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OCCURRENCE, MORTALITY, AND COST OF BRAIN DISORDERS IN DENMARK: A POPULATION-BASED COHORT STUDY

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ABSTRACT

Objectives

To examine the occurrence of brain disorders (*i.e.,* neurological and mental disorders) in Denmark and mortality and cost-of-illness among affected persons.

Design

Matched cohort study.

Setting

We obtained routinely collected registry data on all Danish residents during 1995-2015.

Participants

We identified all persons alive on 1 January 2015 with a diagnosis of 25 specific brain disorders (prevalent cohort) and all persons with an incident diagnosis during 2011-2015 (incident cohort). Each person was matched on age and sex with 10 persons from the general population without a diagnosis of the specific brain disorder at the time of matching.

Primary and secondary outcome measures

Prevalence and incidence of hospital-diagnosed brain disorders, 1-year absolute and relative mortality, and attributable direct and indirect costs-of-illness.

Results

We identified 1,075,081 persons with prevalent brain disorders on 1 January 2015, corresponding to 18.9% of the Danish population. The incidence rate of *any brain disorder* during 2011-2015 was 1,349 per 100,000 person-years (95% confidence interval [CI]: 1,345-1,353). One-year mortality after diagnosis was increased in persons with *any brain disorder* (hazard ratio = 4.7 [95% CI: 4.7-4.8]) and in persons in every group of specific brain disorders compared to the matched cohort from the general population. The total attributable direct costs of brain disorders in 2015 were €5.2 billion and total attributable indirect costs

were €11.2 billion. Traumatic brain injury, stress-related disorders, depression, and stroke were the most common brain disorders. Attributable costs were highest for depression, dementia, stress-related disorders, and stroke.

Conclusions

One in five Danish residents alive on 1 January 2015 had been diagnosed with at least one brain disorder, and mortality was five times higher in persons with any diagnosed brain disorder than in the general population. We found high attributable direct and indirect costs of brain disorders.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- We examined epidemiology and societal costs of hospital-diagnosed brain disorders using individual-level data on a well-defined population with complete follow-up.
- Both epidemiology and cost were estimated among persons with one of 25 specific brain disorders, and among persons with any brain disorders taking into account comorbid disorders.
- We identified persons with incident brain disorders during 2011-2015, whereas persons alive on 1 January 2015 with brain disorders diagnosed from 1995 to 2014 were considered prevalent.
- We estimated 1-year mortality among persons with incident brain disorders, and direct and indirect societal costs among persons with prevalent brain disorders.
- Direct costs included cost of services in primary care, secondary care, and costs of medication, nursing home, sheltered accommodation, personal nursing, home nurse visits, and hospital-based neuro rehabilitation, whereas lost productivity was considered indirect costs.

BACKGROUND

Brain disorders, including both neurological and mental disorders, are the leading cause of years lived with disability worldwide.[1, 2] In 2010, it was estimated that 260 million persons in Europe (~50% of the population) lived with a brain disorder with an estimated total cost-of-illness of €798 billion.[3, 4] Based on this appraisal, mental disorders alone were estimated to account for 4.1% of European countries' combined gross domestic product (GDP) in 2015.[5] The global burden of brain disorders is expected to double between 2010 and 2030.[6, 7]

Previous estimates of overall occurrence and cost of brain disorders relied using heterogeneous data sources without individual-level data. This excluded consideration of comorbid brain disorders in estimates of the incidence, prevalence, mortality, and cost-of-illness of brain disorders.[2, 3, 8] Therefore, single persons with multiple disorders were counted more than once, causing potential overestimation of the occurrence. Previous studies also focused on cause-specific mortality rather than all-cause mortality. This could have led to underestimation of excess mortality associated with brain disorders due to incompletely recorded brain disorders on death certificates.[2, 9] Thus there is a need for valid updated estimates of occurrence, mortality, and cost of brain disorders to better understand the public health burden and healthcare planning needs.[7]

We conducted this population-based study using routinely collected individual-level registry data to examine the prevalence and incidence of brain disorders in the Danish population during 2011-2015, as well as mortality and cost-of-illness in these patients.

METHODS

Setting

We conducted a population-based cohort study encompassing the entire Danish population during 2011-2015. In Denmark, healthcare is primarily tax-funded with equal access for every Danish resident. We examined occurrence, mortality, and costs of brain disorders using nationwide data from healthcare and socioeconomic registries.[10]

Study design and participants

For each of 25 specific brain disorders, we established two cohorts: a prevalent cohort of persons alive on 1 January 2015 who had a diagnosis of the specific brain disorder recorded during the 1995-2014 period and an incident cohort of persons with a first-time diagnosis recorded during the 1 January 2011 to 31 December 2015 period. The following 25 predefined groups of brain disorders were examined: *alcohol abuse, anxiety disorders, bipolar disorder, brain tumours, cerebral palsy, dementia, depression, developmental and behavioural disorders, drug abuse, eating disorders, epilepsy, headache, infections of the central nervous system, intellectual disability, multiple sclerosis, neuromuscular disorders, other neurodegenerative disorders, Parkinson's disease, personality disorders, polyneuropathy, schizophrenia spectrum disorders, sleep disorders, stress-related disorders, stroke, and traumatic brain injury.* We also identified every Danish resident with *any brain disorder*, *i.e.*, each person with any of the specific 25 disorders was identified on the date of his or her first diagnosis.

For each of the 25 groups of brain disorders and the *any brain disorder group*, we created a matched comparison cohort for the incident cohort and a matched comparison cohort for the prevalent cohort. Each person in the two brain disorder cohorts was matched to 10 living persons from the general population on birth year and sex. Matched persons could not have the specific brain disorder as of the index date of the person with the brain disorder. The index dates of matching were the date of the brain disorder diagnosis for the incident cohort and 1 January 2015 for the prevalent cohort.

Variables

The unambiguous personal identifier assigned to every Danish resident enabled us to identify and link every person across national registries to estimate occurrence, mortality, and cost-of-illness of brain disorders on the individual level (see detailed description of the data sources in Appendix 1).[10]

We identified persons with brain disorders by means of inpatient and outpatient hospital diagnoses (both primary and secondary diagnoses) coded in the Danish National Patient Registry according to the *International Classification of Diseases, Tenth Revision* (ICD-10).[11] ICD codes are provided in Appendix 2.

To estimate mortality, we retrieved the dates of death of persons who died during the study period from the Danish Civil Registration System.[10]

To estimate direct costs, we obtained individual-level information on all primary care services provided by general practitioners and dentists from the Danish Health Service Registry,[12] individual-level medication expenditures from the Danish National Prescription Registry,[13] and individual-level information on nursing home or sheltered accommodation, personal nursing and other personal care, home nurse visits, and hospital-based neuro rehabilitation from Statistics Denmark.[14] We also computed costs of secondary care including hospital inpatient admissions, outpatient specialist clinic visits, and emergency room contacts based on the Diagnosis Related Group (DRG) and Danish Ambulatory Grouping System (DAGS) tariffs.[15] Medication costs were computed using market prices for prescriptions filled at outpatient pharmacies and in-hospital medication costs were included in the DRG/DAGS tariffs. To estimate indirect costs, we first estimated lost productivity associated with illness by subtracting the personal income of persons in the matched comparison cohorts from the personal income of persons with brain disorders (all before taxes). We then estimated lost productivity due to premature death (difference in actual age of death and expected age at death based on the average life expectancy of persons of same age and sex in Denmark). We obtained 2015 cost information for persons in the prevalent cohort and their comparison cohort and from index date for persons in the incident cohort and their comparison cohort.

Finally, we obtained information on prior comorbid brain disorders and on prior non-mental disorders included in the Charlson Comorbidity Index (CCI) up to 10 years before the index date of every person in the brain disorder and comparison cohorts.[11] Using the comorbid diseases included in the CCI, we calculated a CCI score for every person (CCI score: 0 = low, 1-2 = medium, 3+ = high comorbidity).[16, 17]

Statistical analyses

Occurrence

We used any diagnosis from 1 January 1995 to 31 December 2014 as the basis for computing the period prevalence of each of the 25 brain disorders in persons alive on 1 January 2015. To estimate the average annual incidence of the different brain disorders, we computed incidence rates (IRs) of newly diagnosed persons per 100 000 person-years at risk between 1 January 2011 and 31 December 2015. We considered a person to be at risk of an incident specific brain disorder only if he or she did not have a diagnosis of that specific brain disorder during 1995-2010. We characterised persons with brain disorders by age, sex, CCI conditions, and CCI score on the index date across the 25 groups of disorders.

Mortality

We computed 1-year mortality for persons with brain disorders and for persons in their matched comparison cohorts and compared these by means of crude and adjusted hazard ratios (HRs) obtained from a Cox regression model adjusted for age, sex, and CCI score.

Cost-of-illness

To estimate the economic burden of the 25 brain disorders, we used the human capital approach to conduct a societal cost-of-illness analysis including both direct and indirect individual-level costs.[18, 19] For each brain disorder, we computed direct and indirect costs-of-illness for every individual in our study population. We estimated both overall annual costs and average annual costs per person. Direct costs were computed both as actual direct costs (*i.e.*, costs of healthcare services) and attributable direct costs (*i.e.*,

the cost of healthcare services for persons with brain disorders minus the cost of healthcare services for persons of the same age and sex in the comparison cohorts). For persons with incident brain disorders, we further computed the distribution of the attributable direct costs per person during the first year after the diagnosis, as we expected substantial direct and indirect costs during this year.

We computed attributable indirect costs (*i.e.,* loss of productivity) in patients of working age, *i.e*., ages 18-65 years. In persons living with brain disorder diagnoses, we computed loss of productivity associated with illness as yearly income before taxes in persons with brain disorders subtracted from the yearly income in living members of the comparison cohorts. For persons who died after diagnoses of brain disorders, we estimated loss of productivity due to premature death as the annual income during the year before death multiplied by the number of lost years of life, assuming that they otherwise would have survived to age 66 years (accounting for the risk of dying each year and discounting future costs with 4% per annum).[18, 19]

Sensitivity analyses

As *alcohol abuse, bipolar disorder, dementia, depression, drug abuse, headache, multiple sclerosis, Parkinson's disease, and sleep disorders* are commonly treated in general practice, we performed sensitivity analyses that included both persons with hospital diagnoses and persons who filled prescriptions for relevant pharmacological treatments (including information on indication for the prescription when relevant).[13] We repeated all occurrence and cost analyses on these extended cohorts.

In addition, we performed attributable cost analyses, in which we modelled the average annual costs per person for each group of brain disorders using an ordinary least squares (OLS) regression, adjusting for comorbid brain disorders in individuals with more than one brain disorder.

Analyses were performed using SAS version 9.4 (Cary, NC, USA), and visualization was made using Tidyverse packages in R version 3.6.1.[20] The study was approved by the Danish Data Protection Agency through registration at Aarhus University (record number 2016-051-000001/603). According to Danish legislation,

no approval from an ethics committee or informed consent from patients is required for registry-based studies.

Patient involvement statement

This study was done without patient involvement. Patients were not invited to comment on the study design, to develop patient relevant outcomes, or interpret the results. Patients were not invited to contribute to the writing or editing of the manuscript.

RESULTS

Patient characteristics

The characteristics of 1 075 081 persons with prevalent brain disorders in 2015 are displayed in Figure 1, and those of 381 759 persons with incident brain disorders during 2011-2015 are displayed in Suppl. Figure 1. Approximately half of persons with *any brain disorder* were female, occurrence was stable across ages, and three out of four persons had no or mild comorbidity (both in the prevalent and incident cohorts) (Figure 1, Suppl. Figure 1, Suppl. Table 1, and Suppl. Table 2). The proportions of persons with specific brain disorders who were diagnosed with specific comorbid somatic or mental disorders before index date are displayed in Suppl. Figure 2.

Occurrence

On 1 January 2015, 18.9% of the Danish population had been diagnosed with *any brain disorder*. Among persons without prior brain disorder diagnoses, the IR of *any brain disorder* was 1 349 per 100 000 person-years during 2011-2015 (Suppl. Table 3).

The prevalence in 2015 and incidence in 2011-2015 of the 25 groups of brain disorders in the Danish population are displayed in Figure 2. *Traumatic brain disorders* were the most common brain disorders, with a prevalence of 4.4% (Figure 2 and Suppl. Table 3), followed by *stress-related disorders* (3.4%) and *depression* (3.2%) (Figure 2).

During 2011-2015, IRs were highest for *stress-related disorders* (286 per 100 000 person-years [95% CI: 284-288]) and *depression* (279 per 100 000 person-years [95% CI: 277-281]) (Figure 2 and Suppl. Table 3).

Mortality in persons with incident brain disorders

One-year mortality was 7.8% among persons with *any brain disorder*, compared to 1.9% in the comparison cohort. After adjustment, persons with *any brain disorder* still had almost five-fold increased mortality (HR=4.7 [95% CI: 4.7-4.8]), and the HRs were increased in every group of brain disorders. One-year mortality was highest in persons with *other neurodegenerative disorders* (28.0%), *brain tumours (*24.5%), *stroke* (20.8%), and *dementia* (20.3%). Of note, mortality was more than ten-fold increased in persons with *other neurodegenerative disorders* (HR of 15.3 [95% CI: 13.2-17.7]), *brain tumours* (HR of 13.2 [95% CI: 12.4-14.0]), and *anxiety disorders* (HR of 12.8 [95% CI: 12.4-13.3]) (Figure 3).

Cost-of-illness

The total direct attributable costs of *any brain disorder* were €5.2 billion in 2015 in Denmark, with increased costs in every group of brain disorders. Specifically, attributable direct costs were highest in patients with prevalent *depression* (€1.2 billion), *dementia* (€1.1 billion), and *stroke* (€1.0 billion) (Figure 4 and Suppl. Table 4). Importantly, the distribution of cost components varied considerably between brain disorders (Figure 4 and Figure 5).

Of note, the highest attributable costs per person in persons with prevalent brain disorders in 2015 was found in persons with *dementia* (€30K) and *Parkinson's disease* (€24K), mainly due to costs of nursing home/sheltered accommodation (Figure 5 and Suppl. Table 4).

The average attributable direct costs of *any brain disorder* during the first year after diagnosis was €13K, though these differed widely between persons with different disorders. Costs were highest during the first year in persons with incident *brain tumours* (€44K) and *schizophrenia spectrum disorders* (€39K) (Suppl. Figure 3 and Suppl. Table 4).

Productivity of persons with brain disorders was reduced in every group of brain disorders. The total indirect costs in 2015 were €11.2 billion in persons with *any brain disorder*, mostly due to loss of productivity associated with illness (€10.9 billion) and less due to loss of productivity due to premature death (€0.3 billion). Specifically, lost productivity was €3.2 billion in persons with *stress-related disorders*, €2.9 billion in persons with *depression*, and €2.2 billion in persons with *alcohol abuse*. Finally, we found that the indirect costs were largely made up of costs due to lost productivity in patients living with illness, while costs due to lost productivity due to premature death contributed little (Figure 6 and Suppl. Table 5).

Sensitivity analyses

Adding persons with filled prescriptions to the hospital-diagnosed cohorts, we found that occurrence of *alcohol abuse*, *bipolar disorder*, and *dementia* increased little, while occurrence of *anxiety disorders*, *depression*, *headache*, *Parkinson's disease*, and *sleep disorders* increased several-fold (Suppl. Figure 4). Prevalence of *any brain disorders* increased to 30.2%, and total attributable costs in these persons in 2015 were €22.5 billion, of which direct costs were €6.5 billion and indirect costs were €16.0 billion (data not shown).

In the OLS regression, we accounted for comorbid brain disorders when estimating per-person costs associated with each brain disorder. We found that *dementia* (€23K) and *Parkinson's disease* (€17K) were associated with the highest per-person additional direct cost-of-illness after adjustment for comorbid brain disorders (Suppl. Figure 5). Of note, removing outliers (the 99% percentile) changed results considerably, indicating that the 1% of persons with highest costs-of-illness contributed a considerable share of the total costs.

DISCUSSION

We performed a study of occurrence, mortality, and cost of hospital-diagnosed brain disorders using high-quality, individual-level data. Brain disorders were common: one in five persons in Denmark had prevalent brain disorders in 2015. We found the most prevalent disorders to be *traumatic brain injury, stress-related*

disorders, and *depression,* whereas the disorders with the highest incidence were *stress-related disorders*, *depression,* and *stroke*. One-year mortality was five-fold increased in persons with *any brain disorder* and was increased in persons with any type of brain disorder. The attributable direct costs of persons with *any brain disorder* were more than €5 billion. The more common brain disorders—*depression, dementia,* and *stroke*—accounted for the highest total attributable direct costs among persons with prevalent disorders. Attributable direct costs per person were highest in persons with *dementia* and *Parkinson's disease*. The total attributable indirect costs due to loss of productivity in persons with any prevalent brain disorder were twice as high as direct costs.

Even though our findings are based on high-quality population-based registries, some limitations should be considered when interpreting our findings. We may have underestimated the prevalence, incidence, and total cost of non-severe brain disorders, as some patients were treated solely in general practice or were undiagnosed. This is especially relevant for disorder that are mainly treated in primary care, or not treated at all, and therefore were not captured in our main analyses such as *anxiety,*[21] *headache,*[22] and *sleep disorders*.[23] We addressed this in a sensitivity analysis that also identified patient-based filled prescriptions for relevant medications.

We estimated the period prevalence among living persons who had been diagnosed with brain disorders during the preceding 20 years, even though some disorders may be reversible. We chose this approach as a period with severe disease may affect future income and use of healthcare services.

Although we used all diseases from the CCI (covering 19 groups of disorders) to describe non-mental comorbidity and to adjust for confounding in our mortality analyses, we cannot rule out residual or unmeasured confounding in our estimates of HRs of death.[16, 17, 24]

While we had detailed data on direct costs, we lacked information on municipally supported rehabilitation, assistance supplies, and transportation costs related to treatment and rehabilitation. Similarly, our cost analyses did not include intangible costs (*e.g.*, due to decreased quality of life) and costs of informal care

provided by relatives, which may be considerable in conditions such as *dementia*.[25] Yet, we included costs of nursing homes, sheltered accommodation, and home nursing, and we found the annual cost per person with *dementia* (€30K) similar to that previously reported.[26, 27]

Our study described the cost-of-illness in patients with brain disorders, but did not isolate the cost of the disease itself as patients with brain disorders are known to have a high load of comorbidity.[28-30]

We estimated the prevalence and incidence of *any brain disorder* using individual-level data, which allowed us to capture concurrent brain disorders,[28] opposed to the prior studies based on literature reviews that included a mix of hospital-diagnosed disorders and disorders reported in population surveys.[3, 5] Beside using different eligibility criteria, double counting of individuals with concurrent brain disorders may explain the previously reported total 1-year prevalence of brain disorders of ~50% (260 million affected among 514 million population in Europe),[3] which is markedly higher than what we found despite including prevalent disorders during a 20-year period.[8, 9]

A recent Danish study reported a 2.5-fold increased mortality rate in persons with hospital-diagnosed mental disorders compared to persons from the general population,[31] which is markedly lower than mortality of *any brain disorders* in our study – likely explained by our use of different length of follow-up (*i.e.,* long-term as opposed to 1-year).

We found that the total attributable direct and indirect costs of brain disorders in Denmark in 2015 were €16.4 billion, equivalent to 5.9% of the Danish GDP (€273 billion in 2015).[32] This is only slightly higher than the recently reported costs of mental illness alone of €15 billion in Denmark in 2015 corresponding to 5.4% of the GDP.[5] However, when we included persons identified from filled prescriptions in addition to hospital-based diagnoses in sensitivity analyses, the prevalence increased and total attributable costs of *any brain disorders* increased substantially, indicating that the costs may be higher than previously estimated when not restricting to hospital-diagnosed persons.[3, 5]

Finally, previous Danish studies of selected brain disorders reported lower total costs of disorders such as dementia,[25] stroke,[33] Parkinson's disease,[34] and epilepsy.[35] These studies did not include costs of home nursing and nursing homes, and when accounting for that, our findings are comparable.[25, 33-35]

As the already large burden of brain disorders is expected to increase in the future,[6] prevention and effective early intervention are essential.[5] The potential to prevent stroke, infections of the central nervous system, and mental disorders is established, whereas the potential to prevent other neurological disorders remains unclear.[36, 37] As comorbidity load is substantial in persons with brain disorders, cost-of-illness may be reduced by preventing and improving treatment of comorbid disorders.[30]

We found that one in five persons alive in Denmark had been diagnosed with a brain disorder. One-year mortality was five-fold increased in persons with an incident brain disorder. Mortality was increased in every group of brain disorders, underscoring the illness of these patients. The severity also was reflected in the very high cost-of-illness in persons with brain disorders, with total attributable costs of €16.4 billion in Denmark in 2015, including direct costs of €5.2 billion and indirect costs of €11.2 billion.

Occurrence of brain disorders is expected to increase in the future. As brain disorders already use a large proportion of healthcare resources and come with high indirect costs, effective prevention and intervention strategies must be developed.

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CONTRIBUTIONS

CFC and HTS contributed to the study conception. CFC, HTS, NS, JO, SS, TBR, and SVV designed the study and wrote a statistical analyses plan. NS, JO, and SS outlined the economic methods, and SS and JO performed the data management and analyses of the economic data. TBR performed the remaining data management and analyses, and performed all final analyses. All authors interpreted the results, and TBR, SVV, and CFC visualized the data. SVV drafted the first manuscript, and all authors revised the manuscript and approved the final version.

COMPETING INTERESTS

The authors have no specific competing interests to declare.

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ETCHICAL APPROVAL

Not required.

DATA SHARING

Data are available as presented in the paper and in the Supporting Information files. According to Danish legislation, our approvals to use the Danish data sources for the current study do not allow us to distribute or make patient data directly available to other parties. Data access and information about availability is accessible through Statistics Denmark (website: https://www.dst.dk/en/TilSalg/Forskningsservice, e-mail: dst@dst.dk).

Figure Legends

Figure 1. Characteristics of patients with prevalent brain disorders in Denmark in 2015 sorted from highest to lowest prevalence (the white line in the age distribution represents the median age in each cohort).

Abbreviations: CNS, central nervous system; CCI, Charlson Comorbidity Index

Figure 2. Occurrence of brain disorders in the Danish population sorted from highest to lowest incidence, including incidence during 2011-2015 and prevalence in 2015.

Abbreviations: CNS, central nervous system

Figure 3. One-year mortality in patients with incident brain disorders in Denmark during 2011-2015 compared with the general population (comparison group). Hazard ratios are adjusted for age, sex, and comorbidity score. Specific disorders are sorted by hazard ratios.

Abbreviations: CI, confidence interval; CNS, central nervous system

Figure 4. Total attributable direct costs in persons with prevalent brain disorders in Denmark in 2015 (in 2015 prices) sorted from highest to lowest costs.

Abbreviations: CNS, central nervous system

Figure 5. Attributable direct costs per person in individuals with prevalent brain disorders in Denmark in 2015 (in 2015 prices) sorted from highest to lowest costs.

Abbreviations: CNS, central nervous system

Figure 6. Total attributable indirect costs due to lost productivity in persons with prevalent brain disorders in Denmark in 2015 (in 2015 prices) sorted from highest to lowest costs.

Abbreviations: CNS, central nervous system

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Figure 1: Characteristics of patients with prevalent brain disorders in Denmark in 2015 sorted from highest to lowest prevalence (the white line in the age distribution represents the median age in each cohort).

Abbreviations: CNS, central nervous system; CCI, Charlson Comorbidity Index

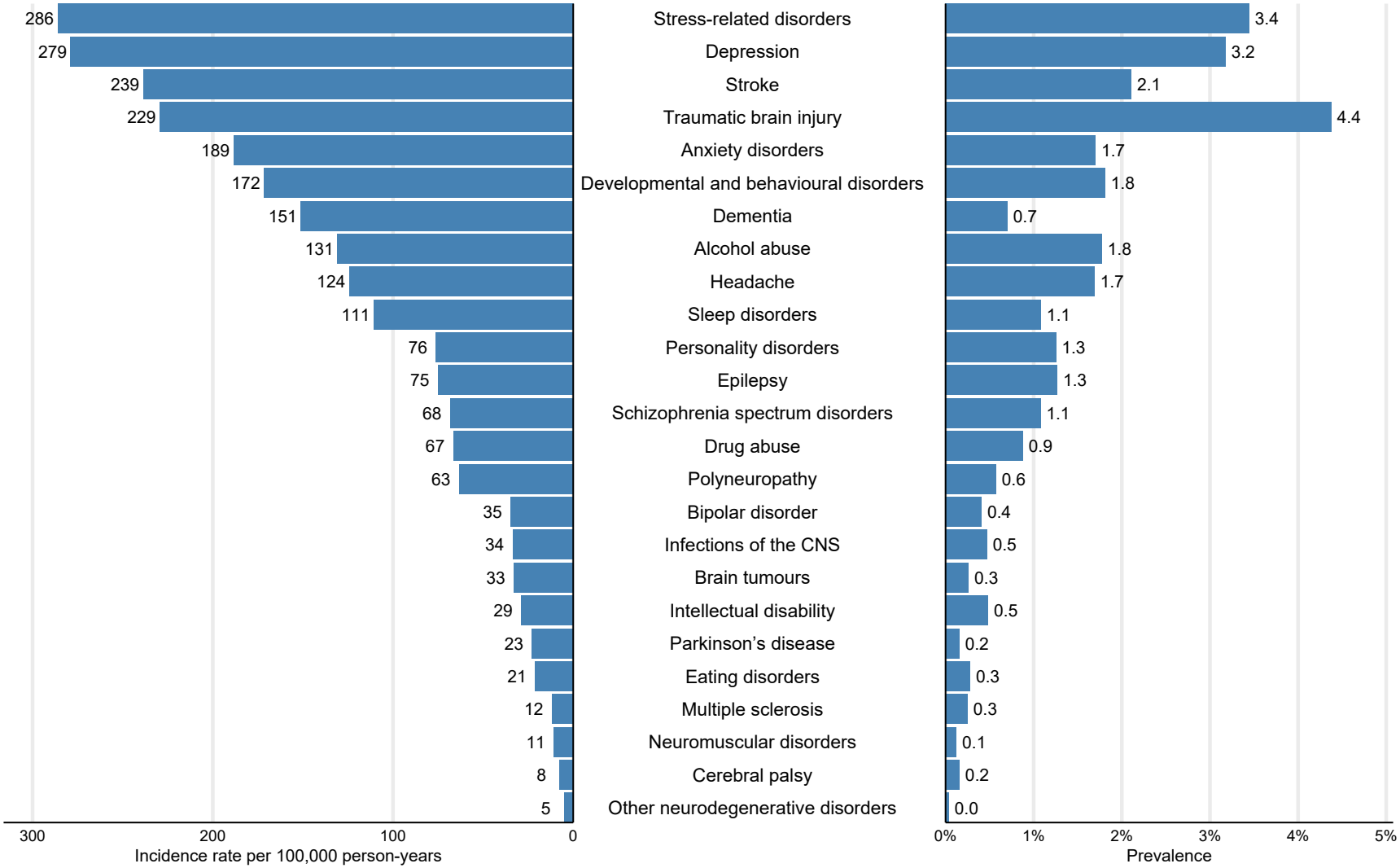


Figure 2: Occurrence of brain disorders in the Danish population sorted from highest to lowest incidence, including incidence during 2011-2015 and prevalence in 2015.
Abbreviations: CNS, central nervous system

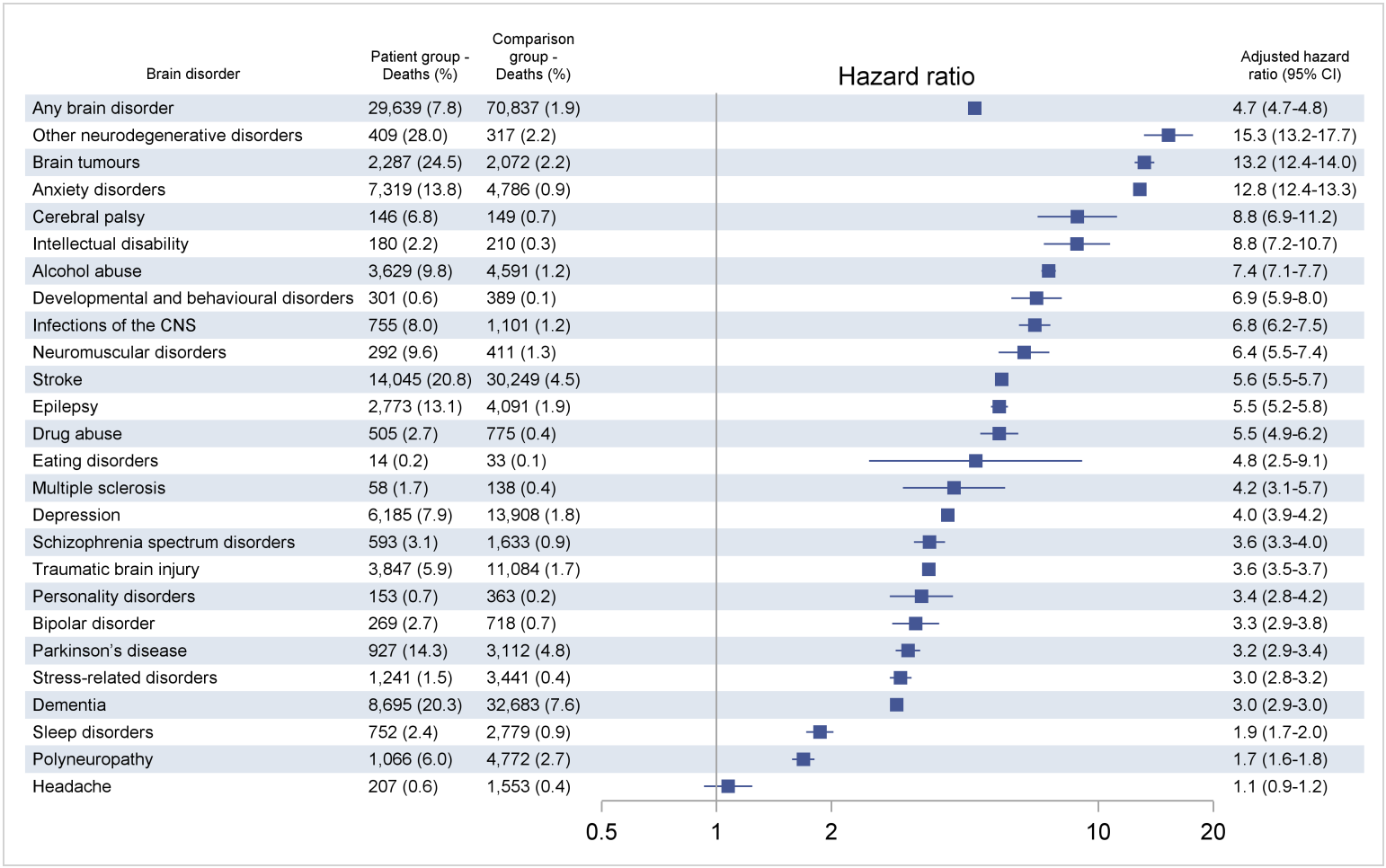


Figure 3: One-year mortality in patients with incident brain disorders in Denmark during 2011-2015 compared with the general population (comparison group). Hazard ratios are adjusted for age, sex, and comorbidity score. Specific disorders are sorted by hazard ratios. Abbreviations: CI, confidence interval; CNS, central nervous system

