordentoft M. Young males have a higher risk of developing schizophrenia: a Danish register study. *Psychol Med*. 2007;37(4):479–484.
4. Kühl JOG, Laursen TM, Thorup A, Nordentoft M. The incidence of schizophrenia and schizophrenia spectrum disorders in Denmark in the period 2000–2012. A register-based study. *Schizophr Res*. 2016;176(2–3):533–539. doi:10.1016/j.schres.2016.06.023
5. Compton M, Broussard B. Conceptualizing the multifaceted determinants of the duration of untreated psychosis. *Curr Psychiatry Rev*. 2011;7(1):1–11. doi:10.2174/157340011795945865
6. Laursen TM, Wahlbeck K, Hällgren J, et al. Life expectancy and death by diseases of the circulatory system in patients with bipolar disorder or schizophrenia in the Nordic countries. *PLoS One*. 2013;8(6):e67133.
7. Seppala J, Korpela H, Jääskeläinen E, et al. Somatic comorbidity and its outcomes in schizophrenia during lifespan. *Eur Psychiatry*. 2016;33:S35–S36. doi:10.1016/J.EURPSY.2016.01.870
8. Laursen TM, Nordentoft M, Mortensen PB. Excess early mortality in schizophrenia. *Annu Rev Clin Psychol*. 2014;10:425–448.
9. Hastrup LH, Kongslev MT, Simonsen E. Low vocational outcome among people diagnosed with borderline personality disorder during first admission to mental health services in Denmark: a nationwide 9-year register-based study. *J Pers Disord*. 2018;5:1–15. doi:10.1521/pedi_2018_32_344
10. Stilo SA, Gayer-Anderson C, Beards S, et al. Further evidence of a cumulative effect of social disadvantage on risk of psychosis. *Psychol Med*. 2017;47(5):913–924.
11. Ramsay CE, Stewart T, Compton MT. Unemployment among patients with newly diagnosed first-episode psychosis: prevalence and clinical correlates in a US sample. *Soc Psychiatry Psychiatr Epidemiol*. 2012;47(5):797–803. doi:10.1007/s00127-011-0386-4
12. Wade D, Harrigan S, Edwards J, Burgess PM, Whelan G, McGorry PD. Substance misuse in first-episode psychosis: 15-month prospective follow-up study. *Br J Psychiatry*. 2006;189:229–234.
13. Barnett JH, Werners U, Secher SM, et al. Substance use in a population-based clinic sample of people with first-episode psychosis. *Br J Psychiatry*. 2007;190:515–520.
14. Wisdom JP, Manuel JI, Drake RE. Substance use disorder among people with first-episode psychosis: a systematic review of course and treatment. *Psychiatr Serv*. 2011;62(9):1007–1012.
15. Fazel S, Gulati G, Linsell L, Geddes JR, Grann M. Schizophrenia and violence: systematic review and meta-analysis. *PLoS Med*. 2009;6(8):e1000120.
16. Munkner R, Hastrup S, Joergensen T, Kramp P. Incipient offending among schizophrenia patients after first contact to the psychiatric hospital system. *Eur Psychiatry*. 2005;20(4):321–326.
17. Maniglio R. Severe mental illness and criminal victimization: a systematic review. *Acta Psychiatr Scand*. 2009;119(3):180–191.
18. Chan SW. Global perspective of burden of family caregivers for persons with schizophrenia. *Arch Psychiatr Nurs*. 2011;25(5):339–349.
19. Lauber C, Eichenberger A, Luginbühl P, Keller C, Rössler W. Determinants of burden in caregivers of patients with exacerbating schizophrenia. *Eur Psychiatry*. 2003;18(6):285–289.

20. Cuijpers P, Stam H. Burnout among relatives of psychiatric patients attending psychoeducational support groups. *Psychiatr Serv*. 2000;51(3):375–379.
21. Martens L, Addington J. The psychological well-being of family members of individuals with schizophrenia. *Soc Psychiatry Psychiatr Epidemiol*. 2001;36(3):128–133.
22. Hastrup LH, Haahr UH, Jansen JE, Simonsen E. Determinants of duration of untreated psychosis among first-episode psychosis patients in Denmark: a nationwide register-based study. *Schizophr Res*. 2018;192:154–158.
