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Estimation of Direct and Indirect Costs of Treating Schizophrenia for Community-Dwelling US Residents

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Dedication

I would like to dedicate this thesis to my parents, Bela and Rajiv Desai.

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Abstract

Estimation of Direct and Indirect Costs of Treating Schizophrenia for Community-Dwelling US Residents

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Schizophrenia is a chronic and debilitating disease that affects approximately one percent of the US population and exerts a disproportionately high financial burden on the society. The objective of this study was to estimate the direct and indirect costs of schizophrenia among community-dwelling US residents and identify patient characteristics associated with high schizophrenia-related direct costs.

Patients with a diagnosis of schizophrenia (ICD-9 code 295) or other non-organic psychoses (ICD-9 code 298) between January 1, 2005 and December 31, 2008 were identified from the Medical Expenditure Panel Survey (MEPS). To estimate direct costs, the following cost categories were identified: inpatient hospitalizations, outpatient visits, emergency department visits, office-based physician visits, home healthcare visits, and prescription medications. The following cost categories were identified to estimate indirect costs: caregivers' costs and cost of lost productivity due to missed work days, reduced employment, and suicide. Logistic regression was used to compare patients belonging to the high-cost group and to the low-cost group. All analyses were carried out using SAS version 9.2 (SAS Institute Inc., Cary, North Carolina).

The weighted average number of patients with schizophrenia identified for each year was 757,893. The annual direct and indirect costs were estimated at $3.96 billion and $15.35 billion, respectively. The mean annual direct medical schizophrenia-related cost per patient was $5,586. For each one-year increase in age, patients were 5.7% less likely to be in the high-cost group. Patients with a spouse were 77.7% less likely than patients without a spouse to be in the high-cost group.

Healthcare providers and policymakers can use these cost estimates to better understand the economic burden of schizophrenia and identify services and subgroups of patients associated with the highest costs. This would help in the provision of healthcare services to patients with schizophrenia and in the optimization of patient outcomes.

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CHAPTER 1: Literature Review

Introduction

Schizophrenia is a chronic debilitating illness that is characterized by disturbances of language, perception, thinking, social activity, behavior, and decision making skills.[1] Several epidemiologic surveys have been conducted to estimate the prevalence of schizophrenia including the Epidemiologic Catchment Area (ECA) study and the National Co-morbidity Survey (NCS). The overall prevalence in the US is estimated to be between 0.3% and 1.6%.[2,3]

Due to the complex nature of the disease, the cause is not explicitly known. However, it has been hypothesized that genetic and environmental factors play a role in triggering the disease.[4] Family history of schizophrenia, exposure to viruses and toxins in the first and second trimester, stressful life, old age of parents, and consumption of psychoactive drugs at a young age are known to be risk factors for schizophrenia.[5] In addition, several studies have reported that season of birth, complications during birth, autoimmune diseases, ethnicity, urban residence, and cannabis use are also risk factors.[6] Schizophrenia generally strikes in late adolescence and progresses slowly, starting with the patient becoming socially withdrawn and having distorted perceptions and moving towards frequent delusions and hallucinations.[1]

Symptoms

Schizophrenia has several symptoms. The patients may have positive symptoms, such as hallucinations, delusions, and conceptual disorientation or negative symptoms, such as loss of function, decreased social engagement, diminished concentration, decreased emotional expression, and inability to feel happiness from pleasurable experiences.[1] A patient must have at least two of these symptoms for one month and must show signs continuously for at least a six-

month period for the diagnosis of schizophrenia to be confirmed. With increasing age, positive symptoms decrease and some amount of social and occupational functioning may be regained. However, the symptoms and course of disease vary and are patient specific.

Types of schizophrenia

Four types of schizophrenia are recognized:[1]

Catatonic schizophrenia: It is characterized by increased motor-activity, negativity, and imitation of speech and movement of others.

Disorganized schizophrenia: There is disorganization of speech and behavior which is accompanied by silly behavior.

Paranoid schizophrenia: Patients are preoccupied with a specific delusional system and do not show signs of disorganized schizophrenia.

Residual schizophrenia: It is characterized by negative symptoms in the absence of delusions, hallucinations, and increased motor activity.

In addition, there are two closely related disorders:

Schizophreniform disorders: Patients have the symptoms of schizophrenia but not for the duration that is required to confirm a schizophrenia diagnosis.

Schizoaffective disorders: Patients have the symptoms of schizophrenia and in addition have independent periods of mood disturbances.

Treatment

Schizophrenia requires lifelong treatment due to its chronic nature. Antipsychotic medications are the cornerstone of treatment for both acute schizophrenia and as maintenance medications. There are two categories of antipsychotics: conventional (or typical) and atypical.[5]

Typical antipsychotics include chlorpromazine, fluphenazine, haloperidol, and perphenazine.[5] They cause a number of neurological side effects including movement disorders, which are often irreversible, and orthostatic hypotension. Atypical antipsychotics are the newer class of drugs and cause less severe side effects. They include aripiprazole, clozapine, olanzapine, paliperidone, quetiapine, risperidone, and ziprasidone. They can cause side effects such as diabetes, high cholesterol, and weight gain. They are more effective in treating negative symptoms and improving cognitive functioning.

Antipsychotic medications are generally effective in patients with a first episode.[1] Improvement is usually seen within months and sometimes even days, but a period of 6-8 weeks may be required for complete remission. Maintenance medication is extremely important as it protects against possible relapse and development of movement disorders. Regular dosing is much more effective than intermittent drug therapy. However, for patients on very high doses, gradual reduction can help improve social functioning. On complete discontinuation of medication therapy, the relapse rate in 6 months is about 60%.

In addition to medication therapy, social skills training, family/individual therapy, vocational rehabilitation, and supported employment can help patients with schizophrenia.[5] Educational efforts directed towards family members and relevant community resources have also proved very advantageous.[1]

Medication adherence

Patients with schizophrenia are known to have poor adherence to medication. For patients to benefit from antipsychotic drugs, they must be adherent to their medication. Maintenance medication is also important to prevent relapse of the disease. Studies have measured adherence subjectively (from patient, family, and clinician reports) and objectively (using electronic monitoring systems).[7] Non-adherence leads to increased symptom severity, aggressive behavior, and increased use of hospitals and emergency departments. This, in turn, leads to increased health care costs associated with schizophrenia. Another important consequence of lack of adherence is relapse which is also responsible for a substantial portion of the total cost of care for schizophrenia.[8]

In addition to lack of medication adherence among patients with schizophrenia, frequent use of inpatient, outpatient, and emergency department services, need for maintenance medications for long periods of time, informal support from family and friends, and presence of co-morbid conditions are responsible for the high costs of schizophrenia. The costs associated with schizophrenia have shown a two-fold increase between 1990 and 2002, with Rice et al.'s[9] estimate for 1990 at $32.5 billion and the most recent estimate in 2002 by Wu et al.[10] at $62.7 billion. The burden of schizophrenia is disproportionately high; in 1990, schizophrenia had a prevalence of 1.1% and an associated expenditure of $32.5 billion while affective disorders had a prevalence of 9.5% and an associated expenditure of $30.4 billion.[9]

The purpose of this study is to estimate the direct and indirect costs of schizophrenia in the US from a societal perspective as well as identify factors that are significantly associated with the high costs of schizophrenia using the Medical Expenditure Panel Survey (MEPS)

database. This chapter contains a literature review of the prevalence of schizophrenia, costs and predictors of high costs of schizophrenia, and the use of MEPS in cost studies to estimate the direct and indirect costs of diseases.

Prevalence

Many studies have assessed the prevalence of schizophrenia and have found varying results depending on several factors such as age, gender, race, social class, and geographic location. These studies have used various approaches including epidemiological surveys, claims-based analyses, and other methods to assess the prevalence of schizophrenia. Two major epidemiological surveys include the Epidemiologic Catchment Area (ECA) study and the National Co-morbidity Survey (NCS). The ECA study was conducted at five different research sites in the US between 1980 and 1985.[11] The NCS, which was conducted in the US between 1990 and 1992, administered structured psychiatric interviews to a nationally representative sample of Americans.[12] The National Co-morbidity Survey Replicate (NCS-R) was conducted between 2000 and 2003. However, little information related specifically to schizophrenia was reported from the NCS or the NCS-R due to the manner in which the mental disorders were classified. Based on these epidemiological survey results, schizophrenia affects about 0.3%-1.6% of the US population.[2,3] However, Kessler et al. noted that this value is an underestimate as patients with schizophrenia are underrepresented in epidemiological surveys.[2]

In 2002, Wu et al. used an alternative method to estimate annual prevalence of diagnosed schizophrenia in the US.[13] They used private insurance claims data, paid claims from California Medicaid, published statistics of Medicare and the Veterans Administration, and other published statistics to estimate schizophrenia prevalence. The prevalence of schizophrenia diagnosis from administrative claims data was estimated to be 0.51%. Schizophrenia diagnosis was most prevalent in the Medicaid population (1.66%) followed by the non-insured population (1.02%), the Medicare population (0.83%), and the least prevalent in the privately insured population (0.13%). Almost one-third (33%) of the patients with schizophrenia in America are covered by

Medicaid, 22% by Medicare, 16% are privately insured, and 30% do not have a form of insurance.

The ECA study found that schizophrenia generally occurs in early adulthood, between 18 and 29 years of age (lifetime prevalence=1.7%) or slightly later, between 30 and 44 years of age (lifetime prevalence=2.3%).[3] The disease often strikes at a time when people are about to complete their education or start a career. The estimated prevalence of schizophrenia diagnosis from the claims data in people under 55 years of age was found to be higher in males than females.[13] The reverse was seen for patients older than 55 years of age. In males, the prevalence peaked in the age range 46 to 55 years, and in females it peaked between 56 and 65 years. Schizophrenia is very rare in children and manifestation of the disease in children under 13 years of age is less than 1 in 10,000.[14] However, cases have been seen in children as young as 3 to 5 years old. Children of parents with schizophrenia have a higher risk of the disease.[15] In cases where one parent has schizophrenia, the risk for the child increases to 13% (compared to 0.8%-1% for the general population) and the risk increases to 35%-40% when both parents are patients with schizophrenia. Complications during pregnancy, childbirth, and early childhood also increase the risk of schizophrenia.[16]

Although the ECA study did not find a significant difference in the schizophrenia prevalence rates by gender, women (lifetime prevalence=1.7%) tended to have higher prevalence rates compared to men (lifetime prevalence=1.2%).[3] This was mainly due to lower socioeconomic status and higher divorce rates in women as compared to men. In women, the initial symptoms are seen later and last for a shorter period of time than in men. Unmarried and divorced people have a higher lifetime prevalence of schizophrenia as compared to those who are married or widowed.

Another important finding of the ECA study was that out of the 1.7 million people affected by schizophrenia in the US, 1.1 million received some form of mental health service.[17] Schizophrenia was the mental disorder that had the highest proportion of patients being treated within a one-year period of being affected by the illness.

Barnes reported in a study published in 2004 that among individuals admitted to state psychiatric hospitals in Indiana between 1988 and 1995, African Americans were more likely to have a diagnosis of schizophrenia compared to whites.[18] Bresnahan et al. reported in an article published in 2007 that in a US birth cohort consisting of children of women enrolled in the Alameda County Kaiser Permanente Medical Care Plan clinics who were followed between 1981 and 1997, African Americans were three times more likely to have a schizophrenia diagnosis compared to whites.[19] Similar to Barnes' and Bresnahan's findings, the ECA study also found that African Americans (lifetime prevalence=2.1%) have a significantly higher lifetime prevalence of schizophrenia than whites (lifetime prevalence=1.4%) and Hispanics (lifetime prevalence=0.8%).[3]

The social class that a person belongs to is also related to the risk of schizophrenia. Bromet and Finneg found that people belonging to the lowest social class are three times more likely to have a schizophrenia diagnosis than those belonging to the highest social class.[16] The ECA study reported that a lower proportion of patients with schizophrenia are able to complete college and maintain a permanent job as compared to the general population.[3]

Although the literature review did not reveal any recent studies providing the geographic distribution of patients with schizophrenia across the US, Torrey and Bowler reported that over the period from 1880 to 1963 the number of cases of schizophrenia and insanity were highest in

the Northwestern and Pacific coast states, followed by the Midwestern and mountain states.[20] The Southeastern and South Central states had the lowest number of schizophrenia and insanity cases. In general, urban areas have a higher prevalence of schizophrenia than rural areas.[21]

Patients with schizophrenia are more likely to suffer from diseases such as diabetes,[22] chronic obstructive pulmonary disease, and cardiovascular diseases as compared to those who do not have schizophrenia.[23] Substance abuse and nicotine dependence are also more common in patients with schizophrenia.

Fischer et al. reported the prevalence of schizophrenia among mentally ill detainees in two correctional facilities in Massachusetts to be 2.5%.[24] Teplin found the schizophrenia prevalence rate among male detainees in the Cook County Department of Corrections in Chicago to be 3.7%.[25] According to the ECA study, the lifetime prevalence of schizophrenia among the prison population was about 6.7%.[3]

Studies evaluating costs associated with schizophrenia

Several studies have been carried out to estimate the cost of schizophrenia. Over the past few decades, the costs associated with schizophrenia have shown a steady rise. Gunderson et al.'s[26] estimate for the total cost of schizophrenia in 1971 was between $11.6 billion and $19.5 billion. In 1985, Rice and Miller[27] estimated the financial burden at $22.7 billion. Rice et al.'s[9] estimate updated to 1990 values was $32.5 billion and that of Wyatt et al.[28] for 1991 was $65.2 billion. The most recent estimate by Wu et al.[10] in 2002 was $62.7 billion. The high costs of the disease are due to several factors including early age of onset of the disease, concurrent medical conditions, frequent hospitalizations, need for prolonged outpatient treatment, functional impairment, need for informal support and supervision, self neglect, and frequent rejection of treatment by the patient.[29] Costs are divided into two major categories, 1) direct costs (including direct medical and direct non-medical costs) and 2) indirect costs. The findings from the literature on cost attributable to schizophrenia have been summarized in Table 1 and Table 2 at the end of this section.

Direct costs

Direct costs include mental health treatment costs, medical services costs, and criminal justice system costs.[30] Expenditures for hospitalizations, nursing facilities, emergency room visits for psychiatric purposes, ambulance services, medications, outpatient treatment, day treatments, and laboratory tests are all included in the mental health treatment costs. Medical services must be included while calculating the cost of schizophrenia as patients with schizophrenia often suffer from several concurrent conditions. Hospitalizations, outpatient visits, emergency room visits, nursing home, and laboratory tests for the co-morbid conditions are

included in the medical treatment costs. Resources spent on the criminal justice system and social services are sometimes related to the illness. Criminal justice system expenses generally include costs due to contact with police, arrests, and jail and probation services. Cost of assisted living facilities and rehabilitation centers are also included in the direct costs. Direct costs are further categorized into direct medical costs and direct non-medical costs.

Direct medical costs

One of the earliest studies for cost of illness for schizophrenia was conducted by Gunderson et al. in 1971.[26] The direct medical costs included inpatient costs, outpatient costs, and the cost of medications. They identified the number of patients suffering from schizophrenia in state and county hospitals, Veterans Affairs (VA) hospitals, private and general hospitals, and community mental health centers. The cost per day for a bed was assumed to be $30 for state and county hospitals and $60 for the other facilities. The cost for inpatients with schizophrenia in 1971 amounted to $3.8 billion. The cost of outpatient care amounted to $57 million and included the cost of antipsychotic drugs and maintenance medication for discharged patients. The cost of half-way houses for patients with schizophrenia ranged from $11 million to $16 million. Therefore, the total estimated direct costs for schizophrenia in 1971 ranged from $2 billion to $4 billion.

In 1985, Rice and Miller used a prevalence-based method to estimate the cost of schizophrenia.[27] The methodology was similar to that used in 'The Economic Costs of Alcohol, Drug Abuse and Mental Illnesses: 1985,' a study conducted for the Alcohol, Drug Abuse and Mental Health Administration (ADAMHA). International Classification of Diseases, 9th Revision (ICD-9) codes for schizophrenia and paranoid states were used to identify patients to be considered in order to determine direct costs. Data on the number of short-stay hospital days was

obtained from the National Hospital Discharge Survey, the number of nursing home residents with primary schizophrenia diagnosis was obtained from the National Nursing Home Survey, and the number of visits to outpatient physicians was obtained from the National Ambulatory Care Survey. Total costs were obtained by multiplying the numbers by the cost per patient. Costs of other services such as social workers and psychologists were estimated from the proportion of the total ambulatory cost for all mental illnesses represented by schizophrenia ambulatory costs. Data from the National Institute of Mental Health was used to calculate the costs of care in mental specialty institutions. Outpatient antipsychotic sales of prescription drugs were obtained from the National Prescription Survey.

The total direct cost for schizophrenia in 1985 was $11.1 billion. Of the total, $4.3 billion (38%) was spent for care in specialty institutions, $1.7 billion (15%) on short-stay hospitals, $3.4 billion (34%) on nursing home services, $239 million (2.4%) on outpatient physician visits, $373 million (3.4%) on psychologists and social workers, $236 million (2.1%) on prescription drugs, and $847 million (8%) on support costs. Other related direct costs included costs for police protection of patients with schizophrenia, legal and judicial services costs, correctional institutions, and costs associated with administration of social welfare programs and these amounted to $439 million.

When Rice and Miller's estimates from 1985 were updated to 1990, the total direct cost for schizophrenia was estimated at $17.3 billion.[9] The new estimates for the component costs in 1990 were as follows: mental health organizations ($6.5 billion; 36% of total direct costs), short-stay hospitals ($2.6 billion; 15% of total direct costs), office-based physicians ($104 million; 0.6% of total direct costs), professional services such as psychologists and social workers ($702 million; 4% of total direct costs), nursing home services ($5.3 billion; 31% of total direct costs),

prescription drug costs ($397 million; 2% of total direct costs), and support costs ($1.35 billion; 8% of total direct costs).

In a cost-of-illness study conducted by Wyatt et al. in 1991, the total direct costs associated with schizophrenia were estimated to be about $19 billion.[28] This included all treatment-related costs, cost of law enforcement and the judicial system, suicide cost, and cost of research for schizophrenia. The components of the treatment-related costs were costs for inpatient services, outpatient services, nursing homes, intermediate and domiciliary care, medications, treatment of alcohol and substance abuse, and supported living facilities. Inpatient costs were calculated for private hospitals, state and county hospitals, VA hospitals, nonfederal general hospitals, the Department of Defense (DOD), and Indian Health Services; which amounted to $10.8 billion. Outpatient costs for independent clinics, VA clinics, DOD, and Indian Health Services were estimated at $1.2 billion. Nursing home expenditures were calculated by multiplying the number of patients with schizophrenia in nursing homes by the mean annual expenditure. To determine the cost estimate of the intermediate and domiciliary facilities provided by the VA, the product of the psychiatric services costs and the number of patients with schizophrenia was found. The total expenditures for nursing homes and intermediate and domiciliary care were estimated to be $5.8 billion. The cost of medications without any form of government subsidy was $115 million. All patients taking antipsychotics were assumed to be patients with schizophrenia; this overestimate was counter-balanced by those individuals having schizophrenia whose costs were not included in this estimate. Cost of treatment for drug and alcohol abuse and the cost of supported living facilities amounted to about $300 million and $410 million, respectively.

Some of the direct cost expenditures, such as the basic cost of living, would have occurred whether or not the patient suffered from schizophrenia. This was called the adjustment for transfer cost and amounted to $2.3 billion. The adjustment for transfer cost was subtracted from the total direct cost in order to prevent overestimation.

A decade after Wyatt et al.'s 1991 study , Wu et al. calculated the costs associated with schizophrenia using private insurance claims data and paid claims from the California Medicaid program.[10] Medi-Cal data included information on copays and deductibles of dual eligible patients. The patients with schizophrenia were matched with non-schizophrenia controls. The excess annual cost for the patients with schizophrenia was calculated as the difference in cost between the patient and their non-schizophrenia control. Cost estimates for privately insured patients and Medicaid patients were obtained directly from the private insurance and Medi-Cal databases. For Medicare beneficiaries, the costs were imputed using the dual-eligible patients' costs and statistics published by the Centers for Medicare and Medicaid Services. Adjustments were made to ensure that the California Medicare and Medicaid costs would represent the costs for the whole country. The total direct health care costs amounted to $22.7 billion. This includes expenditures on drugs (22%), outpatient care and professional fees (31%), hospital inpatient stays and services (12%), and long-term care (35%). The excess (compared to the general population) mean direct health care cost per patient was $15,464.