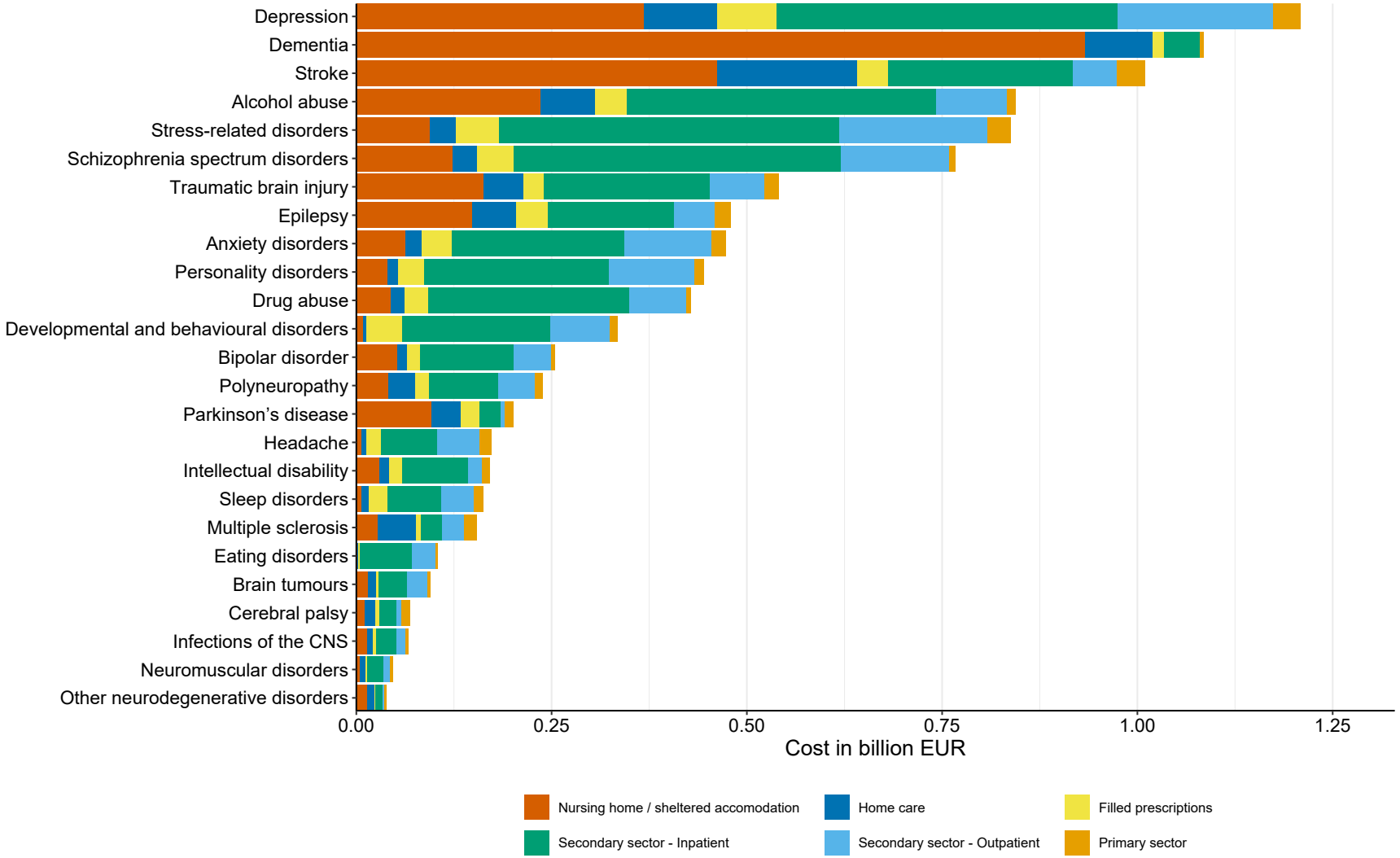


Figure 4: Total attributable direct costs in persons with prevalent brain disorders in Denmark in 2015 (in 2015 prices) sorted from highest to lowest costs.
Abbreviations: CNS, central nervous system

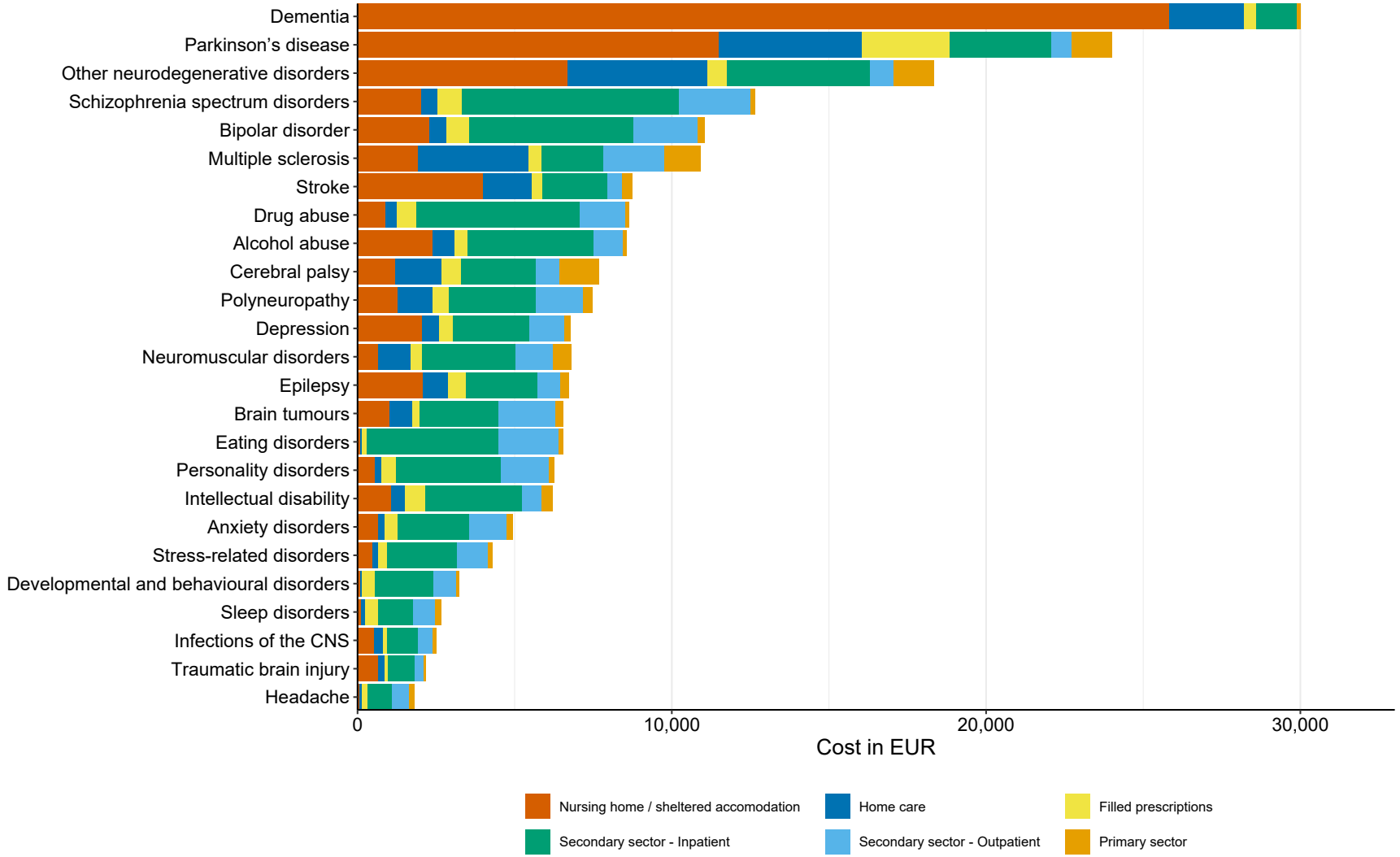


Figure 5: Attributable direct costs per person in individuals with prevalent brain disorders in Denmark in 2015 (in 2015 prices) sorted from highest to lowest costs.
Abbreviations: CNS, central nervous system

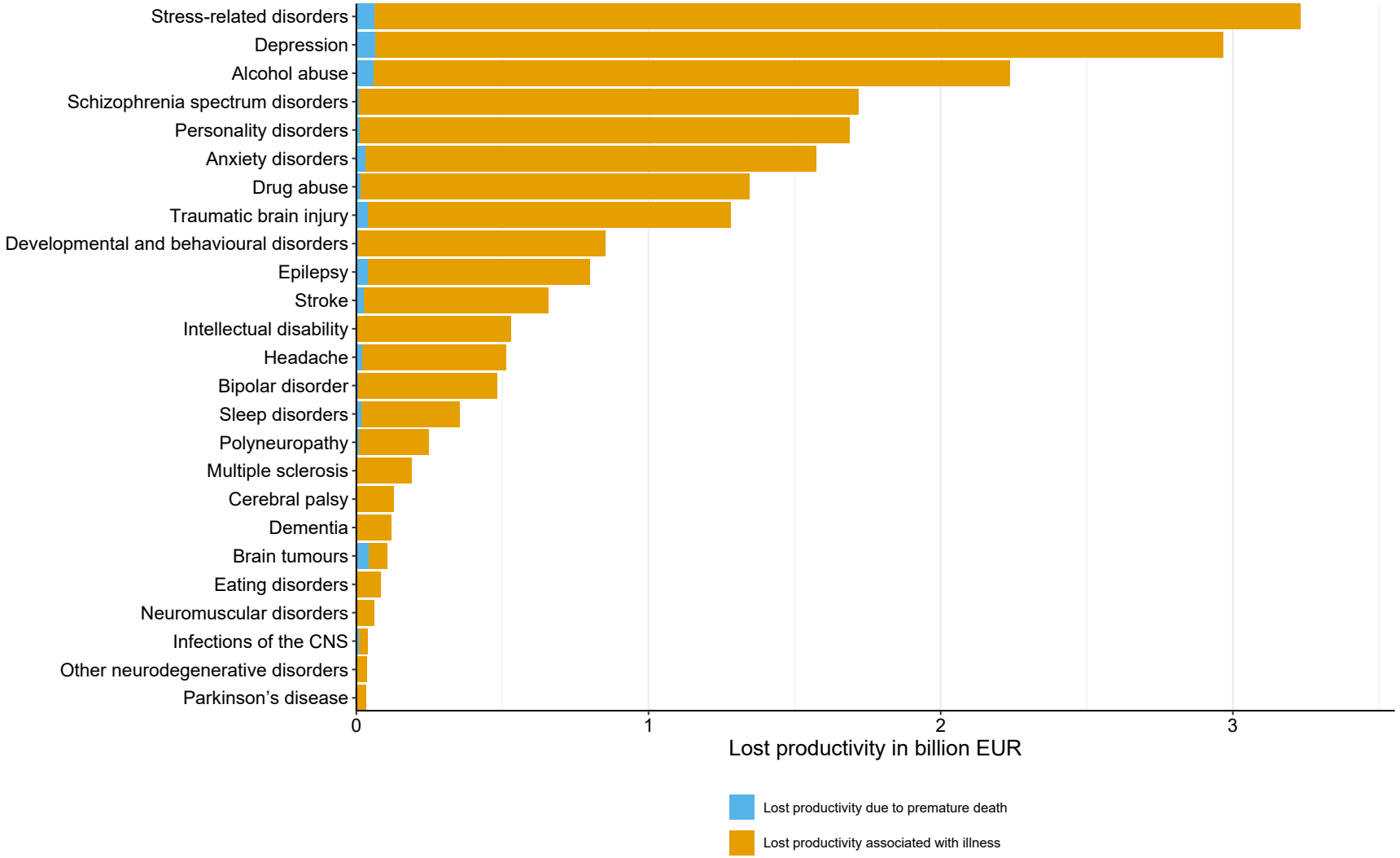


Figure 6: Total attributable indirect costs due to lost productivity in persons with prevalent brain disorders in Denmark in 2015 (in 2015 prices) sorted from highest to lowest costs.
Abbreviations: CNS, central nervous system

APPENDIX 1 – DATA SOURCES

From the Danish Civil Registration System (DCRS), we obtained personal identification numbers (*i.e.*, CPR-numbers, a unique 10-digit number for every Danish citizen given at birth or immigration) to identify individuals across the nationwide registries in both the healthcare and socioeconomic systems. Also, the DCRS holds information on date of birth, sex, vital status, and place of living, of every person in Denmark.[1]

The Danish National Patient Registry (DNPR) holds information on all in- and outpatient hospital contacts since 1995, with details about date of admission and discharge, procedures and operations, and one or more discharge diagnoses.[2] Similarly, all contacts to psychiatric hospitals are recorded in the Danish Psychiatric Central Research Registry, which since 1995 has been included in the DNPR. The discharge diagnoses are recorded using the International Classification of Diseases, Tenth Revision (ICD-10).[3] For every hospital contact, the accumulated costs of the services provided are reimbursed to the hospital department using national reimbursement rates/tariffs based on average costs of the services. Diagnosis-related group (DRG) tariffs are used for inpatient contacts and Danish Ambulatory Grouping System (DAGS) tariffs for outpatient contacts.[4]

The Danish Health Service Registry (DHSR) contains information on services provided by health contractors in primary health care covered by the national health services during consultations, telephone consultations, and home visits. Services are recorded from a wide range of health contractors such as general practitioners, dentists, physiotherapists, chiropodists, chiropractors, psychologists, and other specialists. Every service recorded in the DHSR is accompanied with a corresponding tariff used when the counties reimburse services to the health contractor.[5]

The Danish National Prescription Registry includes nationwide data on all prescriptions filled at outpatient pharmacies since 1995, *e.g.*, drug type, number of packages, package size, and price. Since 2004, indication of prescriptions are recorded, but with missing indication in one third of prescriptions filled. Drug types are classified according to the Anatomical Therapeutic Chemical (ATC) classification system.[6]

Finally, Statistics Denmark hosts registries with information on every Danish resident on whether the person lives in an elderly home or nursery home, on exact time spent by public home help in private households (in hours), and on personal income before taxes.[7] Data on rehabilitation provided by municipalities were not available in any nationwide registry and therefore not included in our analyses.

APPENDIX 2 – CODE BOOKS

ICD-10 and ATC codes

In the main analyses, brain disorders were defined by the "Included diagnosis codes" excluding the codes in "Excluded diagnosis codes". In the sensitivity analyses, brain disorders were defined by either "Included diagnosis codes" excluding the codes in "Excluded diagnosis codes" or by filled prescriptions including "Included ATC codes". For The Anatomical Therapeutic Chemical (ATC) codes, if any indication codes are given, only prescriptions with those ATC and indication codes were used. Diagnosis codes are given as International Classification of Diseases, Tenth Revision (ICD-10) codes. For both ICD-10 and ATC codes, all subcodes were included.

Brain disorder	Included diagnosis codes	Excluded diagnosis codes	Included ATC codes	Included indication codes
Any brain disorder				
Alcohol abuse	F10 E244 G312 G621 G721 I426 K292 K70 K852 K860 Q860	F100	V03AA N07BB	
Anxiety disorders	F40 F41 F42		N06A	371 830 163
Bipolar disorder	F30 F31		N05AN01	
Brain tumours	C70 C71 C72 D32 D33 D42 D43			
Cerebral palsy	G80			
Dementia	F00 F01 F02 F03 G30 G310B G311 G318 G319		N06D	330 331 329 838
Depression	F32 F33		N06A	168 270
Developmental and behavioural disorders	F84 F9	F99		
Drug abuse	F1	F10 F17	N07BC01 N07BC51	
Eating disorders	F500 F501 F502 F503			
Epilepsy	G40			
Headache	G43 G44		N02C	56 269 153
Infections of the central nervous system	G0 A17 A321 A327 A390 A521 A522 A523 A692 A83 A84 A85 A87 A89 B003 B004 B010 B011 B020 B021 B582 B451 B375	G08 G09		
Intellectual disability	F7 Q90 Q992			
Multiple sclerosis	G35			
Neuromuscular disorders	G70 G71 G72 G73			
Other neurodegenerative disorders	G10 G11 G122G G13 G14	G130 G139		
Parkinson's disease	G20 G23		N04BA N04BB N04BD N04BX	
Personality disorders	F60			
Polyneuropathy	G60 G61 G62 G63 G64 G130			
Schizophrenia spectrum disorders	F2			
Sleep disorders	F51 G470 G471 G473 G474		N05CF01 N05CH01	372 165 166 373 170
Stress-related disorders	F43			
Stroke	I60 I61 I63 I64	I608		
Traumatic brain injury	S020 S021 S027 S029 S06			

Charlson Comorbidity Index (CCI)

The codes included were used to identify comorbidity in persons with brain disorders and their comparisons. Persons were considered having the specific type of comorbidity when having at least one of the listed discharge diagnosis codes (including all subcodes) recorded in the Danish National Patient Registry up to 10 years before index date.

CCI disease	Included ICD-8 and ICD-10 diagnosis codes
Myocardial infarction	410 DI21 DI22 DI23
Congestive heart failure	42709 42710 42711 42719 42899 78249 DI50 DI110 DI130 DI132
Peripheral vascular disease	440 441 442 443 444 445 DI70 DI71 DI72 DI73 DI74 DI77
Cerebrovascular disease	430 431 432 433 434 435 436 437 438 DI6 DG45 DG46
Dementia	29009 2901 29309 DF00 DF01 DF02 DF03 DF051 DG30
Chronic pulmonary disease	490 491 492 493 515 516 517 518 DJ40 DJ41 DJ42 DJ43 DJ44 DJ45 DJ46 DJ47 DJ60 DJ61 DJ62 DJ63 DJ64 DJ65 DJ66 DJ67 DJ684 DJ701 DJ703 DJ841 DJ920 DJ961 DJ982 DJ983
Connective tissue disease	712 716 734 446 13599 DM05 DM06 DM08 DM09 DM30 DM31 DM32 DM33 DM34 DM35 DM36 DD86
Ulcer disease	53091 53098 531 532 533 534 DK221 DK25 DK26 DK27 DK28
Mild liver disease	571 57301 57304 DB18 DK700 DK701 DK702 DK703 DK709 DK71 DK73 DK74 DK760
Diabetes without end-organ damage	24900 24906 24907 24909 25000 25006 25007 25009 DE100 DE101 DE109 DE110 DE111 DE119
Hemiplegia	344 DG81 DG82
Moderate to severe renal disease	403 404 580 581 582 583 584 59009 59319 7531 792 DI12 DI13 DN00 DN01 DN02 DN03 DN04 DN05 DN07 DN11 DN14 DN17 DN18 DN19 DQ61
Diabetes with end-organ damage	24901 24902 24903 24904 24905 24908 25001 25002 25003 25004 25005 25008 DE102 DE103 DE104 DE105 DE106 DE107 DE108 DE112 DE113 DE114 DE115 DE116 DE117 DE118
Solid cancer tumour	14 15 16 17 18 190 191 192 193 194 DC0 DC1 DC2 DC3 DC4 DC5 DC6 DC70 DC71 DC72 DC73 DC74 DC75
Leukaemia	204 205 206 207 DC91 DC92 DC93 DC94 DC95
Lymphoma	200 201 202 203 27559 DC81 DC82 DC83 DC84 DC85 DC88 DC90 DC96
Moderate to severe liver disease	07000 07002 07004 07006 07008 57300 4560 DB150 DB160 DB162 DB190 DK704 DK72 DK766 DI85
Metastatic solid tumour	195 196 197 198 199 DC76 DC77 DC78 DC79 DC80
AIDS	07983 DB21 DB22 DB23 DB24

Supplementary tables

Suppl. Table 1. Characteristics of patients with prevalent disorders in Denmark in 2015 sorted in alphabetical order.

	Prevalent cohorts: 2015					
Disease group	Persons, N	Men, N (%)	Age, median (Q1-Q3)	CCI: 0, N (%)	CCI: 1-2, N (%)	CCI: +3, N (%)
Any brain disorder	1,075,081	536,462 (49.9)	46.0 (27.5-63.6)	788,948 (73.4)	222,453 (20.7)	63,680 (5.9)
Alcohol abuse	101,066	67,376 (66.7)	56.5 (46.2-65.8)	59,961 (59.3)	28,397 (28.1)	12,708 (12.6)
Anxiety disorders	96,943	33,768 (34.8)	41.2 (28.8-54.3)	78,009 (80.5)	15,181 (15.7)	3,753 (3.9)
Bipolar disorder	23,364	9,366 (40.1)	52.4 (39.3-64.9)	17,127 (73.3)	4,851 (20.8)	1,386 (5.9)
Brain tumours	14,953	6,101 (40.8)	62.6 (48.6-71.9)	8,718 (58.3)	4,339 (29.0)	1,896 (12.7)
Cerebral palsy	9,083	5,093 (56.1)	22.3 (14.1-37.0)	6,516 (71.7)	2,092 (23.0)	475 (5.2)
Dementia	40,037	15,645 (39.1)	81.7 (73.9-87.5)	8,340 (20.8)	22,655 (56.6)	9,042 (22.6)
Depression	180,886	64,191 (35.5)	49.0 (35.6-64.1)	130,862 (72.3)	38,342 (21.2)	11,682 (6.5)
Developmental and behavioural disorders	103,157	68,589 (66.5)	19.6 (14.2-26.0)	94,745 (91.8)	7,841 (7.6)	571 (0.6)
Drug abuse	50,066	32,295 (64.5)	38.6 (28.4-50.8)	38,657 (77.2)	9,180 (18.3)	2,229 (4.5)
Eating disorders	15,936	750 (4.7)	29.5 (23.0-36.9)	14,484 (90.9)	1,332 (8.4)	120 (0.8)
Epilepsy	72,205	37,047 (51.3)	43.5 (24.8-62.1)	51,701 (71.6)	15,562 (21.6)	4,942 (6.8)
Headache	96,252	32,218 (33.5)	45.4 (31.2-57.6)	75,439 (78.4)	17,566 (18.3)	3,247 (3.4)
Infections of the central nervous system	26,829	14,069 (52.4)	43.1 (22.9-61.5)	20,740 (77.3)	4,709 (17.6)	1,380 (5.1)
Intellectual disability	27,605	16,087 (58.3)	25.4 (17.1-45.1)	23,577 (85.4)	3,501 (12.7)	527 (1.9)
Multiple sclerosis	14,264	4,431 (31.1)	52.6 (42.9-62.7)	11,206 (78.6)	2,559 (17.9)	499 (3.5)
Neuromuscular disorders	7,080	3,649 (51.5)	51.4 (33.3-66.5)	4,427 (62.5)	1,992 (28.1)	661 (9.3)
Other neurodegenerative disorders	2,192	1,143 (52.1)	59.9 (46.2-70.5)	1,381 (63.0)	622 (28.4)	189 (8.6)
Parkinson's disease	8,942	5,083 (56.8)	75.3 (68.4-81.4)	4,430 (49.5)	3,323 (37.2)	1,189 (13.3)
Personality disorders	71,334	24,517 (34.4)	39.9 (30.6-51.0)	58,516 (82.0)	10,824 (15.2)	1,994 (2.8)
Polyneuropathy	32,710	18,918 (57.8)	66.7 (55.0-75.8)	15,900 (48.6)	11,139 (34.1)	5,671 (17.3)
Schizophrenia spectrum disorders	61,346	32,637 (53.2)	45.1 (32.1-57.7)	48,640 (79.3)	10,276 (16.8)	2,430 (4.0)
Sleep disorders	61,666	45,042 (73.0)	55.9 (43.0-66.2)	41,909 (68.0)	15,223 (24.7)	4,534 (7.4)
Stress-related disorders	196,291	77,494 (39.5)	42.3 (29.3-54.1)	158,789 (80.9)	31,138 (15.9)	6,364 (3.2)
Stroke	120,065	64,067 (53.4)	71.0 (61.1-79.9)	23,651 (19.7)	70,389 (58.6)	26,025 (21.7)
Traumatic brain injury	249,348	142,776 (57.3)	34.9 (22.1-53.4)	207,314 (83.1)	34,162 (13.7)	7,872 (3.2)

Abbreviations: Q, quartile; CCI, Charlson Comorbidity Index.

Suppl. Table 2. Characteristics of patients with incident brain disorders in Denmark during 2011-2015 sorted in alphabetical order.

	Incident cohorts: 2011-2015					
Disease group	Persons, N	Men, N (%)	Age, median (Q1-Q3)	CCI: 0, N (%)	CCI: 1-2, N (%)	CCI: +3, N (%)
Any brain disorder	381,759	187,780 (49.2)	46.6 (21.5-68.9)	295,560 (77.4)	64,746 (17.0)	21,453 (5.6)
Alcohol abuse	37,032	25,251 (68.2)	55.8 (42.7-66.8)	25,797 (69.7)	8,347 (22.5)	2,888 (7.8)
Anxiety disorders	53,350	20,013 (37.5)	35.8 (22.3-56.5)	39,034 (73.2)	8,480 (15.9)	5,836 (10.9)
Bipolar disorder	9,838	4,074 (41.4)	40.8 (28.5-55.0)	7,951 (80.8)	1,500 (15.2)	387 (3.9)
Brain tumours	9,336	4,199 (45.0)	64.1 (50.7-72.9)	6,044 (64.7)	2,227 (23.9)	1,065 (11.4)
Cerebral palsy	2,145	1,199 (55.9)	13.7 (3.1-54.3)	1,371 (63.9)	582 (27.1)	192 (9.0)
Dementia	42,798	17,454 (40.8)	81.8 (75.4-87.0)	21,015 (49.1)	15,686 (36.7)	6,097 (14.2)
Depression	78,926	29,379 (37.2)	45.4 (27.9-66.8)	56,768 (71.9)	15,445 (19.6)	6,713 (8.5)
Developmental and behavioural disorders	48,562	29,864 (61.5)	14.1 (8.6-21.9)	43,747 (90.1)	4,445 (9.2)	370 (0.8)
Drug abuse	18,843	12,469 (66.2)	26.9 (20.7-42.3)	15,944 (84.6)	2,322 (12.3)	577 (3.1)
Eating disorders	6,011	321 (5.3)	19.7 (16.0-24.9)	5,683 (94.5)	307 (5.1)	21 (0.3)
Epilepsy	21,255	11,301 (53.2)	53.2 (21.1-70.6)	12,057 (56.7)	6,319 (29.7)	2,879 (13.5)
Headache	35,180	11,547 (32.8)	37.6 (23.4-50.4)	29,066 (82.6)	5,292 (15.0)	822 (2.3)
Infections of the central nervous system	9,501	4,922 (51.8)	44.6 (21.9-64.2)	7,086 (74.6)	1,727 (18.2)	688 (7.2)
Intellectual disability	8,166	4,692 (57.5)	17.3 (9.9-34.8)	7,035 (86.1)	994 (12.2)	137 (1.7)
Multiple sclerosis	3,345	1,070 (32.0)	41.7 (31.9-52.0)	2,833 (84.7)	449 (13.4)	63 (1.9)
Neuromuscular disorders	3,062	1,596 (52.1)	52.8 (32.9-67.8)	1,950 (63.7)	803 (26.2)	309 (10.1)
Other neurodegenerative disorders	1,464	777 (53.1)	65.3 (53.1-73.2)	904 (61.7)	425 (29.0)	135 (9.2)
Parkinson's disease	6,478	3,883 (59.9)	75.5 (68.9-81.4)	3,459 (53.4)	2,236 (34.5)	783 (12.1)
Personality disorders	21,556	6,762 (31.4)	27.2 (21.3-38.6)	19,265 (89.4)	2,030 (9.4)	261 (1.2)
Polyneuropathy	17,925	10,755 (60.0)	65.9 (54.5-75.0)	8,825 (49.2)	6,108 (34.1)	2,992 (16.7)
Schizophrenia spectrum disorders	19,316	10,219 (52.9)	29.7 (21.1-48.9)	16,209 (83.9)	2,483 (12.9)	624 (3.2)
Sleep disorders	31,316	21,769 (69.5)	51.9 (38.5-62.7)	21,974 (70.2)	7,086 (22.6)	2,256 (7.2)
Stress-related disorders	80,953	34,110 (42.1)	34.5 (20.5-48.5)	68,431 (84.5)	10,356 (12.8)	2,166 (2.7)
Stroke	67,539	35,308 (52.3)	71.8 (61.1-81.3)	37,862 (56.1)	21,220 (31.4)	8,457 (12.5)
Traumatic brain injury	64,931	35,456 (54.6)	34.3 (15.7-63.4)	50,924 (78.4)	10,610 (16.3)	3,397 (5.2)

Abbreviations: Q, quartile; CCI, Charlson Comorbidity Index.

Suppl. Table 3. Occurrence of hospital-diagnosed brain disorders in the Danish population including incidence during 2011-2015 and prevalence in 2015 sorted in alphabetical order.

Disease group	Prevalent cohorts: 2015		Incident cohorts: 2011-2015	
	Prevalence, N (%)	Prevalence per 100,000 persons (95% CI)	Incidence, N	Incidence rate per 100,000 person-years (95% CI)
Any brain disorder	1,075,081 (18.9)	18,879 (18,844-18,915)	381,759	1,349 (1,345-1,353)
Alcohol abuse	101,066 (1.8)	1,775 (1,764-1,786)	37,032	131 (130-132)
Anxiety disorders	96,943 (1.7)	1,702 (1,692-1,713)	53,350	189 (187-190)
Bipolar disorder	23,364 (0.4)	410 (405-416)	9,838	35 (34-35)
Brain tumours	14,953 (0.3)	263 (258-267)	9,336	33 (32-34)
Cerebral palsy	9,083 (0.2)	160 (156-163)	2,145	8 (7-8)
Dementia	40,037 (0.7)	703 (696-710)	42,798	151 (150-153)
Depression	180,886 (3.2)	3,176 (3,162-3,191)	78,926	279 (277-281)
Developmental and behavioural disorders	103,157 (1.8)	1,812 (1,800-1,823)	48,562	172 (170-173)
Drug abuse	50,066 (0.9)	879 (872-887)	18,843	67 (66-68)
Eating disorders	15,936 (0.3)	280 (276-284)	6,011	21 (21-22)
Epilepsy	72,205 (1.3)	1,268 (1,259-1,277)	21,255	75 (74-76)
Headache	96,252 (1.7)	1,690 (1,680-1,701)	35,180	124 (123-126)
Infections of the central nervous system	26,829 (0.5)	471 (466-477)	9,501	34 (33-34)
Intellectual disability	27,605 (0.5)	485 (479-491)	8,166	29 (28-29)
Multiple sclerosis	14,264 (0.3)	250 (246-255)	3,345	12 (11-12)
Neuromuscular disorders	7,080 (0.1)	124 (121-127)	3,062	11 (10-11)
Other neurodegenerative disorders	2,192 (0.0)	38 (37-40)	1,464	5 (5-5)
Parkinson's disease	8,942 (0.2)	157 (154-160)	6,478	23 (22-23)
Personality disorders	71,334 (1.3)	1,253 (1,244-1,262)	21,556	76 (75-77)
Polyneuropathy	32,710 (0.6)	574 (568-581)	17,925	63 (62-64)
Schizophrenia spectrum disorders	61,346 (1.1)	1,077 (1,069-1,086)	19,316	68 (67-69)
Sleep disorders	61,666 (1.1)	1,083 (1,074-1,091)	31,316	111 (109-112)
Stress-related disorders	196,291 (3.4)	3,447 (3,432-3,462)	80,953	286 (284-288)
Stroke	120,065 (2.1)	2,108 (2,097-2,120)	67,539	239 (237-240)
Traumatic brain injury	249,348 (4.4)	4,379 (4,362-4,396)	64,931	229 (228-231)

Abbreviations: CI, confidence interval.