23. Marshall M, Lewis S, Lockwood A, Drake R, Jones P, Croudace T. Association between duration of untreated psychosis and outcome in cohorts of first-episode patients: a systematic review. *Arch Gen Psychiatry*. 2005;62(9):975–983.
24. Perkins DO, Gu H, Boteva K, Lieberman JA. Relationship between duration of untreated psychosis and outcome in first-episode schizophrenia: a critical review and meta-analysis. *Am J Psychiatry*. 2005;162(10):1785–1804.
25. Correll CU, Gallinger B, Pawar A, et al. Comparison of early intervention services vs treatment as usual for early-phase psychosis: a systematic review, meta-analysis, and meta-regression. *JAMA Psychiatry*. 2018;75(6):555–565. doi:10.1001/jamapsychiatry.2018.0623
26. Jeppesen P, Petersen L, Thorup A, et al. Integrated treatment of first-episode psychosis: effect of treatment on family burden: OPUS trial. *Br J Psychiatry*. 2005;187(suppl 48):85–90. doi:10.1192/bjp.187.48.s85
27. Nordentoft M, Melau M, Iversen T, et al. From research to practice: how OPUS treatment was accepted and implemented throughout Denmark. *Early Interv Psychiatry*. 2015;9(2):156–162.
28. Hastrup LH, Kronborg C, Bertelsen M, et al. Cost-effectiveness of early intervention in first-episode psychosis: economic evaluation of a randomised controlled trial (the OPUS study). *Br J Psychiatry*. 2013;202(1):35–41.
29. Melle I, Larsen TK, Haahr U, et al. Reducing the duration of untreated first-episode psychosis: effects on clinical presentation. *Arch Gen Psychiatry*. 2004;61(2):143–150.
30. Hegelstad WT, Larsen TK, Auestad B, et al. Long-term follow-up of the TIPS early detection in psychosis study: effects on 10-year outcome. *Am J Psychiatry*. 2012;169(4):374–380.
31. Hastrup LH, Haahr UH, Nordgaard J, Simonsen E. The effect of implementation of an early detection team: a nationwide register-based study of characteristics and help-seeking behavior in first-episode schizophrenia in Denmark. *Schizophr Res*. 2018;201:337–342.
32. Chong HY, Teoh SL, Wu DB, Kotirum S, Chiou CF, Chaiyakunapruk N. Global economic burden of schizophrenia: a systematic review. *Neuropsychiatr Dis Treat*. 2016;12:357–373. <http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=psyc13&NEWS=N&AN=2016-09026-001>.
33. Jin H, Moswew I. The societal cost of schizophrenia: a systematic review. *Pharmacoeconomics*. 2017;35(1):25–42.
34. Chan SW. Global perspective of burden of family caregivers for persons with schizophrenia. *Arch Psychiatr Nurs*. 2011;25(5):339–349.
35. Awad AG, Voruganti LN. The burden of schizophrenia on caregivers: a review. *Pharmacoeconomics*. 2008;26(2):149–162.
36. Mittendorfer-Rutz E, Rahman S, Tanskanen A, et al. Burden for parents of patients with schizophrenia—a nationwide comparative study of parents of offspring with rheumatoid arthritis, multiple sclerosis, epilepsy, and healthy controls. *Schizophr Bull*. 2019;45(4):794–803.
37. Chong HY, Teoh SL, Wu DB-C, Kotirum S, Chiou C-F, Chaiyakunapruk N. Global economic burden of schizophrenia: a systematic review. *Neuropsychiatr Dis Treat*. 2016;12:357–373. <http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=psyc13&NEWS=N&AN=2016-09026-001>.
38. Knapp M, Razzouk D. Costs of schizophrenia. *Psychiatry*. 2008;71(1):491–494. doi:10.1016/j.mpps.2008.08.008
39. Gustavsson A, Svensson M, Jacobi F, et al. Cost of disorders of the brain in Europe 2010. *Eur Neuropsychopharmacol*. 2011;21(Netherlands LG-English PT-Journal: Article EM-201100 DD-20111014):October.