McDonald et al. calculated the direct costs of schizophrenia using the Medical Expenditure Panel Survey (MEPS).[31] A cross-sectional study was conducted to calculate the annual direct medical costs for schizophrenia between 2001 and 2002. Study participants were identified using the AHRQ-based clinical classification codes for 'schizophrenia and other psychoses' (codes 70 and 72 which correspond to the ICD-9 codes 295, 297, 298.1-298.4, 298.8,

298.9, and 299). The direct medical costs, which included inpatient hospitalizations, outpatient visits, physician visits, transportation for medical care visits, and prescription medication, amounted to $2.13 billion. The total direct cost consisted of the following component costs: inpatient hospitalization, $280 million (13.0%); ambulatory and emergency care, $780 million (36.6%); prescription drugs, $820 million (38.7%); and home health care, $250 million (11.8%). Medicaid incurred an expenditure of $1 billion on schizophrenia treatment. Patients with no co-morbidity had a higher schizophrenia-related expenditure ($4,898) as compared to those who had at least one listed co-morbidity ($2,374 to $4,707).

The proportion of total costs accounted for by inpatient costs decreased while the proportion accounted for by outpatient costs increased between 1991 (Wyatt et al.) and 2002 (Wu et al.). This was mainly due to change in the payment practices of Medicaid and careful monitoring of inpatients which helped them return to outpatient status quickly.[32] Introduction of newer drugs in recent years also reduced the number of hospitalized patients.

To better understand how the various components of direct medical costs vary, some studies that only looked at certain components of the direct medical costs will be discussed.

Dixon et al. studied the use and estimated cost of ambulatory care services used by Medicare enrollees with schizophrenia.[33] The study sample consisted of Medicare enrollees diagnosed with schizophrenia or schizoaffective disorder according to ICD-9 codes and having at least one service claim in 1991. The type of ambulatory care service used was identified using the Current Procedural Terminology (4th Edition) codes assigned to the claim. The four ambulatory care services evaluated were: individual therapy, group therapy, family therapy, and psychiatric somatotherapy. The cost of the ambulatory care services varied by the type of service used. The mean cost for each type of ambulatory care service was as follows: individual therapy,

$411 (SD = $719); group therapy, $688 (SD = $2,059); family therapy, $158 (SD = $250); and psychiatric somatotherapy, $160 (SD = $237). Those who received any type of ambulatory care service had a mean annual cost of $470 (SD = $1,045).

Public insurance such as Medicare and Medicaid covers almost two-thirds of the patients with schizophrenia. In order to form a complete picture of the expenditures for schizophrenia through the life of a publicly insured patient, Bartels et al. analyzed the per capita direct cost for dual-eligible (both Medicare and Medicaid) adults.[34] Data were obtained from the paid claims of dual-eligible beneficiaries over 19 years of age from New Hampshire. The study was carried out between January 1 and December 31, 1999. ICD-9 codes were used to identify the psychiatric disorders.

The mean per capita expenditure for patients with schizophrenia increased with increasing age ($25,633 for the age group 19-44 years, $31,529 for 45-54 years, $39,154 for 65-74 years and $43,461 for 75 years and older). Inpatient expenditures were lower for patients in the age group 45-64 years and increased by 80% for those between 65-74 years. Outpatient services and home and community-based services were used most extensively by middle-aged patients and declined with age. At the same time, as age increased, nursing home expenditures also increased. Pharmaceutical expenditures were higher for younger patients and decreased with age, while physician expenses increased slightly with age. The largest bulk of expense for younger patients with schizophrenia was outpatient services and that for older patients was nursing home services. Schizophrenia was therefore associated with high inpatient and nursing home expenses for older patients and high outpatient and medication expenses for the younger patients.

Direct non-medical costs

Direct non-medical costs include all those costs which are not related to the medical treatment of the disease in question. They consist of non-medical goods, services, and resources. Gunderson et al.'s estimate included the cost of public assistance and research costs in their direct non-medical costs estimate. The cost of public assistance for patients with schizophrenia through the Aid to the Permanently and Totally Disabled (APTD), government agencies, Veterans Affairs (VA), Social Security Administration, and state and local government amounted to about $1 billion. A majority of the research at that time was funded by the National Institute of Mental Health (NIMH). In addition, the Scottish Rite Foundation and Universities also supported schizophrenia research. The total research expenditure for schizophrenia in 1971 ranged between $14 million and $15 million.

Rice and Miller's estimate of non-medical direct costs included research, training, program administration, insurance, and criminal justice system costs. The Health Care Financing Administration was the source for federal expenses for medical and health service research, costs of training of physicians and nurses, program administration, and costs for private insurance. Cost to the criminal justice system and social welfare were estimated as the proportion that these costs represented for other mental illnesses reported in the alcohol and drug abuse study. These costs amounted to $439 million.

In the study conducted by Wyatt and his colleagues, non-treatment related costs included law enforcement, suicide and suicide attempt, and research and training costs. Law enforcement and judicial services costs included the costs of police, trial investigations, adjudication, jury, and private defense which amounted to $2 billion. To calculate costs associated with suicide and suicide attempts, it was assumed that the patient would make one serious suicide attempt from

poisoning during the first year of the illness. The medical cost of the suicide attempt and the investigational cost of the suicide amounted to about $190 million. The research and training costs from the National Institute of Mental Health, states, private organizations, and pharmaceutical companies amounted to $71 million.

Wu and his colleagues included the following direct non-health care costs in their estimate: law enforcement costs (obtained from the US Bureau of Justice Statistics and the Criminal Justice Institute Inc.), research and training costs (obtained from the National Institute of Mental Health), and the homeless shelter costs. The total direct non-healthcare costs amounted to $9.3 billion (law enforcement=$2.6 billion, research and training=$300 million and homeless shelters=$6.4 billion). The direct cost-offset was $1.7 billion; therefore the total direct non-medical costs amounted to $7.6 billion.

Indirect costs

Indirect costs mainly include lost productivity due to morbidity and mortality. They also include the opportunity cost of the time spent by friends and family members in caring for the schizophrenia patient (caregivers' costs).

Gunderson et al. estimated that in 1971, the lost productivity due to unemployed patients with schizophrenia ranged from $7.5 billion to $10 billion and the lost productivity due to hospitalization of people with schizophrenia ranged from $1 billion to $1.4 billion.[26] The lost productivity was calculated by finding the product of the work disability, the number of patients who have the disability, and the average expected annual earnings. About 2 million people were unemployed due to schizophrenia. Assuming the average yearly earnings at about $5,000, unemployed people with schizophrenia had a lost productivity of about $10 billion per year.

About 250,000 people suffering from schizophrenia were hospitalized; the total lost productivity due to hospitalization would amount to $1.25 billion.

More than a decade later, Miller and Rice estimated the cost of illness of schizophrenia.[27] The investigators divided the indirect costs into two categories: morbidity costs and mortality costs. Morbidity costs for non-institutionalized patients were calculated using the population size, prevalence rate of the disease, rate of impairment in patients with schizophrenia (or percent decrease in income), the original income of patients without the disorder, and the age and sex of the patients. For institutionalized patients, the number of patients with schizophrenia residing in mental hospitals or nursing homes (adjusted by labor force participation rates) was multiplied by the estimated wage (adjusted for fringe benefits) for a particular age group and gender. The morbidity costs due to schizophrenia amounted to $8.1 billion. The lost productivity for non-institutionalized patients was $6.6 billion and that for institutionalized patients was $1.5 billion in 1985.

Mortality costs were calculated as the product of the number of deaths due to schizophrenia and the individual's projected earnings over the years had they been alive and productive. Schizophrenia was assumed to be the cause of 10% of all the suicides. The earnings were adjusted for age, sex, changing income of individuals over the years due to experience, and changes in the participation rates in the labor force. The amounts were discounted to bring them to present day values. The mortality costs amounted to $1 billion at a 6% discount rate.

Other related indirect costs included the productivity loss for a patient incarcerated due to a schizophrenia-related crime and the cost of care giving time spent by family members and friends. This amounted to $2.1 billion where $2 billion was attributable to the opportunity cost of the family members' care giving time.

When the 1985 estimates were updated to 1990 values, the morbidity costs amounted to $10.7 billion which was 32.9% of the total cost of the illness.[9] The expected lifetime earnings of a schizophrenia patient who died prematurely discounted to present day value (i.e., the mortality costs) were $1.3 billion which was about 4% of the total cost of schizophrenia.

The lost productivity of patients with schizophrenia who were not working due to the illness and those who were partially disabled but were working was calculated by Wyatt et al. in 1991.[28] The lost productivity of institutionalized patients and lost productivity due to suicide were included in the estimate. The lost productivity due to suicide was calculated using the steady state method which assumes that the same number of people die each year. Thus, the lost productivity due to suicide depended on the expected productive lifespan, retirement age, and the number of people who died in that year. The lost productivity of the family caring for the schizophrenia patient was calculated based on a survey of the National Alliance of the Mentally Ill (NAMI) members. An estimate of caregiving time was made for NAMI non-members as well. The total indirect expenditure due to schizophrenia in 1991 amounted to $46.5 billion.

Although Rice and Miller and Wyatt et al. estimated the cost of schizophrenia for about the same time period (1990-1991), there is a vast difference in their estimates of the indirect cost ($12-$15 billion vs. $46.5 billion). This is due to different methods of calculating the indirect cost and use of different sources of data. Wyatt et al. assumed greater number of premature deaths compared to Rice and Miller. While calculating lost productivity due to premature death, Wyatt et al. did not discount the costs to 1991 values while Rice and Miller did the discounting. Productivity for compensated workers has been calculated differently in the two studies.

The latest cost of illness study conducted by Wu et al. estimated the indirect cost due to schizophrenia at $32.4 billion.[10] This figure includes the productivity loss due to increased

unemployment, reduced productivity at work place, premature mortality due to suicide, and caregiving time of the family member of a schizophrenia patient. Estimates for unemployment rates were obtained from the literature, those for wages and suicide rates were obtained from published statistics, and those for caregiving time spent by family members were obtained from values reported by the families and friends of patients with schizophrenia. Lost productivity due to increased unemployment, reduced work place productivity, premature mortality, and caregiving time amounted to $21.6 billion, $1.7 billion, $1.1 billion and $7.9 billion, respectively.

Caregivers' costs

Over the past 50 years, care for schizophrenia has seen a shift from the formal healthcare systems to informal care providers such as families and nonprofit organizations. Costs studies have qualified caregivers' costs using different methods. Rice and Miller's estimate for caregivers' costs was $2 billion. Wyatt and his coworkers estimated the caregivers' costs based on a survey of the National Alliance of the Mentally Ill (NAMI) members. Informal caregivers' costs for NAMI non-members were also calculated. The total caregivers' cost estimate for 1991 was $7 billion. Wu et al. estimated the opportunity cost of the time spent by family members and friends caring for patients with schizophrenia as $7.9 billion in 2002.

Cost of relapse

Although not directly relevant to the study, another category of costs associated with schizophrenia is the cost of treatment following a relapse. Weiden et al. estimated the annual cost due to re-hospitalization of multi-episode patients with schizophrenia and found the proportion of the cost burden that is attributable to loss of medication efficacy and medication non-

compliance.[8] The cost of the initial hospitalization was $2.3 billion (1993 dollars). The cost of re-hospitalization due to loss of medication efficacy was $1.2 billion and that due to non-compliance was $705 million. These costs were incurred within 2 years of first discharge and covered only the direct hospitalization costs.

Ascher-Svanum et al. conducted an observational longitudinal study in the US between 1997 and 2003 to estimate the cost and cost components of relapse in schizophrenia, determine the predictors of relapse, and the role of a prior or recent relapse on the following costs.[35] Relapse was defined as any of the following: psychiatric hospitalization, emergency services use, use of a crisis bed, and suicide attempt. Direct costs for one year were measured and they included costs for medications, psychiatric hospitalizations, day treatment, emergency services, psychosocial group treatment, medication management, individual therapy, and case management.

Prior relapse was an important indicator of subsequent relapse. Patients with a prior relapse had three times the total direct mental health care costs during the one-year study period as compared to those who did not have a prior relapse ($33,187 (SD=$47,616) vs. $11,771 (SD=$10,611)). In addition to higher hospitalization and emergency services costs, patients who relapsed also experienced higher outpatient and medication costs. The major contributors of costs were psychiatric hospitalizations and antipsychotic medications.

A recent study by Nicholl et al. explored the difference between the total health care costs for recently diagnosed and chronic patients with schizophrenia.[36] The PharMetrics Integrated Database for the period between 1998 and 2007 was used. Patients were identified by the ICD-9 code for schizophrenia. Recently diagnosed patients were those who had their first schizophrenia event (index event) within a year of being enrolled in the database. Chronic patients were those

who had the schizophrenia event (index event) at least three years after their first schizophrenia event recorded in the database. The overall health care expenditure was significantly higher for recently diagnosed patients as compared to chronic patients ($20,654 vs. $15,489). Outpatient costs were higher for chronic patients while inpatient costs made up the bulk of the expenditure for recently diagnosed patients.

Table 1 presents a summary of cost-of-illness studies related to schizophrenia and Table 2 presents a distribution of costs in the studies.

Table 1: Cost-of-illness studies for schizophrenia

Authors	Year	Target population	Estimate
Gunderson et al.[26]	1971	Representative US population	$11.6 billion to $19.5 billion Direct costs: $3 billion to $5 billion Indirect costs: $8.5 billion to $11.4 billion
Rice and Miller[27]	1985	Representative US population	$22.7 billion Direct costs: $11.5 billion Indirect costs: $11.2 billion
Rice[9]	1990	Representative US population	$ 32.5 billion Direct costs: $17.3 billion Indirect costs: $15.2 billion
Wyatt et al.[28]	1991	Representative US population	$65.2 billion Direct costs: $19 billion Indirect costs: $46.5 billion
Wu et al.[10]	2002	Medicaid, Medicare and privately insured US patients	$62.7 billion Direct costs: $30.3 billion Indirect costs: $32.4 billion
McDonald et al.[31]	2001-2002	Community-dwelling patients with schizophrenia using MEPS	Direct medical costs: $2.13 billion

Table 2: Distribution of costs in cost-of-illness studies for schizophrenia

Authors	Proportion of direct costs (%)									Proportion of indirect costs (%)				Estimates
	Direct medical costs						Direct non-medical costs							
	IP	OP	Inst	NH	RX	Other	R&D	Judicial	Other	Morbidity	Mortality	Caregivers	Other	
Gunderson et al.[26] (1971)	78	0.6	-	0.3	0.6	-	0.3	-	20[a]	88[b] 12[c]	-	-	-	$11.6 billion to $19.5 billion Direct costs: $3 billion to $5 billion (30%) Indirect costs: $8.5 billion to $11.4 billion (70%)
Rice and Miller[27] (1985)	15	2.1	37	29	2.0	11[d]	-	4	-	72	9	17	1[e]	$22.7 billion Direct costs: $11.5 billion (51%) Indirect costs: $11.2 billion (49%)

Table 2: continued

Authors	Proportion of direct costs (%)									Proportion of indirect costs (%)				Estimates
	Direct medical costs						Direct non-medical costs							
	IP	OP	Inst	NH	RX	Other	R&D	Judicial	Other	Morbidity	Mortality	Caregivers	Other	
Rice[9] (1990)	15	0.6	36	31	2	12[d]	-	-	-	89	11	-	-	$ 32.5 billion Direct costs: $17.3 billion (53%) Indirect costs: $15.2 billion (47%)
Wyatt et al.[28] (1991)	52	6	-	28	0.6	3[f]	0.3	10	1[g]	70	15	15	-	$65.2 billion Direct costs: $19 billion (29%) Indirect costs: $46.5 billion (71%)

Table 2: continued

Authors	Proportion of direct costs (%)									Proportion of indirect costs (%)				Estimates
	Direct medical costs						Direct non-medical costs							
	IP	OP	Inst	NH	RX	Other	R&D	Judicial	Other	Morbidity	Mortality	Caregivers	Other	
Wu et al.[10] (2002)	9	22	-	25	16	-	1	8	20[h]	74	3	24	-	$62.7 billion Direct costs: $30.3 billion (48%) Indirect costs: $32.4 billion (52%)
McDonald et al.[31] (2001-02)	13	37	-	-	39	12[i]	-	-	-	-	-	-	-	Direct costs: $2.13 billion

IP-inpatient hospitalization costs, OP-outpatient visits costs, Inst-institutionalization costs, NH-nursing home costs, RX-prescription drug costs, R&D- research and development costs

[a] Public assistance cost

[b] Lost productivity due to increased unemployment

[c] Lost productivity due to hospitalization

[d] Costs due to psychologists and social workers and support costs

[e] Incarceration due to schizophrenia related crime

[f] Cost of drug and alcohol abuse and cost of supported living facilities

[g] Cost of suicide attempt and investigation

[h] Cost of homeless shelters

[i] Home healthcare costs

Factors associated with high costs for schizophrenia

The 2002 MEPS reports indicated that 5% of the American population was responsible for 49% of the medical expenditure for all conditions, while half the population was responsible for only 3% of the total expenditure.[37] McDonald et al.'s estimate for the direct cost of schizophrenia showed a similar pattern, where a small percentage of the community-dwelling patients with schizophrenia were responsible for a disproportionately large cost.[31] It has been hypothesized that several factors such as early onset of disease, presence of co-morbid conditions, hospitalizations, need for outpatient and emergency department visits, need for maintenance medications for prolonged periods of times, and constant requirement of informal support and supervision are responsible for the high cost of schizophrenia.[29] Identification of the characteristics of patients responsible for the high costs may be useful for health care providers and managed health care organizations to design interventions for schizophrenia treatment that target this high-risk population.

Crowne et al. estimated the difference in cost of privately insured hospitalized and non-hospitalized patients with schizophrenia.[38] They found that the total cost of hospitalized patients was higher than that for non-hospitalized patients. The cost of hospitalization was related to age (higher for older people), subtype of schizoaffective disorder, and whether or not the benefit plan required an inpatient pre-certification for hospitalization (with higher costs associated with pre-certification). For non-hospitalized patients, costs were higher for those who suffered from depression or substance abuse and for those who took clozapine. Zhu et al. also found that psychiatric hospitalizations, suicide attempts, violent behavior, prior arrests, and substance use disorders increased the cost of schizophrenia.[39]

Dixon et al. evaluated the use and cost of ambulatory care services (individual therapy, group therapy, family therapy, and individual somatotherapy) and found that age, race, sex, co-morbidities, and insurance status affect the total outpatient expenditure for the services examined.[33] Women, younger patients, those with drug abuse disorders, Medicaid enrollees, and Caucasians tended to have higher expenditures for outpatient services.

Marcus et al. found that gaps in the use of antipsychotic medication were associated with the cost of schizophrenia.[40] The investigators used California Medicaid data and made adjustments to provide a national estimate of $106 million higher total inpatient costs due to gaps in antipsychotic medication adherence. Svarstad et al. used claims data for severely mentally ill patients in Wisconsin and reached a similar conclusion that irregular medication use increases hospitalizations, which in turn translates to high costs for schizophrenia.[41]

A retrospective study that evaluated the total cost of schizophrenia using olanzapine vs. risperidone as the drug of choice found that several factors were associated with the total cost of schizophrenia.[42] Type of antipsychotic medication used previously, number of antipsychotic medications used, prior hospitalizations, presence of co-morbidities, age, sex, region of residence, previous costs, and the number of treatment days were all significantly associated with the total schizophrenia-related expenditure. Clozapine users and users of depot antipsychotics had higher total costs as compared to risperidone users. The number of antipsychotic medications used, prior hospitalizations, and number of treatment days were associated with higher costs, while the presence of nonorganic mental illnesses was associated with lower total costs. Age was found to be negatively associated with costs, and females had lower expenditures compared to males.

Among dual eligible (Medicare and Medicaid) beneficiaries, age was found to be positively associated with direct costs.[34] The outpatient and prescription drug expenditures were higher for younger patients and the inpatient and nursing home expenditures were higher for the older patients. Patients with a primary diagnosis of schizophrenia who were discharged against medical advice had a significantly higher average cost per hospital day ($1,886) as compared to patients discharged with medical approval ($1,565).[43]

Relapse is quite common in schizophrenia. Prior relapse,[35] non-compliance to medication, loss of medication efficacy,[8] substance abuse, poor alliance of patient with family and health care provider, male gender, and younger age have all been identified as predictors of relapse.[44] If there is a re-hospitalization due to the relapse, the cost of schizophrenia increases tremendously. Antipsychotic medication costs also contributes to the high cost of a relapse.[35]

Use of MEPS in cost-of-illness studies

The 1970s marked the beginning of national surveys that collected medical expenditure data.[45] The National Medical Care Expenditure Survey (NMCES), conducted in 1977, was the first survey of this kind. NMCES collected information from about 14,000 households over a 14-month time period. The survey had three components: the household component, the physician component, and the health insurance provider component. Following NMCES, the National Medical Expenditure Survey (NMES) was conducted in 1987; it interviewed 16,000 households including 2,000 American Indian and Alaskan Native households. Its structure was similar to that of the NMCES. In 1996, the first Medical Expenditure Panel Survey (MEPS) data was collected and the survey has been conducted annually ever since. The household component of MEPS is a subsample of those who participated in the National Health Interview Survey (NHIS) conducted by the National Center for Health Statistics. The household component is supplemented by the medical and health insurance provider components. Several studies have used MEPS data to calculate direct and/or indirect costs of a disease. Different methods have been used for the calculations.