Suppl. Table 4. Actual and attributable costs in total and per person in persons with prevalent brain disorders in 2015, and incident brain disorders during 2011-2015 sorted in alphabetical order and stratified by cost components.

		Prevalent cohort - 2015				Incident cohort - 2011-2015
Brain disorder	Cost component	Actual costs in 2015 (EUR)	Actual costs per person in 2015 (EUR)	Attributable costs in 2015 (EUR)	Attributable costs per person in 2015 (EUR)	Attributable costs per person in the first year after diagnosis (EUR)
Any brain disorder	Primary sector	488,168,143	460	191,774,339	181	175
	Secondary sector - Outpatient	1,491,081,458	1,406	743,338,257	701	2,702
	Secondary sector - Inpatient	2,522,910,114	2,379	1,638,312,025	1,545	8,457
	Filled prescriptions	533,852,195	503	319,922,005	302	211
	Home care	700,068,647	660	529,492,180	499	489
	Nursing home / sheltered accommodation	2,138,655,226	2,017	1,786,588,544	1,685	749
	Total cost (excl. lost productivity)	7,874,735,782	7,426	5,209,427,352	4,912	12,783
Alcohol abuse	Primary sector	43,832,697	444	10,708,496	109	164
	Secondary sector - Outpatient	182,619,411	1,851	90,265,391	915	2,318
	Secondary sector - Inpatient	509,785,016	5,166	396,078,314	4,014	14,252
	Filled prescriptions	70,574,116	715	41,364,956	419	329
	Home care	86,902,799	881	69,319,977	703	686
	Nursing home / sheltered accommodation	272,375,227	2,760	235,944,141	2,391	1,019
	Total cost (excl. lost productivity)	1,166,089,265	11,817	843,681,275	8,550	18,768
Anxiety disorders	Primary sector	46,880,525	488	17,760,012	185	270
	Secondary sector - Outpatient	186,143,973	1,939	112,251,855	1,169	4,937
	Secondary sector - Inpatient	304,572,473	3,172	220,690,805	2,298	8,872
	Filled prescriptions	58,721,973	612	38,187,658	398	502
	Home care	32,889,132	343	20,728,003	216	359
	Nursing home / sheltered accommodation	93,491,816	974	63,280,196	659	368
	Total cost (excl. lost productivity)	722,699,890	7,527	472,898,530	4,925	15,308
Bipolar disorder	Primary sector	12,927,768	561	4,802,917	209	227
	Secondary sector - Outpatient	68,871,491	2,990	47,030,959	2,042	6,368
	Secondary sector - Inpatient	147,299,161	6,395	120,588,736	5,235	17,468
	Filled prescriptions	23,251,036	1,009	16,487,361	716	755
	Home care	17,966,005	780	12,684,093	551	299
	Nursing home / sheltered accommodation	65,937,773	2,863	52,520,523	2,280	680
	Total cost (excl. lost productivity)	336,253,233	14,598	254,114,589	11,032	25,797
Brain tumours	Primary sector	9,283,859	640	3,508,912	242	223
	Secondary sector - Outpatient	42,180,950	2,910	26,480,502	1,827	12,604

		Prevalent cohort - 2015				Incident cohort - 2011-2015
Brain disorder	Cost component	Actual costs in 2015 (EUR)	Actual costs per person in 2015 (EUR)	Attributable costs in 2015 (EUR)	Attributable costs per person in 2015 (EUR)	Attributable costs per person in the first year after diagnosis (EUR)
	Secondary sector - Inpatient	57,321,123	3,954	36,118,409	2,492	29,223
	Filled prescriptions	8,861,608	611	3,527,159	243	295
	Home care	16,473,487	1,136	10,430,046	720	901
	Nursing home / sheltered accommodation	31,261,211	2,157	14,864,894	1,025	302
	Total cost (excl. lost productivity)	165,382,238	11,409	94,929,922	6,549	43,548
Cerebral palsy	Primary sector	13,167,622	1,462	11,318,548	1,256	960
	Secondary sector - Outpatient	11,430,545	1,269	6,723,166	746	2,731
	Secondary sector - Inpatient	27,487,812	3,051	21,438,091	2,380	11,838
	Filled prescriptions	6,630,687	736	5,437,246	604	567
	Home care	13,763,599	1,528	13,328,070	1,479	2,111
	Nursing home / sheltered accommodation	11,864,848	1,317	10,870,651	1,207	3,193
	Total cost (excl. lost productivity)	84,345,114	9,363	69,115,771	7,672	21,400
Dementia	Primary sector	24,098,562	667	4,596,178	127	137
	Secondary sector - Outpatient	43,138,878	1,193	-5,214,136	-144	1,567
	Secondary sector - Inpatient	140,689,111	3,891	46,270,459	1,280	6,237
	Filled prescriptions	35,544,655	983	14,366,512	397	458
	Home care	148,296,718	4,102	85,823,645	2,374	3,175
	Nursing home / sheltered accommodation	1,079,664,024	29,862	933,749,795	25,826	10,891
	Total cost (excl. lost productivity)	1,471,431,949	40,698	1,079,592,452	29,860	22,465
Depression	Primary sector	95,893,225	539	34,953,943	196	294
	Secondary sector - Outpatient	353,092,962	1,983	198,404,020	1,115	4,415
	Secondary sector - Inpatient	632,094,332	3,551	437,349,885	2,457	11,336
	Filled prescriptions	123,586,689	694	75,514,229	424	447
	Home care	147,797,688	830	94,735,383	532	817
	Nursing home / sheltered accommodation	510,771,406	2,869	367,705,421	2,066	1,275
	Total cost (excl. lost productivity)	1,863,236,302	10,466	1,208,662,881	6,789	18,584
Developmental and behavioural disorders	Primary sector	27,337,787	266	10,369,345	101	104
	Secondary sector - Outpatient	116,363,305	1,130	75,097,169	729	3,890
	Secondary sector - Inpatient	236,746,401	2,299	190,215,735	1,847	5,695
	Filled prescriptions	53,648,059	521	45,268,384	440	477
	Home care	5,642,767	55	4,450,425	43	28
	Nursing home / sheltered accommodation	11,467,658	111	8,904,950	86	39

		Prevalent cohort - 2015				Incident cohort - 2011-2015
Brain disorder	Cost component	Actual costs in 2015 (EUR)	Actual costs per person in 2015 (EUR)	Attributable costs in 2015 (EUR)	Attributable costs per person in 2015 (EUR)	Attributable costs per person in the first year after diagnosis (EUR)
	Total cost (excl. lost productivity)	451,205,976	4,382	334,306,007	3,247	10,235
Drug abuse	Primary sector	18,789,575	379	6,103,985	123	173
	Secondary sector - Outpatient	104,455,802	2,110	71,938,513	1,453	3,539
	Secondary sector - Inpatient	294,331,957	5,944	257,849,075	5,207	14,939
	Filled prescriptions	39,585,700	799	30,697,450	620	525
	Home care	21,420,415	433	17,004,322	343	320
	Nursing home / sheltered accommodation	55,090,031	1,113	44,708,406	903	324
	Total cost (excl. lost productivity)	533,673,480	10,778	428,301,752	8,650	19,820
Eating disorders	Primary sector	6,954,226	438	2,231,551	141	112
	Secondary sector - Outpatient	41,617,887	2,621	30,089,653	1,895	8,660
	Secondary sector - Inpatient	78,974,413	4,973	66,777,164	4,205	21,099
	Filled prescriptions	5,121,915	323	2,656,004	167	108
	Home care	1,027,908	65	768,275	48	40
	Nursing home / sheltered accommodation	1,702,989	107	1,282,483	81	65
	Total cost (excl. lost productivity)	135,399,338	8,526	103,805,130	6,536	30,084
Epilepsy	Primary sector	41,173,985	580	19,904,667	280	350
	Secondary sector - Outpatient	108,270,760	1,524	51,399,429	723	3,615
	Secondary sector - Inpatient	236,872,420	3,334	162,384,494	2,286	13,573
	Filled prescriptions	56,830,263	800	39,757,000	560	539
	Home care	71,643,564	1,008	57,009,489	802	1,439
	Nursing home / sheltered accommodation	186,490,441	2,625	148,199,767	2,086	3,600
	Total cost (excl. lost productivity)	701,281,434	9,871	478,654,845	6,737	23,117
Headache	Primary sector	45,555,311	475	15,231,927	159	213
	Secondary sector - Outpatient	133,513,223	1,393	53,710,708	560	1,579
	Secondary sector - Inpatient	165,735,926	1,729	72,915,060	761	2,660
	Filled prescriptions	41,304,678	431	18,445,725	192	144
	Home care	18,540,020	193	5,347,719	56	24
	Nursing home / sheltered accommodation	38,547,780	402	7,238,248	76	-2
	Total cost (excl. lost productivity)	443,196,937	4,625	172,889,385	1,804	4,618
Infections of the central nervous system	Primary sector	11,203,340	421	3,297,607	124	168
	Secondary sector - Outpatient	33,558,808	1,262	12,417,210	467	2,276
	Secondary sector - Inpatient	53,806,027	2,023	25,888,210	974	19,530
	Filled prescriptions	9,714,465	365	3,292,758	124	181

		Prevalent cohort - 2015				Incident cohort - 2011-2015
Brain disorder	Cost component	Actual costs in 2015 (EUR)	Actual costs per person in 2015 (EUR)	Attributable costs in 2015 (EUR)	Attributable costs per person in 2015 (EUR)	Attributable costs per person in the first year after diagnosis (EUR)
	Home care	12,811,201	482	7,584,973	285	563
	Nursing home / sheltered accommodation	27,418,463	1,031	14,310,372	538	461
	Total cost (excl. lost productivity)	148,512,305	5,585	66,791,130	2,512	23,180
Intellectual disability	Primary sector	15,988,512	583	9,893,121	361	278
	Secondary sector - Outpatient	33,228,973	1,213	17,182,705	627	3,055
	Secondary sector - Inpatient	102,644,232	3,746	84,346,003	3,078	9,397
	Filled prescriptions	21,583,017	788	17,432,722	636	538
	Home care	13,976,239	510	12,449,542	454	393
	Nursing home / sheltered accommodation	32,339,423	1,180	29,128,690	1,063	598
	Total cost (excl. lost productivity)	219,760,396	8,020	170,432,783	6,220	14,258
Multiple sclerosis	Primary sector	21,206,010	1,503	16,200,681	1,148	583
	Secondary sector - Outpatient	40,714,728	2,885	27,233,358	1,930	10,465
	Secondary sector - Inpatient	43,448,943	3,079	27,817,864	1,971	4,925
	Filled prescriptions	9,720,026	689	5,629,372	399	189
	Home care	51,880,624	3,676	49,746,582	3,525	644
	Nursing home / sheltered accommodation	31,328,567	2,220	27,272,490	1,933	335
	Total cost (excl. lost productivity)	198,298,897	14,051	153,900,347	10,905	17,140
Neuromuscular disorders	Primary sector	6,282,164	901	3,972,937	570	353
	Secondary sector - Outpatient	14,433,119	2,071	8,172,495	1,172	3,211
	Secondary sector - Inpatient	29,246,940	4,196	20,898,189	2,998	16,132
	Filled prescriptions	4,437,530	637	2,451,542	352	389
	Home care	8,986,447	1,289	7,194,501	1,032	544
	Nursing home / sheltered accommodation	8,955,012	1,285	4,625,467	664	147
	Total cost (excl. lost productivity)	72,341,211	10,378	47,315,130	6,788	20,777
Other neurodegenerative disorders	Primary sector	3,467,634	1,660	2,695,799	1,290	1,214
	Secondary sector - Outpatient	3,744,735	1,792	1,557,828	746	2,623
	Secondary sector - Inpatient	12,458,820	5,963	9,519,636	4,556	18,250
	Filled prescriptions	2,025,361	969	1,312,465	628	1,152
	Home care	9,972,538	4,773	9,295,614	4,449	5,491
	Nursing home / sheltered accommodation	15,620,797	7,476	13,965,869	6,684	3,904
	Total cost (excl. lost productivity)	47,289,884	22,634	38,347,211	18,354	32,634
Parkinson's disease	Primary sector	14,860,564	1,776	10,688,805	1,278	910

		Prevalent cohort - 2015				Incident cohort - 2011-2015
Brain disorder	Cost component	Actual costs in 2015 (EUR)	Actual costs per person in 2015 (EUR)	Attributable costs in 2015 (EUR)	Attributable costs per person in 2015 (EUR)	Attributable costs per person in the first year after diagnosis (EUR)
	Secondary sector - Outpatient	17,312,390	2,069	5,323,437	636	2,069
	Secondary sector - Inpatient	46,402,317	5,546	27,109,682	3,240	8,711
	Filled prescriptions	27,652,172	3,305	23,257,252	2,780	1,178
	Home care	45,766,641	5,470	38,139,915	4,559	3,594
	Nursing home / sheltered accommodation	118,302,501	14,140	96,210,216	11,499	5,067
	Total cost (excl. lost productivity)	270,296,586	32,307	200,729,307	23,992	21,530
Personality disorders	Primary sector	33,726,394	475	12,370,687	174	180
	Secondary sector - Outpatient	161,704,804	2,280	108,438,891	1,529	5,307
	Secondary sector - Inpatient	294,012,210	4,145	237,084,594	3,342	10,946
	Filled prescriptions	47,982,591	676	33,993,717	479	391
	Home care	18,267,898	258	13,204,541	186	60
	Nursing home / sheltered accommodation	50,162,995	707	39,971,083	563	175
	Total cost (excl. lost productivity)	605,856,892	8,541	445,063,513	6,274	17,058
Polyneuropathy	Primary sector	22,995,926	721	9,555,562	300	324
	Secondary sector - Outpatient	84,279,793	2,643	47,316,582	1,484	3,465
	Secondary sector - Inpatient	144,827,869	4,542	88,462,288	2,775	8,416
	Filled prescriptions	30,234,724	948	16,995,029	533	569
	Home care	53,022,119	1,663	35,217,614	1,105	773
	Nursing home / sheltered accommodation	92,592,235	2,904	40,739,401	1,278	-89
	Total cost (excl. lost productivity)	427,952,666	13,423	238,286,476	7,474	13,458
Schizophrenia spectrum disorders	Primary sector	25,870,906	427	7,901,500	130	130
	Secondary sector - Outpatient	184,183,351	3,039	138,302,570	2,282	7,692
	Secondary sector - Inpatient	471,018,165	7,773	418,546,262	6,907	28,598
	Filled prescriptions	60,736,022	1,002	47,173,595	778	584
	Home care	40,669,756	671	31,640,056	522	328
	Nursing home / sheltered accommodation	144,768,784	2,389	123,117,720	2,032	1,259
	Total cost (excl. lost productivity)	927,246,985	15,302	766,681,703	12,652	38,591
Sleep disorders	Primary sector	31,353,798	512	11,799,623	193	238
	Secondary sector - Outpatient	98,914,079	1,616	41,921,108	685	2,096
	Secondary sector - Inpatient	145,942,944	2,385	69,035,777	1,128	3,396
	Filled prescriptions	41,479,250	678	23,820,309	389	394
	Home care	20,461,339	334	9,184,546	150	217

		Prevalent cohort - 2015				Incident cohort - 2011-2015
Brain disorder	Cost component	Actual costs in 2015 (EUR)	Actual costs per person in 2015 (EUR)	Attributable costs in 2015 (EUR)	Attributable costs per person in 2015 (EUR)	Attributable costs per person in the first year after diagnosis (EUR)
	Nursing home / sheltered accommodation	31,784,606	519	6,941,740	113	45
	Total cost (excl. lost productivity)	369,936,015	6,045	162,703,103	2,659	6,386
Stress-related disorders	Primary sector	86,677,745	444	29,534,278	151	251
	Secondary sector - Outpatient	334,672,975	1,716	190,005,389	974	3,344
	Secondary sector - Inpatient	594,516,328	3,048	435,161,116	2,231	8,650
	Filled prescriptions	94,996,342	487	55,121,881	283	263
	Home care	52,036,361	267	33,412,202	171	132
	Nursing home / sheltered accommodation	136,104,200	698	94,380,524	484	302
	Total cost (excl. lost productivity)	1,299,003,951	6,660	837,615,391	4,295	12,942
Stroke	Primary sector	87,618,648	759	36,193,449	313	275
	Secondary sector - Outpatient	200,887,719	1,740	56,107,195	486	1,741
	Secondary sector - Inpatient	462,612,656	4,006	236,363,400	2,047	24,956
	Filled prescriptions	92,706,631	803	39,925,529	346	356
	Home care	262,819,364	2,276	179,189,377	1,552	1,443
	Nursing home / sheltered accommodation	710,435,792	6,152	461,833,282	4,000	1,882
	Total cost (excl. lost productivity)	1,817,080,811	15,736	1,009,612,232	8,743	30,654
Traumatic brain injury	Primary sector	83,545,461	338	18,644,498	75	140
	Secondary sector - Outpatient	239,309,856	968	69,116,574	280	707
	Secondary sector - Inpatient	428,225,272	1,732	212,472,590	859	7,836
	Filled prescriptions	75,591,648	306	26,356,451	107	117
	Home care	92,933,811	376	50,946,346	206	438
	Nursing home / sheltered accommodation	277,317,019	1,122	163,141,079	660	950
	Total cost (excl. lost productivity)	1,196,923,068	4,841	540,677,538	2,187	10,188

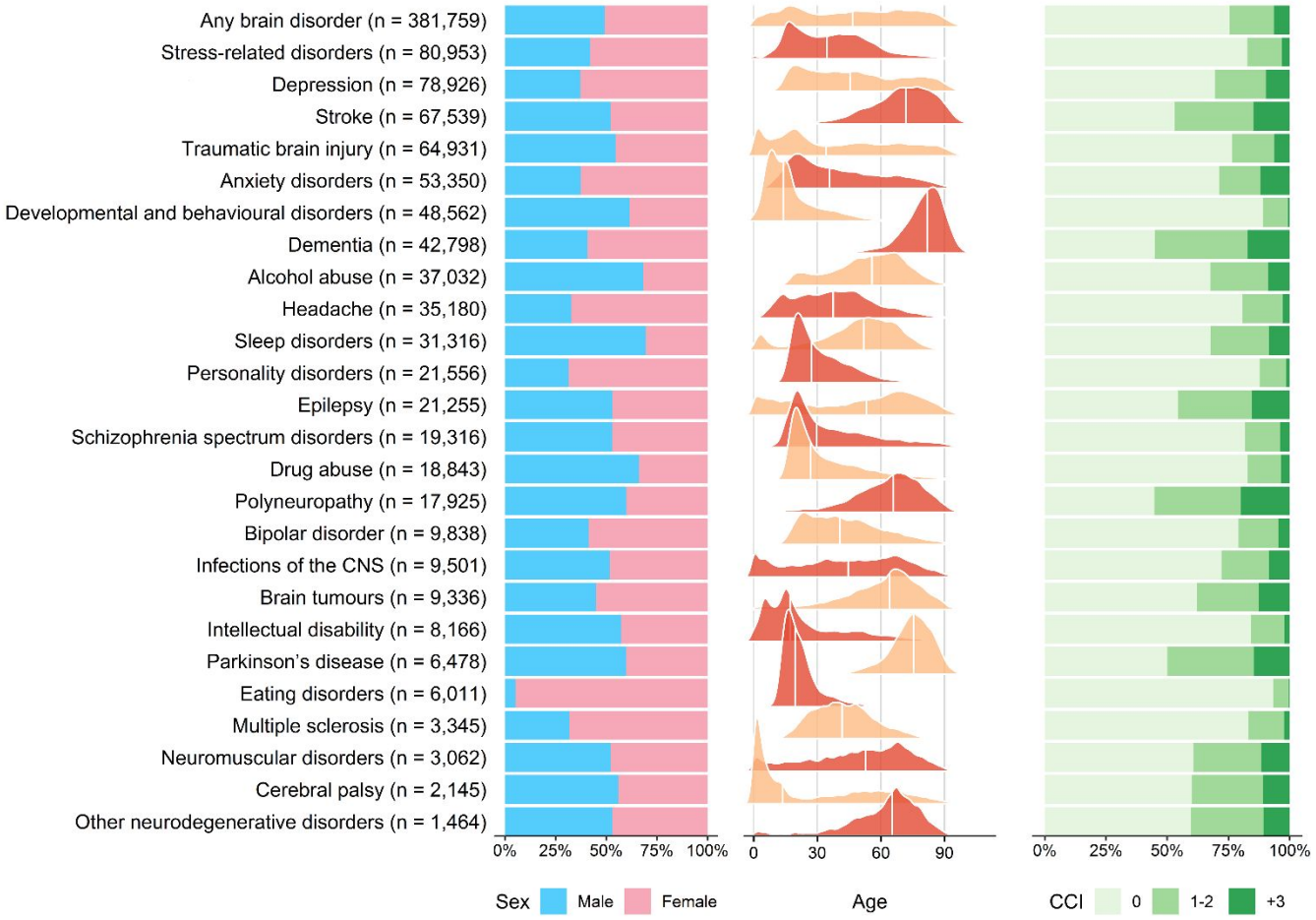
Abbreviations: EUR, Euro.

Suppl. Table 5. Lost productivity in persons with prevalent brain disorders in Denmark in 2015, and incident brain disorders in Denmark during 2011-2015.

	Lost productivity associated with illness			Lost productivity due to premature death		
Brain disorder	Attributable lost production in 2015 (EUR)	Attributable lost production per person in 2015 (EUR)	Attributable lost production per person in the year after diagnosis (EUR)	Attributable lost production among patients who died in 2015 (EUR)	Attributable lost production per person among patients who died in 2015 (EUR)	Attributable lost production per person among patients who died within one year after diagnosis (EUR)
Any brain disorder	10,871,306,597	15,471	11,501	310,599,261	66,595	176,821
Alcohol abuse	2,177,095,714	30,509	26,454	60,885,257	30,519	83,486
Anxiety disorders	1,540,715,518	19,281	19,717	32,197,400	59,515	145,515
Bipolar disorder	474,459,456	27,521	25,383	6,136,984	37,883	136,861
Brain tumours	62,414,375	8,259	15,068	44,062,492	174,851	205,107
Cerebral palsy	126,484,627	24,291	31,767	487,951	7,999	55,995
Dementia	118,974,339	32,436	28,305	1,408,193	8,140	28,505
Depression	2,900,683,027	21,708	20,838	64,470,952	63,706	162,215
Developmental and behavioural disorders	845,403,290	14,455	22,423	6,886,963	47,171	96,899
Drug abuse	1,330,382,612	29,742	24,512	14,271,378	22,908	67,596
Eating disorders	83,103,235	5,798	6,941	1,407,442	54,132	25,604
Epilepsy	757,818,260	16,449	18,764	39,647,665	61,469	167,731
Headache	490,757,570	6,493	6,165	21,177,971	101,330	174,465
Infections of the central nervous system	30,214,014	1,814	2,093	9,137,033	103,830	152,402
Intellectual disability	528,043,228	29,465	30,237	278,285	1,457	9,078
Multiple sclerosis	189,128,371	16,804	9,354	1,721,160	15,367	142,356
Neuromuscular disorders	61,263,234	14,022	9,262	1,733,127	36,875	106,274
Other neurodegenerative disorders	31,346,429	27,716	21,953	3,829,300	55,497	134,409
Parkinson's disease	32,248,038	22,662	14,259	3,565	105	49,396
Personality disorders	1,675,321,683	25,663	22,217	13,071,803	34,858	105,239
Polyneuropathy	238,332,654	16,662	16,701	8,543,728	29,873	78,341
Schizophrenia spectrum disorders	1,707,738,198	33,710	26,581	9,960,281	17,173	90,396
Sleep disorders	336,760,666	8,691	8,554	18,811,390	79,373	133,551
Stress-related disorders	3,167,569,516	19,310	19,520	63,414,446	69,917	175,773
Stroke	630,213,779	16,502	14,382	25,874,307	39,085	140,923
Traumatic brain injury	1,241,809,744	7,179	7,245	41,136,013	48,739	121,008

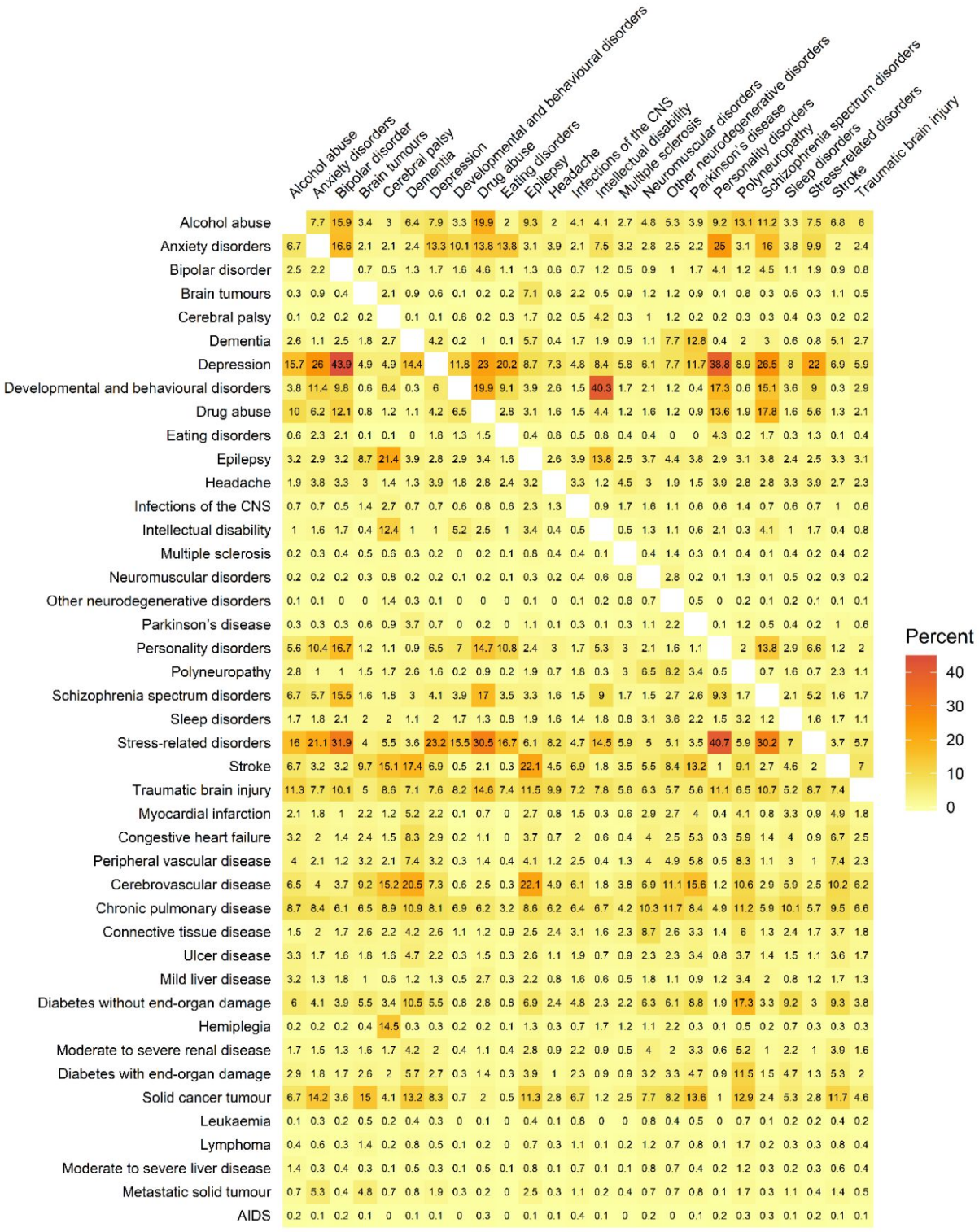
Abbreviations: EUR, Euro.

Supplementary figures



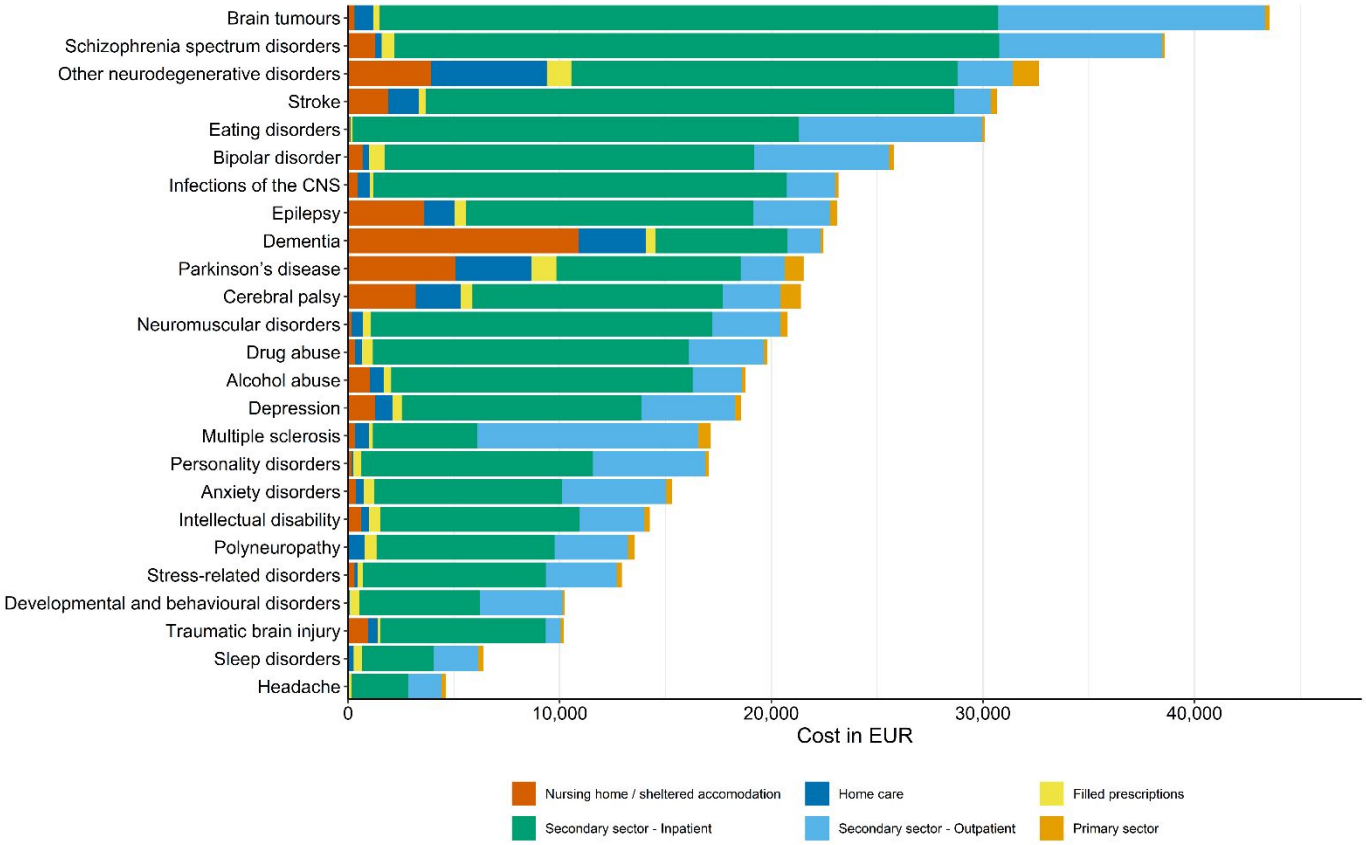
Suppl. Figure 1. Characteristics of patients with incident brain disorders in Denmark during 2011-2015 sorted from highest to lowest incidence (the white line in the age distribution represents the median age in each cohort).