40. Wittchen HU, Jacobi F, Rehm J, et al. The size and burden of mental disorders and other disorders of the brain in Europe 2010. *Eur Neuropsychopharmacol*. 2011;21(9):655–679. doi:10.1016/j.euroneuro.2011.07.018
41. Razzouk D. (Ed) *Mental Health Economics: The Costs and Benefits of Psychiatric Care*. Springer International Publishing 2017. doi:10.1007/978-3-319-55266-8
42. Olesen J, Gustavsson A, Svensson M, Wittchen H-U. The economic cost of brain disorders in Europe. *Eur J Neurol*. 2012;19(1):155–162. <http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed14&NEWS=N&AN=363134089>
43. Chisholm D, Knapp M. The economics of schizophrenia care in Europe: the EPSILON study. *Epidemiol Psychiatr Soc*. 2002;11(1):12–17.
44. Ekman M, Granström O, Omérov S, Jacob J, Landén M. The societal cost of schizophrenia in Sweden. *J Ment Health Policy Econ*. 2013. doi:10.1016/S1098-3015(10)72536-5
45. Sruamsiri R, Mori Y, Mahlich J, Rg Mahlich J. Productivity loss of caregivers of schizophrenia patients: a cross-sectional survey in Japan. *J Ment Heal*. 2018;27(6):583–587. doi:10.1080/09638237.2018.1466048
46. Evensen S, Wisløff T, Lystad JU, Bull H, Ueland T, Falkum E. Prevalence, employment rate, and cost of schizophrenia in a high-income welfare society: a population-based study using comprehensive health and welfare registers. *Schizophr Bull*. 2016;42(2):476–483.
47. Evensen S, Ueland T, Lystad JU, Bull H. Cost effectiveness of the jobmanagement program (JUMP). *Schizophr Res*. 2014;153:S240–S241. <http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed16&NEWS=N&AN=71728955>.
48. Ekman M, Granström O, Omerov S, Jacob J. The societal cost of schizophrenia in Sweden. *Value Heal*. 2010;13(3):A111–A112. <http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed12&NEWS=N&AN=70523189>.
49. Lynge E, Sandegaard JL, Rebolj M. The Danish national patient register. *Scand J Public Health*. 2011;39(7):30–33. doi:10.1177/1403494811401482
50. Pedersen CB. The Danish civil registration system. *Scand J Public Health*. 2011;39(suppl 7):22–25.
51. Hassink W, van den Berg B. Methods and instruments for the estimation of production changes in economic evaluations. In: Razzouk D, ed. *Mental Health Economics: The Costs and Benefits of Psychiatric Care*. Springer International Publishing; 2017. 431–440.
52. Gold MR. *Cost-Effectiveness in Health and Medicine*. Oxford University Press; 1996. https://global.oup.com/academic/product/cost-effectiveness-in-health-and-medicine-9780195108248#.XG_oMoO_3Sk.mendeley. Accessed February 22, 2019.
53. Andersen JS, Olivarius Nde F, Krasnik A. The Danish National Health Service Register. *Scand J Public Health*. 2011;39(suppl 7):34–37.

54. Kildemoes HW, Sørensen HT, Hallas J. The Danish National Prescription Registry. *Scand J Public Health*. 2011;39(suppl 7):38–41.
55. Baadsgaard M, Quitzau J. Danish registers on personal income and transfer payments. *Scand J Public Health*. 2011;39(suppl 7):103–105.
56. Becker P, Razzouk D. Estimation of costs for community mental health services. In: Razzouk D, ed. *Mental Health Economics: The Costs and Benefits of Psychiatric Care*. Springer International Publishing; 2017:239–251. doi:10.1007/978-3-319-55266-8_15
57. Kruse M, Sørensen J, Gyrd-Hansen D. Future costs in cost-effectiveness analysis: an empirical assessment. *Eur J Health Econ*. 2012;13(1):63–70.
58. Glick HA, Doshi JA, Sonnad SS, Polsky D. *Economic Evaluation in Clinical Trials*. Oxford University Press; 2007.
59. Mors O, Perto GP, Mortensen PB. The Danish Psychiatric Central Research Register. *Scand J Public Health*. 2011;39(suppl 7):54–57.
60. Agerbo E, Byrne M, Eaton WW, Mortensen PB. Marital and labor market status in the long run in schizophrenia. *Arch Gen Psychiatry*. 2004;61(1):28–33.
61. Frahm-Falkenberg S, Ibsen R, Kjellberg J, Jennum P. Health, social and economic consequences of dementias: a comparative national cohort study. *Eur J Neurol*. 2016;23(9):1400–1407.