Malone et al. used NMES to determine the total direct and indirect cost of allergic rhinitis.[46] Patients were selected using ICD-9 codes. Direct costs included medication and medical visits. The prescribed medication data of NMES were used to obtain information about the respondent-reported medications that were prescribed by a medical practitioner. Costs of over-the-counter medications purchased by the respondent were also included in the estimate. Those medications classified by investigators as ‘most likely’ and ‘possibly’ used for allergic rhinitis were included. The medical visits included office and clinic visits to medical providers,

emergency department (ED) visits, and outpatient hospital visits. ED and hospital visits include both the facility and provider expenditures.

Indirect cost measurement was conducted using NMES estimates of number of work or school days missed and number of restricted activity days due to allergic rhinitis. To obtain the daily wage rate, total income was divided by the number of days worked during the year. The product of the daily wage and the number of days of work missed gave the lost productivity. To measure lost productivity due to missed school days in children under 12 years, the lost productivity of the parent taking care of the child was taken into consideration. When two people were linked to taking care of the child, the lower income was used. If the person taking care of the child was not working, no economic value was attached. For children between 13 and 17 years, lost productivity was not included as they do not work and no one needs to miss work to take care of them. Restricted activity days were valued at a quarter of the person's daily wage. A restricted activity day was counted as 5/7 as each day of the week has equal probability of being a work day or a leisure day. Restricted activity days were not considered for children below 18 years of age. A similar method was also used to estimate the total cost due to asthma.[47]

Another study that used NMES data to estimate the total financial burden of a disease was conducted by Strassels et al.[48] They used NMES to estimate the direct and indirect cost of COPD in the United States. ICD-9 codes were used to identify patients. Direct costs included inpatient visits, emergency department visits, office visits, outpatient clinic visits, and prescription drug costs. Indirect costs included lost work days, restricted activity days, and bed days.

Cost-of-illness (COI) estimates have also been calculated using MEPS. Wang et al. estimated the total cost of asthma in school-age children using MEPS.[49] Children having asthma were identified using ICD-9 codes. Direct medical costs included prescription drugs, hospitalizations, emergency department visits, outpatient visits to the hospital, office visits to medical practitioners, medical equipment, and home health care. The excess medical cost for children with asthma (as compared to those without asthma) was calculated using linear regression controlling for age, sex, race, mother's education level, poverty status, and health insurance coverage. Indirect costs included the lost productivity of the parent because of missed work when the child misses school (product of missed work days and wage per day) and the lost productivity due to premature mortality (calculated as the product of the mortality due to asthma and future earnings discounted to present day value). The average daily wage rate, mortality due to asthma, and average present day value of future earnings were obtained from recent published literature.

Kamble et al. calculated the incremental direct cost of treating asthma using MEPS.[50] The costs included were prescription drugs, emergency department visits, inpatient visits, outpatient visits, office-based visits, and other costs. The independent variable was presence or absence of asthma. Covariates included were age, sex, race, ethnicity, education, insurance status, geographic location, marital status, and co-morbidities. Multivariate regression models were used to calculate the excess direct cost of asthma.

Miller et al. used a similar multivariate regression model to estimate the direct costs of chronic obtrusive pulmonary disease (COPD).[51] After identifying COPD patients using ICD-9 codes, socio-demographic factors (including age, sex, race, marital status, education level, employment status, income, and insurance coverage) and clinical factors (including health status,

smoking status, presence of co-morbidity, and MEPS eligibility) were assessed. Direct costs included inpatient, outpatient, and pharmacy costs. Inpatient costs included hospital room, lab and diagnostic tests, x-rays, and other such costs. Outpatient costs included clinic, office, emergency department, and home visits. Pharmacy costs included prescription medication expenditure. Two approaches were used: the attributable cost approach measured the expenditure due to COPD and the excess cost approach measured the excess cost due to COPD as the difference in expenditures between those with and without COPD.

Chan et al. estimated the difference in expenditures among children with ADHD, asthma, and the general population using MEPS.[52] ICD-9 codes were used to identify children with ADHD and asthma. The presence of prescriptions for two psychostimulants was also used as an indicator for the presence of ADHD. Direct costs such as hospitalizations, ED visits, outpatient visits, prescription medication, and home health care were considered. The effects of child and parent characteristics (age, sex, race, parent education, marital status of parents, and perceived maternal health) and access to care variables (poverty level, insurance coverage, having a usual care source, region of US, and living in an urban metropolitan area) were studied. Analysis of variance (ANOVA) was used to compare the costs between the three groups. Linear regression was used to find the relation between cost and group status controlling for demographic and access to care variables. The excess cost of asthma and ADHD children compared to the general population was also found using linear regression analysis.

A different methodology was used by Lauri et al. to find the difference in expenditures between people who suffered from depression and those who suffered from some other chronic disease.[53] To find the difference in cost, a matched case control design was used. In order to ensure that confounding variables were controlled, propensity score matching was used. Since it

is difficult to match the cases and controls on all their characteristics, the baseline characteristics were summarized into a single propensity score. The propensity score was obtained using a probit regression model. Each case was then matched with the control that had the closest propensity score using nearest neighbor matching. The effect of depression was then measured as the difference in cost between the case/control pairs.

Akazawa et al. estimated the indirect cost of influenza using MEPS.[54] They determined the number of missed work days due to influenza-like illness controlling for health status, demographic characteristics, and employment characteristics. A binomial distribution was used. The incremental work days missed due to the disease were calculated. The difference in the number of workdays missed when all individuals suffered from influenza-like illness and when no individual suffered from the illness was determined. The number of hours worked per week and the hourly wages were used to calculate the weekly income. This was divided by 5 (assuming that individuals work 5 days a week) to get the daily wage. The daily wage multiplied by the number of missed days gave the lost productivity.

MEPS was used to find the incremental cost of arthritis and other rheumatoid conditions (AORD) by finding the difference in expenditure between those suffering from AORD and those not suffering from the disease.[55] ICD-9 codes were used to identify participants for the study. Costs for ambulatory care, inpatient care, prescription drugs, and residual care were included.

For ambulatory care, inpatient care, prescription drugs, and residual care, Yelin et al. used a two-stage method. First, logistic regression was used to estimate if an individual had any expenditure at all. This was followed by an ordinary least squares regression to estimate the level of expenditure (log transformation of cost) for those who had positive expenditure. To predict

the incremental cost, a four-stage model was used where a logistic regression was conducted to predict the probability of medical expenditure. A different logistic regression predicted the probability of hospital expenditure in the presence of medical expenditure. The third stage used an ordinary least squares regression to predict the total cost (logarithmic function) of those who did not have prior hospitalizations. The fourth stage used an ordinary least squares regression to predict the total expenditures (logarithmic function) of those who had a prior hospitalization. Age, sex, race, ethnicity, marital status, education level, health insurance status, and presence of co-morbidities were also included in the models.

Indirect costs were calculated as lost earnings and this included the lost wages for those who were not working at all and the lost wages for those who were working but with reduced productivity due to the disease. The method used to estimate indirect costs was similar to that used to for direct costs. The variables included in the model were the same as those included in the model for direct costs.

Trasande et al. used a similar two-stage regression model to determine the excess prescription drug, emergency department visit, hospitalization, and outpatient visit expenditure of overweight and obese children (based on BMI) as compared to those who had a normal BMI.[56] In the first stage, a logistic regression was used to identify presence or absence of expenditures based on BMI while controlling for insurance status, family income, region of residence, gender, and race. The second stage calculated the incremental expenditure (for those cases which had non-zero values for expenditure) using a gamma distribution.

As mentioned earlier, McDonald et al. estimated the direct costs for community-dwelling patients with schizophrenia using MEPS. The costs were estimated for the years 2001-2002.

Clinical classification codes were used to identify patients and mean costs were calculated using the 'surveymeans' procedure in SAS.[31]

Several studies have used MEPS to estimate direct and indirect costs attributable to a particular disease. MEPS is a good data source to estimate total costs associated with diseases as it includes expenditures from several sources including private and public insurance providers and out-of-pocket expenditure. It also includes information on limited activity work days and missed work days which may be used for indirect cost estimation. MEPS also allows the use of both the incremental cost approach and the attributable cost approach for estimation of the disease associated expenditures.

Study rationale

Schizophrenia is a chronic, debilitating disease that affects approximately 1% of the US population.[2,3] The costs associated with schizophrenia have shown a steady rise in the past couple of decades. The most recent cost-of-illness study was conducted by Wu et al. on 2002 and estimated the annual US costs at $62.7 billion.[10] A large proportion of the expenditure is attributable to the indirect costs (i.e., lost productivity due to morbidity and mortality). Several investigators have estimated the total national costs associated with schizophrenia. Most studies have used estimates from epidemiologic surveys and claims databases while calculating the total cost. Several factors such as medication non-compliance, hospitalization, drug abuse, co-morbid conditions, relapse, and others have been hypothesized to be the major contributors towards the high cost of the disease.[29]

There was only one study that used the Medical Expenditure Panel Survey (MEPS) database to estimate the total direct cost of schizophrenia for community-dwelling patients with schizophrenia.[31] This study, by McDonald et al., estimated the total direct costs at $2.13 billion for the years 2001-2002. An advantage of using MEPS is that the figures reported include the total payments, including the patient out-of-pocket expenditure and the third-party payer expenses. MEPS includes information on hospitalizations, outpatient visits, emergency department visits, home health visits, and prescription medications. In addition, data on disability days and income is also included which enables determination of indirect costs.

Several studies have shown that age, gender, insurance status, and presence of co-morbid conditions affect the costs associated with schizophrenia.[33,34,38,42] The prevalence of schizophrenia varies by age, gender, race, insurance status, socioeconomic status and marital

status. [3,13] Thus, we would expect the costs to vary by these factors. In addition, we will also look at how perceived health status and mental health status affects the associated costs.

Objectives and hypotheses

The objectives of this study are:

1. To describe the demographic characteristics of the schizophrenia population with respect to age, gender, race, marital status, insurance status, socioeconomic status, and region of residence and the clinical characteristics with respect to perceived health status, mental health status, and presence of co-morbidities using means and standard errors (age) and frequencies and percentages (all other variables).
2. To estimate the *direct medical costs* associated with schizophrenia from the societal perspective.
3. To estimate the *indirect costs* associated with schizophrenia from the societal perspective.

   Total costs were calculated as the sum of the direct and indirect costs.
4. To identify the factors significantly associated with 'high' schizophrenia-related *direct medical costs* from among the following demographic and clinical factors: age, gender, race, marital status, insurance status, region of residence, socioeconomic status, perceived health status, mental health status, and presence of co-morbidities.

The hypotheses of this study are:

Hypothesis 1: Compared to younger age, older age is significantly associated with high schizophrenia-related *direct medical costs* versus low costs after controlling for all other factors.

Hypothesis 2: Compared to being male, being female is significantly associated with high schizophrenia-related *direct medical costs* versus low costs after controlling for other factors.

Hypothesis 3: Compared to all other races, white race is significantly associated with high schizophrenia-related *direct medical costs* versus low costs after controlling for all other factors.

Hypothesis 4: Compared to not having a spouse, having a spouse is significantly associated with high schizophrenia-related *direct medical costs* versus low costs after controlling for other factors.

Hypothesis 5: Compared to private insurance or no insurance, public insurance is significantly associated with high schizophrenia-related *direct medical costs* versus low costs after controlling for all other factors.

Hypothesis 6: Region of residence is not significantly associated with high schizophrenia-related *direct medical costs* versus low costs after controlling for other factors.

Hypothesis 7: Compared to high socioeconomic status, low socioeconomic status is significantly associated with high schizophrenia-related *direct medical costs* versus low costs after controlling for all other factors.

Hypothesis 8: Compared to 'excellent' perceived health status, 'poor' perceived health status is significantly associated with high schizophrenia-related *direct medical costs* versus low costs after controlling for other factors.

Hypothesis 9: Compared to 'excellent' mental health status, 'poor' mental health status is significantly associated with high schizophrenia-related *direct medical costs* versus low costs after controlling for other factors.

Hypothesis 10: Compared to absence of co-morbidities, presence of co-morbidities is significantly associated with high schizophrenia-related *direct medical costs* versus low costs after controlling for other factors.

CHAPTER 2: Methods

Study design

The study was a retrospective database analysis. Patient-level data was extracted from the Medical Expenditure Panel Survey (MEPS). Demographic information such as age, gender, race, marital status, insurance status, region of residence, and socioeconomic status as well as expenditure data and other required data were utilized as available. There are two methods for calculations of costs: the attributable cost approach and the excess cost approach. In the attributable cost approach, the cost attributable to the disease is estimated. In the excess cost approach, the additional cost for people with the disease (as compared to people without the disease) is calculated. For this study, the attributable cost approach was used.

Study population

Patients from the MEPS dataset were selected using the following International Classification of Disease 9th revision (ICD-9) codes: 295 (schizophrenic disorders) and 298 (other nonorganic psychoses).The broad inclusion criteria ensured that most conditions in which psychotic symptoms are seen were captured. The medical conditions are reported directly by the respondents and are coded into ICD-9 codes by professional coders. Participants of all ages, genders, and ethnicities were included in the study.

Data source

The Medical Expenditure Panel Survey (MEPS) was used for the study. It was first conducted in 1996 and is now being carried out annually for civilian non-institutionalized Americans.[45] It collects information from individuals and families, their medical providers, and their employers. The information collected includes the type, usage frequency, cost, and method

of payment for various medical services, details about the type of insurance the participants have, access to care, satisfaction with care, employment information, and demographic characteristics.

Survey components

MEPS has three components: household component (HC), medical provider component (MPC), and insurance component (IC). For the purpose of this study, only the household component was used.[45] However, in order to provide a better understanding of MEPS, a brief overview of all three components of the survey is provided.

Household Component (HC): Data for the household component is collected from a nationally representative sample of individuals and families, which are a subsample of those who participated in the previous year's National Health Interview Survey. Detailed information is collected which includes demographics, health conditions, current state of health, types of medical services used, medical expenditures and sources of payment, access to care, satisfaction with the medical care received, type of health insurance, income, and employment data.

Medical Provider Component (MPC): The information collected from the household component is supplemented using the MPC in order to reduce bias due to non-response and questionable data quality. The information is collected from physicians, hospitals, pharmacists, and home health agencies from whom the HC respondents obtain medical care. It collects information regarding dates of visits, diagnoses leading to the visits, and the utilization, charge, and source of payment for the medical services.

Insurance Component (IC): Information is collected from employers regarding the type of insurance plans offered to their employees. The details collected include information on

premiums paid, any contributions made by employer or worker, eligibility requirements, and benefits of the plans.

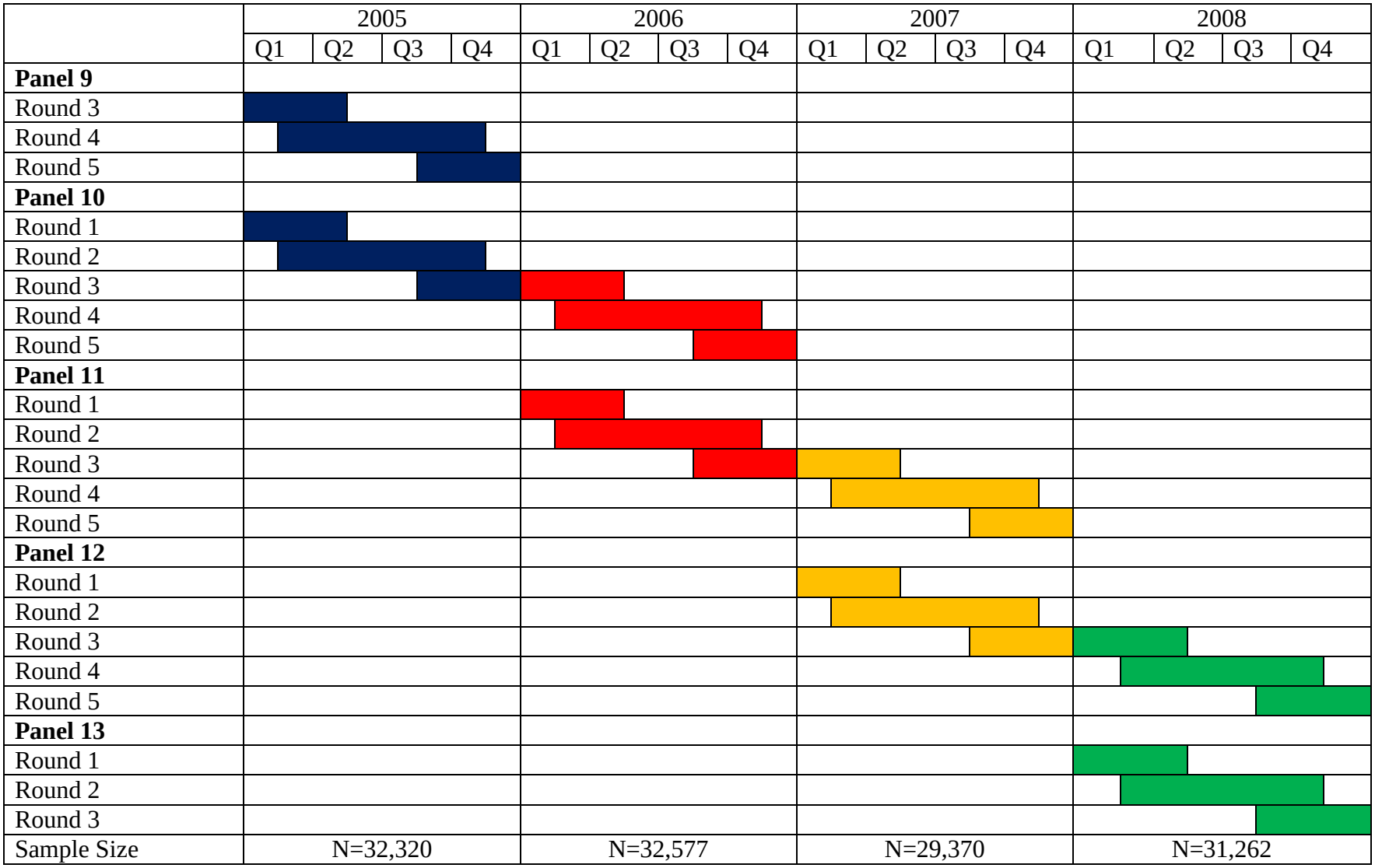
Data collection and survey design for household component

As mentioned earlier, the household component collects data from a nationally representative sample of civilian, non-institutionalized Americans. An overlapping panel design is used for this purpose.[58] Each panel collects data for two calendar years using five rounds of interviews.

Figure 1 shows that out of the five rounds in Panel 10, rounds 1-3 are in 2005 and rounds 3-5 are in 2006. Additionally, 2006 consists of data collected in rounds 3-5 of Panel 10 and rounds 1-3 of Panel 11. This overlapping pattern ensures that continuous and up-to-date information is collected.

Each round has a 'reference period' for which data is collected. For Round 1 of Panel 10, the reference period starts on January 1, 2005 and ends when all the units have reported data from the Round 1 interviews (in the 2nd quarter of 2005, i.e., June 2005).The reference periods for rounds 2-4 vary depending on interview dates of previous and current rounds. The last reference period (for Round 5) ends on December 31, 2006.

Figure 1: MEPS panel design: data reference periods[58]



The HC component of MEPS has different sections covering specific topics. There are a series of CAPI (computer-assisted personal interview) screens which have the instructions, questions, and skip patterns for each section. In addition to the computer-assisted questions, paper-based questionnaires are administered to supplement the information collected. The paper-based questionnaires include the Adult Self-Administered Questionnaire (SAQ), Parent Administered Questionnaire (PAQ), and Diabetes Care Survey (DCS). Interview showcards assist the respondents during the CAPI by providing them with response categories of the questions asked on the computer.

Weighted estimates

The MEPS datasets provide person weights which are year specific. These weights take into account the post-stratification adjustments and non-response. In order to get accurate estimates of the civilian non-institutionalized population using MEPS, the survey weights must be used and appropriate techniques must be used to derive the standard errors associated with the weighted estimates. Thus, in order to account for the complex multistage cluster sampling design, the survey procedure of SAS was used to get accurate estimates of the standard errors.

Dataset

Data collected in MEPS are reported in public use data files (PUFs) for that particular year. These files can be downloaded from the AHRQ website (http://www.meps.ahrq.gov). There are three types of files:

(1) The full-year consolidated data file contains the population characteristics including demographics, income, insurance status, missed work days due to the condition, total expenditure, and utilization summaries for each person;

(2) The medical condition file contains the health condition for each patient. It has unique condition identification (CONDIDX) which can be linked to the corresponding events related to the condition using the event identification number (EVNTIDX). The events are in separate event files. The condition file contains the ICD-9-CM code and the clinical classification code for the condition and the number of events that the condition is linked to (prescription drugs, inpatient visits, outpatient visits, emergency department visits, office-based provider visits, and home healthcare visits); and

(3) There are eight event files with one each for prescription medications, inpatient visits, outpatient visits, emergency department visits, home health visits, dental visits, other medical equipment, and office-based medical provider visits. The unit of analysis (i.e. the unit represented by a single record in that particular event file) for the inpatient file is per stay and that for all other files is per visit.