Abbreviations: CNS, central nervous system; CCI, Charlson Comorbidity Index



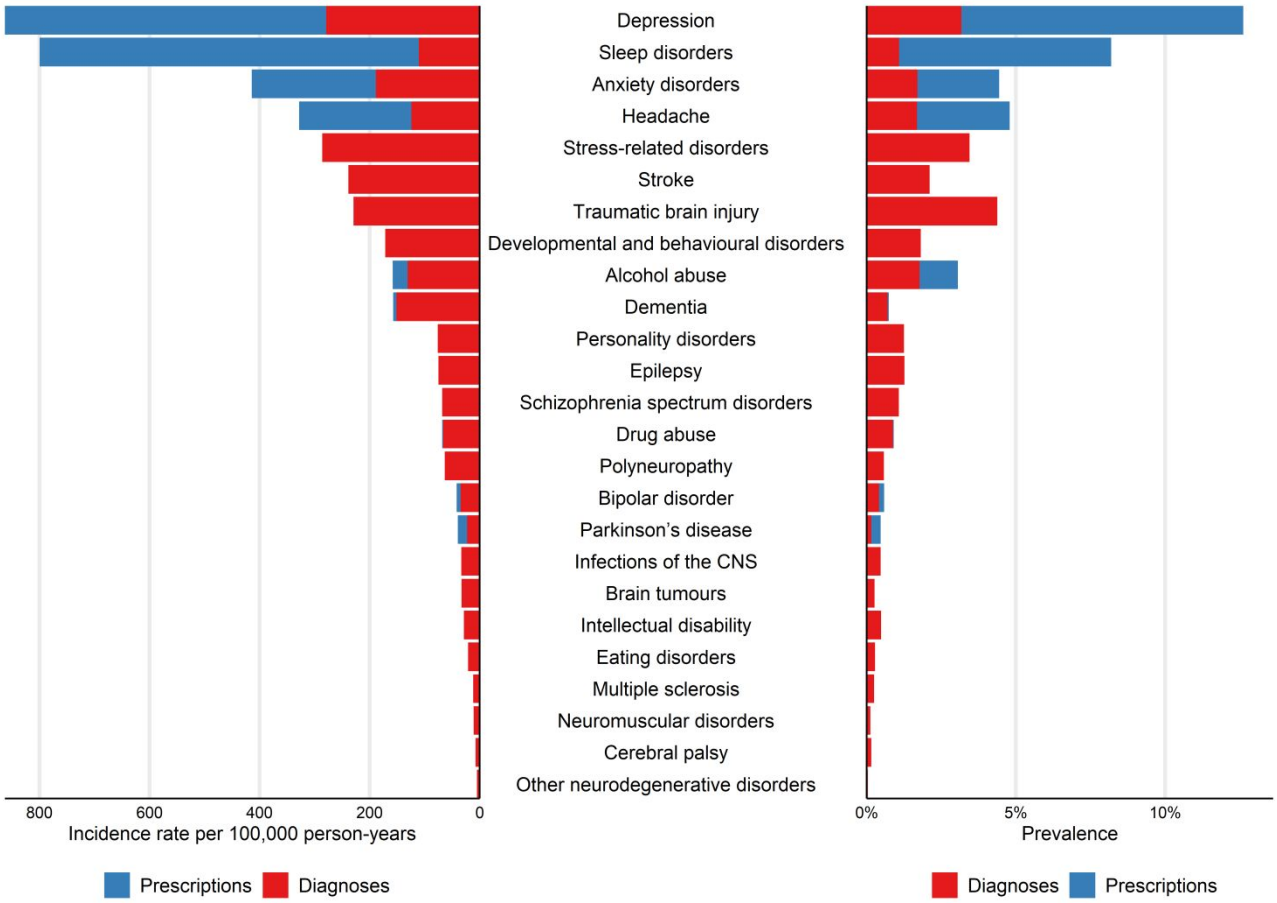
Suppl. Figure 2. Proportion of persons with incident brain disorders in the Danish population during 2011-2015 (columns), who had been diagnosed with comorbid brain or non-psychiatric disorders included in the Charlson Comorbidity Index up to 10 years before the index date of the brain disorder (rows).

Abbreviations: CNS, central nervous system



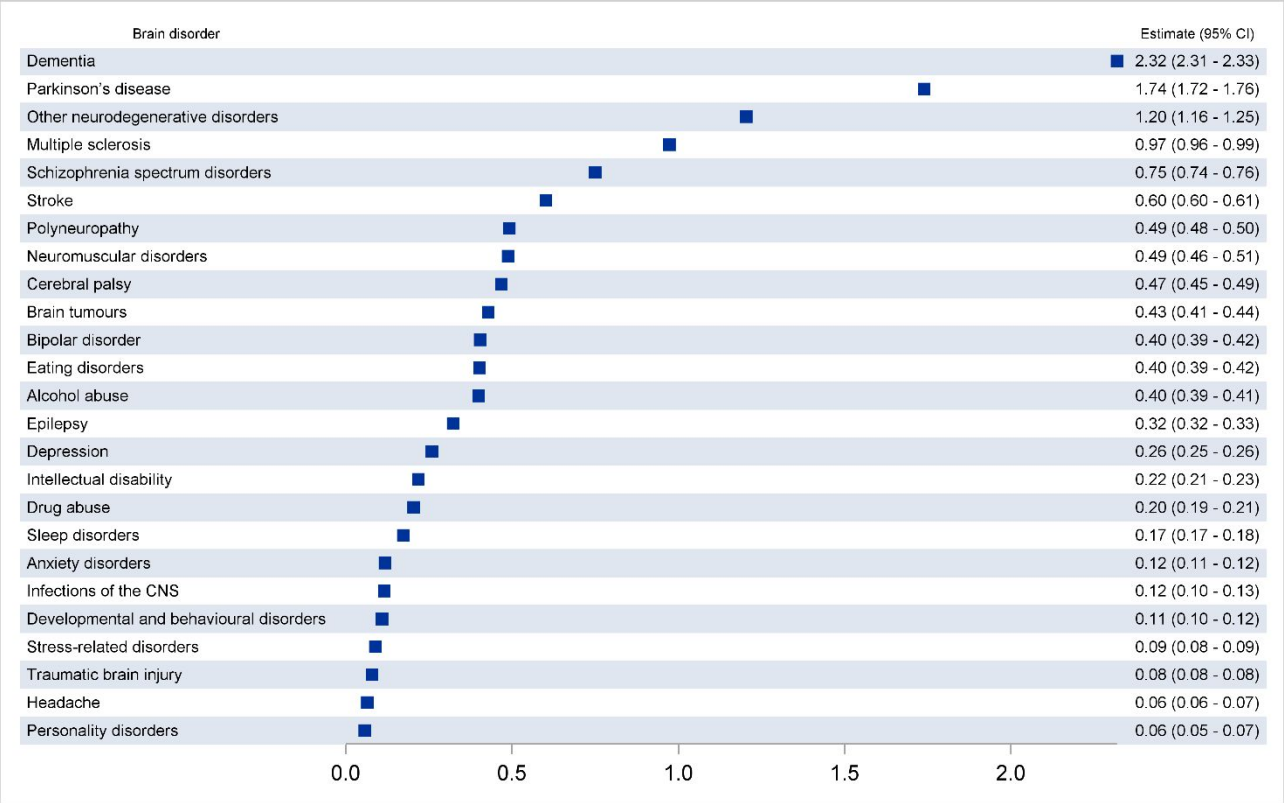
Suppl. Figure 3. Attributable direct costs per person during the first year after diagnosis in persons with incident brain disorders in Denmark during 2011-2015 (in 2015 prices) sorted from highest to lowest costs.

Abbreviations: CNS, central nervous system



Suppl. Figure 4. Occurrence of brain disorders in the Danish population including incidence during 2011-2015 and prevalence in 2015. Alcohol abuse, bipolar disorder, dementia, depression, drug abuse, headache, multiple sclerosis, Parkinson's disease, and sleep disorders were identified by either recorded hospital diagnoses or filled prescriptions of relevant medication, and all other brain disorders were identified by recorded hospital diagnoses.

Abbreviations: CNS, central nervous system



Suppl. Figure 5. Costs in €10,000 associated with each of 25 groups of brain disorders adjusted for comorbid brain disorders in persons with prevalent brain disorders in Denmark in 2015 (2015 prices).
Abbreviations: CI, confidence interval; CNS, central nervous system

Supplementary references

1. Schmidt M, Schmidt SAJ, Adelborg K, et al. The Danish health care system and epidemiological research: from health care contacts to database records. *Clin Epidemiol* 2019;11:563-91. doi: 10.2147/clep.S179083

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STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	title page
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	page 3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	page 6
Objectives	3	State specific objectives, including any prespecified hypotheses	page 6
Methods			
Study design	4	Present key elements of study design early in the paper	page 7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	page 7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	page 7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	page 7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	page 8-9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	page 8-9 + Appendix 1
Bias	9	Describe any efforts to address potential sources of bias	page 10-11
Study size	10	Explain how the study size was arrived at	page 7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	page 8-9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	page 9-10
		(*b*) Describe any methods used to examine subgroups and interactions	page 9-10
		(*c*) Explain how missing data were addressed	NA
		(*d*) If applicable, explain how loss to follow-up was addressed	NA
		(*e*) Describe any sensitivity analyses	page 10
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	page 11
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	page 11+22
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) Summarise follow-up time (eg, average and total amount)	-
Outcome data	15*	Report numbers of outcome events or summary measures over time	page 11-12
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	page 12
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	page 13
Discussion			
Key results	18	Summarise key results with reference to study objectives	page 13-14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	page 14-15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	page 15-16
Generalisability	21	Discuss the generalisability (external validity) of the study results	page 15-16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	page 17

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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OCCURRENCE, MORTALITY, AND COST OF BRAIN DISORDERS IN DENMARK: A POPULATION-BASED COHORT STUDY

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OCCURRENCE, MORTALITY, AND COST OF BRAIN DISORDERS IN DENMARK: A POPULATION-BASED COHORT STUDY

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Keywords: Brain disorders, mental disorders, neurologic disorders, epidemiology, cost-of-illness

ABSTRACT

Objectives

To examine the occurrence of brain disorders (*i.e.,* neurological and mental disorders) in Denmark and mortality and cost-of-illness among affected persons.

Design

Matched cohort study.

Setting

We obtained routinely collected registry data on all Danish residents during 1995-2015.

Participants

We identified all persons alive on 1 January 2015 with a diagnosis of 25 specific brain disorders (prevalent cohort) and all persons with an incident diagnosis during 2011-2015 (incident cohort). Each person was matched on age and sex with 10 persons from the general population without the brain disorder of interest.

Primary and secondary outcome measures

Prevalence and incidence of hospital-diagnosed brain disorders, 1-year absolute and relative mortality, and attributable direct and indirect costs-of-illness compared with the corresponding matched cohorts.

Results

We identified 1,075,081 persons with at least one prevalent brain disorder (*any brain disorder*) on 1 January 2015, corresponding to 18.9% of the Danish population. The incidence rate of *any brain disorder* during 2011-2015 was 1,349 per 100,000 person-years (95% confidence interval [CI]: 1,345-1,353). One-year mortality after diagnosis was increased in persons with *any brain disorder* (hazard ratio = 4.7 [95% CI: 4.7-4.8]) and in persons in every group of specific brain disorders compared to the matched cohort from the general population. The total attributable direct costs of brain disorders in 2015 were €5.2 billion and

total attributable indirect costs were €11.2 billion. Traumatic brain injury, stress-related disorders, depression, and stroke were the most common brain disorders. Attributable costs were highest for depression, dementia, stress-related disorders, and stroke.

Conclusions

One in five Danish residents alive on 1 January 2015 had been diagnosed with at least one brain disorder, and mortality was five times higher in persons with any diagnosed brain disorder than in the general population. We found high attributable direct and indirect costs of brain disorders.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- We examined epidemiology and societal costs of hospital-diagnosed brain disorders using individual-level data on a well-defined population with complete follow-up.
- Both epidemiology and cost were estimated among persons with one of 25 specific brain disorders, and among persons with any brain disorders taking into account comorbid disorders.
- We identified persons with incident brain disorders during 2011-2015, whereas persons alive on 1 January 2015 with brain disorders diagnosed from 1995 to 2014 were considered prevalent.
- We estimated 1-year mortality among persons with incident brain disorders, and direct and indirect societal costs among persons with prevalent brain disorders.
- Direct costs included cost of services in primary care, secondary care, and costs of medication, nursing home, sheltered accommodation, personal nursing, home nurse visits, and hospital-based neuro rehabilitation, whereas lost productivity was considered indirect costs.

BACKGROUND

Brain disorders, including both neurological and mental disorders, are the leading cause of years lived with disability worldwide.[1, 2] In 2010, it was estimated that 260 million persons in Europe (~50% of the population) lived with a brain disorder with an estimated total cost-of-illness of €798 billion.[3, 4] Based on this appraisal, mental disorders alone were estimated to account for 4.1% of European countries' combined gross domestic product (GDP) in 2015.[5] The global burden of brain disorders is expected to double between 2010 and 2030.[6, 7]

Previous estimates of overall occurrence and cost of brain disorders relied on heterogeneous data sources without individual-level data. This excluded consideration of comorbid brain disorders in estimates of the incidence, prevalence, mortality, and cost-of-illness of brain disorders.[2, 3, 8] Therefore, single persons with multiple disorders were counted more than once, causing potential overestimation of the occurrence. Previous studies also focused on cause-specific mortality rather than all-cause mortality. This could have led to underestimation of excess mortality associated with brain disorders due to incompletely recorded brain disorders on death certificates.[2, 9] Thus, there is a need for valid updated estimates of occurrence, mortality, and cost of brain disorders to better understand the public health burden and healthcare planning needs.[7]

We conducted this population-based study using routinely collected individual-level registry data to examine the prevalence and incidence of brain disorders in the Danish population during 2011-2015, as well as mortality and cost-of-illness in these patients.

METHODS

Setting

We conducted a population-based cohort study encompassing the entire Danish population during 2011-2015. In Denmark, healthcare is primarily tax-funded with equal access for every Danish resident. We examined occurrence, mortality, and costs of brain disorders using nationwide data from healthcare and socioeconomic registries.[10]

Study design and participants

The following 25 predefined groups of brain disorders were examined: *alcohol abuse, anxiety disorders, bipolar disorder, brain tumours, cerebral palsy, dementia, depression, developmental and behavioural disorders, drug abuse, eating disorders, epilepsy, headache, infections of the central nervous system, intellectual disability, multiple sclerosis, neuromuscular disorders, other neurodegenerative disorders, Parkinson's disease, personality disorders, polyneuropathy, schizophrenia spectrum disorders, sleep disorders, stress-related disorders, stroke, and traumatic brain injury.* Disorders were selected if expected to be common or critical, and we prioritized to select groups of disorders examined in previous studies to enable comparison of our results.[2, 3] For each of 25 specific brain disorders, we established two cohorts: a prevalent cohort of persons alive on 1 January 2015 who had a diagnosis of the specific brain disorder recorded during the 1995-2014 period and an incident cohort of persons with a first-time diagnosis recorded during the 1 January 2011 to 31 December 2015 period. We also identified every Danish resident with *any brain disorder*, *i.e.*, each person with any of the specific 25 disorders was identified on the date of his or her first diagnosis. To avoid double-counting, every person could only be included once in the *any brain disorder* cohort.

For each of the 25 specific brain disorder cohorts and the *any brain disorder* cohort, we created a matched comparison cohort for the incident cohort and a matched comparison cohort for the prevalent cohort. Each person in the brain disorder cohorts was matched to 10 living persons from the general population on birth

year and sex (sampled with replacement).[11] Matched persons could not have the brain disorder of interest as of the index date of the person with the brain disorder. The index dates of matching were the date of the brain disorder diagnosis for the incident cohort and 1 January 2015 for the prevalent cohort.

Variables

The unambiguous personal identifier assigned to every Danish resident enabled us to identify and link every person across national registries to estimate occurrence, mortality, and cost-of-illness of brain disorders on the individual level (see detailed description of the data sources in Appendix 1).[10]

We identified persons with brain disorders by means of inpatient and outpatient hospital diagnoses (both primary and secondary diagnoses) coded in the Danish National Patient Registry according to the *International Classification of Diseases, Tenth Revision* (ICD-10).[12] ICD codes are provided in Appendix 2.

To estimate mortality, we retrieved the dates of death of persons who died during the study period from the Danish Civil Registration System.[10]

To estimate direct costs, we obtained individual-level information on all primary care services provided by general practitioners and dentists from the Danish Health Service Registry,[13] individual-level medication expenditures from the Danish National Prescription Registry,[14] and individual-level information on nursing home or sheltered accommodation, personal nursing and other personal care, home nurse visits, and hospital-based neuro rehabilitation from Statistics Denmark.[15] We also computed costs of secondary care including hospital inpatient admissions, outpatient specialist clinic visits, and emergency room contacts based on the Diagnosis Related Group (DRG) and Danish Ambulatory Grouping System (DAGS) tariffs.[16] Medication costs were computed using market prices for prescriptions filled at outpatient pharmacies and in-hospital medication costs were included in the DRG/DAGS tariffs. To estimate indirect costs, we first estimated lost productivity associated with illness by subtracting the personal income of persons in the matched comparison cohorts from the personal income of persons with brain disorders (all before taxes). We then estimated lost productivity due to premature death (difference in actual age of death and

expected age at death based on the average life expectancy of persons of same age and sex in Denmark). We obtained 2015 cost information for persons in the prevalent cohort and their comparison cohort and from index date for persons in the incident cohort and their comparison cohort.

Finally, we obtained information on prior comorbid brain disorders and on prior non-mental disorders included in the Charlson Comorbidity Index (CCI) up to 10 years before the index date of every person in the brain disorder and comparison cohorts.[12] Using the comorbid diseases included in the CCI, we calculated a CCI score for every person (CCI score: 0 = low, 1-2 = medium, 3+ = high comorbidity).[17, 18]

Statistical analyses

Occurrence

We used any diagnosis from 1 January 1995 to 31 December 2014 as the basis for computing the period prevalence of each of the 25 brain disorders in persons alive on 1 January 2015. To estimate the average annual incidence of the different brain disorders, we computed incidence rates (IRs) of newly diagnosed persons per 100 000 person-years at risk between 1 January 2011 and 31 December 2015. We considered a person to be at risk of an incident specific brain disorder only if he or she did not have a diagnosis of that specific brain disorder during 1995-2010. We characterised persons with brain disorders by age, sex, CCI conditions, and CCI score on the index date across the 25 groups of disorders.

Mortality

We computed 1-year mortality for persons with brain disorders and for persons in their matched comparison cohorts and compared these by means of crude and adjusted hazard ratios (HRs) obtained from a Cox regression model adjusted for age, sex, and CCI score.

Cost-of-illness

To estimate the economic burden of the 25 brain disorders, we used the human capital approach to conduct a societal cost-of-illness analysis including both direct and indirect individual-level costs.[19, 20] For

each brain disorder, we computed direct and indirect costs-of-illness for every individual in our study population. We estimated both overall annual costs and average annual costs per person. Direct costs were computed both as actual direct costs (*i.e.*, costs of healthcare services) and attributable direct costs (*i.e.*, the cost of healthcare services for persons with brain disorders minus the cost of healthcare services for persons of the same age and sex in the comparison cohorts). For persons with incident brain disorders, we further computed the distribution of the attributable direct costs per person during the first year after the diagnosis, as we expected substantial direct and indirect costs during this year.

We computed attributable indirect costs (*i.e.,* loss of productivity) in patients of working age, *i.e.*, ages 18-65 years. In persons living with brain disorder diagnoses, we computed loss of productivity associated with illness as yearly income before taxes in persons with brain disorders subtracted from the yearly income in living members of the comparison cohorts. For persons who died after diagnoses of brain disorders, we estimated loss of productivity due to premature death as the annual income during the year before death multiplied by the number of lost years of life, assuming that they otherwise would have survived to age 66 years (accounting for the risk of dying each year and discounting future costs with 4% per annum).[19, 20]

Sensitivity analyses

Patients with *alcohol abuse, bipolar disorder, dementia, depression, drug abuse, headache, multiple sclerosis, Parkinson's disease, and sleep disorders* are commonly treated in general practice with medication specific for those disorders. Thus, we performed sensitivity analyses that included both persons with hospital diagnoses and persons who filled prescriptions for relevant pharmacological treatments of these disorders (including information on indication for the prescription when relevant).[14] We repeated all occurrence and cost analyses on these extended cohorts.

In addition, we performed attributable cost analyses, in which we modelled the average annual costs per person for each group of brain disorders using an ordinary least squares (OLS) regression, adjusting for comorbid brain disorders in individuals with more than one brain disorder.

Analyses were performed using SAS version 9.4 (Cary, NC, USA), and visualization was made using Tidyverse packages in R version 3.6.1.[21] The study was approved by the Danish Data Protection Agency through registration at Aarhus University (record number 2016-051-000001/603). According to Danish legislation, no approval from an ethics committee or informed consent from patients is required for registry-based studies.

Patient involvement statement

This study was done without patient involvement. Patients were not invited to comment on the study design, to develop patient relevant outcomes, or interpret the results. Patients were not invited to contribute to the writing or editing of the manuscript.

RESULTS

Patient characteristics

The characteristics of 1 075 081 persons with prevalent brain disorders in 2015 are displayed in Figure 1, and those of 381 759 persons with incident brain disorders during 2011-2015 are displayed in Suppl. Figure 1. Approximately half of persons with *any brain disorder* were female, occurrence was stable across ages, and three out of four persons had no or mild comorbidity (both in the prevalent and incident cohorts) (Figure 1, Suppl. Figure 1, Suppl. Table 1, and Suppl. Table 2). The proportions of persons with specific brain disorders who were diagnosed with specific comorbid somatic or mental disorders before index date are displayed in Suppl. Figure 2.

Occurrence

On 1 January 2015, 18.9% of the Danish population had been diagnosed with *any brain disorder*. Among persons without prior brain disorder diagnoses, the IR of *any brain disorder* was 1 349 per 100 000 person-years during 2011-2015 (Suppl. Table 3).

The prevalence in 2015 and incidence in 2011-2015 of the 25 groups of brain disorders in the Danish population are displayed in Figure 2. *Traumatic brain disorders* were the most common brain disorders, with a prevalence of 4.4% (Figure 2 and Suppl. Table 3), followed by *stress-related disorders* (3.4%) and *depression* (3.2%) (Figure 2).

During 2011-2015, IRs were highest for *stress-related disorders* (286 per 100 000 person-years [95% CI: 284-288]) and *depression* (279 per 100 000 person-years [95% CI: 277-281]) (Figure 2 and Suppl. Table 3).

Mortality in persons with incident brain disorders

One-year mortality was 7.8% among persons with *any brain disorder*, compared to 1.9% in the comparison cohort. After adjustment, persons with *any brain disorder* still had almost five-fold increased mortality (HR=4.7 [95% CI: 4.7-4.8]), and the HRs were increased in every group of brain disorders. One-year mortality was highest in persons with *other neurodegenerative disorders* (28.0%), *brain tumours (*24.5%), *stroke* (20.8%), and *dementia* (20.3%). Of note, mortality was more than ten-fold increased in persons with *other neurodegenerative disorders* (HR of 15.3 [95% CI: 13.2-17.7]), *brain tumours* (HR of 13.2 [95% CI: 12.4-14.0]), and *anxiety disorders* (HR of 12.8 [95% CI: 12.4-13.3]) (Figure 3).

Cost-of-illness

The total direct attributable costs of *any brain disorder* were €5.2 billion in 2015 in Denmark, with increased costs in every group of brain disorders. Specifically, attributable direct costs were highest in patients with prevalent *depression* (€1.2 billion), *dementia* (€1.1 billion), and *stroke* (€1.0 billion) (Figure 4 and Suppl. Table 4). Importantly, the distribution of cost components varied considerably between brain disorders (Figure 4 and Figure 5).

Of note, the highest attributable costs per person in persons with prevalent brain disorders in 2015 was found in persons with *dementia* (€30K) and *Parkinson's disease* (€24K), mainly due to costs of nursing home/sheltered accommodation (Figure 5 and Suppl. Table 4).

The average attributable direct costs of *any brain disorder* during the first year after diagnosis was €13K, though these differed widely between persons with different disorders. Costs were highest during the first year in persons with incident *brain tumours* (€44K) and *schizophrenia spectrum disorders* (€39K) (Suppl. Figure 3 and Suppl. Table 4).

Productivity of persons with brain disorders was reduced in every group of brain disorders. The total indirect costs in 2015 were €11.2 billion in persons with *any brain disorder*, mostly due to loss of productivity associated with illness (€10.9 billion) and less due to loss of productivity due to premature death (€0.3 billion). Specifically, lost productivity was €3.2 billion in persons with *stress-related disorders*, €2.9 billion in persons with *depression*, and €2.2 billion in persons with *alcohol abuse*. Finally, we found that the indirect costs were largely made up of costs due to lost productivity in patients living with illness, while costs due to lost productivity due to premature death contributed little (Figure 6 and Suppl. Table 5).

Sensitivity analyses

Adding persons with filled prescriptions to the hospital-diagnosed cohorts, we found that occurrence of *alcohol abuse*, *bipolar disorder*, and *dementia* increased little, while occurrence of *anxiety disorders*, *depression*, *headache*, *Parkinson's disease*, and *sleep disorders* increased several-fold (Suppl. Figure 4). Prevalence of *any brain disorders* increased to 30.2%, and total attributable costs in these persons in 2015 were €22.5 billion, of which direct costs were €6.5 billion and indirect costs were €16.0 billion (data not shown).

In the OLS regression, we accounted for comorbid brain disorders when estimating per-person costs associated with each brain disorder. We found that *dementia* (€23K) and *Parkinson's disease* (€17K) were associated with the highest per-person additional direct cost-of-illness after adjustment for comorbid brain disorders (Suppl. Figure 5). Of note, removing outliers (the 99% percentile) changed results considerably, indicating that the 1% of persons with highest costs-of-illness contributed a considerable share of the total costs.

DISCUSSION

We performed a study of occurrence, mortality, and cost of hospital-diagnosed brain disorders using high-quality, individual-level data. Brain disorders were common: one in five persons in Denmark had prevalent brain disorders in 2015. We found the most prevalent disorders to be *traumatic brain injury, stress-related disorders,* and *depression,* whereas the disorders with the highest incidence were *stress-related disorders*, *depression,* and *stroke*. One-year mortality was five-fold increased in persons with *any brain disorder* and was increased in persons with any type of brain disorder. The attributable direct costs of persons with *any brain disorder* were more than €5 billion. The more common brain disorders—*depression, dementia,* and *stroke*—accounted for the highest total attributable direct costs among persons with prevalent disorders. Attributable direct costs per person were highest in persons with *dementia* and *Parkinson's disease*. The total attributable indirect costs due to loss of productivity in persons with any prevalent brain disorder were twice as high as direct costs.

Even though our findings are based on high-quality population-based registries, some limitations should be considered when interpreting our findings. We may have underestimated the prevalence, incidence, and total cost of non-severe brain disorders, as some patients were treated solely in general practice, or were undiagnosed or untreated. This is especially relevant for disorder that are mainly treated in primary care, or not treated at all, and therefore were not captured in our main analyses such as *anxiety,*[22] *headache,*[23] and *sleep disorders*.[24] We addressed this in a sensitivity analysis that also identified patient-based filled prescriptions for relevant medications.

We estimated the period prevalence among living persons who had been diagnosed with brain disorders during the preceding 20 years, even though some disorders may be reversible. We chose this approach as a period with severe disease may affect future income and use of healthcare services.

We described non-mental comorbidity as the proportions of persons in each cohort previously diagnosed with diseases from the CCI covering 19 groups of disorders. CCI score was used to adjust for confounding in

our mortality analyses, and as CCI score is an aggregated measure of comorbidity we cannot rule out residual or unmeasured confounding in our estimates of HRs of death.[17, 18, 25]

While we had detailed data on direct costs, we lacked information on municipally supported rehabilitation, assistance supplies, and transportation costs related to treatment and rehabilitation. Similarly, our cost analyses did not include intangible costs (*e.g.*, due to decreased quality of life) and costs of informal care provided by relatives, which may be considerable in conditions such as *dementia*.[26] Yet, we included costs of nursing homes, sheltered accommodation, and home nursing, and we found the annual cost per person with *dementia* (€30K) similar to that previously reported in developed countries.[27, 28]

In estimating the indirect costs (i.e. loss of productivity) of illness and premature death we applied the human capital approach. In the literature, this approach has been discussed and among others it has been argued that application of the human capital approach leads to an over-estimation of the productivity costs. Hence, alternative methods like the friction cost method have been proposed.[19] The idea behind the friction cost method is that the amount of production lost due to disease depends on the time (friction period) organizations need to restore the initial production level. Friction periods will differ by industry, type of work etc. and the challenge is to estimate relevant friction periods but application of the friction cost method leads to lower productivity cost estimates.[19] Taking these considerations into account, we present our indirect cost estimates separately (Figure 6) making it possible to assess the results without inclusion of the indirect costs.

Of note, our study described the cost-of-illness in patients with brain disorders, but did not isolate the cost of the disease itself as patients with brain disorders are known to have a high load of comorbidity.[29-31]

We estimated the prevalence and incidence of *any brain disorder* using individual-level data, which allowed us to capture concurrent brain disorders,[29] opposed to the prior studies based on literature reviews that included a mix of hospital-diagnosed disorders and disorders reported in population surveys.[3, 5] Beside using different eligibility criteria, double counting of individuals with concurrent brain disorders may

explain the previously reported total 1-year prevalence of brain disorders of ~50% (260 million affected among 514 million population in Europe),[3] which is markedly higher than what we found despite including prevalent disorders during a 20-year period.[8, 9] Compared to the reported prevalence of separate disorders, we found markedly lower prevalence of anxiety (1.7% vs 12%), headache (1.7% vs 10%), depression (3.2% vs 6.5%), and sleep disorders (1.1% vs 8.7%), despite the longer lookback in our study (20-years vs. 1-year prevalence).[3] This may be explained by different data sources, as we in the main analyses only included persons with hospital-diagnosed disorders. Importantly, when we included persons with filled prescriptions in sensitivity analyses, the prevalence increased considerably indicating that we underestimated the occurrence of these disorders in our main analyses.

A recent Danish study reported a 2.5-fold increased mortality rate in persons with hospital-diagnosed mental disorders compared to persons from the general population,[32] which is markedly lower than mortality of *any brain disorders* in our study – likely explained by our use of different length of follow-up (*i.e.,* long-term as opposed to 1-year).