62. Jennum P, Ibsen R, Petersen ER, Knudsen S, Kjellberg J. Health, social, and economic consequences of narcolepsy: a controlled national study evaluating the societal effect on patients and their partners. *Sleep Med*. 2012;13(8):1086–1093.
63. Jennum P, Gyllenberg J, Kjellberg J. The social and economic consequences of epilepsy: a controlled national study. *Epilepsia*. 2011;52(5):949–956.
64. Jennum P, Wanscher B, Frederiksen J, Kjellberg J. The socioeconomic consequences of multiple sclerosis: a controlled national study. *Eur Neuropsychopharmacol*. 2012;22(1):36–43.
65. Frey S. The economic burden of schizophrenia in Germany: a population based retrospective cohort study using genetic matching *Eur Psychiatry*. 2014;2(8):479–489.
66. Guest JF, Cookson RF. Cost of schizophrenia to UK Society. An incidence-based cost-of-illness model for the first 5 years following diagnosis. *Pharmacoeconomics*. 1999;15(6):597–610.
67. Mangalore R, Knapp M. Cost of schizophrenia in England. *J Ment Health Policy Econ*. 2007;10(1):23–41.
68. Nordsletten AE, Larsson H, Crowley JJ, Almqvist C, Lichtenstein P, Mataix-Cols D. Patterns of nonrandom mating within and across 11 major psychiatric disorders. *JAMA Psychiatry*. 2016;73(4):354–361.
69. Kvig EI, Brinchmann B, Moe C, Nilssen S, Larsen TK, Sørgeard K. “Lanthanic presentation” in first-episode psychosis predicts long service delay: the challenge of detecting masked psychosis. *Psychopathology*. 2017;50(4):282–289.
70. Kahn RS, Keefe RSE. Schizophrenia is a cognitive illness: time for a change in focus. *JAMA Psychiatry*. 2013;70(10):1107–1112. doi:10.1001/jamapsychiatry.2013.155
71. Bora E, Lin A, Wood SJ, Yung AR, McGorry PD, Pantelis C. Cognitive deficits in youth with familial and clinical high risk to psychosis: a systematic review and meta-analysis. *Acta Psychiatr Scand*. 2014;130(1):1–15.
72. Simonsen E, Newton-Howes G. Personality pathology and schizophrenia. *Schizophr Bull*. 2018;44(6):1180–1184.
73. Nørgaard H, Søndergaard Pedersen H, Fenger-Grøn M, et al. Increased use of primary care during 6 years of prodromal schizophrenia. *Acta Psychiatr Scand*. 2016;134(3):225–233. doi:10.1111/acps.12600
74. Sørensen HJ, Nielsen PR, Benros ME, Pedersen CB, Mortensen PB. Somatic diseases and conditions before the first diagnosis of schizophrenia: a nationwide population-based cohort study in more than 900000 individuals. *Schizophr Bull*. 2014;41(2):513–521. doi:10.1093/schbul/sbu110
75. Salokangas RK, Honkonen T, Stengård E, Koivisto AM. To be or not to be married—that is the question of quality of life in men with schizophrenia. *Soc Psychiatry Psychiatr Epidemiol*. 2001;36(8):381–390.
76. Hastrup LH, Van Den Berg B, Gyrd-Hansen D. Do informal caregivers in mental illness feel more burdened? A comparative study of mental versus somatic illnesses. *Scand J Public Health*. 2011;39(6):598–607.
77. Knapp M, Mangalore R, Simon J. The global costs of schizophrenia. *Schizophr Bull*. 2004;30(2):279–293. <http://www.ncbi.nlm.nih.gov/pubmed/15279046>. Accessed July 5, 2018.
78. McGorry P, Bates T, Birchwood M. Designing youth mental health services for the 21st century: examples from Australia, Ireland and the UK. *Br J Psychiatry Suppl*. 2013;54:30–35. doi:10.1192/bjp.bp.112.119214
79. Modini M, Tan L, Brinchmann B, et al. Supported employment for people with severe mental illness: systematic review and meta-analysis of the international evidence. *Br J Psychiatry*. 2016;209(1):14–22.
80. Christensen TN, Nielsen IG, Stenager E, et al. Individual placement and support supplemented with cognitive remediation and work-related social skills training in Denmark: study protocol for a randomized controlled trial. *Trials*. 2015;16:280.