Since the information required for the study is spread over different data files, the various files must be integrated to form the analytical dataset. Patients with a schizophrenic disorder diagnosis (ICD-9 code 295) or other non-organic psychoses diagnosis (ICD-9 code 298) were flagged in the medical conditions file. The conditions file was linked to the events files using the conditions-event link file which ensured that all those events which are associated with a condition were captured. The linkage was based on the event identification number (EVNTIDX) which was present in both the conditions file and the event files. One condition may be linked to more than one event. The combination of the conditions file and the event files was linked to the full year consolidated data file which contains the demographic information. This linkage was done using the unique patient identifier, DUPERSID, which was present in all the data files. The combination of the conditions, events, and full-year consolidated data files gave the final dataset

for a single year. This linkage was done for the 2005, 2006, 2007, and 2008 files. The four datasets were stacked to obtain the final analytical dataset for the present study.

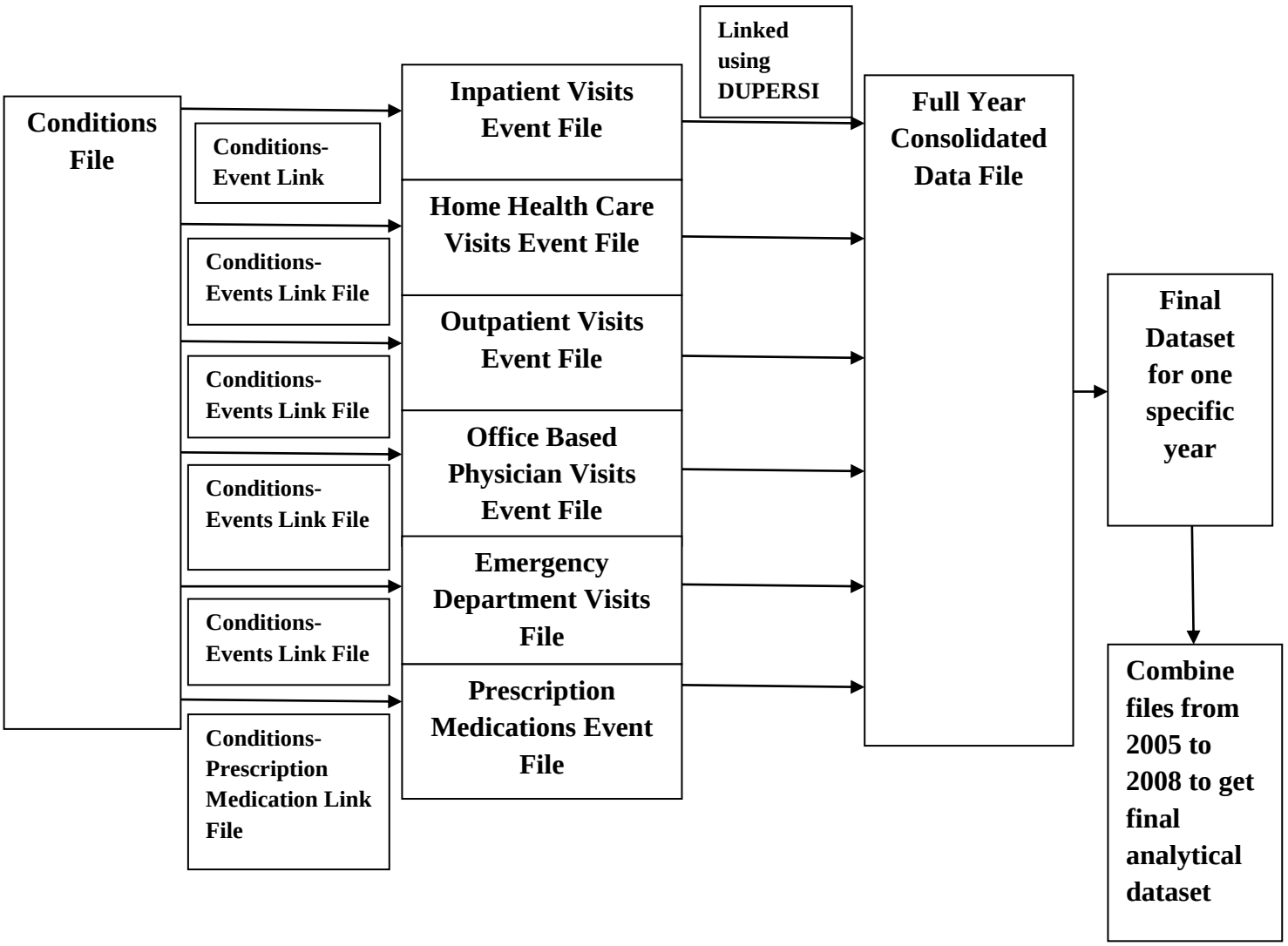
The table below provides the number of the various files from MEPS that were used in the study.

Table 3: MEPS files used in the study

Year	Full-year consolidated data file	Medical conditions file	Event files
2005	HC-097	HC-096	HC-094A, HC-094D, HC-094E, HC-094F, HC-094G, HC-094H
2006	HC-105	HC-104	HC-102A, HC-102D, HC-102E, HC-102F, HC-102G, HC-102H
2007	HC-113	HC-112	HC-110A, HC-110D, HC-110E, HC-110F, HC-110G, HC-110H
2008	HC-121	HC-120	HC-118A, HC-118D, HC-118E, HC118F, HC-118G, HC-118H

The data linkage process to create the analytic dataset is shown in Figure 2. For the study, only six event files were included: inpatient visits, home health care visits, outpatient visits, office-based medical provider visits, emergency department visits, and prescription medications. The dental visits and medical equipment files were not included in the analysis as these events are not relevant in calculating the direct costs associated with schizophrenia.

Figure 2: **File linkage method to obtain final analytic dataset**



Time frame

The annual costs were calculated for the time period from January 1, 2005 to December 31, 2008.

Study variables

This section provides operational definitions for all the dependent and independent variables of interest.

Dependent variables

Direct medical costs

The direct medical costs included costs of hospital inpatient stays, outpatient visits, emergency room visits, office-based medical provider visits, home healthcare visits, and prescription medications. These events were obtained from the MEPS event files. The total expenditure was the sum total of expenditures from 12 sources of payments: self and family, Medicare, Medicaid, private insurance, Veterans Administration, Tricare, other federal sources, state and local government, workers compensation, other private sources, other public sources, and other sources of insurance. The inpatient, emergency department, and outpatient events had facility expenditures, which cover room and board, diagnostic and laboratory work, x-rays, and physician services, and the separately billed doctor's expenditure which included all those services of the physician not included in the facility expenditures.

Indirect costs

The indirect costs include lost productivity costs, reduced employment costs, mortality costs, and costs of caregivers' services. For respondents equal to and over 18 years of age,

number of missed work days due to illness and the number of missed work days due to staying in bed were identified. This information was obtained from the full-year consolidated data file. The daily wage rate was calculated by dividing the total wage income of the person by 260 (assuming that they work or are paid for 5 days a week for 52 weeks a year). In 2008, only hourly wages were collected from the respondents. Thus, for 2008, the daily wage was calculated by multiplying the hourly wages by 8 (assuming the individuals work 8 hours a day). The daily wage was multiplied by the number of missed work days due to illness or staying in bed to calculate the total lost productivity.

Using a method similar to that used by Wu et al.,[10] the loss due to decreased employment of patients with schizophrenia was calculated as the product of the difference between the employment level in the general population (62.2% in 2008, 63% in 2007, 63.1% in 2006, 62.7% in 2005)[59] and the schizophrenia population (21.3%)[10,60,61,62] and the lost earnings, which were estimated using the mean annual wage (calculated from the hourly wage by assuming that an individual works or is paid for 8 hours a day and 260 days a year) reported by US Bureau of Labor Statistics and obtained from the literature (mean hourly wage in 2008 = $20.32; 2007 = $19.56; 2006 = $18.84; 2005 = $18.21 for the general population[63] vs. $7.05 for patients with schizophrenia[64]). The calculation was done as follows:

Lost Earnings =

[(0.627 * # of PWS in 2005 * annual wages for PWOS)

+ (0.631 * # of PWS in 2006 * annual wages for PWOS)

+ (0.630 * # of PWS in 2007 * annual wages for PWOS)

+ (0.622 * # of PWS in 2008 * annual wages for PWOS)]

– [(0.213 * # of PWS in 2005 * annual wage for PWS)

+ (0.213 * # of PWS in 2006 * annual wage for PWS)

+ (0.213 * # of PWS in 2007 * annual wage for PWS)

+ (0.213 * # of PWS in 2008 * annual wage for PWS)]

where PWOS = patients without schizophrenia,

PWS=patients with schizophrenia

Suicide is a major cause of death among patients with schizophrenia. To find the lost productivity due to suicide, the percentage of patients with schizophrenia who commit suicide (5% per year)[65,66] was used to estimate the number of suicides due to schizophrenia among community dwelling patients with schizophrenia. Using the number of deaths and the employment rate among patients with schizophrenia, the annual lost productivity due to premature death was calculated. As mentioned earlier, the daily wages and employment rate among patients with schizophrenia were obtained from literature. The daily wage obtained from literature was for 2003 and it was adjusted to 2005, 2006, 2007, and 2008 values.[67] The average wage for the general population was estimated from the reports of the US Bureau of Labor Statistics.[63]

To calculate the informal caregivers' cost (friends and family members missing work to care for the schizophrenia patient), the family affiliations of the patients with schizophrenia were identified by combining the FAMIDYR and DUID variables to form a new family identification variable. The lost productivity cost for all the family members for each schizophrenia patient was calculated as the product of the number of work days missed in caring for another person and the daily wage. This was done under the assumption that if a schizophrenia patient had a family member who reported a missed work day to care for another person, it was to take care of the

schizophrenia patient. The numbers of missed work days caring for other's health problems were calculated only for persons who had their age reported and were above 16 years of age.

Estimates of caregivers' costs were also obtained from the literature and adjusted to 2005, 2006, 2007, and 2008 values.[67]

Independent variables

Demographic variables

Age was used as a continuous variable and was obtained from the full-year consolidated data file of MEPS.

Gender was used a dichotomous categorical variable (male/female) and was obtained from the full-year consolidated data file of MEPS.

Race was used as a categorical variable with the following categories: black, white, American Indian/Alaskan Native, Asian, Native Hawaiian/Pacific Islander, and multiple races reported. This information was obtained from the full-year consolidated data file of MEPS.

Marital status was used as a categorical variable with the following categories: not ascertained, married, widowed, divorced, separated, never married, and inapplicable for respondents under 16 years of age. This information was obtained from the full-year consolidated data file of MEPS.

Insurance status was used as a categorical variable with the following categories: private insurance, public insurance, and uninsured. This information was obtained from the full-year consolidated data file of MEPS.

Region was used as a categorical variable with the following categories: Northeast, Midwest, South, West, and inapplicable. This information was obtained from the full-year consolidated data file of MEPS.

Socioeconomic status was used as a categorical variable with the following categories: poor/negative, poor, low income, middle income, and high income. This information was obtained from the full-year consolidated data file of MEPS. The socioeconomic status was defined as follows- Poor/negative: Less than 1.00 times poverty line; Poor:1.01 to 1.24 times poverty line; Low income: 1.25 to 1.99 times poverty line; Middle income: 2.00 to 3.99 times poverty line; High income: 4.0 or more times poverty line.

Perceived health status was used as a categorical variable with the following categories: excellent, very good, good, fair, and poor. It was obtained from the full-year consolidated data file of MEPS.

Mental health status was used as a categorical variable with the following categories: excellent, very good, good, fair, and poor. It was obtained from the full-year consolidated data file of MEPS.

Presence of co-morbidities was used as a dichotomous variable (yes/no) and was generated from the event files of MEPS.

Data analysis

This section describes the analytical methods used in the study. The a priori alpha level used was $p < 0.05$ and the statistical tests were two-tailed. All the statistical analyses were conducted using SAS version 9.2 (SAS Institute Inc., Cary, North Carolina).

Determination of demographic characteristics of patients with schizophrenia

Using the 'surveymeans' and 'surveyfreq' procedure of SAS, the demographic distribution of the schizophrenia population with respect to age, sex, race, marital status, insurance status, region of residence, and socioeconomic status was described. The distribution of the population with respect to the perceived health status, mental health status, and presence of co-morbidities was also described using the same procedure. Means and standard errors were calculated for continuous variables and frequencies and percentages were calculated for categorical variables.

Determination of total costs associated with schizophrenia

In order to determine the mean cost per patient for each cost component of the direct cost and the mean overall cost, the 'surveymeans' procedure of SAS was used. The costs for the following categories were identified: inpatient hospitalizations, outpatient visits, emergency department visits, physician office visits, home healthcare visits, and prescription medication costs. The mean weighted cost per patient for each category was multiplied by the weighted frequency of the number of people having a visit (or prescription) in that category to find the total weighted direct cost.

For the indirect costs, the lost productivity due to missed work days for each patient was calculated using the previously described method. The product of the weighted mean per patient estimate and the weighted number of patients who reported a missed work day gave the total lost productivity cost due to missed work days. The caregivers' cost was calculated by the method previously described. The total caregivers' cost for patients with schizophrenia was calculated as the product of the weighted mean caregivers' cost per patient and the weighted number of

patients who reported positive values for caregivers' costs. The obtained lost productivity cost and caregivers' cost was added to the estimates of lost productivity due to premature death and reduced employment to obtain the total indirect costs.

Table 4 summarizes the procedures that were used to calculate various costs.

Table 4: Cost calculations

Type of Cost	Calculation
Direct Medical Costs	
Inpatient hospitalizations cost	Product of weighted average inpatient hospitalization cost per person and weighted frequency of people having inpatient hospitalizations
Outpatient visits cost	Product of weighted average outpatient visits cost per person and weighted frequency of people having outpatient visits
Emergency department visits cost	Product of weighted average emergency department visits cost per person and weighted frequency of people having emergency department visits
Office-based visits cost	Product of weighted average office-based visits cost per person and weighted frequency of people having office-based visits
Prescription medications cost	Product of weighted average prescription medication cost per person and weighted frequency of people who purchased prescription medication
Home healthcare visits cost	Product of weighted average home healthcare cost per person and weighted frequency of people having home healthcare visits
Indirect Costs	
Lost productivity due to missed work days	Number of work days missed was multiplied by the daily wage rate. Product of weighted lost productivity cost due to missed work day per person and weighted frequency of people having missed work days gave the total lost productivity cost due to missed work days.
Lost productivity due to reduced employment among patients with schizophrenia	The employment rate among the general population was found from the Bureau of Labor Statistics and that among patients with schizophrenia was found from literature. The product of the difference in employment rate, average wage (obtained from the Bureau of Labor Statistics), and the weighted average of the number of patients with schizophrenia gave the lost productivity due to reduced employment among patients with schizophrenia.
Lost productivity due to premature death (suicide)	Percent of patients with schizophrenia committing suicide was obtained from the literature. This was used to find the number of patients with schizophrenia who committed suicide. The lost productivity of the year in which the patient committed suicide was calculated under the assumption that the suicide was committed in the middle of the year.

Type of Cost	Calculation
Caregivers' cost	The cost of missed work by family and friends taking care of patients with schizophrenia was calculated as the product of the weighted mean caregivers' cost per patient and the weighted frequency of the people who reported a positive value for caregivers' costs.
Total Costs	Sum of direct and indirect costs.

Determination of factors associated with high costs

Determinants of high costs were identified based on the direct medical costs. The cost variable was dichotomized into high costs (expenditures that are more than or equal to $16,000) and low costs (expenditures that are less than $16,000). Logistic regression was carried out using age, sex, race, marital status, insurance status, socioeconomic status, region of residence, perceived health status, mental health status, and presence of co-morbidities as independent variables and the dichotomized cost variable as the dependent variable. The 'surveylogistic' procedure in SAS was used to determine the relationship between the independent variables and the costs and identify those factors which are statistically significantly related to a patient belonging to a particular cost category.

Due to the limited sample size, accurate estimates of odds ratios may not be obtained. Therefore, as a sub-analysis, linear regression was carried out with total cost as the dependent variable and age, sex, race, marital status, insurance status, region of residence, socioeconomic status, perceived health status, mental health status, and presence of co-morbidities as the independent variables. The 'surveyreg' procedure of SAS was used for this process. Due to the positively skewed nature of the cost data, the total cost variable was log transformed and the regression procedure using 'surveyreg' was repeated with the log-transformed cost variable as the dependent variable and age, sex, race, marital status, insurance status, socioeconomic status,

region of residence, perceived health status, mental health status, and presence of co-morbidities as the independent variables. The following assumptions were checked before carrying out the regression procedure:

- Normality of residuals;
- Linear relationship of residuals with dependent variables;
- Homoscedasticity; and
- Independence of prediction errors.

All the regression assumptions were met.

Note: The plot used to evaluate the above assumptions is provided in the appendix (Figure A1).

Sensitivity analyses

In order to ensure the robustness of the estimate, sensitivity analyses were conducted on the following:

- The employment rate among patients with schizophrenia
- Mean annual wage among patients with schizophrenia
- Cost of lost productivity due to missed work days
- Suicide rate among patients with schizophrenia
- Caregivers' costs

The estimates were varied over a range of ±50%.

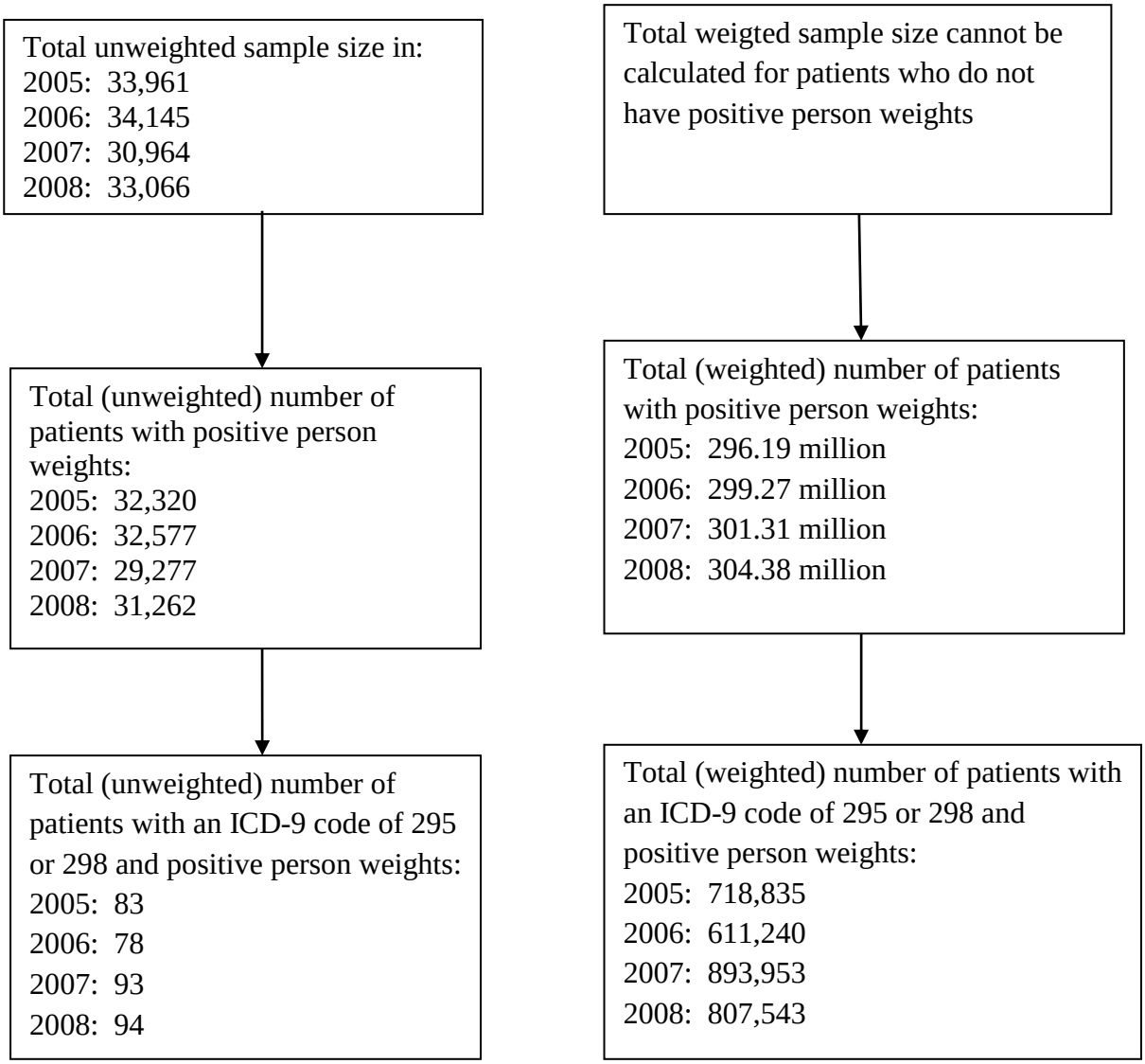
CHAPTER 3: Results

This section provides the results of the analysis. The results are organized and summarized by objective.