We found that the total attributable direct and indirect costs of brain disorders in Denmark in 2015 were €16.4 billion, equivalent to 5.9% of the Danish GDP (€273 billion in 2015).[33] This is only slightly higher than the recently reported costs of mental illness alone of €15 billion in Denmark in 2015 corresponding to 5.4% of the GDP.[5] However, when we included persons identified from filled prescriptions in addition to hospital-based diagnoses in sensitivity analyses, the prevalence increased and total attributable costs of *any brain disorders* increased substantially, indicating that the costs may be higher than previously estimated when not restricting to hospital-diagnosed persons.[3, 5]

Finally, previous Danish studies of selected brain disorders reported lower total costs of disorders such as dementia,[26] stroke,[34] Parkinson's disease,[35] and epilepsy.[36] These studies did not include costs of home nursing and nursing homes, and when accounting for that, our findings are comparable.[26, 34-36]

As the already large burden of brain disorders is expected to increase in the future,[6] prevention and effective early intervention are essential.[5] The potential to prevent stroke, infections of the central nervous system, and mental disorders is established, whereas the potential to prevent other neurological disorders remains unclear.[37, 38] As comorbidity load is substantial in persons with brain disorders, cost-of-illness may be reduced by preventing and improving treatment of comorbid disorders.[31]

We found that one in five persons alive in Denmark had been diagnosed with a brain disorder. One-year mortality was five-fold increased in persons with an incident brain disorder. Mortality was increased in every group of brain disorders, underscoring the illness of these patients. The severity also was reflected in the very high cost-of-illness in persons with brain disorders, with total attributable costs of €16.4 billion in Denmark in 2015, including direct costs of €5.2 billion and indirect costs of €11.2 billion.

Occurrence of brain disorders is expected to increase in the future. As brain disorders already use a large proportion of healthcare resources and come with high indirect costs, effective prevention and intervention strategies must be developed.

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CONTRIBUTIONS

CFC and HTS contributed to the study conception. CFC, HTS, NS, JO, SS, TBR, and SVV designed the study and wrote a statistical analyses plan. NS, JO, and SS outlined the economic methods, and SS and JO performed the data management and analyses of the economic data. TBR performed the remaining data management and analyses, and performed all final analyses. All authors interpreted the results, and TBR, SVV, and CFC visualized the data. SVV drafted the first manuscript, and all authors revised the manuscript and approved the final version. All authors agree to be accountable for all aspects of the work.

COMPETING INTERESTS

The authors have no specific competing interests to declare.

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ETHICAL APPROVAL

Not required.

DATA SHARING

Data are available as presented in the paper and in the Supporting Information files. According to Danish legislation, our approvals to use the Danish data sources for the current study do not allow us to distribute or make patient data directly available to other parties. Data access and information about availability is accessible through Statistics Denmark (website: https://www.dst.dk/en/TilSalg/Forskningsservice, e-mail: dst@dst.dk).

Figure Legends

Figure 1. Characteristics of patients with prevalent brain disorders in Denmark in 2015 sorted from highest to lowest prevalence (the white line in the age distribution represents the median age in each cohort).

Abbreviations: CNS, central nervous system; CCI, Charlson Comorbidity Index

Figure 2. Occurrence of brain disorders in the Danish population sorted from highest to lowest incidence, including incidence during 2011-2015 and prevalence in 2015.

Abbreviations: CNS, central nervous system

Figure 3. One-year mortality in patients with incident brain disorders in Denmark during 2011-2015 compared with the general population (comparison group). Hazard ratios are adjusted for age, sex, and comorbidity score. Specific disorders are sorted by hazard ratios.

Abbreviations: CI, confidence interval; CNS, central nervous system

Figure 4. Total attributable direct costs in persons with prevalent brain disorders in Denmark in 2015 (in 2015 prices) sorted from highest to lowest costs.

Abbreviations: CNS, central nervous system

Figure 5. Attributable direct costs per person in individuals with prevalent brain disorders in Denmark in 2015 (in 2015 prices) sorted from highest to lowest costs.

Abbreviations: CNS, central nervous system

Figure 6. Total attributable indirect costs due to lost productivity in persons with prevalent brain disorders in Denmark in 2015 (in 2015 prices) sorted from highest to lowest costs.

Abbreviations: CNS, central nervous system

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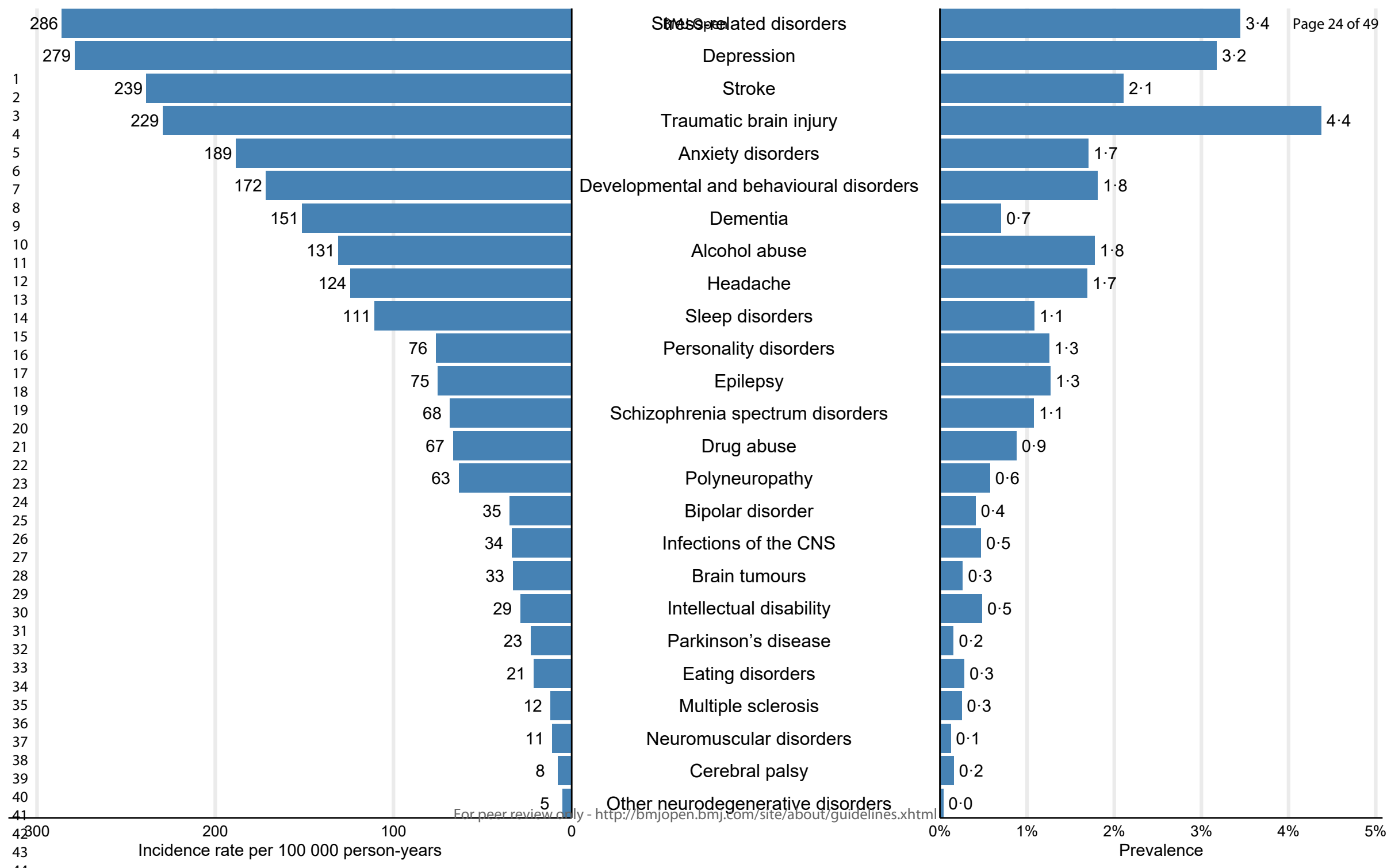
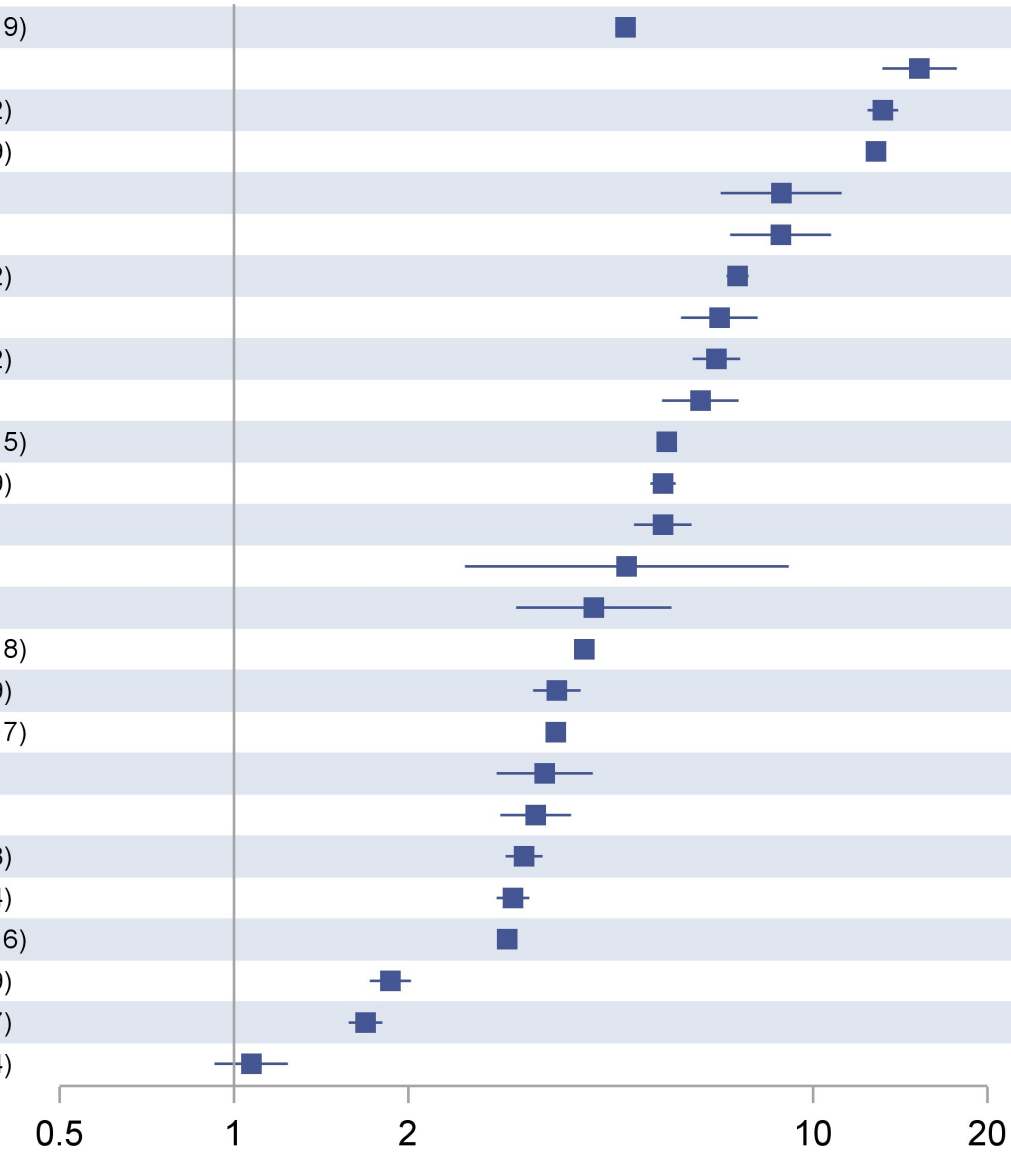
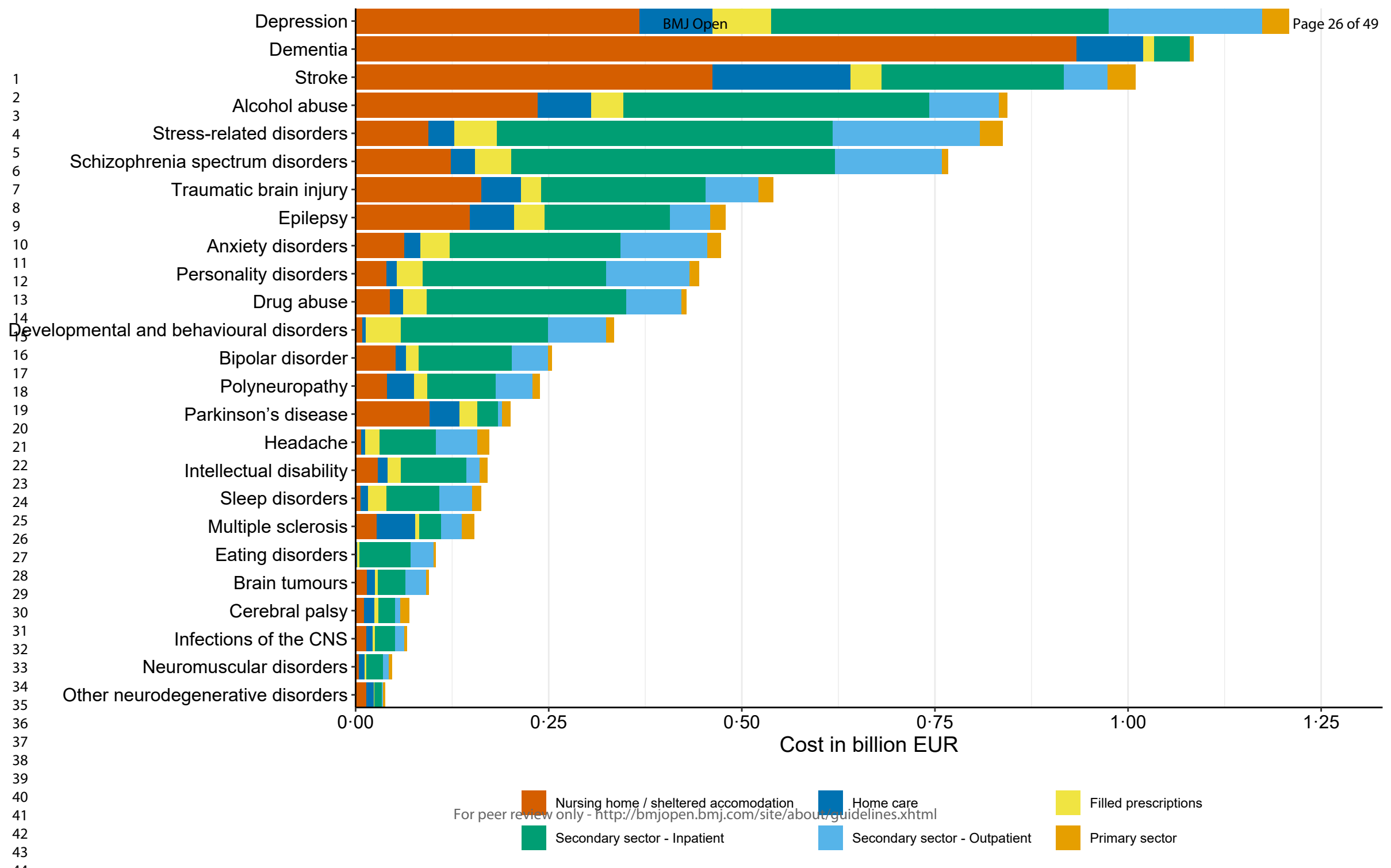
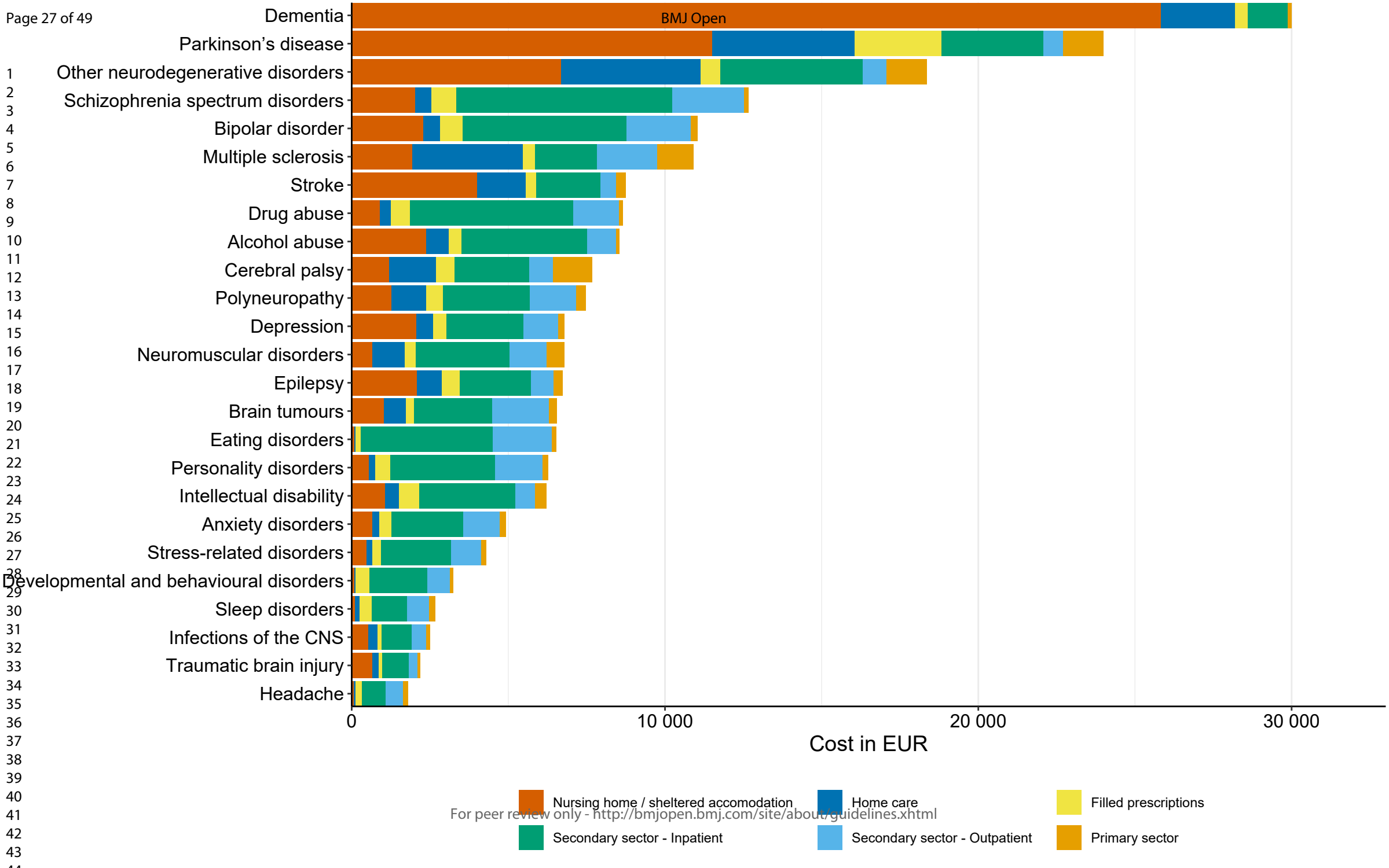
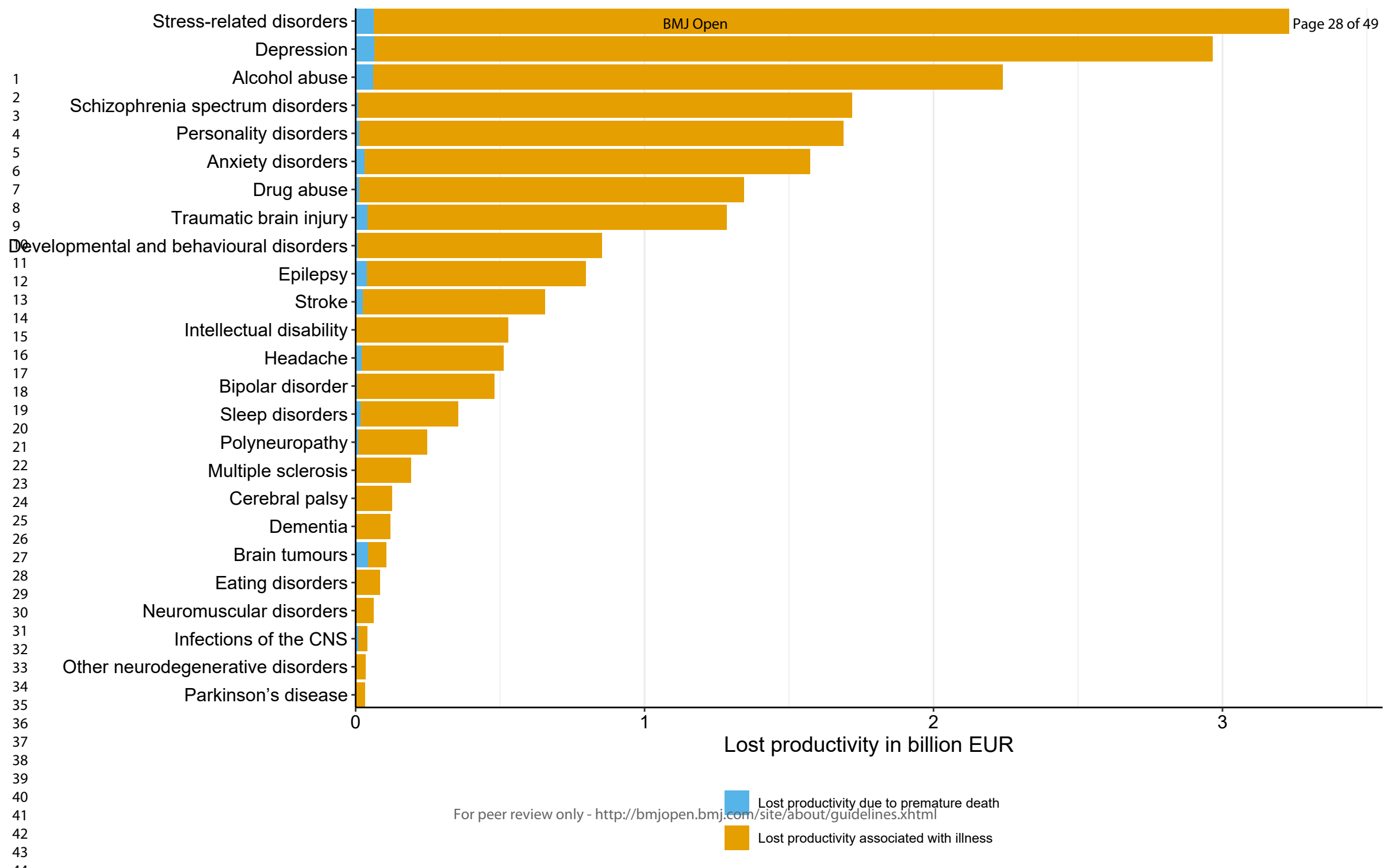


Brain disorder	Patient group - Deaths (%)	Comparison group - Deaths (%)	Adjusted hazard ratio (95% CI)
Any brain disorder	29 639 (7·8)	70 837 (1·9)	4·7 (4·7-4·8)
Other neurodegenerative disorders	409 (28·0)	317 (2·2)	15·3 (13·2-17·7)
Brain tumours	2 287 (24·5)	2 072 (2·2)	13·2 (12·4-14·0)
Anxiety disorders	7 319 (13·8)	4 786 (0·9)	12·8 (12·4-13·3)
Cerebral palsy	146 (6·8)	149 (0·7)	8·8 (6·9-11·2)
Intellectual disability	180 (2·2)	210 (0·3)	8·8 (7·2-10·7)
Alcohol abuse	3 629 (9·8)	4 591 (1·2)	7·4 (7·1-7·7)
Developmental and behavioural disorders	301 (0·6)	389 (0·1)	6·9 (5·9-8·0)
Infections of the CNS	755 (8·0)	1 101 (1·2)	6·8 (6·2-7·5)
Neuromuscular disorders	292 (9·6)	411 (1·3)	6·4 (5·5-7·4)
Stroke	14 045 (20·8)	30 249 (4·5)	5·6 (5·5-5·7)
Epilepsy	2 773 (13·1)	4 091 (1·9)	5·5 (5·2-5·8)
Drug abuse	505 (2·7)	775 (0·4)	5·5 (4·9-6·2)
Eating disorders	14 (0·2)	33 (0·1)	4·8 (2·5-9·1)
Multiple sclerosis	58 (1·7)	138 (0·4)	4·2 (3·1-5·7)
Depression	6 185 (7·9)	13 908 (1·8)	4·0 (3·9-4·2)
Schizophrenia spectrum disorders	593 (3·1)	1 633 (0·9)	3·6 (3·3-4·0)
Traumatic brain injury	3 847 (5·9)	11 084 (1·7)	3·6 (3·5-3·7)
Personality disorders	153 (0·7)	363 (0·2)	3·4 (2·8-4·2)
Bipolar disorder	269 (2·7)	718 (0·7)	3·3 (2·9-3·8)
Parkinson's disease	927 (14·3)	3 112 (4·8)	3·2 (2·9-3·4)
Stress-related disorders	1 241 (1·5)	3 441 (0·4)	3·0 (2·8-3·2)
Dementia	8 695 (20·3)	32 683 (7·6)	3·0 (2·9-3·0)
Sleep disorders	752 (2·4)	2 779 (0·9)	1·9 (1·7-2·0)
Polyneuropathy	1 066 (6·0)	4 772 (2·7)	1·7 (1·6-1·8)
Headache	207 (0·6)	1 553 (0·4)	1·1 (0·9-1·2)









APPENDIX 1 – DATA SOURCES

From the Danish Civil Registration System (DCRS), we obtained personal identification numbers (*i.e.*, CPR-numbers, a unique 10-digit number for every Danish citizen given at birth or immigration) to identify individuals across the nationwide registries in both the healthcare and socioeconomic systems. Also, the DCRS holds information on date of birth, sex, vital status, and place of living, of every person in Denmark.[1]

The Danish National Patient Registry (DNPR) holds information on all in- and outpatient hospital contacts since 1995, with details about date of admission and discharge, procedures and operations, and one or more discharge diagnoses.[2] Similarly, all contacts to psychiatric hospitals are recorded in the Danish Psychiatric Central Research Registry, which since 1995 has been included in the DNPR. The discharge diagnoses are recorded using the International Classification of Diseases, Tenth Revision (ICD-10).[3] For every hospital contact, the accumulated costs of the services provided are reimbursed to the hospital department using national reimbursement rates/tariffs based on average costs of the services. Diagnosis-related group (DRG) tariffs are used for inpatient contacts and Danish Ambulatory Grouping System (DAGS) tariffs for outpatient contacts.[4]

The Danish Health Service Registry (DHSR) contains information on services provided by health contractors in primary health care covered by the national health services during consultations, telephone consultations, and home visits. Services are recorded from a wide range of health contractors such as general practitioners, dentists, physiotherapists, chiropodists, chiropractors, psychologists, and other specialists. Every service recorded in the DHSR is accompanied with a corresponding tariff used when the counties reimburse services to the health contractor.[5]

The Danish National Prescription Registry includes nationwide data on all prescriptions filled at outpatient pharmacies since 1995, *e.g.*, drug type, number of packages, package size, and price. Since 2004, indication of prescriptions are recorded, but with missing indication in one third of prescriptions filled. Drug types are classified according to the Anatomical Therapeutic Chemical (ATC) classification system.[6]

Finally, Statistics Denmark hosts registries with information on every Danish resident on whether the person lives in an elderly home or nursery home, on exact time spent by public home help in private households (in hours), and on personal income before taxes.[7] Data on rehabilitation provided by municipalities were not available in any nationwide registry and therefore not included in our analyses.

APPENDIX 2 – CODE BOOKS

ICD-10 and ATC codes

In the main analyses, brain disorders were defined by the "Included diagnosis codes" excluding the codes in "Excluded diagnosis codes". In the sensitivity analyses, brain disorders were defined by either "Included diagnosis codes" excluding the codes in "Excluded diagnosis codes" or by filled prescriptions including "Included ATC codes". For The Anatomical Therapeutic Chemical (ATC) codes, if any indication codes are given, only prescriptions with those ATC and indication codes were used. Diagnosis codes are given as International Classification of Diseases, Tenth Revision (ICD-10) codes. For both ICD-10 and ATC codes, all subcodes were included.

Brain disorder	Included diagnosis codes	Excluded diagnosis codes	Included ATC codes	Included indication codes
Any brain disorder				
Alcohol abuse	F10 E244 G312 G621 G721 I426 K292 K70 K852 K860 Q860	F100	V03AA N07BB	
Anxiety disorders	F40 F41 F42		N06A	371 830 163
Bipolar disorder	F30 F31		N05AN01	
Brain tumours	C70 C71 C72 D32 D33 D42 D43			
Cerebral palsy	G80			
Dementia	F00 F01 F02 F03 G30 G310B G311 G318 G319		N06D	330 331 329 838
Depression	F32 F33		N06A	168 270
Developmental and behavioural disorders	F84 F9	F99		
Drug abuse	F1	F10 F17	N07BC01 N07BC51	
Eating disorders	F500 F501 F502 F503			
Epilepsy	G40			
Headache	G43 G44		N02C	56 269 153
Infections of the central nervous system	G0 A17 A321 A327 A390 A521 A522 A523 A692 A83 A84 A85 A87 A89 B003 B004 B010 B011 B020 B021 B582 B451 B375	G08 G09		
Intellectual disability	F7 Q90 Q992			
Multiple sclerosis	G35			
Neuromuscular disorders	G70 G71 G72 G73			
Other neurodegenerative disorders	G10 G11 G122G G13 G14	G130 G139		
Parkinson's disease	G20 G23		N04BA N04BB N04BD N04BX	
Personality disorders	F60			
Polyneuropathy	G60 G61 G62 G63 G64 G130			
Schizophrenia spectrum disorders	F2			
Sleep disorders	F51 G470 G471 G473 G474		N05CF01 N05CH01	372 165 166 373 170
Stress-related disorders	F43			
Stroke	I60 I61 I63 I64	I608		
Traumatic brain injury	S020 S021 S027 S029 S06			

Charlson Comorbidity Index (CCI)

The codes included were used to identify comorbidity in persons with brain disorders and their comparisons. Persons were considered having the specific type of comorbidity when having at least one of the listed discharge diagnosis codes (including all subcodes) recorded in the Danish National Patient Registry up to 10 years before index date.

CCI disease	Included ICD-8 and ICD-10 diagnosis codes
Myocardial infarction	410 DI21 DI22 DI23
Congestive heart failure	42709 42710 42711 42719 42899 78249 DI50 DI110 DI130 DI132
Peripheral vascular disease	440 441 442 443 444 445 DI70 DI71 DI72 DI73 DI74 DI77
Cerebrovascular disease	430 431 432 433 434 435 436 437 438 DI6 DG45 DG46
Dementia	29009 2901 29309 DF00 DF01 DF02 DF03 DF051 DG30
Chronic pulmonary disease	490 491 492 493 515 516 517 518 DJ40 DJ41 DJ42 DJ43 DJ44 DJ45 DJ46 DJ47 DJ60 DJ61 DJ62 DJ63 DJ64 DJ65 DJ66 DJ67 DJ684 DJ701 DJ703 DJ841 DJ920 DJ961 DJ982 DJ983
Connective tissue disease	712 716 734 446 13599 DM05 DM06 DM08 DM09 DM30 DM31 DM32 DM33 DM34 DM35 DM36 DD86
Ulcer disease	53091 53098 531 532 533 534 DK221 DK25 DK26 DK27 DK28
Mild liver disease	571 57301 57304 DB18 DK700 DK701 DK702 DK703 DK709 DK71 DK73 DK74 DK760
Diabetes without end-organ damage	24900 24906 24907 24909 25000 25006 25007 25009 DE100 DE101 DE109 DE110 DE111 DE119
Hemiplegia	344 DG81 DG82
Moderate to severe renal disease	403 404 580 581 582 583 584 59009 59319 7531 792 DI12 DI13 DN00 DN01 DN02 DN03 DN04 DN05 DN07 DN11 DN14 DN17 DN18 DN19 DQ61
Diabetes with end-organ damage	24901 24902 24903 24904 24905 24908 25001 25002 25003 25004 25005 25008 DE102 DE103 DE104 DE105 DE106 DE107 DE108 DE112 DE113 DE114 DE115 DE116 DE117 DE118
Solid cancer tumour	14 15 16 17 18 190 191 192 193 194 DC0 DC1 DC2 DC3 DC4 DC5 DC6 DC70 DC71 DC72 DC73 DC74 DC75
Leukaemia	204 205 206 207 DC91 DC92 DC93 DC94 DC95
Lymphoma	200 201 202 203 27559 DC81 DC82 DC83 DC84 DC85 DC88 DC90 DC96
Moderate to severe liver disease	07000 07002 07004 07006 07008 57300 4560 DB150 DB160 DB162 DB190 DK704 DK72 DK766 DI85
Metastatic solid tumour	195 196 197 198 199 DC76 DC77 DC78 DC79 DC80
AIDS	07983 DB21 DB22 DB23 DB24

Supplementary tables

Suppl. Table 1. Characteristics of patients with prevalent disorders in Denmark in 2015 sorted in alphabetical order.