Case Identification

The total unweighted sample size in 2005, 2006, 2007, and 2008 was 33,961; 34,145; 30,964; and 33,066, respectively. Only 32,320; 32,577; 29,277; and 31,262 individuals in 2005, 2006, 2007, and 2008, respectively had positive weights and were used for calculations. Of the total, 83, 78, 93, and 94 individuals in 2005, 2006, 2007, and 2008, respectively had an ICD-9 code of 295 (schizophrenic disorder) or 289 (other non-organic psychoses). The total weighted sample size was 296.19 million, 299.27 million, 301.31 million, and 304.38 million and the weighted sample size for individuals with a diagnosis of schizophrenia was 718,835; 611,240; 893,953; and 807,543 in 2005, 2006, 2007, and 2008, respectively (Figure 3).

Figure 3: Flowchart for patient inclusion criteria



Objective 1

The purpose of objective 1 was to describe the demographic characteristics of the schizophrenia population with respect to age, gender, race, marital status, insurance status, region of residence, and socioeconomic status and the clinical characteristics with respect to perceived health status, mental health status, and presence of co-morbidities using means and standard errors (age) and frequencies and percentages (all other variables).

Of the 296.19 million, 299.27 million, 301.31 million, and 304.38 million individuals (unweighted frequency= 32,320; 32,577; 29,277; 31,262 individuals) represented in MEPS, 718,835; 611,240; 893,953; and 807,543 (unweighted frequency=83, 78, 93, 94) individuals had a schizophrenia diagnosis in 2005, 2006, 2007, and 2008, respectively and were included in the analytical cohort.

The population was predominantly male (55.4%). The mean age of the patients with schizophrenia was 40.2 (±2.1) years, 39.4 (±1.9) years, 47.6 (±2.5) years, and 43.4 (±2.1) years in 2005, 2006, 2007, and 2008, respectively. The average age over the four-year period was 42.7 years. The patients with schizophrenia were mainly whites (71.1%) and 23.7% were blacks. A majority of the patients with schizophrenia had only public insurance (72.8%). In terms of marital status, classification as 'never married' (53.1%) was most common.

Only 5.8% of the patients with schizophrenia rated their perceived health status as excellent, 19.2% as very good, 33.4% as good, 31.6% as fair, and 10.1% as poor. The mental health status ratings reported by the patients with schizophrenia were as follows: 2.7% rated mental health status as excellent, 11.4% as very good, 26.3% as good, 41.1% as fair, and 18.6% as poor. Presence of co-morbidities was reported in 40.2% of the patients with schizophrenia.

Tables 5 and 6 provide the demographic and clinical characteristics of the patients with schizophrenia by year as well as the overall average. Table 7 provides the unweighted frequency of schizophrenia patients categorized by demographic/ clinical characteristics and year.

Table 5: Demographic characteristics of the schizophrenia population by year

Demographic characteristics	Categories	2005		2006		2007		2008		Average	
		Weighted N	%	Weighted N	%	Weighted N	%	Weighted N	%	Weighted N	%
Gender	Male	362,965	50.49	354,742	58.04	466,113	52.14	491,174	60.82	418,749	55.37
	Female	355,870	49.51	256,498	41.96	427,840	47.86	316,369	39.18	339,144	44.63
Race	White	479,056	66.64	460,882	75.40	653,013	73.05	559,880	69.33	538,208	71.11
	Black	202,780	28.21	125,736	20.57	201,956	22.59	189,475	23.46	179,987	23.71
	American Indian/Alaska Native	8,793	1.22	-	0.00	-	0.00	3,674	0.45	3,117	0.42
	Asian	-	0.00	-	0.00	-	0.00	12,100	1.50	3,025	0.37
	Native Hawaiian/Pacific Islander	1,869	0.26	-	0.00	-	0.00	-	0.00	467	0.07
	Multiple races reported	26,338	3.66	24,622	4.03	38,984	4.36	42,415	5.25	33,090	4.33
Insurance status	Any private	150,575	20.95	102,404	16.75	244,678	27.37	120,130	14.88	154,447	19.99
	Public only	521,615	72.56	470,407	76.96	583,751	65.30	616,955	76.40	548,182	72.81
	No insurance	46,645	6.49	38,428	6.29	65,524	7.33	70,458	8.72	55,264	7.21
Marital status	Married	103,171	14.35	90,211	14.76	148,031	16.56	77,175	9.56	104,647	13.81

Table 5: continued

Demographic characteristics	Categories	2005		2006		2007		2008		Average	
		Weighted N	%	Weighted N	%	Weighted N	%	Weighted N	%	Weighted N	%
	Widowed	54,217	7.54	22,188	3.63	111,750	12.50	65,150	8.07	63,326	7.94
	Divorced	121,896	16.96	139,619	22.84	183,705	20.55	144,030	17.84	147,313	19.55
	Separated	6,447	0.90	18,664	3.05	27,812	3.11	17,716	2.19	17,660	2.31
	Never married	404,431	56.26	302,290	49.46	407,965	45.64	492,858	61.03	401,886	53.10
	In applicable-below 16 years	28,674	3.99	38,269	6.26	14,689	1.64	10,614	1.31	23,062	3.30
Region of residence	Northwest	147,487	20.52	173,066	28.32	188,150	21.05	167,981	20.80	169,171	22.67
	Midwest	173,122	24.08	158,425	25.92	166,702	18.65	101,760	12.60	150,002	20.31
	South	251,631	35.01	183,555	30.03	299,138	33.46	294,208	36.43	257,133	33.73
	West	109,887	15.29	73,168	11.97	183,042	20.48	224,980	27.86	147,769	18.90
	Inapplicable	36,707	5.11	22,998	3.76	56,922	6.37	18,615	2.31	33,811	4.39
Socioeconomic status*	Poor/negative	198,697	27.64	204,149	33.40	333,750	37.33	295,376	36.58	257,993	33.74
	Poor	142,942	19.89	60,841	9.95	40,287	4.51	136,753	16.93	95,206	12.82
	Low income	96,546	13.43	165,627	27.10	151,903	16.99	140,522	17.40	138,650	18.73
	Mid income	213,467	29.70	61,163	10.01	242,901	27.17	149,143	18.47	166,669	21.34

Table 5: continued

Demographic characteristics	Categories	2005		2006		2007		2008		Average	
		Weighted N	%	Weighted N	%	Weighted N	%	Weighted N	%	Weighted N	%
	High income	67,183	9.35	119,459	19.54	125,111	14.00	85,750	10.62	99,376	13.38

***** The socioeconomic status was defined as follows- Poor/negative: Less than 1.00 times poverty line; Poor:1.01 to 1.24 times poverty line; Low income: 1.25 to 1.99 times poverty line; Middle income: 2.00 to 3.99 times poverty line; High income: 4.0 or more time poverty line

Table 6: Clinical characteristics of the schizophrenia population by year

Clinical characteristics	Categories	2005		2006		2007		2008		Average	
		Weighted N	%	Weighted N	%	Weighted N	%	Weighted N	%	Weighted N	%
Perceived health status	Excellent	24,848	3.46	20,630	3.38	45,990	5.18	90,497	11.21	45,491	5.80
	Very good	184,494	25.67	93,858	15.36	113,687	12.81	184,619	22.86	144,165	19.17
	Good	232,546	32.35	206,777	33.83	276,014	31.09	291,773	36.13	251,778	33.35
	Fair	227,474	31.64	243,918	39.91	327,374	36.87	146,016	18.08	236,196	31.63
	Poor	49,474	6.88	46,057	7.54	124,735	14.05	94,639	11.72	78,726	10.05
Mental health status	Excellent	12,605	1.75	6,222	1.02	27,694	3.12	38,301	4.74	21,206	2.66
	Very good	80,276	11.17	90,958	14.88	100,255	11.29	65,189	8.07	84,170	11.35
	Good	173,526	24.14	153,733	25.15	205,487	23.15	263,519	32.63	199,066	26.27
	Fair	374,118	52.04	213,684	34.96	393,537	44.33	267,800	33.16	312,285	41.12
	Poor	78,311	10.89	146,643	23.99	160,827	18.12	172,733	21.39	139,629	18.60
Presence of co-morbidities	No	423,503	59.52	305,783	54.45	478,584	58.72	514,559	66.73	430,607	59.85
	Yes	288,028	40.48	255,850	45.55	336,424	41.28	256,515	33.27	284,204	40.15

Table 7: Unweighted frequency of the schizophrenia population categorized by demographic/ clinical characteristics and year

Demographic/ clinical characteristics	Categories	Year			
		2005	2006	2007	2008
Gender	Male	40	45	52	59
	Female	43	33	41	35
Race	White	55	55	61	55
	Black	22	20	29	31
	American Indian/Alaska Native [a]	1	0	0	1
	Asian [a]	0	0	0	3
	Native Hawaiian/Pacific Islander [a]	1	0	0	0
	Multiple races reported [a]	4	3	3	4
Insurance status	Any private	13	12	21	12
	Public only	66	61	65	74
	No insurance	4	5	7	8
Marital status	Married [b]	9	13	20	12
	Widowed [c]	8	2	6	9
	Divorced [c]	16	16	17	12
	Separated [c]	3	3	3	2
	Never married [c]	41	39	45	58
	In applicable-below 16 years [b]	6	5	2	2
Region of residence	Northwest	18	22	20	19
	Midwest	19	19	18	12
	South	29	26	34	35
	West	13	9	18	26
	Inapplicable	4	2	3	2
Socioeconomic status	Poor/negative [e]	32	31	39	41
	Poor [e]	17	8	8	15
	Low income [e]	11	20	15	17
	Mid income	15	8	21	16
	High income	8	11	10	5
Perceived health status	Excellent [f]	4	3	4	8
	Very good [f]	18	12	13	17
	Good [g]	29	28	29	37
	Fair [g]	25	30	34	20
	Poor	7	5	12	12

Table 7: continued

Demographic/ clinical characteristics	Categories	Year			
		2005	2006	2007	2008
Mental health status	Excellent [h]	2	1	2	4
	Very good [h]	11	12	12	9
	Good [i]	23	22	18	30
	Fair [i]	35	26	41	28
	Poor	12	17	19	23
Presence of co-morbidities*	No	45	39	51	57
	Yes	37	32	34	32

[a, b, c, d, e, f, g, h, i] Categories combined for statistical analysis

[*] Comorbidities were only determined for patients who had a schizophrenia-related event

Objective 2

The purpose of objective 2 was to estimate the direct medical costs associated with schizophrenia.

The direct medical costs consisted of the following: inpatient hospitalizations, outpatient visits, emergency department visits, office based physician visits, home healthcare visits, and prescription medication.

The mean expenditure per person with schizophrenia amounted to $5,238 (SE = $1,906), $6,254 (SE = $1,349), $5,169 (SE = $998), and $5,683 (SE = $896) for 2005, 2006, 2007, and 2008, respectively. This was based on 327 (weighted frequency = 2.86 million) patients with schizophrenia. The mean cost per person for the 54,590 patients each year who had an emergency department (ED) visit was $688. The mean cost per person for the 70,684 patients who had inpatient hospitalizations (IH) each year was $12,088. Outpatient visits (OV) cost an average of $1,480 per patient for the 61,354 patients who had OVs each year. The mean cost per patient for the 594,956 patients who had an office-based physician visit (MDV) each year was $1,701. Home health care visits (HHCVs) cost an average of $6,852 per patient for the 72,822 patients with HHCVs each year. The mean cost of prescription medication (RX) per person was $2,501, for the 608,278 patients who had purchased prescription medications each year (Table 8).

The total expenditure estimates during the 2005 to 2008 time period for each category were as follows: $135.28 million (0.9%) for EDs, $3.27 billion (20.6%) for IHs, $370.46 million (2.3%) for OVs, $4.03 billion (25.4%) for MDVs, $1.89 billion (11.9%) for HHCVs, and $6.16 billion (38.9%) for RX purchases. The total direct costs estimate for the period between 2005

and 2008 was $15.85 billion. The annual average direct costs amounted to $3.96 billion (Table 9).

The mean direct cost per patient categorized by year and type of service is provided in Table 8. The total direct cost per category per year is provided in Table 9. The total direct costs per year were $3.73 billion, $3.51 billion, $4.21 billion, and $4.39 billion for 2005, 2006, 2007, and 2008, respectively. Figure 4 provides the percentage of components of direct costs from 2005-2008.

Table 8: Mean direct medical cost per patient categorized by year and type of service

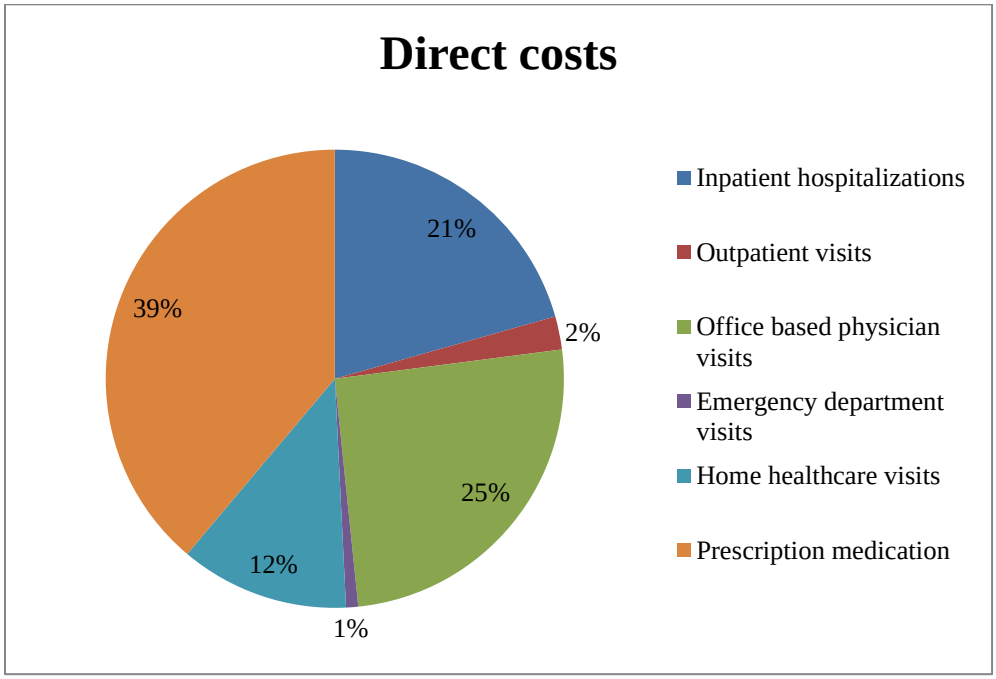
	2005		2006		2007		2008		
Type of service	**# people with service**	**Mean cost per patient (SE)**	**# people with service**	**Mean cost per patient (SE)**	**# people with service**	**Mean cost per patient (SE)**	**# people with service**	**Mean cost per patient (SE)**	**Mean annual cost per patient**
Inpatient visits	110,016	$11,909 ($3,574)	61,435	$17,163 ($6,837)	78,437	$5,910 ($1,229)	32,848	$13,368 ($9,459)	**$13,152**
Outpatient visits	55,539	$1,557 ($704)	55,124	$2,115 ($786)	56,846	$367 ($122)	77,908	$1,881 ($1,441)	**$1,480**
Office-based physician visits	579,691	$1,238 ($388)	471,051	$2,009 ($640)	667,570	$1,680 ($474)	661,512	$1,876 ($546)	**$1,737**
Emergency department visits	80,215	$645 ($288)	39,113	$379 ($113)	66,898	$320 ($86)	33,573	$1,409 ($224)	**$726**
Home healthcare visits	37,892	$4,983 ($2,646)	51,464	$5,727 ($2,954)	71,665	$13,129 ($9,446)	130,265	$3,569 ($861)	**$7,786**
Prescription medication	589,088	$2,330 ($447)	497,232	$2,183 ($389)	669,109	$2,458 ($348)	677,684	$3,033 ($508)	**$2,501**

Table 9: Total direct medical costs categorized by year and type of service (costs are in million USD)

	Direct Costs (%)[a]				
Cost category	**2005**	**2006**	**2007**	**2008**	**Total direct costs per category[b]**
Inpatient visits	$1,310 (35.2)	$1,054 (30.0)	$464 (11.0)	$439 (10.0)	**$3,267**
Outpatient visits	$86 (2.3)	$117 (3.3)	$21 (0.5)	$147 (3.3)	**$370**
Office-based physician visits	$718 (19.3)	$946 (26.9)	$1,122 (26.6)	$1,241 (28.2)	**$4,027**
Emergency department visits	$52 (1.4)	$15 (0.4)	$21 (0.5)	$47 (1.1)	**$135**
Home healthcare visits	$189 (5.1)	$295 (8.4)	$941 (22.3)	$465 (10.6)	**$1,889**
Prescription medications	$1,373 (36.8)	$1,085 (30.9)	$1,644 (39)	$2,056 (46.8)	**$6,158**
Total direct costs per year[b]	**$3,727**	**$3,512**	**$4,213**	**$4,394**	**$15,850**

[a] Per cent of total direct costs for that year
[b] Totals might not add up due to rounding

Figure 4: Percentage of components of direct medical costs (2005-2008)



Mean direct costs for each year categorized by demographic factors such as gender, race, insurance status, marital status, region of residence, and socioeconomic status are presented in Table 10. Mean direct costs for each year categorized by clinical factors such as perceived health status, mental health status, and presence of co-morbidities are presented in Table 11.