	Prevalent cohorts: 2015					
Disease group	Persons, N	Men, N (%)	Age, median (Q1-Q3)	CCI: 0, N (%)	CCI: 1-2, N (%)	CCI: +3, N (%)
Any brain disorder	1,075,081	536,462 (49.9)	46.0 (27.5-63.6)	788,948 (73.4)	222,453 (20.7)	63,680 (5.9)
Alcohol abuse	101,066	67,376 (66.7)	56.5 (46.2-65.8)	59,961 (59.3)	28,397 (28.1)	12,708 (12.6)
Anxiety disorders	96,943	33,768 (34.8)	41.2 (28.8-54.3)	78,009 (80.5)	15,181 (15.7)	3,753 (3.9)
Bipolar disorder	23,364	9,366 (40.1)	52.4 (39.3-64.9)	17,127 (73.3)	4,851 (20.8)	1,386 (5.9)
Brain tumours	14,953	6,101 (40.8)	62.6 (48.6-71.9)	8,718 (58.3)	4,339 (29.0)	1,896 (12.7)
Cerebral palsy	9,083	5,093 (56.1)	22.3 (14.1-37.0)	6,516 (71.7)	2,092 (23.0)	475 (5.2)
Dementia	40,037	15,645 (39.1)	81.7 (73.9-87.5)	8,340 (20.8)	22,655 (56.6)	9,042 (22.6)
Depression	180,886	64,191 (35.5)	49.0 (35.6-64.1)	130,862 (72.3)	38,342 (21.2)	11,682 (6.5)
Developmental and behavioural disorders	103,157	68,589 (66.5)	19.6 (14.2-26.0)	94,745 (91.8)	7,841 (7.6)	571 (0.6)
Drug abuse	50,066	32,295 (64.5)	38.6 (28.4-50.8)	38,657 (77.2)	9,180 (18.3)	2,229 (4.5)
Eating disorders	15,936	750 (4.7)	29.5 (23.0-36.9)	14,484 (90.9)	1,332 (8.4)	120 (0.8)
Epilepsy	72,205	37,047 (51.3)	43.5 (24.8-62.1)	51,701 (71.6)	15,562 (21.6)	4,942 (6.8)
Headache	96,252	32,218 (33.5)	45.4 (31.2-57.6)	75,439 (78.4)	17,566 (18.3)	3,247 (3.4)
Infections of the central nervous system	26,829	14,069 (52.4)	43.1 (22.9-61.5)	20,740 (77.3)	4,709 (17.6)	1,380 (5.1)
Intellectual disability	27,605	16,087 (58.3)	25.4 (17.1-45.1)	23,577 (85.4)	3,501 (12.7)	527 (1.9)
Multiple sclerosis	14,264	4,431 (31.1)	52.6 (42.9-62.7)	11,206 (78.6)	2,559 (17.9)	499 (3.5)
Neuromuscular disorders	7,080	3,649 (51.5)	51.4 (33.3-66.5)	4,427 (62.5)	1,992 (28.1)	661 (9.3)
Other neurodegenerative disorders	2,192	1,143 (52.1)	59.9 (46.2-70.5)	1,381 (63.0)	622 (28.4)	189 (8.6)
Parkinson's disease	8,942	5,083 (56.8)	75.3 (68.4-81.4)	4,430 (49.5)	3,323 (37.2)	1,189 (13.3)
Personality disorders	71,334	24,517 (34.4)	39.9 (30.6-51.0)	58,516 (82.0)	10,824 (15.2)	1,994 (2.8)
Polyneuropathy	32,710	18,918 (57.8)	66.7 (55.0-75.8)	15,900 (48.6)	11,139 (34.1)	5,671 (17.3)
Schizophrenia spectrum disorders	61,346	32,637 (53.2)	45.1 (32.1-57.7)	48,640 (79.3)	10,276 (16.8)	2,430 (4.0)
Sleep disorders	61,666	45,042 (73.0)	55.9 (43.0-66.2)	41,909 (68.0)	15,223 (24.7)	4,534 (7.4)
Stress-related disorders	196,291	77,494 (39.5)	42.3 (29.3-54.1)	158,789 (80.9)	31,138 (15.9)	6,364 (3.2)
Stroke	120,065	64,067 (53.4)	71.0 (61.1-79.9)	23,651 (19.7)	70,389 (58.6)	26,025 (21.7)
Traumatic brain injury	249,348	142,776 (57.3)	34.9 (22.1-53.4)	207,314 (83.1)	34,162 (13.7)	7,872 (3.2)

Abbreviations: Q, quartile; CCI, Charlson Comorbidity Index.

Suppl. Table 2. Characteristics of patients with incident brain disorders in Denmark during 2011-2015 sorted in alphabetical order.

	Incident cohorts: 2011-2015					
Disease group	Persons, N	Men, N (%)	Age, median (Q1-Q3)	CCI: 0, N (%)	CCI: 1-2, N (%)	CCI: +3, N (%)
Any brain disorder	381,759	187,780 (49.2)	46.6 (21.5-68.9)	295,560 (77.4)	64,746 (17.0)	21,453 (5.6)
Alcohol abuse	37,032	25,251 (68.2)	55.8 (42.7-66.8)	25,797 (69.7)	8,347 (22.5)	2,888 (7.8)
Anxiety disorders	53,350	20,013 (37.5)	35.8 (22.3-56.5)	39,034 (73.2)	8,480 (15.9)	5,836 (10.9)
Bipolar disorder	9,838	4,074 (41.4)	40.8 (28.5-55.0)	7,951 (80.8)	1,500 (15.2)	387 (3.9)
Brain tumours	9,336	4,199 (45.0)	64.1 (50.7-72.9)	6,044 (64.7)	2,227 (23.9)	1,065 (11.4)
Cerebral palsy	2,145	1,199 (55.9)	13.7 (3.1-54.3)	1,371 (63.9)	582 (27.1)	192 (9.0)
Dementia	42,798	17,454 (40.8)	81.8 (75.4-87.0)	21,015 (49.1)	15,686 (36.7)	6,097 (14.2)
Depression	78,926	29,379 (37.2)	45.4 (27.9-66.8)	56,768 (71.9)	15,445 (19.6)	6,713 (8.5)
Developmental and behavioural disorders	48,562	29,864 (61.5)	14.1 (8.6-21.9)	43,747 (90.1)	4,445 (9.2)	370 (0.8)
Drug abuse	18,843	12,469 (66.2)	26.9 (20.7-42.3)	15,944 (84.6)	2,322 (12.3)	577 (3.1)
Eating disorders	6,011	321 (5.3)	19.7 (16.0-24.9)	5,683 (94.5)	307 (5.1)	21 (0.3)
Epilepsy	21,255	11,301 (53.2)	53.2 (21.1-70.6)	12,057 (56.7)	6,319 (29.7)	2,879 (13.5)
Headache	35,180	11,547 (32.8)	37.6 (23.4-50.4)	29,066 (82.6)	5,292 (15.0)	822 (2.3)
Infections of the central nervous system	9,501	4,922 (51.8)	44.6 (21.9-64.2)	7,086 (74.6)	1,727 (18.2)	688 (7.2)
Intellectual disability	8,166	4,692 (57.5)	17.3 (9.9-34.8)	7,035 (86.1)	994 (12.2)	137 (1.7)
Multiple sclerosis	3,345	1,070 (32.0)	41.7 (31.9-52.0)	2,833 (84.7)	449 (13.4)	63 (1.9)
Neuromuscular disorders	3,062	1,596 (52.1)	52.8 (32.9-67.8)	1,950 (63.7)	803 (26.2)	309 (10.1)
Other neurodegenerative disorders	1,464	777 (53.1)	65.3 (53.1-73.2)	904 (61.7)	425 (29.0)	135 (9.2)
Parkinson's disease	6,478	3,883 (59.9)	75.5 (68.9-81.4)	3,459 (53.4)	2,236 (34.5)	783 (12.1)
Personality disorders	21,556	6,762 (31.4)	27.2 (21.3-38.6)	19,265 (89.4)	2,030 (9.4)	261 (1.2)
Polyneuropathy	17,925	10,755 (60.0)	65.9 (54.5-75.0)	8,825 (49.2)	6,108 (34.1)	2,992 (16.7)
Schizophrenia spectrum disorders	19,316	10,219 (52.9)	29.7 (21.1-48.9)	16,209 (83.9)	2,483 (12.9)	624 (3.2)
Sleep disorders	31,316	21,769 (69.5)	51.9 (38.5-62.7)	21,974 (70.2)	7,086 (22.6)	2,256 (7.2)
Stress-related disorders	80,953	34,110 (42.1)	34.5 (20.5-48.5)	68,431 (84.5)	10,356 (12.8)	2,166 (2.7)
Stroke	67,539	35,308 (52.3)	71.8 (61.1-81.3)	37,862 (56.1)	21,220 (31.4)	8,457 (12.5)
Traumatic brain injury	64,931	35,456 (54.6)	34.3 (15.7-63.4)	50,924 (78.4)	10,610 (16.3)	3,397 (5.2)

Abbreviations: Q, quartile; CCI, Charlson Comorbidity Index.

Suppl. Table 3. Occurrence of hospital-diagnosed brain disorders in the Danish population including incidence during 2011-2015 and prevalence in 2015 sorted in alphabetical order.

Disease group	Prevalent cohorts: 2015		Incident cohorts: 2011-2015	
	Prevalence, N (%)	Prevalence per 100,000 persons (95% CI)	Incidence, N	Incidence rate per 100,000 person-years (95% CI)
Any brain disorder	1,075,081 (18.9)	18,879 (18,844-18,915)	381,759	1,349 (1,345-1,353)
Alcohol abuse	101,066 (1.8)	1,775 (1,764-1,786)	37,032	131 (130-132)
Anxiety disorders	96,943 (1.7)	1,702 (1,692-1,713)	53,350	189 (187-190)
Bipolar disorder	23,364 (0.4)	410 (405-416)	9,838	35 (34-35)
Brain tumours	14,953 (0.3)	263 (258-267)	9,336	33 (32-34)
Cerebral palsy	9,083 (0.2)	160 (156-163)	2,145	8 (7-8)
Dementia	40,037 (0.7)	703 (696-710)	42,798	151 (150-153)
Depression	180,886 (3.2)	3,176 (3,162-3,191)	78,926	279 (277-281)
Developmental and behavioural disorders	103,157 (1.8)	1,812 (1,800-1,823)	48,562	172 (170-173)
Drug abuse	50,066 (0.9)	879 (872-887)	18,843	67 (66-68)
Eating disorders	15,936 (0.3)	280 (276-284)	6,011	21 (21-22)
Epilepsy	72,205 (1.3)	1,268 (1,259-1,277)	21,255	75 (74-76)
Headache	96,252 (1.7)	1,690 (1,680-1,701)	35,180	124 (123-126)
Infections of the central nervous system	26,829 (0.5)	471 (466-477)	9,501	34 (33-34)
Intellectual disability	27,605 (0.5)	485 (479-491)	8,166	29 (28-29)
Multiple sclerosis	14,264 (0.3)	250 (246-255)	3,345	12 (11-12)
Neuromuscular disorders	7,080 (0.1)	124 (121-127)	3,062	11 (10-11)
Other neurodegenerative disorders	2,192 (0.0)	38 (37-40)	1,464	5 (5-5)
Parkinson's disease	8,942 (0.2)	157 (154-160)	6,478	23 (22-23)
Personality disorders	71,334 (1.3)	1,253 (1,244-1,262)	21,556	76 (75-77)
Polyneuropathy	32,710 (0.6)	574 (568-581)	17,925	63 (62-64)
Schizophrenia spectrum disorders	61,346 (1.1)	1,077 (1,069-1,086)	19,316	68 (67-69)
Sleep disorders	61,666 (1.1)	1,083 (1,074-1,091)	31,316	111 (109-112)
Stress-related disorders	196,291 (3.4)	3,447 (3,432-3,462)	80,953	286 (284-288)
Stroke	120,065 (2.1)	2,108 (2,097-2,120)	67,539	239 (237-240)
Traumatic brain injury	249,348 (4.4)	4,379 (4,362-4,396)	64,931	229 (228-231)

Abbreviations: CI, confidence interval.

Suppl. Table 4. Actual and attributable costs in total and per person in persons with prevalent brain disorders in 2015, and incident brain disorders during 2011-2015 sorted in alphabetical order and stratified by cost components.

		Prevalent cohort - 2015				Incident cohort - 2011-2015
Brain disorder	Cost component	Actual costs in 2015 (EUR)	Actual costs per person in 2015 (EUR)	Attributable costs in 2015 (EUR)	Attributable costs per person in 2015 (EUR)	Attributable costs per person in the first year after diagnosis (EUR)
Any brain disorder	Primary sector	488,168,143	460	191,774,339	181	175
	Secondary sector - Outpatient	1,491,081,458	1,406	743,338,257	701	2,702
	Secondary sector - Inpatient	2,522,910,114	2,379	1,638,312,025	1,545	8,457
	Filled prescriptions	533,852,195	503	319,922,005	302	211
	Home care	700,068,647	660	529,492,180	499	489
	Nursing home / sheltered accommodation	2,138,655,226	2,017	1,786,588,544	1,685	749
	Total cost (excl. lost productivity)	7,874,735,782	7,426	5,209,427,352	4,912	12,783
Alcohol abuse	Primary sector	43,832,697	444	10,708,496	109	164
	Secondary sector - Outpatient	182,619,411	1,851	90,265,391	915	2,318
	Secondary sector - Inpatient	509,785,016	5,166	396,078,314	4,014	14,252
	Filled prescriptions	70,574,116	715	41,364,956	419	329
	Home care	86,902,799	881	69,319,977	703	686
	Nursing home / sheltered accommodation	272,375,227	2,760	235,944,141	2,391	1,019
	Total cost (excl. lost productivity)	1,166,089,265	11,817	843,681,275	8,550	18,768
Anxiety disorders	Primary sector	46,880,525	488	17,760,012	185	270
	Secondary sector - Outpatient	186,143,973	1,939	112,251,855	1,169	4,937
	Secondary sector - Inpatient	304,572,473	3,172	220,690,805	2,298	8,872
	Filled prescriptions	58,721,973	612	38,187,658	398	502
	Home care	32,889,132	343	20,728,003	216	359
	Nursing home / sheltered accommodation	93,491,816	974	63,280,196	659	368
	Total cost (excl. lost productivity)	722,699,890	7,527	472,898,530	4,925	15,308
Bipolar disorder	Primary sector	12,927,768	561	4,802,917	209	227
	Secondary sector - Outpatient	68,871,491	2,990	47,030,959	2,042	6,368
	Secondary sector - Inpatient	147,299,161	6,395	120,588,736	5,235	17,468
	Filled prescriptions	23,251,036	1,009	16,487,361	716	755
	Home care	17,966,005	780	12,684,093	551	299
	Nursing home / sheltered accommodation	65,937,773	2,863	52,520,523	2,280	680
	Total cost (excl. lost productivity)	336,253,233	14,598	254,114,589	11,032	25,797
Brain tumours	Primary sector	9,283,859	640	3,508,912	242	223
	Secondary sector - Outpatient	42,180,950	2,910	26,480,502	1,827	12,604

		Prevalent cohort - 2015				Incident cohort - 2011-2015
Brain disorder	Cost component	Actual costs in 2015 (EUR)	Actual costs per person in 2015 (EUR)	Attributable costs in 2015 (EUR)	Attributable costs per person in 2015 (EUR)	Attributable costs per person in the first year after diagnosis (EUR)
	Secondary sector - Inpatient	57,321,123	3,954	36,118,409	2,492	29,223
	Filled prescriptions	8,861,608	611	3,527,159	243	295
	Home care	16,473,487	1,136	10,430,046	720	901
	Nursing home / sheltered accommodation	31,261,211	2,157	14,864,894	1,025	302
	Total cost (excl. lost productivity)	165,382,238	11,409	94,929,922	6,549	43,548
Cerebral palsy	Primary sector	13,167,622	1,462	11,318,548	1,256	960
	Secondary sector - Outpatient	11,430,545	1,269	6,723,166	746	2,731
	Secondary sector - Inpatient	27,487,812	3,051	21,438,091	2,380	11,838
	Filled prescriptions	6,630,687	736	5,437,246	604	567
	Home care	13,763,599	1,528	13,328,070	1,479	2,111
	Nursing home / sheltered accommodation	11,864,848	1,317	10,870,651	1,207	3,193
	Total cost (excl. lost productivity)	84,345,114	9,363	69,115,771	7,672	21,400
Dementia	Primary sector	24,098,562	667	4,596,178	127	137
	Secondary sector - Outpatient	43,138,878	1,193	-5,214,136	-144	1,567
	Secondary sector - Inpatient	140,689,111	3,891	46,270,459	1,280	6,237
	Filled prescriptions	35,544,655	983	14,366,512	397	458
	Home care	148,296,718	4,102	85,823,645	2,374	3,175
	Nursing home / sheltered accommodation	1,079,664,024	29,862	933,749,795	25,826	10,891
	Total cost (excl. lost productivity)	1,471,431,949	40,698	1,079,592,452	29,860	22,465
Depression	Primary sector	95,893,225	539	34,953,943	196	294
	Secondary sector - Outpatient	353,092,962	1,983	198,404,020	1,115	4,415
	Secondary sector - Inpatient	632,094,332	3,551	437,349,885	2,457	11,336
	Filled prescriptions	123,586,689	694	75,514,229	424	447
	Home care	147,797,688	830	94,735,383	532	817
	Nursing home / sheltered accommodation	510,771,406	2,869	367,705,421	2,066	1,275
	Total cost (excl. lost productivity)	1,863,236,302	10,466	1,208,662,881	6,789	18,584
Developmental and behavioural disorders	Primary sector	27,337,787	266	10,369,345	101	104
	Secondary sector - Outpatient	116,363,305	1,130	75,097,169	729	3,890
	Secondary sector - Inpatient	236,746,401	2,299	190,215,735	1,847	5,695
	Filled prescriptions	53,648,059	521	45,268,384	440	477
	Home care	5,642,767	55	4,450,425	43	28
	Nursing home / sheltered accommodation	11,467,658	111	8,904,950	86	39

		Prevalent cohort - 2015				Incident cohort - 2011-2015
Brain disorder	Cost component	Actual costs in 2015 (EUR)	Actual costs per person in 2015 (EUR)	Attributable costs in 2015 (EUR)	Attributable costs per person in 2015 (EUR)	Attributable costs per person in the first year after diagnosis (EUR)
	Total cost (excl. lost productivity)	451,205,976	4,382	334,306,007	3,247	10,235
Drug abuse	Primary sector	18,789,575	379	6,103,985	123	173
	Secondary sector - Outpatient	104,455,802	2,110	71,938,513	1,453	3,539
	Secondary sector - Inpatient	294,331,957	5,944	257,849,075	5,207	14,939
	Filled prescriptions	39,585,700	799	30,697,450	620	525
	Home care	21,420,415	433	17,004,322	343	320
	Nursing home / sheltered accommodation	55,090,031	1,113	44,708,406	903	324
	Total cost (excl. lost productivity)	533,673,480	10,778	428,301,752	8,650	19,820
Eating disorders	Primary sector	6,954,226	438	2,231,551	141	112
	Secondary sector - Outpatient	41,617,887	2,621	30,089,653	1,895	8,660
	Secondary sector - Inpatient	78,974,413	4,973	66,777,164	4,205	21,099
	Filled prescriptions	5,121,915	323	2,656,004	167	108
	Home care	1,027,908	65	768,275	48	40
	Nursing home / sheltered accommodation	1,702,989	107	1,282,483	81	65
	Total cost (excl. lost productivity)	135,399,338	8,526	103,805,130	6,536	30,084
Epilepsy	Primary sector	41,173,985	580	19,904,667	280	350
	Secondary sector - Outpatient	108,270,760	1,524	51,399,429	723	3,615
	Secondary sector - Inpatient	236,872,420	3,334	162,384,494	2,286	13,573
	Filled prescriptions	56,830,263	800	39,757,000	560	539
	Home care	71,643,564	1,008	57,009,489	802	1,439
	Nursing home / sheltered accommodation	186,490,441	2,625	148,199,767	2,086	3,600
	Total cost (excl. lost productivity)	701,281,434	9,871	478,654,845	6,737	23,117
Headache	Primary sector	45,555,311	475	15,231,927	159	213
	Secondary sector - Outpatient	133,513,223	1,393	53,710,708	560	1,579
	Secondary sector - Inpatient	165,735,926	1,729	72,915,060	761	2,660
	Filled prescriptions	41,304,678	431	18,445,725	192	144
	Home care	18,540,020	193	5,347,719	56	24
	Nursing home / sheltered accommodation	38,547,780	402	7,238,248	76	-2
	Total cost (excl. lost productivity)	443,196,937	4,625	172,889,385	1,804	4,618
Infections of the central nervous system	Primary sector	11,203,340	421	3,297,607	124	168
	Secondary sector - Outpatient	33,558,808	1,262	12,417,210	467	2,276
	Secondary sector - Inpatient	53,806,027	2,023	25,888,210	974	19,530
	Filled prescriptions	9,714,465	365	3,292,758	124	181

		Prevalent cohort - 2015				Incident cohort - 2011-2015
Brain disorder	Cost component	Actual costs in 2015 (EUR)	Actual costs per person in 2015 (EUR)	Attributable costs in 2015 (EUR)	Attributable costs per person in 2015 (EUR)	Attributable costs per person in the first year after diagnosis (EUR)
	Home care	12,811,201	482	7,584,973	285	563
	Nursing home / sheltered accommodation	27,418,463	1,031	14,310,372	538	461
	Total cost (excl. lost productivity)	148,512,305	5,585	66,791,130	2,512	23,180
Intellectual disability	Primary sector	15,988,512	583	9,893,121	361	278
	Secondary sector - Outpatient	33,228,973	1,213	17,182,705	627	3,055
	Secondary sector - Inpatient	102,644,232	3,746	84,346,003	3,078	9,397
	Filled prescriptions	21,583,017	788	17,432,722	636	538
	Home care	13,976,239	510	12,449,542	454	393
	Nursing home / sheltered accommodation	32,339,423	1,180	29,128,690	1,063	598
	Total cost (excl. lost productivity)	219,760,396	8,020	170,432,783	6,220	14,258
Multiple sclerosis	Primary sector	21,206,010	1,503	16,200,681	1,148	583
	Secondary sector - Outpatient	40,714,728	2,885	27,233,358	1,930	10,465
	Secondary sector - Inpatient	43,448,943	3,079	27,817,864	1,971	4,925
	Filled prescriptions	9,720,026	689	5,629,372	399	189
	Home care	51,880,624	3,676	49,746,582	3,525	644
	Nursing home / sheltered accommodation	31,328,567	2,220	27,272,490	1,933	335
	Total cost (excl. lost productivity)	198,298,897	14,051	153,900,347	10,905	17,140
Neuromuscular disorders	Primary sector	6,282,164	901	3,972,937	570	353
	Secondary sector - Outpatient	14,433,119	2,071	8,172,495	1,172	3,211
	Secondary sector - Inpatient	29,246,940	4,196	20,898,189	2,998	16,132
	Filled prescriptions	4,437,530	637	2,451,542	352	389
	Home care	8,986,447	1,289	7,194,501	1,032	544
	Nursing home / sheltered accommodation	8,955,012	1,285	4,625,467	664	147
	Total cost (excl. lost productivity)	72,341,211	10,378	47,315,130	6,788	20,777
Other neurodegenerative disorders	Primary sector	3,467,634	1,660	2,695,799	1,290	1,214
	Secondary sector - Outpatient	3,744,735	1,792	1,557,828	746	2,623
	Secondary sector - Inpatient	12,458,820	5,963	9,519,636	4,556	18,250
	Filled prescriptions	2,025,361	969	1,312,465	628	1,152
	Home care	9,972,538	4,773	9,295,614	4,449	5,491
	Nursing home / sheltered accommodation	15,620,797	7,476	13,965,869	6,684	3,904
	Total cost (excl. lost productivity)	47,289,884	22,634	38,347,211	18,354	32,634
Parkinson's disease	Primary sector	14,860,564	1,776	10,688,805	1,278	910

		Prevalent cohort - 2015				Incident cohort - 2011-2015
Brain disorder	Cost component	Actual costs in 2015 (EUR)	Actual costs per person in 2015 (EUR)	Attributable costs in 2015 (EUR)	Attributable costs per person in 2015 (EUR)	Attributable costs per person in the first year after diagnosis (EUR)
	Secondary sector - Outpatient	17,312,390	2,069	5,323,437	636	2,069
	Secondary sector - Inpatient	46,402,317	5,546	27,109,682	3,240	8,711
	Filled prescriptions	27,652,172	3,305	23,257,252	2,780	1,178
	Home care	45,766,641	5,470	38,139,915	4,559	3,594
	Nursing home / sheltered accommodation	118,302,501	14,140	96,210,216	11,499	5,067
	Total cost (excl. lost productivity)	270,296,586	32,307	200,729,307	23,992	21,530
Personality disorders	Primary sector	33,726,394	475	12,370,687	174	180
	Secondary sector - Outpatient	161,704,804	2,280	108,438,891	1,529	5,307
	Secondary sector - Inpatient	294,012,210	4,145	237,084,594	3,342	10,946
	Filled prescriptions	47,982,591	676	33,993,717	479	391
	Home care	18,267,898	258	13,204,541	186	60
	Nursing home / sheltered accommodation	50,162,995	707	39,971,083	563	175
	Total cost (excl. lost productivity)	605,856,892	8,541	445,063,513	6,274	17,058
Polyneuropathy	Primary sector	22,995,926	721	9,555,562	300	324
	Secondary sector - Outpatient	84,279,793	2,643	47,316,582	1,484	3,465
	Secondary sector - Inpatient	144,827,869	4,542	88,462,288	2,775	8,416
	Filled prescriptions	30,234,724	948	16,995,029	533	569
	Home care	53,022,119	1,663	35,217,614	1,105	773
	Nursing home / sheltered accommodation	92,592,235	2,904	40,739,401	1,278	-89
	Total cost (excl. lost productivity)	427,952,666	13,423	238,286,476	7,474	13,458
Schizophrenia spectrum disorders	Primary sector	25,870,906	427	7,901,500	130	130
	Secondary sector - Outpatient	184,183,351	3,039	138,302,570	2,282	7,692
	Secondary sector - Inpatient	471,018,165	7,773	418,546,262	6,907	28,598
	Filled prescriptions	60,736,022	1,002	47,173,595	778	584
	Home care	40,669,756	671	31,640,056	522	328
	Nursing home / sheltered accommodation	144,768,784	2,389	123,117,720	2,032	1,259
	Total cost (excl. lost productivity)	927,246,985	15,302	766,681,703	12,652	38,591
Sleep disorders	Primary sector	31,353,798	512	11,799,623	193	238
	Secondary sector - Outpatient	98,914,079	1,616	41,921,108	685	2,096
	Secondary sector - Inpatient	145,942,944	2,385	69,035,777	1,128	3,396
	Filled prescriptions	41,479,250	678	23,820,309	389	394
	Home care	20,461,339	334	9,184,546	150	217

		Prevalent cohort - 2015				Incident cohort - 2011-2015
Brain disorder	Cost component	Actual costs in 2015 (EUR)	Actual costs per person in 2015 (EUR)	Attributable costs in 2015 (EUR)	Attributable costs per person in 2015 (EUR)	Attributable costs per person in the first year after diagnosis (EUR)
	Nursing home / sheltered accommodation	31,784,606	519	6,941,740	113	45
	Total cost (excl. lost productivity)	369,936,015	6,045	162,703,103	2,659	6,386
Stress-related disorders	Primary sector	86,677,745	444	29,534,278	151	251
	Secondary sector - Outpatient	334,672,975	1,716	190,005,389	974	3,344
	Secondary sector - Inpatient	594,516,328	3,048	435,161,116	2,231	8,650
	Filled prescriptions	94,996,342	487	55,121,881	283	263
	Home care	52,036,361	267	33,412,202	171	132
	Nursing home / sheltered accommodation	136,104,200	698	94,380,524	484	302
	Total cost (excl. lost productivity)	1,299,003,951	6,660	837,615,391	4,295	12,942
Stroke	Primary sector	87,618,648	759	36,193,449	313	275
	Secondary sector - Outpatient	200,887,719	1,740	56,107,195	486	1,741
	Secondary sector - Inpatient	462,612,656	4,006	236,363,400	2,047	24,956
	Filled prescriptions	92,706,631	803	39,925,529	346	356
	Home care	262,819,364	2,276	179,189,377	1,552	1,443
	Nursing home / sheltered accommodation	710,435,792	6,152	461,833,282	4,000	1,882
	Total cost (excl. lost productivity)	1,817,080,811	15,736	1,009,612,232	8,743	30,654
Traumatic brain injury	Primary sector	83,545,461	338	18,644,498	75	140
	Secondary sector - Outpatient	239,309,856	968	69,116,574	280	707
	Secondary sector - Inpatient	428,225,272	1,732	212,472,590	859	7,836
	Filled prescriptions	75,591,648	306	26,356,451	107	117
	Home care	92,933,811	376	50,946,346	206	438
	Nursing home / sheltered accommodation	277,317,019	1,122	163,141,079	660	950
	Total cost (excl. lost productivity)	1,196,923,068	4,841	540,677,538	2,187	10,188

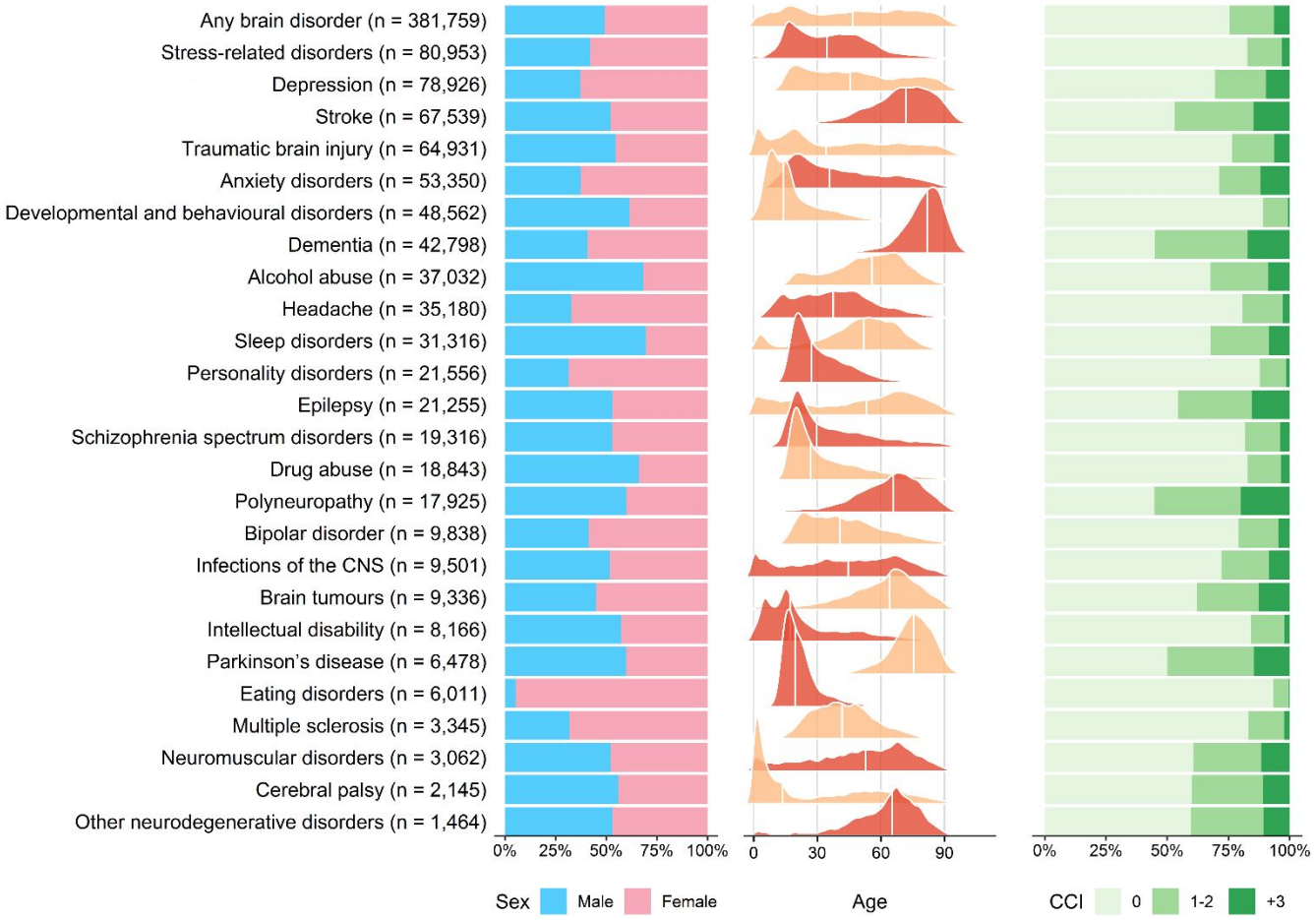
Abbreviations: EUR, Euro.