Table 10: Mean direct costs categorized by demographic factors and years

		2005		2006		2007		2008	
		Direct cost (SE)	Weighted N	Direct cost (SE)	Weighted N	Direct cost (SE)	Weighted N	Direct cost (SE)	Weighted N
Gender	Male	$6,345 ($1,594)	355,661	$6,904 ($1,922)	352,408	$3,300 ($523)	448,123	$6,510 ($1,449)	458,789
	Female	$3,890 ($1,382)	355,870	$5,158 ($1,856)	209,225	$7,452 ($2,074)	366,885	$4,469 ($739)	312,285
Race	White	$3,433 ($918)	471,752	$5,543 ($1,373)	421,964	$4,227 ($707)	592,057	$4,675 ($756)	531,492
	Black	$6,114 ($2,545)	202,780	$9,238 ($3,705)	115,047	$8,144 ($3,663)	191,812	$8,561 ($2,889)	185,478
	American Indian/Alaska Native	$40,178 -[a]	8,793	NA	-	NA	-	$19,366 -[a]	3,674
	Asian	NA	-	NA	-	NA	-	$11,077 ($2,453)	12,100
	Native Hawaiian/Pacific Islander	$1,979 -[a]	1,869	NA	-	NA	-	NA	-
	Multiple races reported	$16,111 ($14,389)	26,388	$4,487 ($2,576)	14,334	$4,764 ($2,068)	31,138	$2,725 ($957)	38,331
Insurance status	Any private	$7,311 ($3,306)	150,575	$327,665 ($2,693)	102,404	$3,261 ($789)	222,736	$4,593 ($1,620)	110,414
	Public only	$4,868 ($1,185)	514,312	$5,720 ($1,369)	420,800	$6,301 ($1,448)	532,848	$6,311 ($1,010)	608,874
	No insurance	$521 ($220)	46,645	$14,360 ($7,998)	38,428	$2,175 ($1,180)	59,423	$635 ($247)	51,787
Marital status	Married	$5,018 ($2,199)	103,171	$4,710 ($2,854)	90,211	$1,869 ($466)	132,459	$2,679 ($654)	67,459
	Widowed	$1,267 ($598)	54,217	$366 -[a]	14,904	$1,592 ($530)	71,219	$3,642 ($1,333)	65,150

Table 10: continued

		2005		2006		2007		2008	
		Direct cost (SE)	Weighted N	Direct cost (SE)	Weighted N	Direct cost (SE)	Weighted N	Direct cost (SE)	Weighted N
	Divorced	$2,399 ($744)	121,896	$3,863 ($821)	135,227	$6,040 ($1,784)	177,604	$4,273 ($1,300)	144,030
	Separated	$2,421 ($1,618)	6,447	$2,327 ($807)	12,609	$4,343 ($2,771)	27,812	$13,216 ($4,120)	17,716
	Never married	$5,771 ($1,553)	397,128	$8,796 ($2,345)	272,748	$6,726 ($1,943)	391,223	$6,599 ($1,417)	466,105
	In applicable-below 16 years	$15,858 ($12,136)	28,674	$463,971 ($2,016)	35,935	$1,832 ($1,676)	14,689	$3,681 ($390)	10,614
Region of residence	Northwest	$6,754 ($2,907)	140,183	$6,740 ($2,195)	168,674	$6,268 ($1,396)	184,057	$6,995 ($1,926)	163,897
	Midwest	$5,530 ($1,611)	173,122	$6,721 ($2,150)	142,595	$4,695 ($1,330)	147,752	$3,634 ($1,133)	101,760
	South	$4,693 ($2,226)	2,511,631	$2,162 ($433)	183,555	$5,219 ($2,544)	277,514	$4,848 ($1,296)	294,208
	West	$1,466 ($694)	109,887	$23,020 ($10,566)	43,810	$4,237 ($1,055)	175,196	$5,450 ($1,265)	192,595
	Inapplicable	$10,750 ($8,967)	36,707	$507 ($129)	22,998	$5,739 ($1,558)	30,488	$20,956 ($15,850)	18,615
Socioeconomic status	Poor/negative	$2,138 ($543)	198,697	$9,398 ($3,429)	163,174	$7,304 ($2,471)	299,179	$7,184 ($1,965)	277,654
	Poor	$8,736 ($3,162)	135,639	$2,939 ($1,001)	60,841	$8,342 ($3,881)	29,333	$4,707 ($1,302)	136,753
	Low income	$2,819 ($1,504)	96,546	$5,673 ($1,662)	163,294	$3,107 ($788)	137,807	$4,715 ($1,438)	136,525
	Mid income	$7,440 ($2,961)	213,467	$3,444 ($1,446)	54,865	$5,162 ($1,304.92)	235,056	$3,681 ($775)	144,108
	High income	$2,537 ($1,162)	67,183	$5,731 ($2,759)	119,459	$1,244.53 ($679.28)	113,632	$7,492 ($2,729)	76,034

[a] No standard error reported as there was only 1 person (unweighted frequency) in that particular group

Table 11: Mean direct costs categorized by clinical factors and years

		2005		2006		2007		2008	
		Direct cost (SE)	Weighted N	Direct cost (SE)	Weighted N	Direct cost (SE)	Weighted N	Direct cost (SE)	Weighted N
Perceived health status	Excellent	$2,098 ($486)	24,848	$2,881 ($1,349)	20,630	$1,902 ($1,820)	31,894	$19.843 ($6,712)	62,109
	Very good	$4,856 ($2,472)	177,190	$7,479 ($3,929)	93,858	$2,456 ($970)	109,594	$5,867 ($1,162)	184,619
	Good	$7,134 ($2,362)	232,546	$3,192 ($718)	176,991	$5,765 ($1,220)	250,588	$3,500 ($547)	283,692
	Fair	$2,733 ($706)	227,474	$7,816 ($2,521)	224,097	$4,102 ($868)	296,896	$5,997 ($1,856)	146,016
	Poor	$9,051 ($6,370)	49,474	$9,428 ($6,905)	46,057	$10,170 ($5,747)	119,882	$2,092 ($614)	94,639
Mental health status	Excellent	$1,632 ($869)	12,605	$5,049 -[a]	6,222	$99 ($71)	27,694	$4,022 ($368)	28,585
	Very good	$5,803 ($2,799)	80,276	$2,078 ($887)	77,618	$1,238 ($577)	76,837	$7,471 ($1,715)	65,189
	Good	$4,098 ($2,424)	173,526	$12,364 ($4,863)	121,857	$5,514 $889	191,390	$3,283 ($796)	258,485
	Fair	$4,868 ($1,560)	374,118	$3,458 ($866)	209,292	$4,833 ($992)	356,958	$7,564 ($1,782)	263,716
	Poor	$8,810 ($4,374)	71,008	$7,427 ($2,016)	146,643	$8,546 ($4,605)	155,974	$6,041 ($2,290)	155,099
Presence of co-morbidities	No	$5,486 ($1,655)	423,503	$5,345 ($1,931)	305,783	$4,219 ($780)	478,584	$5,776 ($1,161)	514,559
	Yes	$4,874 ($1,258)	288,028	$7,339 ($1,786)	255,850	$6,521 ($2,157)	336,424	$5,497 ($1,278)	256,515

[a] No standard error reported as there was only 1 person (unweighted frequency) in that particular group

Objective 3

The purpose of objective 3 was to estimate the indirect costs associated with schizophrenia.

Indirect costs consist of lost productivity due to missed work days, lost productivity due to reduced employment, lost productivity due to premature death, and caregivers' costs. The results for each component are presented below.

Lost productivity due to missed work days

The mean lost productivity cost per patient per year due to missed work days was $1,533, $687, $1,482 and $1,008 in 2005, 2006, 2007, and 2008, respectively. If a patient had an ICD-9 code of 295 (schizophrenic disorders) or 298 (other non-organic psychoses) for a condition, we assumed that the missed work days were attributable to schizophrenia even if the patients had other conditions in addition to schizophrenia. This estimate was for adult patients (age $\geq$ 18 years) who had positive values for missed work days. If a patient had a positive value for missed work days and a value for wages, it was assumed that he was over 18 years of age, even if the age was not reported for the patient. The weighted frequency of the number of people who reported having a positive value for missed work days was 126,642, 42,045, 74,789 and 12,402 in 2005, 2006, 2007, and 2008, respectively. Therefore, the total lost productivity cost due to missed work days for adult patients with schizophrenia amounted to $346.38 million (Table 12).

Table 12: Annual lost productivity cost due to missed work days

Year	Mean lost productivity cost per patient	Weighted # of patients	Lost productivity cost (in million)
2005	$1,533	126,642	$197.17
2006	$687	42,045	$28.89
2007	$1,482	74,789	$110.82
2008	$1,008	12,402	$12.50
Total			**$346.38**

Lost productivity due to reduced employment

The cost of lost productivity of adult patients with schizophrenia in the dataset was estimated by finding the difference between the productivity for the 'no schizophrenia' and the 'with schizophrenia' cases. First, the product of the number of employed people and the mean annual wage of the patients with schizophrenia was calculated (the employment rate of 21.3%[10,60,61,62] and the mean hourly wage of $7.50[64] for 2003 was obtained from the literature). The productivity cost of the same population was then calculated assuming that these patients did not have schizophrenia. A higher employment rate and mean hourly wage was used when it was assumed that the patients did not suffer from schizophrenia (mean hourly wage in 2008 = $20.32; 2007 = $19.56; 2006 = $18.84; and 2005 = $18.21 for the general population[63]; employment rate: 62.2% in 2008, 63% in 2007, 63.1% in 2006, and 62.7% in 2005[59]). The employment rates and the daily wages were obtained from Bureau of Labor Statistics. The total lost productivity cost due to reduced employment between 2005 and 2008 amounted to $60.71 billion. Table 13 provides the annual lost productivity due to reduced employment for each year from 2005 to 2008.

Table 13: Annual lost productivity due to reduced employment

Year	Employment rate	# of people	Wage per annum	Total productivity (in billions)
No schizophrenia				
2005	62.2%	650,221	$37,877	$15.44
2006	63.0%	541,275	$39,187	$13.38
2007	63.1%	822,341	$40,685	$21.08
2008	62.7%	778,314	$42,266	$20.46
Total productivity over the period between 2005 to 2008				$70.37
With schizophrenia				
2005	21.3%	650,221	$15,421	$2.14
2006	21.3%	541,275	$15,884	$1.83
2007	21.3%	822,341	$16,424	$2.88
2008	21.3%	778,314	$16,933	$2.81
Total productivity for patients with schizophrenia between 2005 and 2008				$9.65
Lost productivity due to reduced employment among patients with schizophrenia				**$60.71**

Lost productivity due to premature death

The annual lost productivity due to premature death (suicide) was estimated as the lost productivity for that particular year for the patients with schizophrenia. It was assumed that the suicide would occur in the middle of the year, so only half of the year's income was counted as 'lost productivity.' The daily wages of patients with schizophrenia and the proportion of patients with schizophrenia who commit suicide were obtained from literature. The daily wage rate for patients with schizophrenia was found to be $7.05 in 2003.[64] This value was converted to the particular year's dollar value prior to analyses. Using that assumption that 5% of the patients per year would commit suicide,[65] the lost productivity due to premature death amounted to $187.88 million for the period between 2005 and 2008 (Table 14).

Table 14: Annual lost productivity due to premature death

Year	Weighted frequency of # of people with schizophrenia	Proportion of patients who are employed	Proportion of patients who commit suicide	Annual lost wages in USD	Lost earnings (in millions)
2005	650,221	21.3%	5%	$15,421	$53.40
2006	541,275	21.3%	5%	$15,884	$45.78
2007	822,341	21.3%	5%	$16,424	$71.92
2008	778,314	21.3%	5%	$16,933	$70.18
Total					**$241.28**

Lost productivity due to the opportunity costs of friends and family members caring for the patients with schizophrenia

The mean caregivers' cost per patient was calculated by the previously described method. The mean cost per patient multiplied by the number of patients who reported positive values for caregivers' cost gave the total caregivers' cost. Table 15 gives the estimated annual caregivers' costs from 2005 to 2008.

Table 15: Annual caregivers' costs

Year	Mean cost	Weighted frequency of number of patients with schizophrenia who reported positive caregivers costs	Caregivers' costs
2005	$1,016.96	52,899	$53,773,520
2006	$333.26	62,896	$20,960,648
2007	$587.67	65,774	$38,653,105
2008	$511.96	71,783	$36,750,267
Total			**$150,137,540**

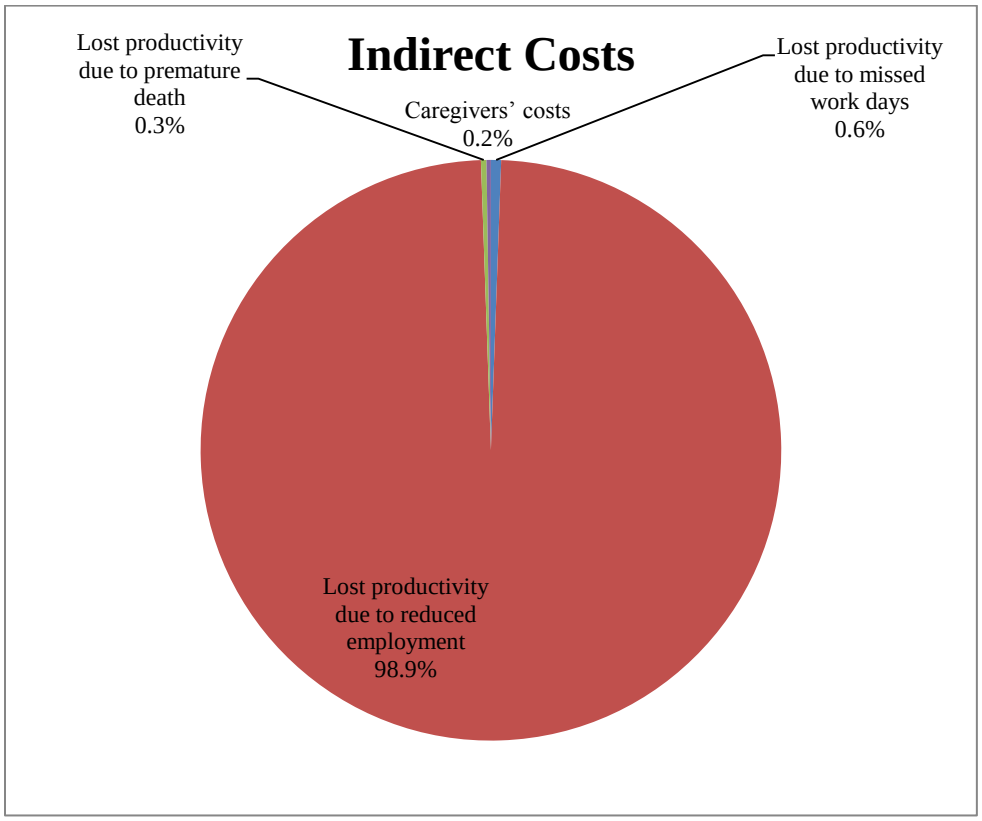
Total indirect costs

The total indirect cost estimate for the period from 2005-2008 was $61.40 billion. The mean indirect cost per year was $15.42 billion. The annual indirect costs were $13.61 billion, $11.65 billion, and $18.42 billion, and $17.77 billion for 2005, 2006, 2007, and 2008, respectively (Table 16). Figure 5 gives the percentages of the components of the indirect costs from 2005-2008.

Table 16: Total indirect cost categorized by year and type of cost (costs are in million USD)

	Indirect costs				
Cost Category	**2005**	**2006**	**2007**	**2008**	**Total**
Lost productivity due to missed work days	$197.17	$28.89	$111.02	$12.69	$346.38
Lost productivity due to reduced employment	$13,306.12	$11,552.88	$18,200.95	$17,654.05	$60,713.99
Lost productivity due to premature death	$53.40	$45.78	$71.92	$70.18	$187.88
Caregivers' costs	$53.77	$20.96	$38.65	$36.75	$150.14
Annual total	**$13,610.46**	**$11,648.51**	**$18,422.54**	**$17,773.67**	**$61,398.39**

Figure 5: Percentage of components of indirect costs (2005-2008)



Objective 4

The purpose of objective 4 was to determine factors associated with high schizophrenia-related direct medical costs.

The model contained 10 independent variables. The minimum required sample size was calculated using the formula N>=104+#IV.[68] Therefore, for the current study, the minimum sample size would have to be 104+10=124. Our sample size was 348 patients with positive person weights.

Checking for multicollinearity

The variance inflation factors (VIFs) for all the independent variables were calculated and are reported in Table 17. Since all the VIF values are less than 10, we can assume that there was no significant multicollinearity.

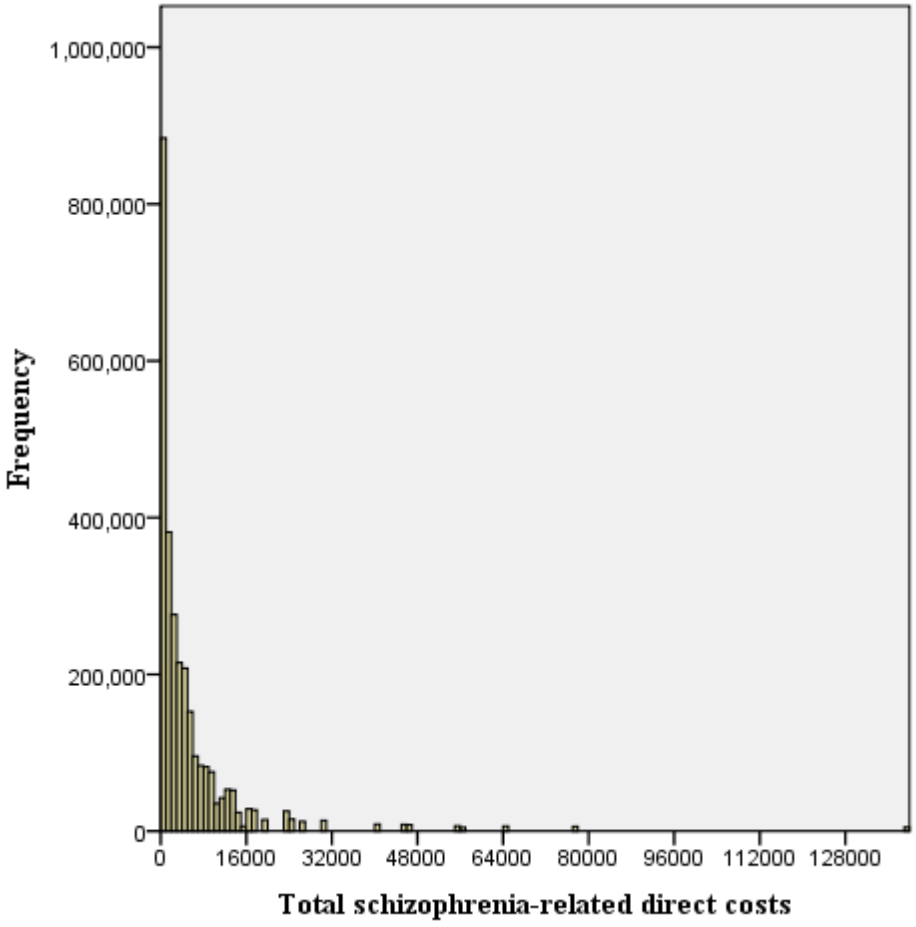
Table 17: Variance inflation factors

Variable	Variance inflation factor (VIF)
Age	1.2293
Gender	1.0125
Race	1.0394
Marital status	1.0746
Insurance status	1.2471
Region of residence	1.0275
Socioeconomic status	1.2952
Perceived health status	1.6917
Mental health status	1.5713
Presence of co-morbidities	1.0053

Identification of patients with high costs

Inspection of the histogram showing the frequency distribution of the weighted direct costs of the patients with schizophrenia showed that $16,000 was an appropriate cut-off point for the high-cost group. Although $20,000 seemed to be a natural cut-off point, when it was used the high-cost group had very few patients which led to spurious odds-ratios. Therefore, $16,000 was used as the cut-off point. Figure 6 gives the histogram for the frequency distribution of the weighted costs for the patients with schizophrenia.

Figure 6: Distribution of schizophrenia-related direct costs



Patients with costs greater than $16,000 were categorized into the ‘high cost’ category and the others were categorized into the ‘low cost’ category. The mean cost for the low-cost group was $3,592 (SE=$283) and that for the high-cost group was $29,099 (SE=$4,422).

Distributions for the high- and low-cost groups by demographic and clinical characteristics are reported in Table 18 and Table 19, respectively. The Rao-Scott Chi-square tests demonstrated that there were no statistically significant differences between the two groups with respect to any of the demographic or clinical characteristics except marital status. More patients in the high-cost group, as compared to the low-cost group, had no spouse while more patients in the low-cost group reported having a spouse or being under 16 years of age.

Table 18: Distribution of high- and low-cost groups by demographic characteristics

Demographic/ Clinical variables	Categories of costs for demographic variables	Low-cost group		High-cost group		Rao-Scott Chi-square test	p-value
		Weighted N	Percentage	Weighted N	Percentage		
Gender	**Male**	1,482,414	56.06	132,567	61.71	0.2401	0.6241
	Female	1,162,023	43.94	82,243	38.29		
Race	**Black**	607,886	22.99	87,231	40.61	5.2094	0.0739
	White	1,911,516	72.28	105,750	49.23		
	Other	125,036	4.73	21,829	10.16		
Marital Status	**Has spouse or is less than 16 years of age**	472,354	17.86	10,858	5.05	4.3681	0.0366
	No spouse	2,172,083	82.14	203,951	94.95		
Insurance coverage	**Private insurance**	561,615	21.24	24,514	11.41	1.3372	0.5124
	Public Insurance	1,904,059	72.00	172,775	80.43		
	No insurance	178,763	6.76	17,520	8.16		
Region	**Northwest**	602,839	23.62	53,972	27.29	1.6792	0.6416
	Midwest	521,040	20.41	44,189	22.34		
	South	961,127	37.65	45,781	23.14		
	West	467,628	18.32	53,861	27.23		
Socioeconomic status	**Low income**	1,681,148	63.57	154,295	71.83	0.4261	0.5139
	High income	963,289	36.43	60,515	28.17		

Table 19: Distribution of high- and low-cost groups by clinical characteristics

Demographic/ Clinical variables	Categories of costs for demographic variables	Low-cost group		High-cost group		Rao-Scott Chi-square test	p-value
		Weighted N	%	Weighted N	%		
Perceived health status	**Excellent**	657,223	24.91	47,518	22.12	1.8022	0.4061
	Good	1,713,355	64.94	124,945	58.17		
	Poor	267,705	10.15	42,347	19.71		
Mental health status	**Excellent**	346,167	8.05	28,859	13.43	0.0114	0.9943
	Good	1,804,829	41.95	144,514	67.28		
	Poor	2,150,996	50.00	41,436	19.29		
Presence of co-morbidities	**No**	4,301,992	72.74	214,809	66.01	0.7133	0.3983
	Yes	1,611,828	27.26	110,601	33.99		

A logistic regression procedure was carried out with cost categories (based on direct costs) high (more than or equal to $16,000) and low (less than $16,000) as the dependent variable and age, gender, race, marital status, insurance coverage, socioeconomic status, region of residence, perceived health status, mental health status, and presence of co-morbidities as the independent variables. Table 20 provides the regression coefficients, Wald's Chi-square values, odds ratios, and 95% confidence intervals of the odds ratios for all the variables included in the model.