Suppl. Table 5. Lost productivity in persons with prevalent brain disorders in Denmark in 2015, and incident brain disorders in Denmark during 2011-2015.

	Lost productivity associated with illness			Lost productivity due to premature death		
Brain disorder	Attributable lost production in 2015 (EUR)	Attributable lost production per person in 2015 (EUR)	Attributable lost production per person in the year after diagnosis (EUR)	Attributable lost production among patients who died in 2015 (EUR)	Attributable lost production per person among patients who died in 2015 (EUR)	Attributable lost production per person among patients who died within one year after diagnosis (EUR)
Any brain disorder	10,871,306,597	15,471	11,501	310,599,261	66,595	176,821
Alcohol abuse	2,177,095,714	30,509	26,454	60,885,257	30,519	83,486
Anxiety disorders	1,540,715,518	19,281	19,717	32,197,400	59,515	145,515
Bipolar disorder	474,459,456	27,521	25,383	6,136,984	37,883	136,861
Brain tumours	62,414,375	8,259	15,068	44,062,492	174,851	205,107
Cerebral palsy	126,484,627	24,291	31,767	487,951	7,999	55,995
Dementia	118,974,339	32,436	28,305	1,408,193	8,140	28,505
Depression	2,900,683,027	21,708	20,838	64,470,952	63,706	162,215
Developmental and behavioural disorders	845,403,290	14,455	22,423	6,886,963	47,171	96,899
Drug abuse	1,330,382,612	29,742	24,512	14,271,378	22,908	67,596
Eating disorders	83,103,235	5,798	6,941	1,407,442	54,132	25,604
Epilepsy	757,818,260	16,449	18,764	39,647,665	61,469	167,731
Headache	490,757,570	6,493	6,165	21,177,971	101,330	174,465
Infections of the central nervous system	30,214,014	1,814	2,093	9,137,033	103,830	152,402
Intellectual disability	528,043,228	29,465	30,237	278,285	1,457	9,078
Multiple sclerosis	189,128,371	16,804	9,354	1,721,160	15,367	142,356
Neuromuscular disorders	61,263,234	14,022	9,262	1,733,127	36,875	106,274
Other neurodegenerative disorders	31,346,429	27,716	21,953	3,829,300	55,497	134,409
Parkinson's disease	32,248,038	22,662	14,259	3,565	105	49,396
Personality disorders	1,675,321,683	25,663	22,217	13,071,803	34,858	105,239
Polyneuropathy	238,332,654	16,662	16,701	8,543,728	29,873	78,341
Schizophrenia spectrum disorders	1,707,738,198	33,710	26,581	9,960,281	17,173	90,396
Sleep disorders	336,760,666	8,691	8,554	18,811,390	79,373	133,551
Stress-related disorders	3,167,569,516	19,310	19,520	63,414,446	69,917	175,773
Stroke	630,213,779	16,502	14,382	25,874,307	39,085	140,923
Traumatic brain injury	1,241,809,744	7,179	7,245	41,136,013	48,739	121,008

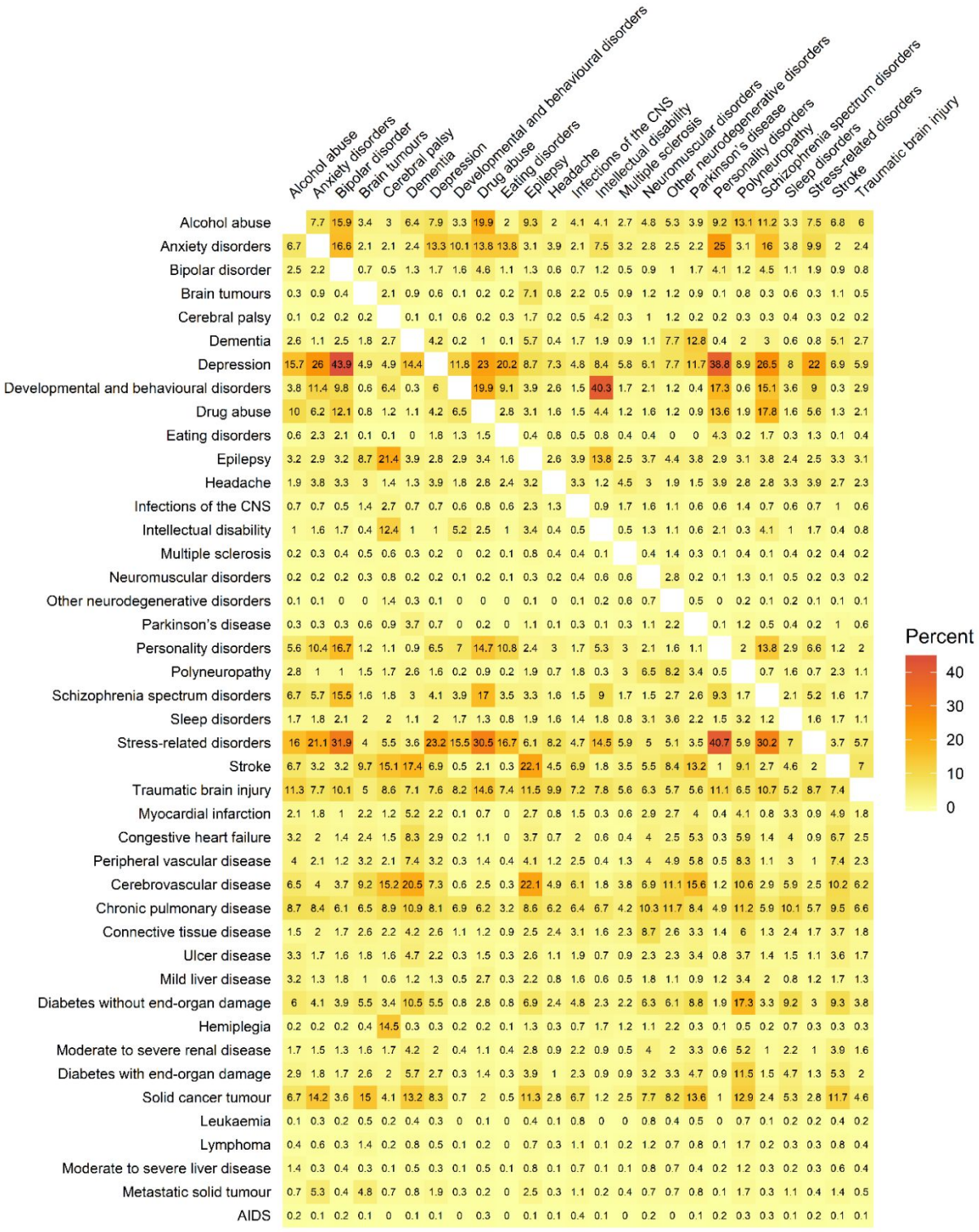
Abbreviations: EUR, Euro.

Supplementary figures



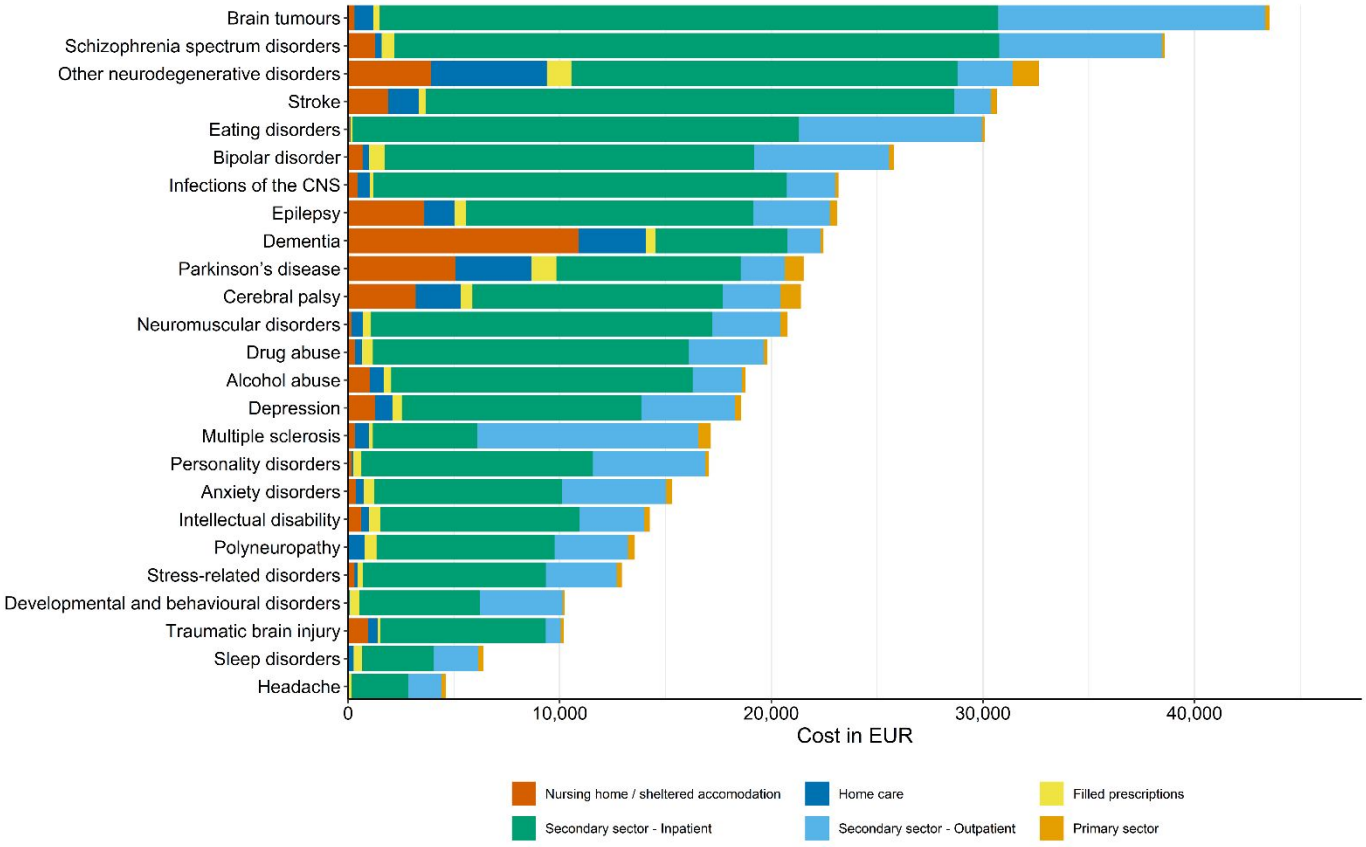
Suppl. Figure 1. Characteristics of patients with incident brain disorders in Denmark during 2011-2015 sorted from highest to lowest incidence (the white line in the age distribution represents the median age in each cohort).

Abbreviations: CNS, central nervous system; CCI, Charlson Comorbidity Index



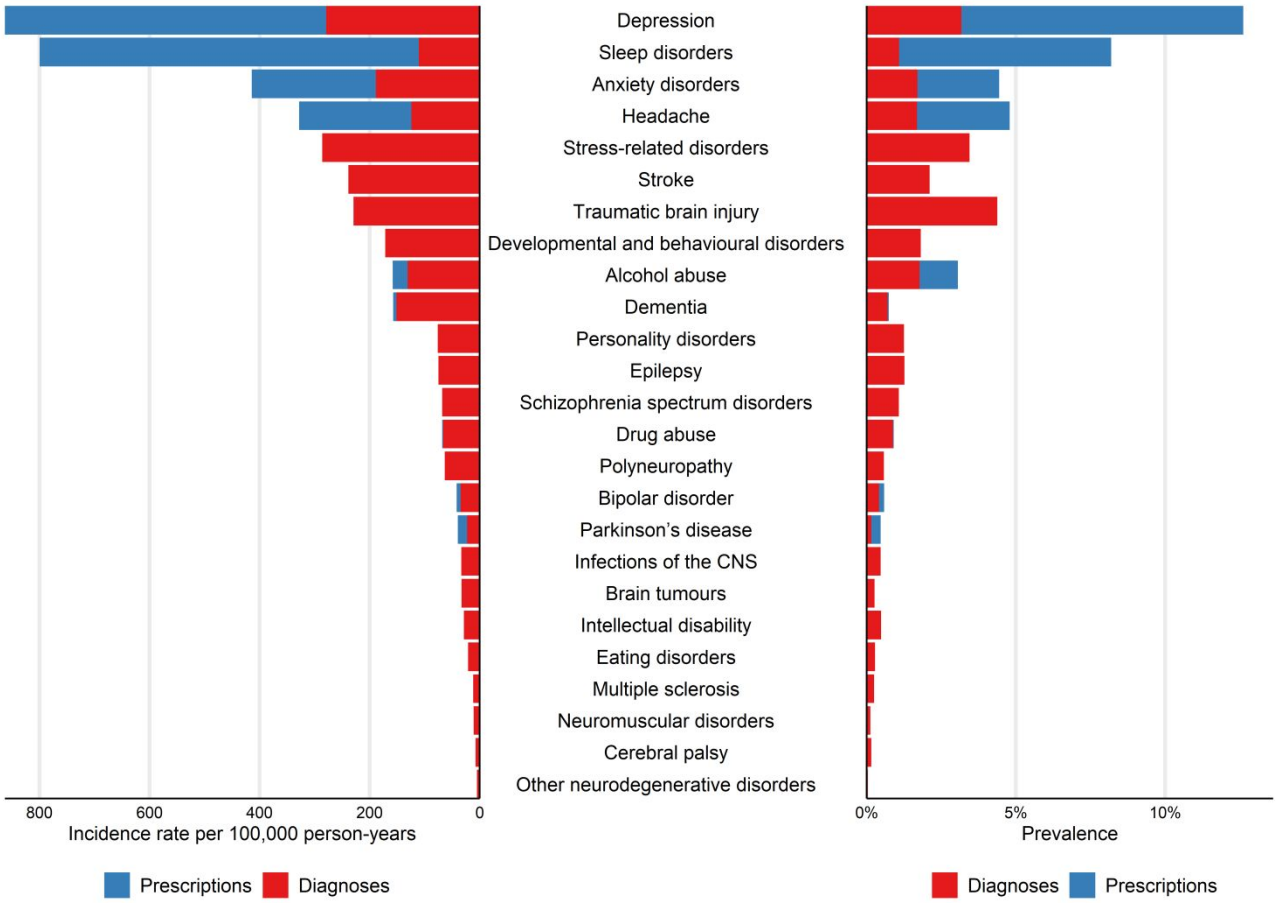
Suppl. Figure 2. Proportion of persons with incident brain disorders in the Danish population during 2011-2015 (columns), who had been diagnosed with comorbid brain or non-psychiatric disorders included in the Charlson Comorbidity Index up to 10 years before the index date of the brain disorder (rows).

Abbreviations: CNS, central nervous system



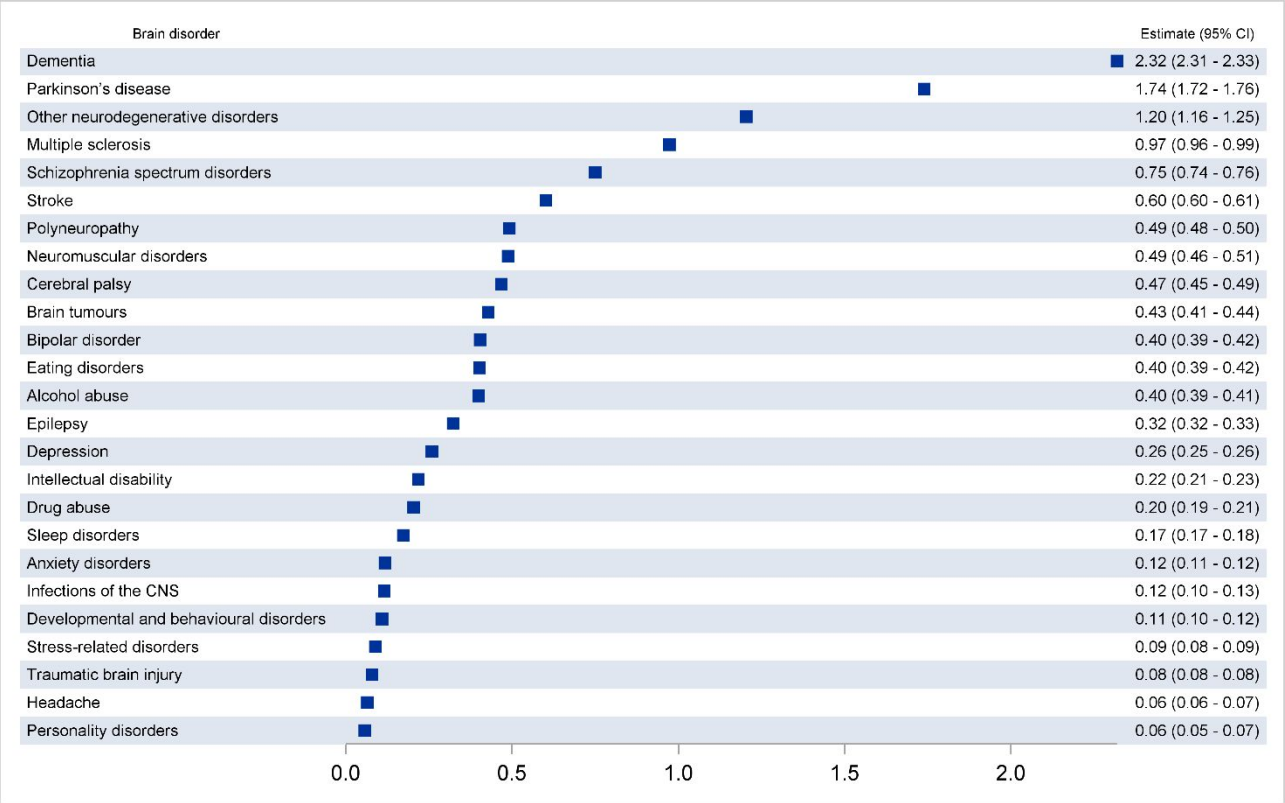
Suppl. Figure 3. Attributable direct costs per person during the first year after diagnosis in persons with incident brain disorders in Denmark during 2011-2015 (in 2015 prices) sorted from highest to lowest costs.

Abbreviations: CNS, central nervous system



Suppl. Figure 4. Occurrence of brain disorders in the Danish population including incidence during 2011-2015 and prevalence in 2015. Alcohol abuse, bipolar disorder, dementia, depression, drug abuse, headache, multiple sclerosis, Parkinson's disease, and sleep disorders were identified by either recorded hospital diagnoses or filled prescriptions of relevant medication, and all other brain disorders were identified by recorded hospital diagnoses.

Abbreviations: CNS, central nervous system



Suppl. Figure 5. Costs in €10,000 associated with each of 25 groups of brain disorders adjusted for comorbid brain disorders in persons with prevalent brain disorders in Denmark in 2015 (2015 prices).
Abbreviations: CI, confidence interval; CNS, central nervous system

Supplementary references

1. Schmidt M, Schmidt SAJ, Adelborg K, et al. The Danish health care system and epidemiological research: from health care contacts to database records. *Clin Epidemiol* 2019;11:563-91. doi: 10.2147/clep.S179083

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STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	title page
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	page 3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	page 6
Objectives	3	State specific objectives, including any prespecified hypotheses	page 6
Methods			
Study design	4	Present key elements of study design early in the paper	page 7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	page 7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	page 7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	page 7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	page 8-9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	page 8-9 + Appendix 1
Bias	9	Describe any efforts to address potential sources of bias	page 10-11
Study size	10	Explain how the study size was arrived at	page 7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	page 8-9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	page 9-10
		(*b*) Describe any methods used to examine subgroups and interactions	page 9-10
		(*c*) Explain how missing data were addressed	NA
		(*d*) If applicable, explain how loss to follow-up was addressed	NA
		(*e*) Describe any sensitivity analyses	page 10
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	page 11
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	page 11+22
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) Summarise follow-up time (eg, average and total amount)	-
Outcome data	15*	Report numbers of outcome events or summary measures over time	page 11-12
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	page 12
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	page 13
Discussion			
Key results	18	Summarise key results with reference to study objectives	page 13-14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	page 14-15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	page 15-16
Generalisability	21	Discuss the generalisability (external validity) of the study results	page 15-16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	page 17

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

BMJ Open

OCCURRENCE, MORTALITY, AND COST OF BRAIN DISORDERS IN DENMARK: A POPULATION-BASED COHORT STUDY

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OCCURRENCE, MORTALITY, AND COST OF BRAIN DISORDERS IN DENMARK: A POPULATION-BASED COHORT STUDY

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ABSTRACT

Objectives

To examine the occurrence of brain disorders (*i.e.,* neurological and mental disorders) in Denmark and mortality and cost-of-illness among affected persons.

Design

Matched cohort study.

Setting

We obtained routinely collected registry data on all Danish residents during 1995-2015.

Participants

We identified all persons alive on 1 January 2015 with a diagnosis of 25 specific brain disorders (prevalent cohort) and all persons with an incident diagnosis during 2011-2015 (incident cohort). Each person was matched on age and sex with 10 persons from the general population without the brain disorder of interest.

Primary and secondary outcome measures

Prevalence and incidence of hospital-diagnosed brain disorders, 1-year absolute and relative mortality, and attributable direct and indirect costs-of-illness compared with the corresponding matched cohorts.

Results

We identified 1,075,081 persons with at least one prevalent brain disorder (*any brain disorder*) on 1 January 2015, corresponding to 18.9% of the Danish population. The incidence rate of *any brain disorder* during 2011-2015 was 1,349 per 100,000 person-years (95% confidence interval [CI]: 1,345-1,353). One-year mortality after diagnosis was increased in persons with *any brain disorder* (hazard ratio = 4.7 [95% CI: 4.7-4.8]) and in persons in every group of specific brain disorders compared to the matched cohort from the general population. The total attributable direct costs of brain disorders in 2015 were €5.2 billion and

total attributable indirect costs were €11.2 billion. Traumatic brain injury, stress-related disorders, depression, and stroke were the most common brain disorders. Attributable costs were highest for depression, dementia, stress-related disorders, and stroke.

Conclusions

One in five Danish residents alive on 1 January 2015 had been diagnosed with at least one brain disorder, and mortality was five times higher in persons with any diagnosed brain disorder than in the general population. We found high attributable direct and indirect costs of brain disorders.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- We examined epidemiology and societal costs of hospital-diagnosed brain disorders using individual-level data on a well-defined population with complete follow-up.
- Both epidemiology and cost were estimated among persons with one of 25 specific brain disorders, and among persons with any brain disorders taking into account comorbid disorders.
- We identified persons with incident brain disorders during 2011-2015, whereas persons alive on 1 January 2015 with brain disorders diagnosed from 1995 to 2014 were considered prevalent.
- We estimated 1-year mortality among persons with incident brain disorders, and direct and indirect societal costs among persons with prevalent brain disorders.
- Direct costs included cost of services in primary care, secondary care, and costs of medication, nursing home, sheltered accommodation, personal nursing, home nurse visits, and hospital-based neuro rehabilitation, whereas lost productivity was considered indirect costs.

BACKGROUND

Brain disorders, including both neurological and mental disorders, are the leading cause of years lived with disability worldwide.[1, 2] In 2010, it was estimated that 260 million persons in Europe (~50% of the population) lived with a brain disorder with an estimated total cost-of-illness of €798 billion.[3, 4] Based on this appraisal, mental disorders alone were estimated to account for 4.1% of European countries' combined gross domestic product (GDP) in 2015.[5] The global burden of brain disorders is expected to double between 2010 and 2030.[6, 7]

Previous estimates of overall occurrence and cost of brain disorders relied on heterogeneous data sources without individual-level data. This excluded consideration of comorbid brain disorders in estimates of the incidence, prevalence, mortality, and cost-of-illness of brain disorders.[2, 3, 8] Therefore, single persons with multiple disorders were counted more than once, causing potential overestimation of the occurrence. Previous studies also focused on cause-specific mortality rather than all-cause mortality. This could have led to underestimation of excess mortality associated with brain disorders due to incompletely recorded brain disorders on death certificates.[2, 9] Thus, there is a need for valid updated estimates of occurrence, mortality, and cost of brain disorders to better understand the public health burden and healthcare planning needs.[7]

We conducted this population-based study using routinely collected individual-level registry data to examine the prevalence and incidence of brain disorders in the Danish population during 2011-2015, as well as mortality and cost-of-illness in these patients.

METHODS

Setting

We conducted a population-based cohort study encompassing the entire Danish population during 2011-2015. In Denmark, healthcare is primarily tax-funded with equal access for every Danish resident. We examined occurrence, mortality, and costs of brain disorders using nationwide data from healthcare and socioeconomic registries.[10]

Study design and participants

The following 25 predefined groups of brain disorders were examined: *alcohol abuse, anxiety disorders, bipolar disorder, brain tumours, cerebral palsy, dementia, depression, developmental and behavioural disorders, drug abuse, eating disorders, epilepsy, headache, infections of the central nervous system, intellectual disability, multiple sclerosis, neuromuscular disorders, other neurodegenerative disorders, Parkinson's disease, personality disorders, polyneuropathy, schizophrenia spectrum disorders, sleep disorders, stress-related disorders, stroke, and traumatic brain injury.* Disorders were selected if expected to be common or critical, and we prioritized to select groups of disorders examined in previous studies to enable comparison of our results.[2, 3] For each of 25 specific brain disorders, we established two cohorts: a prevalent cohort of persons alive on 1 January 2015 who had a diagnosis of the specific brain disorder recorded during the 1995-2014 period and an incident cohort of persons with a first-time diagnosis recorded during the 1 January 2011 to 31 December 2015 period. We also identified every Danish resident with *any brain disorder*, *i.e.*, each person with any of the specific 25 disorders was identified on the date of his or her first diagnosis. To avoid double-counting, every person could only be included once in the *any brain disorder* cohort.

For each of the 25 specific brain disorder cohorts and the *any brain disorder* cohort, we created a matched comparison cohort for the incident cohort and a matched comparison cohort for the prevalent cohort. Each person in the brain disorder cohorts was matched to 10 living persons from the general population on birth

year and sex (sampled with replacement).[11] Matched persons could not have the brain disorder of interest as of the index date of the person with the brain disorder. The index dates of matching were the date of the brain disorder diagnosis for the incident cohort and 1 January 2015 for the prevalent cohort.

Variables

The unambiguous personal identifier assigned to every Danish resident enabled us to identify and link every person across national registries to estimate occurrence, mortality, and cost-of-illness of brain disorders on the individual level (see detailed description of the data sources in Appendix 1).[10]

We identified persons with brain disorders by means of inpatient and outpatient hospital diagnoses (both primary and secondary diagnoses) coded in the Danish National Patient Registry according to the *International Classification of Diseases, Tenth Revision* (ICD-10).[12] ICD codes are provided in Appendix 2.

To estimate mortality, we retrieved the dates of death of persons who died during the study period from the Danish Civil Registration System.[10]

To estimate direct costs, we obtained individual-level information on all primary care services provided by general practitioners and dentists from the Danish Health Service Registry,[13] individual-level medication expenditures from the Danish National Prescription Registry,[14] and individual-level information on nursing home or sheltered accommodation, personal nursing and other personal care, home nurse visits, and hospital-based neuro rehabilitation from Statistics Denmark.[15] We also computed costs of secondary care including hospital inpatient admissions, outpatient specialist clinic visits, and emergency room contacts based on the Diagnosis Related Group (DRG) and Danish Ambulatory Grouping System (DAGS) tariffs.[16] Medication costs were computed using market prices for prescriptions filled at outpatient pharmacies and in-hospital medication costs were included in the DRG/DAGS tariffs. To estimate indirect costs, we first estimated lost productivity associated with illness by subtracting the personal income of persons in the matched comparison cohorts from the personal income of persons with brain disorders (all before taxes). We then estimated lost productivity due to premature death (difference in actual age of death and

expected age at death based on the average life expectancy of persons of same age and sex in Denmark). We obtained 2015 cost information for persons in the prevalent cohort and their comparison cohort and from index date for persons in the incident cohort and their comparison cohort.

Finally, we obtained information on prior comorbid brain disorders and on prior non-mental disorders included in the Charlson Comorbidity Index (CCI) up to 10 years before the index date of every person in the brain disorder and comparison cohorts.[12] Using the comorbid diseases included in the CCI, we calculated a CCI score for every person (CCI score: 0 = low, 1-2 = medium, 3+ = high comorbidity).[17, 18]

Statistical analyses

Occurrence

We used any diagnosis from 1 January 1995 to 31 December 2014 as the basis for computing the period prevalence of each of the 25 brain disorders in persons alive on 1 January 2015. To estimate the average annual incidence of the different brain disorders, we computed incidence rates (IRs) of newly diagnosed persons per 100 000 person-years at risk between 1 January 2011 and 31 December 2015. We considered a person to be at risk of an incident specific brain disorder only if he or she did not have a diagnosis of that specific brain disorder during 1995-2010. We characterised persons with brain disorders by age, sex, CCI conditions, and CCI score on the index date across the 25 groups of disorders.