Table 20: Results of logistic regression procedure for dichotomized direct costs by demographic and clinical variables

Demographic/Clinical characteristic	Estimate	Wald's Chi-square	p-value	Odds ratio	95% CI of odds ratio	
					Lower	Higher
Age*	-0.0592	9.8906	0.0017	0.943	0.908	0.978
Gender (males = reference group)						
Females	-0.1390	0.2194	0.6395	0.757	0.237	2.423
Race (black = reference group)						
White	-0.8481	3.2872	0.0698	0.277	0.070	1.099
Other	0.4132	0.4603	0.4975	0.979	0.145	6.612
Marital status (no spouse = reference group)						
Has spouse*	-0.7503	3.9778	0.0461	0.223	0.051	0.974
Insurance coverage (private insurance = reference group)						
Public insurance	0.1577	0.1752	0.6756	0.963	0.248	3.745
No insurance	-0.353	0.4004	0.5269	0.587	0.082	4.054
Region (Northeast = reference group)						
Midwest	0.0240	0.0034	0.9534	0.899	0.214	3.777
South	-0.4714	1.2063	0.2721	0.548	0.122	2.465
West	0.3166	0.6755	0.4111	1.204	0.278	5.224
Socioeconomic status (high income = reference group)						
Low income	-0.1355	0.1269	0.7217	0.763	0.172	3.389

Table 20: continued

Demographic/Clinical characteristic	Estimate	Wald's Chi-square	p-value	Odds ratio	95% CI of odds ratio	
					Lower	Higher
Perceived health status (excellent = reference group)						
Good	-0.2834	0.4300	0.5120	1.762	0.315	9.854
Poor*	1.1332	4.0634	0.0438	7.264	0.880	59.936
Mental health status (excellent = reference group)						
Good	0.086	0.0345	0.8527	0.522	0.071	3.825
Poor	-0.8221	1.9715	0.1603	0.211	0.020	2.172
Presence of co-morbidities (no = reference group)						
Yes	0.3688	1.6815	0.1947	2.091	0.686	6.375

Overall model statistics: Wald's Chi-square=38.10; p=0.0015

*statistically significant at p=0.05

The overall model was statistically significant (Wald's Chi-square=38.10, p=0.0015). Age, marital status, and perceived health status were found to be statistically significant at an α level of 0.05. Gender, race, insurance status, region of residence, socioeconomic status, mental health status, and presence of co-morbidities were not significantly related to whether the patient belonged to the high-cost group as compared to the low-cost group.

While controlling for other factors, with a one-year increase in the age, the patient was 5.7% less likely to be in the high-cost group as compared to the low-cost group (OR=0.943, 95% CI= [0.908, 0.978]). Patients who had a spouse were 77.7% less likely than those without a spouse to be in the high-cost group as compared to the low cost group (OR=0.223, 95% CI= [0.051, 0.974]) when all other factors were controlled for. When controlling for all other factors, patients who rated their perceived health status as 'poor' were 7.3 times more likely than those who rated it as 'excellent' to be in the high-cost group as compared to the low-cost group(OR=7.264, 95% CI= [0.880, 59.936]). Although the p-value was significant for the perceived health status, the 95% confidence interval for the odds ratio crosses 1. Therefore, the significance in the p-value may be due to the limited sample size.

Due to the limited sample size, some of the confidence intervals of the odds ratios were very wide and may not be accurate. Therefore, an ordinary least squares regression was also carried out to evaluate the relationships between the independent variables and the direct cost. The overall model was found to be statistically significant (F=616.20, p<0.0001). The adjusted R^2 was 0.0732. Therefore, the independent variables were only able to explain about 7% of the variability in the direct costs.

Age and race were found to be statistically significant. Controlling for all other factors, with a one-year increase in age, the schizophrenia-related direct costs decreased by about $85.

White people spent about $4,304 less on schizophrenia-related direct medical costs as compared to black people. All other variables were not statistically significant (Table 21).

Table 21: Linear regression results for direct costs by demographic and clinical variables

Variable	Estimate	t-value	p-value
Age*	-85.29	-3.08	0.0022
Gender (male = reference group)			
Female	672.50	0.57	0.5698
Race (black = reference group)			
White*	-4303.96	-2.11	0.0353
Other	-2610.13	-0.74	0.4618
Marital status (no spouse = reference group)			
With spouse	-683.65	-0.65	0.5136
Insurance status (private insurance = reference group)			
Public insurance	-220.35	-0.17	0.8615
No insurance	-2825.69	-1.24	0.2140
Region (Northwest = reference group)			
Midwest	-1641.94	-1.04	0.3012
South	-2699.50	-1.71	0.0883
West	-296.97	-0.16	0.8718
Socioeconomic status (high = reference group)			
Low	-547.34	-0.39	0.6954
Perceived health status (excellent = reference group)			
Good	-1911.59	-1.20	0.2305
Poor	260.41	0.09	0.9297
Mental health status (excellent = reference group)			
Good	1794.02	1.12	0.2649
Poor	2767.55	1.43	0.1525
Presence of co-morbidities (no = reference group)			
Yes	1727.10	1.19	0.2334

Overall model statistics: $F=616.20$; $p<0.0001$
*statistically significant at $p<0.05$

As marital status status was significantly related to the patient's cost category, we failed to reject hypothesis 4. As region of residence was not significantly associated with cost category, we failed to reject hypothesis 6. As gender, race, insurance status, socioeconomic status, mental

health status, and presence of co-morbidities were not significantly related to the patient's cost category, we rejected hypotheses 2, 3, 5, 7, 9 and 10, respectively. Even though the p-value for age was statistically significant, we rejected hypothesis 1 as the direction of the relationship was opposite of the one hypothesized. Although the p-value for perceived health status was statistically significant, the 95% confidence interval of the odds ratio crossed 1 and therefore we rejected hypothesis 8. Results of the hypothesis tests are shown in Table 22.

Table 22: Results of hypotheses tests

	Hypothesis	Result
H1:	Compared to younger age, older age is significantly associated with high schizophrenia-related costs versus low costs after controlling for all other factors.	Rejected
H2:	Compared to being male, being female is significantly associated with high schizophrenia-related costs versus low costs after controlling for other factors.	Rejected
H3:	Compared to all other races, white race is significantly associated with high schizophrenia-related costs versus low costs after controlling for all other factors.	Rejected
H4:	Compared to not having a spouse, having a spouse is significantly associated with high schizophrenia-related costs versus low costs after controlling for other factors.	Fail to reject
H5:	Compared to private insurance or no insurance, public insurance is significantly associated with high schizophrenia-related costs versus low costs after controlling for all other factors.	Rejected
$H_0$6:	Region of residence is **not** significantly associated with high schizophrenia-related costs versus low costs after controlling for other factors.	Fail to rejected
H7:	Compared to high socioeconomic status, low socioeconomic status is significantly associated with high schizophrenia-related costs versus low costs after controlling for all other factors.	Rejected
H8:	Compared to 'excellent' perceived health status, 'poor' perceived health status is significantly associated with high schizophrenia-related costs versus low costs after controlling for other factors.	Rejected
H9:	Compared to 'excellent' mental health status, 'poor' mental health status is significantly associated with high schizophrenia-related costs versus low costs after controlling for other factors.	Rejected
H10:	Compared to absence of co-morbidities, presence of co-morbidities is significantly associated with high schizophrenia-related costs versus low costs after controlling for other factors.	Rejected

Sensitivity analyses

Uncertainty exists regarding estimates of the employment level, annual wages of patients with schizophrenia, suicide rates, and caregivers' costs. To test the robustness of the cost estimates to variability in these variables, sensitivity analyses were conducted with varying values for these variables (Table 23).

Because of the uncertainty associated with the number of work days missed by the patient due to schizophrenia-related symptoms, the cost of lost productivity due to missed work days was varied over a ±50% range. The cost of lost productivity varied between $173.58 million and $519.96 million (original estimate $346.48 million) and the indirect costs varied between $61.23 billion and $61.57 billion (original estimate $61.40 billion).

The employment level among patients with schizophrenia (21.3%) was varied 50% above and below the estimate resulting in the cost due to reduced employment among patients with schizophrenia varying between $55.89 billion and $65.54 billion (original estimate $60.71 billion) and the cost due to premature death varying between $93.95 million and $218.82 million (original estimate $187.88 million). Therefore, the indirect costs range between $56.67 billion and $66.13 billion (original estimate $61.40 billion).

Due to the way in which productivity was calculated, the same results were obtained when the mean annual wages of patients with schizophrenia was varied by ±50%. Since the lost productivity was calculated as the product of the employment level and annual wages, when either variable (employment level or annual wages) was varied over ±50%, the same final results for lost productivity were obtained. After conducting the sensitivity analysis, the cost due to reduced employment among patients with schizophrenia ranged between $55.89 billion and $65.54 billion (original estimate $60.71 billion) and the cost due to premature death varying between $93.95 million and $218.82 million (original estimate $187.88 million). Thus, the

indirect cost estimate ranged between $56.67 billion and $66.31 billion (original estimate $61.40 billion).

Again due to the way in which lost productivity due to premature death was calculated (product of annual wage and percent of people who commit suicide), when the suicide rate was varied by ±50%, the lost productivity due to premature death ranged between $93.95 million and $281.82 million (original estimate $187.88 million) and the indirect costs ranged between $61.30 billion and $61.49 billion (original estimate $61.40 billion).

The caregivers' costs were varied 50% above and below their estimate and ranged between $75.07 million and $225.21 million (original estimate $150.14 million); therefore, the indirect costs ranged between $61.32 billion and $61.47 billion (original estimate $61.40 billion).

Table 23: Minimum and maximum values of indirect costs from sensitivity analyses

	Indirect costs (in billion USD)		
Estimate varied	**Original value**	**Minimum estimate**	**Maximum estimate**
Lost productivity due to missed work days	$61.40	$61.23	$61.57
Employment rate of patients with schizophrenia (21.3%)	$61.40	$56.67	$66.13
Annual wage of patients with schizophrenia	$61.40	$56.67	$66.13
Suicide rate among patients with schizophrenia (5%)	$61.40	$61.30	$61.49
Caregivers' costs	$61.40	$61.32	$61.47

Sensitivity analyses were also performed on some of the analyses pertaining to direct costs. Due to the positively skewed nature of the cost data, a separate regression analysis was conducted to address the skewed data. Another linear regression analysis was conducted using log-transformed direct medical costs as the dependent variable. The overall model was found to be statistically significant ($F=973.72$, $p<0.001$). Mental health status was found to be significant. The adjusted R^2 value was 0.1111. Therefore, the independent variables explained about 11% of the variability in the dependent variable. Poor mental health status had a positive association with log-transformed costs; those who rated their mental health status as 'poor' were more likely to have higher schizophrenia-related direct medical costs than those who rated it as 'excellent.' The results are provided in the appendix (Table A1).

In the initial logistic regression analyses, some patients had missing values on their age and region of residence. We performed a mean imputation for the age and a mode imputation for the region of residence. After making these changes in the data, the logistic regression model to predict "high-cost" group membership was repeated. The overall model was statistically significant (Wald's Chi-square= 37.07, $p=0.0021$). In addition to the age, marital status, and perceived health status which were found to be statistically significant in the initial analysis, race was also found to be significantly related to the cost category. After controlling for all other factors, with a one year increase in age, the likelihood of being in the high-cost group decreased by 5.3%. Whites were 73.8% less likely to be in the high-cost group as compared to black people, when all other factors were controlled for. Patients who had a spouse were 80.7% less likely to be in the high-cost group as compared to those who did not have a spouse. Those who reported their perceived health status as 'poor' were almost 6 times more likely to be in the high-cost group as compared to those who reported it as 'excellent'. Although the p-value for

perceived health status was statistically significant, the 95% confidence interval of the odds ratio crossed 1. Therefore, it is not a good predictor of high-cost group membership. The significance with respect to the p-value was probably due to the limited sample size. The results are provided in the appendix (Table A2).

CHAPTER 4: Discussion

Overview

The purpose of this chapter is to discuss the results and implications of this study. The following section contains a summary of the results and the related discussion for each objective.

Case selection

The current study found that approximately 0.24%, 0.20%, 0.30%, and 0.27% of the community-dwelling US residents had schizophrenia in 2005, 2006, 2007, and 2008, respectively. The Epidemiologic Catchment Area (ECA) study, the National Co-morbidity Survey (NCS), and the National Co-morbidity Survey-Replicate (NCS-R) estimated the prevalence of the disease at about 0.6%-1%[2,3] of the US population. The prevalence in the MEPS population is less perhaps because only community-dwellers are included in the survey; a large number of patients with schizophrenia may be institutionalized, in prisons, or homeless and therefore, are not included in the survey. Due to the stigma associated with the disease, a patient is usually diagnosed as having schizophrenia only when their physician is absolutely certain. Often times, patients who are suspected of having schizophrenia are given an interim diagnosis until schizophrenia is confirmed. That may be another reason for the lower number of patients with schizophrenia in this study as compared to that found in prior prevalence studies which were based on broader inclusion criteria. MEPS gives the 'treated prevalence' of the disease rather than the absolute prevalence and therefore our estimate may be lesser than the previous ones.

Two ICD-9 codes, 295 (schizophrenic disorders) and 298 (other non-organic psychoses) were used as the selection criteria for the present study. Rice and Miller's[27] inclusion criteria for their total cost estimate for the year 1991 were ICD-9 codes of 295 (schizophrenic disorders) and 297 (paranoid states). Wu et al.[10] included patients with ICD-9 codes of 295 and McDonald and her colleagues[31] used clinical classification codes of 70 and 72 which included ICD-9 codes of 295 (schizophrenic disorders), 297 (delusional disorders), 298.1 (excitative type psychosis), 298.2 (reactive confusion), 298.3 (acute paranoid reaction), 298.4 (psychogenic paranoid psychosis), 298.8 (other and unspecified reactive psychosis), 298.9 (unspecified psychosis), and 299 (pervasive developmental disorders) for their direct cost estimate for 2001-2002. Our inclusion criteria were intended to ensure that patients with an interim diagnosis (before confirmation of the schizophrenia diagnosis) were included in the study, while avoiding an overestimation of costs due to overly broad inclusion criteria.

Demographic and clinical characteristics

According to the study by Wu et al.[13] that used a claims-based approach, the highest prevalence of schizophrenia was seen in the age-group of 46-55 years. The ECA study reported the highest prevalence in the 30-44 years age group.[3] In the present study, the mean age of the patients with schizophrenia was 43 years which is in agreement with the previous findings. The ECA reports a slightly higher prevalence of schizophrenia in women as compared to men.[3] However, in our study sample, a majority of the patients were male (55%). This is in accordance to the findings of Wu et al.[13] who reported a higher prevalence of schizophrenia among men as compared to women between 2000 and 2002 in the US. Although several studies[3,18,19] in the past have reported a higher prevalence of schizophrenia among blacks as compared to whites, the sample for the current study had more whites. This is probably due to under-representation of blacks with schizophrenia in the MEPS. It is also possible that there was under reporting of schizophrenia among black people during the interviews due to the stigma associated with the disease. As expected based on the results of the ECA study,[3] prevalence of the disease among patients with public insurance was higher than that in patients with private insurance or no insurance. Also, patients without a spouse had a higher prevalence of schizophrenia as compared to those who had a spouse, which was also as seen in the ECA study. The ECA study and a study by Bromet et al.[16] showed that the prevalence of schizophrenia is higher in patients having a lower socioeconomic status as compared to those who have a high socioeconomic status and a similar pattern was observed in this study.

Direct costs

Our direct cost estimate was $15.85 billion for the four-year period from 2005-2008. The mean annual direct medical cost estimate was $3.96 billion. McDonald et al.'s[31] estimate for the direct costs for 2001 and 2002 was $2.13 billion (mean annual cost of $1.07 billion). The difference between the two estimates is likely due to inflation, an increase in the amount of services utilized, different criteria for patient selection, and difference in types of services included while calculating direct costs. Wu et al.'s[10] estimate for the direct cost for 2002 was $30.3 billion, of which $9.3 billion was attributed to direct non-medical costs. Yet, the annual direct health care costs estimate of $22.7 billion was also much higher than our annual estimate of $3.96 billion. The difference in Wu et al.'s and our estimate was probably because our estimate was limited to community-dwelling people and did not include the cost of long-term care. According to Wu and his colleagues, long-term care costs account for nearly 35% of the total direct medical costs. In addition, different methods were used for the cost calculations in the two studies. Wu et al. used the incremental cost approach while we used the attributable cost approach. Also, in the study by Wu et al., a combination of Medicare, Medicaid, and private insurance databases were used while we used MEPS which has patient reported information collected through interviews. The mean cost per patient according to Wu et al.'s study was $15,464 while in our study the mean per patient cost estimate was $5,586. The difference is likely due to a combination of several factors including inflation, increase in utilization of services, and including costs for different services.

The inpatient hospitalization costs accounted for about 21% of the total costs. A review of the previous cost-of illness studies for schizophrenia has shown a decrease in inpatient hospitalization costs as a proportion of the total direct medical costs over the years.[9,10,26,27,28,31]

The weighted number of patients with inpatient hospitalizations was only 282,736 out of a possible 3.03 million patients with schizophrenia. However, the mean cost per patient for those who had inpatient hospitalizations was $12,088. Thus, although the number of inpatient hospitalizations was relatively low, the cost per patient for hospitalizations was very high and therefore, they contributed a major proportion of the direct health-related costs for the disease. McEvory suggests that the decrease in inpatient hospitalizations with time is probably due to the introduction of new second-generation antipsychotic medications and careful monitoring of patients by the hospital staff which enable them to achieve outpatient status quickly.[32]

Prescription medications accounted for 39% of the direct costs and this is in agreement with that reported by McDonald et al.[31] The high proportion of prescription medication costs is because medications are cornerstones for treatment in schizophrenia, for both acute schizophrenia and as maintenance medications. Outpatient visits, emergency department visits, and physician visits together accounted for 29% of the direct costs. This number is similar to the 31% reported by Wu et al.[10] but slightly less than the 37% reported by McDonald et al.[31] The differences are probably due to the differences in the methods of calculations and types of costs included. A general trend of increase in the proportion of outpatient costs and decrease in the proportion of inpatient costs has been observed over the past few years due to the availability of a variety of services such as psychologists, physicians, social workers, and others[32] Home healthcare costs accounted for 12% of the direct costs in this study. This is very similar to that from the study conducted by McDonald et al. Although the number of people with home healthcare visits was not very large (291,286) as compared to 3.03 million patients with schizophrenia, the cost per patient was quite high $6,852, which contributes to the total cost of home healthcare.

Although some health care services (inpatient hospitalizations and home healthcare) were found to be expensive, studies conducted in the past have shown that assisted living facilities are far more expensive than patients living independently.[69] The use of outpatient services and medications was found to be higher among patients living in long-term care facilities. This difference may be due to poorer health of patients living in such facilities as compared to those living in their own homes. However, according to Gilmer et al., homeless people are more likely to stay in group or community housing facilities than live independently.[60] Therefore, in order to care for homeless patients with schizophrenia, policies aimed at subsidizing such facilities for mentally ill patients might help improve outcomes and control costs due to hospitalizations and emergency room visits.

In this study, males had slightly higher schizophrenia-related costs (on an average) as compared to females. This was consistent with that observed by Rascati et al.[42] who reported that females were associated with lower schizophrenia-related direct costs as compared to males. Dixon et al. also observed that Caucasians have higher expenditures as compared to blacks;[33] however, the opposite was observed in this study. This is probably due to the higher utilization of more expensive services (e.g., inpatient hospitalizations, home healthcare) among black people. Medicaid enrollees were found to have high schizophrenia-related ambulatory costs in a study conducted by Dixon et al.; a similar trend was seen in this study where patients with public insurance had higher schizophrenia-related costs as compared to those with private or no insurance. Married patients have higher schizophrenia-related direct cost expenditures as compared to widowed patients probably because they have a lot of family support which enables them to be proactive and regular in utilizing the necessary health services to manage their schizophrenia symptoms. Divorced and separated patients had high schizophrenia-related costs

probably due to absence of family support and therefore, presence of more severe symptoms. Patients having a low socioeconomic status had higher expenditures than those having a high socioeconomic status. This is probably because those who are in the low-income category do not have insurance and therefore, wait too long before going to the physician to get help for their symptoms. By the time they do get help, their condition has reached an advanced stage where expensive services like hospitalizations are the only option.

Patients who rated their perceived health status as 'excellent' and those who rated it as 'poor' both had high costs. The reason for the high costs among those who rated their health state as 'excellent' is probably their proactive nature which may lead to higher use of the health services available to them. While for those who rated their health state as 'poor,' the reason for the high cost may be an inability to get timely help in the form of medications and ambulatory services due to their ill health. Patients who rated their mental health status as 'poor' also had higher direct costs as compared to the other patients. This is probably because these are the patients who are experiencing the symptoms of schizophrenia and hence, make maximum use of the health services available to them. According to Rascati et al.,[42] direct schizophrenia-related costs were higher for those patients who did not have co-morbidities as compared to those who did. However, the reverse was observed in this study.

Indirect costs

The annual indirect costs in the current study amounted to $15.35 billion. This is less than the most recent estimate of $32.4 billion obtained by Wu et al. in 2002.[10] This difference is likely due to the difference in methods of calculation of the components of the indirect costs. Our estimate of the annual indirect costs due to reduced work place productivity was $86.59 million which is much less than the estimate of $1.7 billion by Wu et al. This is probably due to the fact that Wu et al.'s estimate included institutionalized and non-institutionalized patients while our estimate was limited to community-dwelling US residents who suffered from schizophrenia.

The annual lost productivity due to increased unemployment was estimated at $21.6 billion by Wu et al. and $15.18 billion in the current study. Again, the difference can be attributed to the difference in the study population between the two studies.

Our estimate of annual lost productivity due to premature death was $46.97 million which is much less than Wu et al.'s estimate of $1.1 billion. This is due to the difference in the method of calculation of lost productivity due to suicide between the two studies. Wu et al. calculated the projected future earnings due to lost productivity over the expected life span of the patient and discounted them to 2002 values. We calculated the lost productivity due to premature death only for the year of death. Another reason for the vast difference between the two studies' estimates could be the difference in severity of the disease and likelihood of committing suicide between institutionalized people and community-dwelling patients with schizophrenia.

The annual caregivers' cost for this study calculated using the MEPS database was $37.53 million. Several studies have estimated caregivers' costs for people with schizophrenia. The values of the caregivers' cost obtained from literature and adjusted to 2005, 2006, 2007, and 2008 values were $8.54 billion, $8.79 billion, $9.09 billion, and $9.37 billion, respectively.[10]

The average value of the annual caregivers' cost obtained from literature would be $8.95 billion. Although one would expect the caregivers' costs for non-institutionalized patients to be more than that for institutionalized patients, our estimate was significantly less than the value obtained from literature. This is probably because limited number of schizophrenia patients due to the low prevalence of community-dwelling patients with schizophrenia in the MEPS dataset.

Kessler et al.[70] conducted a study using prevalence rates from the National Co-morbidity Survey Replicate (NCS-R) to evaluate the difference in earnings between those who have mental illnesses versus those who do not. It that study, mental illnesses were associated with a loss in personal earnings of $193.3 billion in 2002. Another study found that one-third of the days that people cannot perform their required tasks due to illness are a result of mental illness and not physical illnesses.[71] Yet, only 6.2% of the US budget is allocated to mental health.[72] Most people do not get treatment for mental health[73] and the treatment is much higher for physical disabilities as compared to mental disabilities with the same level of impairment.[74] The introduction of the Mental Health Parity and Addiction Equality Act ensures that if a group health plan or health insurance issuer offers both mental health and substance abuse benefit, these benefits must be on parity with the surgical/medical benefits.[75] Therefore, if out-of-network surgical and medical benefits are included, then out-of-network mental health and substance abuse benefits must also be included. This act prevents plans from imposing treatment limitations or financial requirements for mental health benefits or substance abuse coverage that are different from those for medical and surgical benefits.

The financial burden imposed by schizophrenia is disproportionately high. In 2000, depression had a prevalence of 8.7% (according to the National Co-morbidity Survey) and an associated expenditure of $83.08 billion.[76] According to the current study, the total annual cost

for community-dwelling patients with schizophrenia was $19.31 billion. Schizophrenia has a prevalence of 0.3%-1.6%;[2,3] however, our sample consisted of only community-dwelling patients with schizophrenia with an approximate prevalence of approximately 0.25%. Therefore, although the prevalence of depression is about 40 times more than that of schizophrenia, the costs associated with depression are only 4 times those associated with schizophrenia. However, one must note that the depression estimate is for 2000 and a more recent estimate will be much higher due to inflation, increase in utilization of services, and other factors.

Identification of factors associated with high direct costs

We did not find any study in the literature which used a logistic regression approach, as used in this study, to identify factors associated with high schizophrenia-related costs in the US. The logistic regression procedure demonstrated a significant negative relationship between age and cost category. Bartels et al.[34] found that younger patients were associated with higher expenditures for medications and outpatient services while older patients were associated with higher nursing home costs. Although the current study included home healthcare costs and inpatient costs, it did not include nursing home costs which was probably the reason for the negative relationship between age and costs. Patients with a spouse had significantly lower schizophrenia-related expenditures as compared to those without a spouse. This is probably due to the presence of family support which caused them to be more proactive in taking medications which leads to lesser use of expensive services like hospitalizations and this in turn decreases overall schizophrenia-related direct medical costs. These results are quite different from what could be predicted looking at the raw costs for each category. This is probably because the logistic regression procedure controls for other factors. Those who rated their perceived health status as 'poor' were more likely to be in the high-cost group as compared to those who rated it as 'excellent'. However, since the 95% confidence interval of the odds ratio crossed 1, we do not think that this variable significantly predicts high-cost group membership.

Recognizing that the limited sample size within each cost category may give inaccurate odds ratio estimates, ordinary least square regression was carried out. In this analysis, it was seen that older patients had lower costs compared to younger patients and white people had significantly lower costs compared to blacks. Since the costs were positively skewed, a log transformation was applied to the cost variable and the regression was repeated as a part of

sensitivity analysis. The only significant relationship seen here was that patients who rated their mental health status as ‘poor’ had higher costs compared to those who rated it as ‘excellent’. This is consistent with our hypothesis and is probably due to the presence a more advanced stage of the disease in the ‘poor’ raters which leads to higher schizophrenia-related expenditure. The log-transformed analysis was not included as a part of the main results due to the issues associated with interpreting coefficients for log-transformed dependent variables.

Identifying the high-risk population may help healthcare providers at the grass root level to be mindful of patients most likely to have high expenditures. Such patients may be assigned case managers early on during the course of their disease or healthcare providers could be extra careful to ensure that these patients are regular with their physician visits and take medications on a daily basis.

Limitations

The selection of the patients was done based on ICD-9 codes only. Physicians are known to give patients an interim non-schizophrenia diagnosis when uncertain about schizophrenia until it can be confirmed due to the stigma associated with the disease. Thus, some patients with schizophrenia may not have been identified. However, in order to capture patients who may be given an interim non-schizophrenia diagnosis, we used the ICD-9 code for non-organic psychoses in addition to that for schizophrenic disorder. One must also keep in mind that MEPS collects information about conditions through patient interviews and ability of the household participant to describe the condition in a way that it can be accurately coded using ICD-9 codes must not be assumed.[46] There are possibilities of miscoding of the ICD-9 codes.

We could not include direct non-medical costs due to the limited data available from MEPS. Travel time to the physician's office, cost for homeless shelters for patients with schizophrenia, law and order costs, cost for training physicians and nurses, and research costs also contribute substantially to the direct costs but were not included in the current study.

The estimate of the proportion of patients with schizophrenia who are employed, the proportion who commit suicide, the annual wages of the patients with schizophrenia, and the caregivers' costs were all obtained from literature. It must be recognized that there may be some uncertainty associated with these estimates. We did conduct sensitivity analyses around some of the important variables and have reported the results.

The cut-off point for the 'high' costs was arbitrarily chosen. This was done in order to ensure that each cost category had a sufficient number of cases and that we could get a clear demarcation between the cost categories.

While calculating the lost productivity costs for patients with schizophrenia, it was assumed that the days of work missed were due to the schizophrenia-related symptoms. The patients with schizophrenia could have been suffering from other diseases as a result of which they may have missed work. Thus, a sensitivity analysis was conducted around the cost of lost productivity due to missed work days which were varied over a ±50% range.

In the calculations of the caregivers' costs, it was assumed that if a schizophrenia patient had a family member who reported missed work days in caring for another person, it would be because the family member was taking care of the schizophrenia patient. This might not be the case, as the caregiver could have missed work to care for a person other than the schizophrenia patient. Because of this uncertainty, a sensitivity analysis was conducted on the caregivers' costs and they were varied over a ±50% range.

The lost productivity cost per person for the patients with schizophrenia and caregivers' was calculated as the product of the daily wages and the number of missed work days. People who had missed work due to an illness or in order to care for an ailing family member would have lower wages than what they should be earning as a result of the missed work. Thus, using these wages to estimate the lost productivity cost due to missed work days would underestimate the indirect cost. An option would be to use the wages reported by the Bureau of Labor Statistics for each occupation, but even this this case some assumptions would have to be made as the wages are reported for broad occupational categories.

Due to the overlapping panel design in MEPS, half the patients from each year were included in the following year's sample. Therefore, the patients used for the logistic regression procedure, which was carried out on a sample of all the patients with schizophrenia between 2005 and 2008, were not mutually independent. However, if the costs for the same patient from

consecutive years were added, then for patients with schizophrenia from 2006 and 2007, costs from two years would be counted while for patients from 2005 and 2008 (the first and last year included in the analyses) the costs from only one year would be accounted for. In order to avoid the inconsistency of costs accounted for by different patients, we chose to treat the patients as independent observations. According to MEPS documentation, it is valid keep all observations and treat them as independent as each year's data is designed to be nationally representative.

For the regression procedure, the data were not normally distributed. However, the surveyreg command is quite robust to non-normality in the presence of a sufficiently large sample size and therefore, was used for this analysis. As a method for sensitivity analysis, we carried out a log-transformation of the costs and repeated the regression procedure. However, one must recognize the limitations to interpreting the regression coefficients when the dependent variable is log-transformed.

The number of patients who had a diagnosis for schizophrenia based on ICD-9 codes in our final analytical file was 362. Of that, only 348 patients had positive person weights. Of the 348, some patients had missing ages and regions of residence. Therefore, even fewer were included in the final logistic regression analyses. As a sensitivity analysis, the missing ages were imputed using the mean and the missing regions of residence were imputed with the modal value for the region of residence and the results have been reported in Appendix A. The limitation of a small sample size for this study must be recognized.

The R^2 for the regression procedure was about 0.0734. Therefore, the variables included in the model only explained about 7% of the variance in the dependent variable. The remaining 93% of the variability is not explained by the current predictors. This must be kept in mind while interpreting the results.

Strengths

The dataset used for the current study, the Medical Expenditure Panel Survey, is representative of the non-institutionalized US population. Therefore, the sample used in this study represents the intended population fairly well. This study provides the most recent direct medical and indirect cost estimates for community-dwelling US residents with schizophrenia using a representative population. The costs were calculated from a societal perspective and hence, included all the costs paid by private insurance companies, public insurance programs, and patient out-of-pocket expenses as determined via face-to-face interviews with patients. The information collected from the patients via interviews was supplemented by that collected from their medical care providers to ensure good quality data.

The costs for a large variety of services commonly used by community-dwelling patients with schizophrenia were included in this estimate. Sensitivity analyses were conducted around those estimates that were obtained from the literature and therefore, might have some associated uncertainty.

This was the first study that conducted a logistic regression procedure to identify patients in the US associated with high and low schizophrenia-related costs. Regression was also carried out to determine the strength of association between the predictors and costs. Several predictors that could affect the schizophrenia-related direct costs were included in the model.

Future research

Replication of the study using a dataset obtained by combining MEPS data from several years in order to obtain a larger sample size might help clarify the relationship of the various independent variables with costs. Inclusion of other components of cost, such as research costs, criminal justice system costs, homeless shelter costs, cost of presenteeism, and others would give a more accurate estimate of the costs associated with the disease. The present study only looked at the costs for community-dwelling patients. Inclusion of patients in prisons, institutions, nursing homes, assisted living facilities, and homeless patients would give a more inclusive estimate of the financial burden of schizophrenia.

Future research could focus on investigating how new pharmaceutical treatments and easy access to help in the form of psychiatrists and social workers could lead to potential reduction in expensive services such as inpatient hospitalizations.

Inclusion of other factors such as past hospitalizations, professional status, duration of disease, and others in the regression model that may be able to explain some of the unexplained variability in the costs would be helpful. This may provide a better picture of the contribution of different factors to the overall cost.

Conclusions

Cost-of-illness studies for diseases are important because indicators such as prevalence and mortality cannot convey the true economic burden of the disease.[77] Decision makers can benefit from such estimates as cost containment efforts directed at only one or two cost categories of schizophrenia-related costs could have unintended consequences. For instance, if medication costs are increased, it has been seen that patients forego 5% of their antipsychotic medications when faced with financial barriers. In addition, gaps in antipsychotic therapy is an important predictor of inpatient hospitalizations,[40] one of the most expensive healthcare services. Cost-of-illness studies may also help highlight the need for funding for effective mental health programs such as rehabilitation and first-episode treatment programs and also for research and development. Finally, such studies pave the path for cost-effectiveness and modeling studies in which different treatments can be compared in real or hypothetical populations.

Several studies have been conducted worldwide to estimate the financial burden of schizophrenia and all the studies have found that despite its low prevalence, schizophrenia is associated with very high costs.[78,79] This cost-of-illness study provides the most recent estimate for the direct medical and indirect costs of schizophrenia for community-dwelling US residents. The total cost for the 4-year period from 2005 to 2008 was estimated at $77.25 billion dollars which is about $19.31 billion annually. This highlights the financial burden of schizophrenia on society. Costs for each category of health care services were evaluated which helps identify the expensive services. The logistic regression procedure aids in the identification of demographic and clinical characteristics associated with high costs. This could help policymakers identify high-risk groups.

In recent years, policy makers and researchers have been trying to find ways to improve the delivery of healthcare while preventing a further rise in healthcare costs, especially for the subset of patients who are responsible for a disproportionately large share of the overall health care spending.[80] This study provides the most recent estimate of the cost-of-illness for community-dwelling patients with schizophrenia who are responsible for a disproportionately high financial burden on the US economy. This cost estimate may help health care providers and policymakers better understand the economic burden of schizophrenia and identify services associated with the highest costs so that the provision of healthcare services to patients with schizophrenia and patient outcomes can be optimized.

Appendix

<u>Figure A1:</u> Plot of predicted values vs. residuals which satisfies regression assumptions

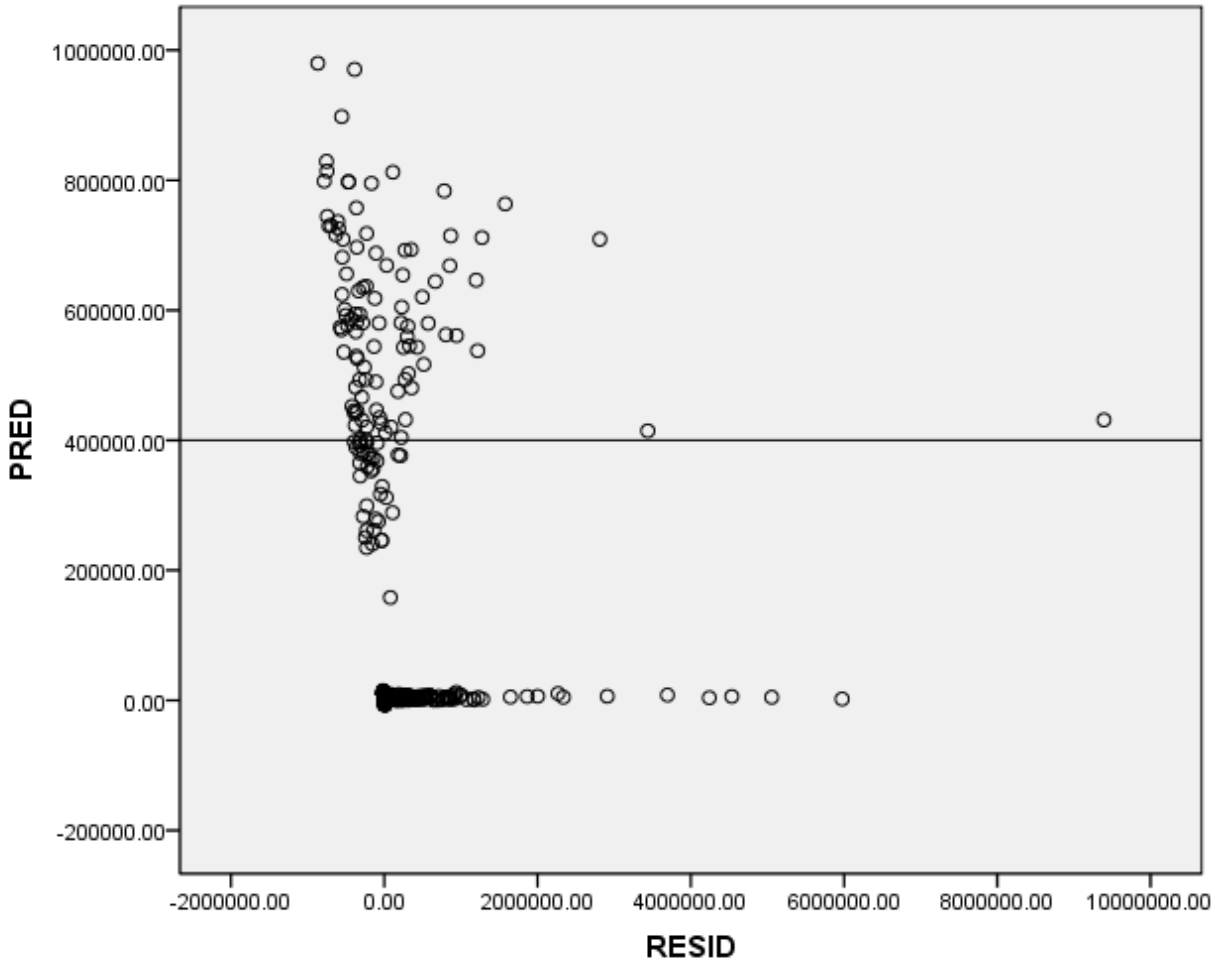


Table A1: Results of linear regression of the log-transformed direct costs by demographic and clinical variables

Variable	Estimate	t-value	p-value
Age	-0.0075	-0.87	0.4187
Gender (male = reference group)			
Female	-0.3100	-1.09	0.2750
Race (white = reference group)			
Black	-0.4472	-1.25	0.2126
Other	-0.2208	-0.36	0.7220
Marital status (no spouse = reference group)			
With spouse	0.2011	0.67	0.5063
Insurance status (private insurance = reference group)			
Public	0.3208	0.89	0.3750
No insurance	-0.8615	-1.47	0.1426
Region (Northwest = reference group)			
Midwest	-0.0890	-0.21	0.8355
South	-0.5563	-1.40	0.1618
West	-0.1203	-0.22	0.8222
Socioeconomic status (high = reference group)			
Low	-0.1592	-0.54	0.5874
Perceived health status (excellent = reference group)			
Good	-0.1987	-0.57	0.5713
Poor	-0.7524	-1.12	0.2650
Mental health status (excellent = reference group)			
Good	0.6236	1.42	0.1566
Poor*	1.2399	2.54	0.0144
Presence of co-morbidities (no = reference group)			
Yes	0.3902	1.42	0.1559

Overall model statistics: $F=973.72$; $p<0.001$
*statistically significant at $p<0.05$

Table A2: Sensitivity analyses- Results of logistic regression procedure for dichotomized direct costs by demographic and clinical variables

Demographic/Clinical characteristic	Estimate	Wald's Chi-square	p-value	Odds ratio	95% CI of odds ratio	
					Lower	Higher
Age*	-0.0547	9.0849	0.0026	0.947	0.914	0.981
Gender (males = reference group)						
Females	-0.1936	0.5959	0.4401	0.679	0.254	1.815
Race (black = reference group)						
White*	-1.0342	6.144	0.0132	0.262	0.071	0.966
Other	0.7299	1.6098	0.2045	1.531	0.235	9.961
Marital status (no spouse = reference group)						
Has spouse*	-0.8234	4.0286	0.0447	0.193	0.039	0.962
Insurance coverage (private insurance = reference group)						
Public insurance	0.3233	0.8089	0.3684	1.428	0.381	5.35
No insurance	-0.2902	0.3195	0.5719	0.773	0.126	4.745
Region (Northeast = reference group)						
Midwest	-0.0184	0.0019	0.965	0.965	0.225	4.129
South	-0.3753	1.0359	0.3088	0.675	0.172	2.657
West	0.3761	1.0357	0.3088	1.431	0.35	5.858
Socioeconomic status (high income = reference group)						
Low income	-0.1144	0.1198	0.7293	0.796	0.218	2.906
Perceived health status (excellent = reference group)						
Good	-0.3561	0.8530	0.3557	1.397	0.273	7.161
Poor*	1.0467	5.0562	0.0245	5.682	0.886	36.449
Mental health status (excellent = reference group)						
Good	-0.0696	0.0267	0.8702	0.624	0.085	4.562

Table A2: continued

Demographic/Clinical characteristic	Estimate	Wald's Chi-square	p-value	Odds ratio	95% CI of odds ratio	
					Lower	Higher
Poor	-0.3331	0.4052	0.5244	0.479	0.051	4.511
Presence of co-morbidities (no = reference group)						
Yes	0.2776	1.0880	0.2969	1.742	0.614	4.945

Overall model statistics: Wald's Chi-square= 37.07; p=0.0021
*significant at p<0.05

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