Mortality

We computed 1-year mortality for persons with brain disorders and for persons in their matched comparison cohorts and compared these by means of crude and adjusted hazard ratios (HRs) obtained from an unstratified Cox regression model adjusted for age, sex, and CCI score.

Cost-of-illness

To estimate the economic burden of the 25 brain disorders, we used the human capital approach to conduct a societal cost-of-illness analysis including both direct and indirect individual-level costs.[19, 20] For

each brain disorder, we computed direct and indirect costs-of-illness for every individual in our study population. We estimated both overall annual costs and average annual costs per person. Direct costs were computed both as actual direct costs (*i.e.*, costs of healthcare services) and attributable direct costs (*i.e.*, the cost of healthcare services for persons with brain disorders minus the cost of healthcare services for persons of the same age and sex in the comparison cohorts). For persons with incident brain disorders, we further computed the distribution of the attributable direct costs per person during the first year after the diagnosis, as we expected substantial direct and indirect costs during this year.

We computed attributable indirect costs (*i.e.,* loss of productivity) in patients of working age, *i.e.*, ages 18-65 years. In persons living with brain disorder diagnoses, we computed loss of productivity associated with illness as yearly income before taxes in persons with brain disorders subtracted from the yearly income in living members of the comparison cohorts. For persons who died after diagnoses of brain disorders, we estimated loss of productivity due to premature death as the annual income during the year before death multiplied by the number of lost years of life, assuming that they otherwise would have survived to age 66 years (accounting for the risk of dying each year and discounting future costs with 4% per annum).[19, 20]

Sensitivity analyses

Patients with *alcohol abuse, bipolar disorder, dementia, depression, drug abuse, headache, multiple sclerosis, Parkinson's disease, and sleep disorders* are commonly treated in general practice with medication specific for those disorders. Thus, we performed sensitivity analyses that included both persons with hospital diagnoses and persons who filled prescriptions for relevant pharmacological treatments of these disorders (including information on indication for the prescription when relevant).[14] We repeated all occurrence and cost analyses on these extended cohorts.

In addition, we performed an ordinary least squares (OLS) regression to compute attributable direct costs, in which we modelled the average annual costs per person for each group of brain disorders. This OLS regression included every Danish resident (not only the matched cohorts) with age, sex, and each of the 25

brain disorders as explanatory variables, and thus, costs of every brain disorder was adjusted for costs of comorbid brain disorders.

Analyses were performed using SAS version 9.4 (Cary, NC, USA), and visualization was made using Tidyverse packages in R version 3.6.1.[21] The study was approved by the Danish Data Protection Agency through registration at Aarhus University (record number 2016-051-000001/603). According to Danish legislation, no approval from an ethics committee or informed consent from patients is required for registry-based studies.

Patient involvement statement

This study was done without patient involvement. Patients were not invited to comment on the study design, to develop patient relevant outcomes, or interpret the results. Patients were not invited to contribute to the writing or editing of the manuscript.

RESULTS

Patient characteristics

The characteristics of 1 075 081 persons with prevalent brain disorders in 2015 are displayed in Figure 1, and those of 381 759 persons with incident brain disorders during 2011-2015 are displayed in Suppl. Figure 1. Approximately half of persons with *any brain disorder* were female, occurrence was stable across ages, and three out of four persons had no or mild comorbidity (both in the prevalent and incident cohorts) (Figure 1, Suppl. Figure 1, Suppl. Table 1, and Suppl. Table 2). The proportions of persons with specific brain disorders who were diagnosed with specific comorbid somatic or mental disorders before index date are displayed in Suppl. Figure 2.

Occurrence

On 1 January 2015, 18.9% of the Danish population had been diagnosed with *any brain disorder*. Among persons without prior brain disorder diagnoses, the IR of *any brain disorder* was 1 349 per 100 000 person-years during 2011-2015 (Suppl. Table 3).

The prevalence in 2015 and incidence in 2011-2015 of the 25 groups of brain disorders in the Danish population are displayed in Figure 2. *Traumatic brain disorders* were the most common brain disorders, with a prevalence of 4.4% (Figure 2 and Suppl. Table 3), followed by *stress-related disorders* (3.4%) and *depression* (3.2%) (Figure 2).

During 2011-2015, IRs were highest for *stress-related disorders* (286 per 100 000 person-years [95% CI: 284-288]) and *depression* (279 per 100 000 person-years [95% CI: 277-281]) (Figure 2 and Suppl. Table 3).

Mortality in persons with incident brain disorders

One-year mortality was 7.8% among persons with *any brain disorder*, compared to 1.9% in the comparison cohort. After adjustment, persons with *any brain disorder* still had almost five-fold increased mortality (HR=4.7 [95% CI: 4.7-4.8]), and the HRs were increased in every group of brain disorders. One-year mortality was highest in persons with *other neurodegenerative disorders* (28.0%), *brain tumours (*24.5%), *stroke* (20.8%), and *dementia* (20.3%). Of note, mortality was more than ten-fold increased in persons with *other neurodegenerative disorders* (HR of 15.3 [95% CI: 13.2-17.7]), *brain tumours* (HR of 13.2 [95% CI: 12.4-14.0]), and *anxiety disorders* (HR of 12.8 [95% CI: 12.4-13.3]) (Figure 3).

Cost-of-illness

The total direct attributable costs of *any brain disorder* were €5.2 billion in 2015 in Denmark, with increased costs in every group of brain disorders. Specifically, attributable direct costs were highest in patients with prevalent *depression* (€1.2 billion), *dementia* (€1.1 billion), and *stroke* (€1.0 billion) (Figure 4 and Suppl. Table 4). Importantly, the distribution of cost components varied considerably between brain disorders (Figure 4 and Figure 5).

Of note, the highest attributable costs per person in persons with prevalent brain disorders in 2015 was found in persons with *dementia* (€30K) and *Parkinson's disease* (€24K), mainly due to costs of nursing home/sheltered accommodation (Figure 5 and Suppl. Table 4).

The average attributable direct costs of *any brain disorder* during the first year after diagnosis was €13K, though these differed widely between persons with different disorders. Costs were highest during the first year in persons with incident *brain tumours* (€44K) and *schizophrenia spectrum disorders* (€39K) (Suppl. Figure 3 and Suppl. Table 4).

Productivity of persons with brain disorders was reduced in every group of brain disorders. The total indirect costs in 2015 were €11.2 billion in persons with *any brain disorder*, mostly due to loss of productivity associated with illness (€10.9 billion) and less due to loss of productivity due to premature death (€0.3 billion). Specifically, lost productivity was €3.2 billion in persons with *stress-related disorders*, €2.9 billion in persons with *depression*, and €2.2 billion in persons with *alcohol abuse*. Finally, we found that the indirect costs were largely made up of costs due to lost productivity in patients living with illness, while costs due to lost productivity due to premature death contributed little (Figure 6 and Suppl. Table 5).

Sensitivity analyses

Adding persons with filled prescriptions to the hospital-diagnosed cohorts, we found that occurrence of *alcohol abuse*, *bipolar disorder*, and *dementia* increased little, while occurrence of *anxiety disorders*, *depression*, *headache*, *Parkinson's disease*, and *sleep disorders* increased several-fold (Suppl. Figure 4). Prevalence of *any brain disorders* increased to 30.2%, and total attributable costs in these persons in 2015 were €22.5 billion, of which direct costs were €6.5 billion and indirect costs were €16.0 billion (data not shown).

In the OLS regression, we accounted for comorbid brain disorders when estimating per-person costs associated with each brain disorder. We found that *dementia* (€23K) and *Parkinson's disease* (€17K) were associated with the highest per-person additional direct cost-of-illness after adjustment for comorbid brain

disorders (Suppl. Figure 5). Of note, removing outliers (the 99% percentile) changed results considerably, indicating that the 1% of persons with highest costs-of-illness contributed a considerable share of the total costs.

DISCUSSION

We performed a study of occurrence, mortality, and cost of hospital-diagnosed brain disorders using high-quality, individual-level data. Brain disorders were common: one in five persons in Denmark had prevalent brain disorders in 2015. We found the most prevalent disorders to be *traumatic brain injury, stress-related disorders,* and *depression,* whereas the disorders with the highest incidence were *stress-related disorders*, *depression,* and *stroke*. One-year mortality was five-fold increased in persons with *any brain disorder* and was increased in persons with any type of brain disorder. The attributable direct costs of persons with *any brain disorder* were more than €5 billion. The more common brain disorders—*depression, dementia,* and *stroke*—accounted for the highest total attributable direct costs among persons with prevalent disorders. Attributable direct costs per person were highest in persons with *dementia* and *Parkinson's disease*. The total attributable indirect costs due to loss of productivity in persons with any prevalent brain disorder were twice as high as direct costs.

Even though our findings are based on high-quality population-based registries, some limitations should be considered when interpreting our findings. We may have underestimated the prevalence, incidence, and total cost of non-severe brain disorders, as some patients were treated solely in general practice, or were undiagnosed or untreated. This is especially relevant for disorder that are mainly treated in primary care, or not treated at all, and therefore were not captured in our main analyses such as *anxiety,*[22] *headache,*[23] and *sleep disorders*.[24] We addressed this in a sensitivity analysis that also identified patient-based filled prescriptions for relevant medications.

We estimated the period prevalence among living persons who had been diagnosed with brain disorders during the preceding 20 years, even though some disorders may be reversible. We chose this approach as a period with severe disease may affect future income and use of healthcare services.

We described non-mental comorbidity as the proportions of persons in each cohort previously diagnosed with diseases from the CCI covering 19 groups of disorders. CCI score was used to adjust for confounding in our mortality analyses, and as CCI score is an aggregated measure of comorbidity we cannot rule out residual or unmeasured confounding in our estimates of HRs of death.[17, 18, 25]

While we had detailed data on direct costs, we lacked information on municipally supported rehabilitation, assistance supplies, and transportation costs related to treatment and rehabilitation. Similarly, our cost analyses did not include intangible costs (*e.g.*, due to decreased quality of life) and costs of informal care provided by relatives, which may be considerable in conditions such as *dementia*.[26] Yet, we included costs of nursing homes, sheltered accommodation, and home nursing, and we found the annual cost per person with *dementia* (€30K) similar to that previously reported in developed countries.[27, 28]

In estimating the indirect costs (i.e. loss of productivity) of illness and premature death we applied the human capital approach. In the literature, this approach has been discussed and among others it has been argued that application of the human capital approach leads to an over-estimation of the productivity costs. Hence, alternative methods like the friction cost method have been proposed.[19] The idea behind the friction cost method is that the amount of production lost due to disease depends on the time (friction period) organizations need to restore the initial production level. Friction periods will differ by industry, type of work etc. and the challenge is to estimate relevant friction periods but application of the friction cost method leads to lower productivity cost estimates.[19] Taking these considerations into account, we present our indirect cost estimates separately (Figure 6) making it possible to assess the results without inclusion of the indirect costs.

Of note, our study described the cost-of-illness in patients with brain disorders, but did not isolate the cost of the disease itself as patients with brain disorders are known to have a high load of comorbidity.[29-31]

We estimated the prevalence and incidence of *any brain disorder* using individual-level data, which allowed us to capture concurrent brain disorders,[29] opposed to the prior studies based on literature reviews that included a mix of hospital-diagnosed disorders and disorders reported in population surveys.[3, 5] Beside using different eligibility criteria, double counting of individuals with concurrent brain disorders may explain the previously reported total 1-year prevalence of brain disorders of ~50% (260 million affected among 514 million population in Europe),[3] which is markedly higher than what we found despite including prevalent disorders during a 20-year period.[8, 9] Compared to the reported prevalence of separate disorders, we found markedly lower prevalence of anxiety (1.7% vs 12%), headache (1.7% vs 10%), depression (3.2% vs 6.5%), and sleep disorders (1.1% vs 8.7%), despite the longer lookback in our study (20-years vs. 1-year prevalence).[3] This may be explained by different data sources, as we in the main analyses only included persons with hospital-diagnosed disorders. Importantly, when we included persons with filled prescriptions in sensitivity analyses, the prevalence increased considerably indicating that we underestimated the occurrence of these disorders in our main analyses.

A recent Danish study reported a 2.5-fold increased mortality rate in persons with hospital-diagnosed mental disorders compared to persons from the general population,[32] which is markedly lower than mortality of *any brain disorders* in our study – likely explained by our use of different length of follow-up (*i.e.,* long-term as opposed to 1-year).

We found that the total attributable direct and indirect costs of brain disorders in Denmark in 2015 were €16.4 billion, equivalent to 5.9% of the Danish GDP (€273 billion in 2015).[33] This is only slightly higher than the recently reported costs of mental illness alone of €15 billion in Denmark in 2015 corresponding to 5.4% of the GDP.[5] However, when we included persons identified from filled prescriptions in addition to hospital-based diagnoses in sensitivity analyses, the prevalence increased and total attributable costs of *any brain*

disorders increased substantially, indicating that the costs may be higher than previously estimated when not restricting to hospital-diagnosed persons.[3, 5]

Finally, previous Danish studies of selected brain disorders reported lower total costs of disorders such as dementia,[26] stroke,[34] Parkinson's disease,[35] and epilepsy.[36] These studies did not include costs of home nursing and nursing homes, and when accounting for that, our findings are comparable.[26, 34-36]

As the already large burden of brain disorders is expected to increase in the future,[6] prevention and effective early intervention are essential.[5] The potential to prevent stroke, infections of the central nervous system, and mental disorders is established, whereas the potential to prevent other neurological disorders remains unclear.[37, 38] As comorbidity load is substantial in persons with brain disorders, cost-of-illness may be reduced by preventing and improving treatment of comorbid disorders.[31]

We found that one in five persons alive in Denmark had been diagnosed with a brain disorder. One-year mortality was five-fold increased in persons with an incident brain disorder. Mortality was increased in every group of brain disorders, underscoring the illness of these patients. The severity also was reflected in the very high cost-of-illness in persons with brain disorders, with total attributable costs of €16.4 billion in Denmark in 2015, including direct costs of €5.2 billion and indirect costs of €11.2 billion.

Occurrence of brain disorders is expected to increase in the future. As brain disorders already use a large proportion of healthcare resources and come with high indirect costs, effective prevention and intervention strategies must be developed.

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CONTRIBUTIONS

CFC and HTS contributed to the study conception. CFC, HTS, NS, JO, SS, TBR, and SVV designed the study and wrote a statistical analyses plan. NS, JO, and SS outlined the economic methods, and SS and JO performed the data management and analyses of the economic data. TBR performed the remaining data management and analyses, and performed all final analyses. All authors interpreted the results, and TBR, SVV, and CFC visualized the data. SVV drafted the first manuscript, and all authors revised the manuscript and approved the final version. All authors agree to be accountable for all aspects of the work.

COMPETING INTERESTS

The authors have no specific competing interests to declare.

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ETHICAL APPROVAL

Not required.

DATA SHARING

Data are available as presented in the paper and in the Supporting Information files. According to Danish legislation, our approvals to use the Danish data sources for the current study do not allow us to distribute or make patient data directly available to other parties. Data access and information about availability is accessible through Statistics Denmark (website: https://www.dst.dk/en/TilSalg/Forskningsservice, e-mail: dst@dst.dk).

Figure Legends

Figure 1. Characteristics of patients with prevalent brain disorders in Denmark in 2015 sorted from highest to lowest prevalence (the white line in the age distribution represents the median age in each cohort).

Abbreviations: CNS, central nervous system; CCI, Charlson Comorbidity Index

Figure 2. Occurrence of brain disorders in the Danish population sorted from highest to lowest incidence, including incidence during 2011-2015 and prevalence in 2015.

Abbreviations: CNS, central nervous system

Figure 3. One-year mortality in patients with incident brain disorders in Denmark during 2011-2015 compared with the general population (comparison group). Hazard ratios are adjusted for age, sex, and comorbidity score. Specific disorders are sorted by hazard ratios.

Abbreviations: CI, confidence interval; CNS, central nervous system

Figure 4. Total attributable direct costs in persons with prevalent brain disorders in Denmark in 2015 (in 2015 prices) sorted from highest to lowest costs.

Abbreviations: CNS, central nervous system

Figure 5. Attributable direct costs per person in individuals with prevalent brain disorders in Denmark in 2015 (in 2015 prices) sorted from highest to lowest costs.

Abbreviations: CNS, central nervous system

Figure 6. Total attributable indirect costs due to lost productivity in persons with prevalent brain disorders in Denmark in 2015 (in 2015 prices) sorted from highest to lowest costs.

Abbreviations: CNS, central nervous system

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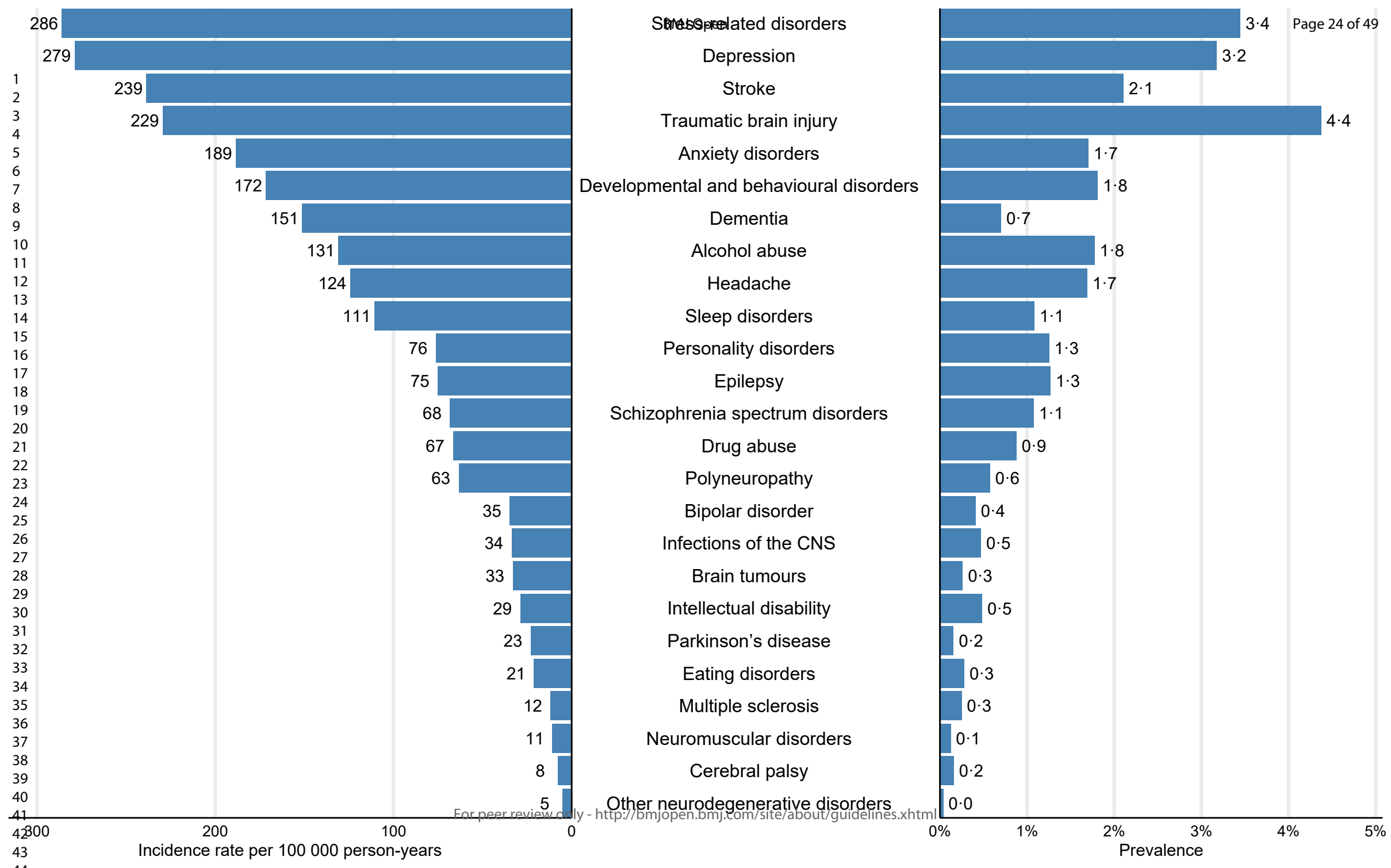
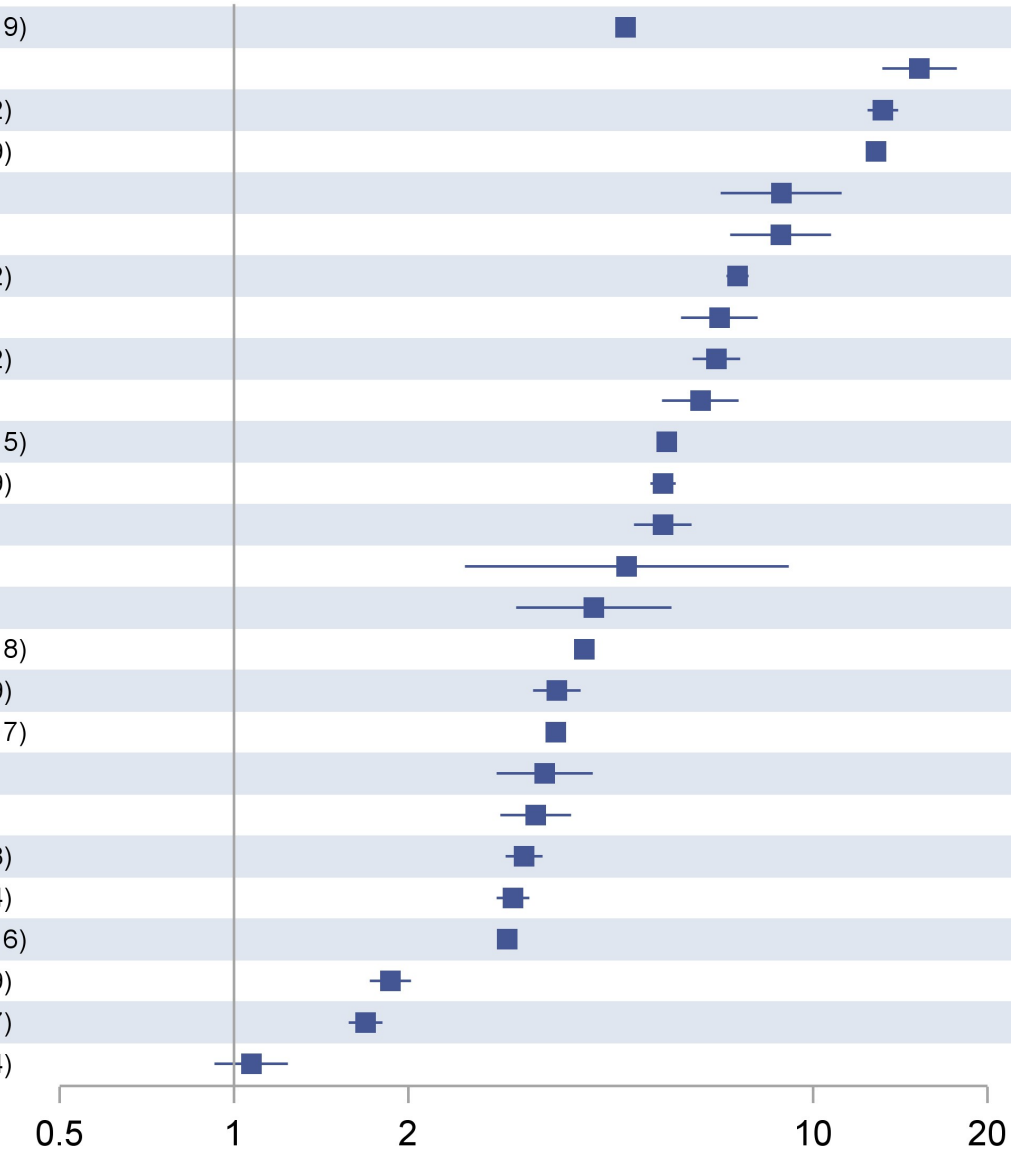
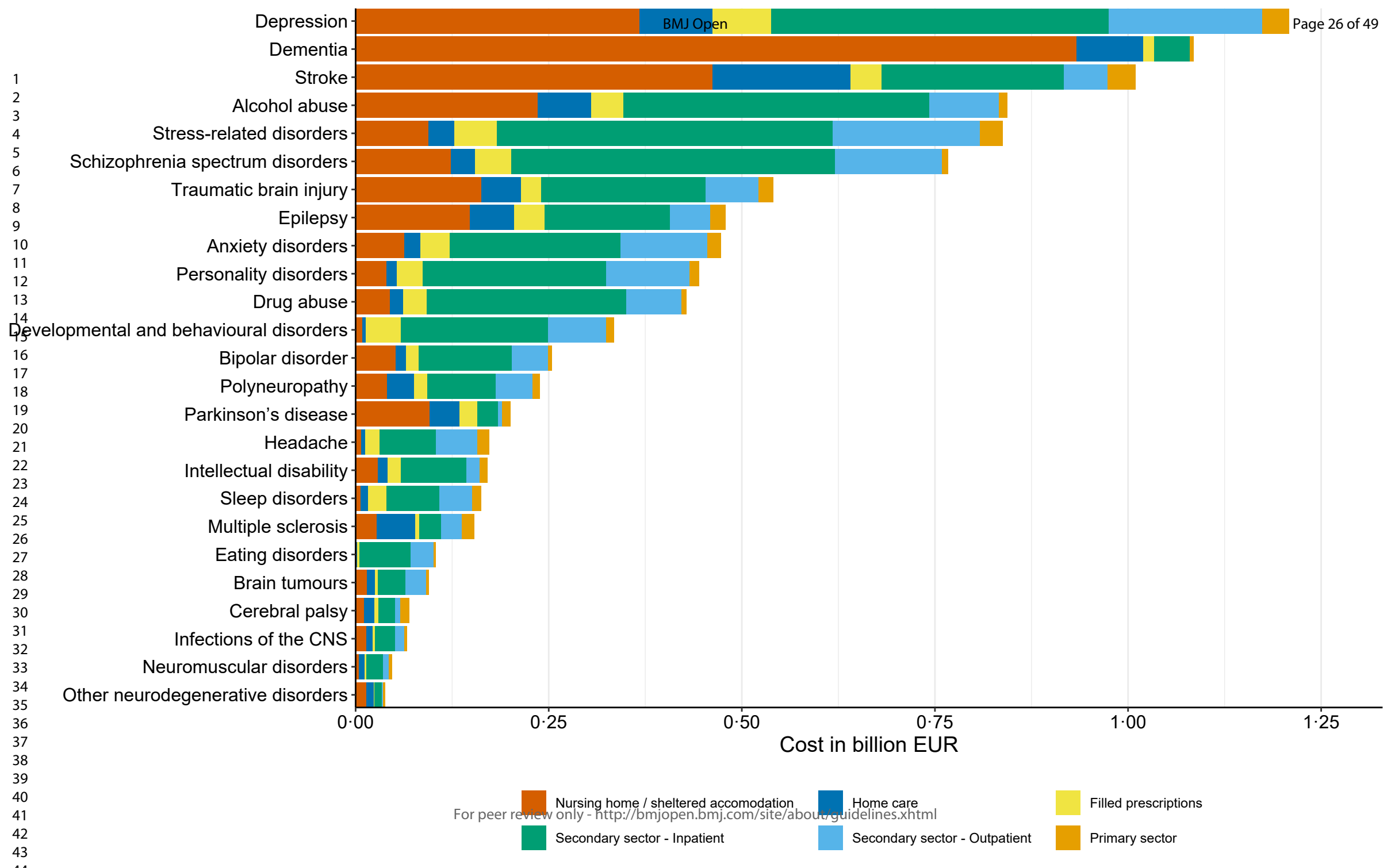
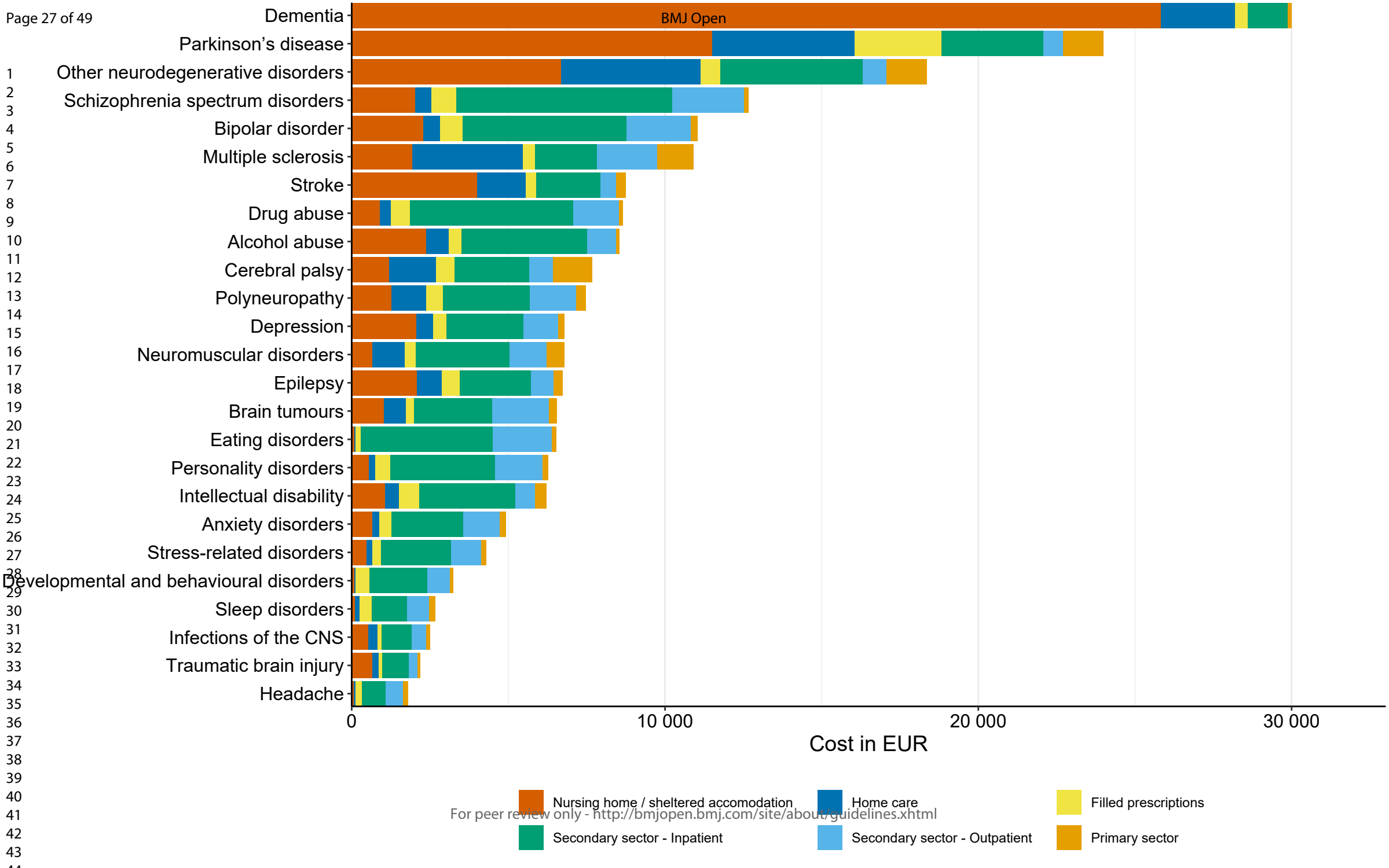
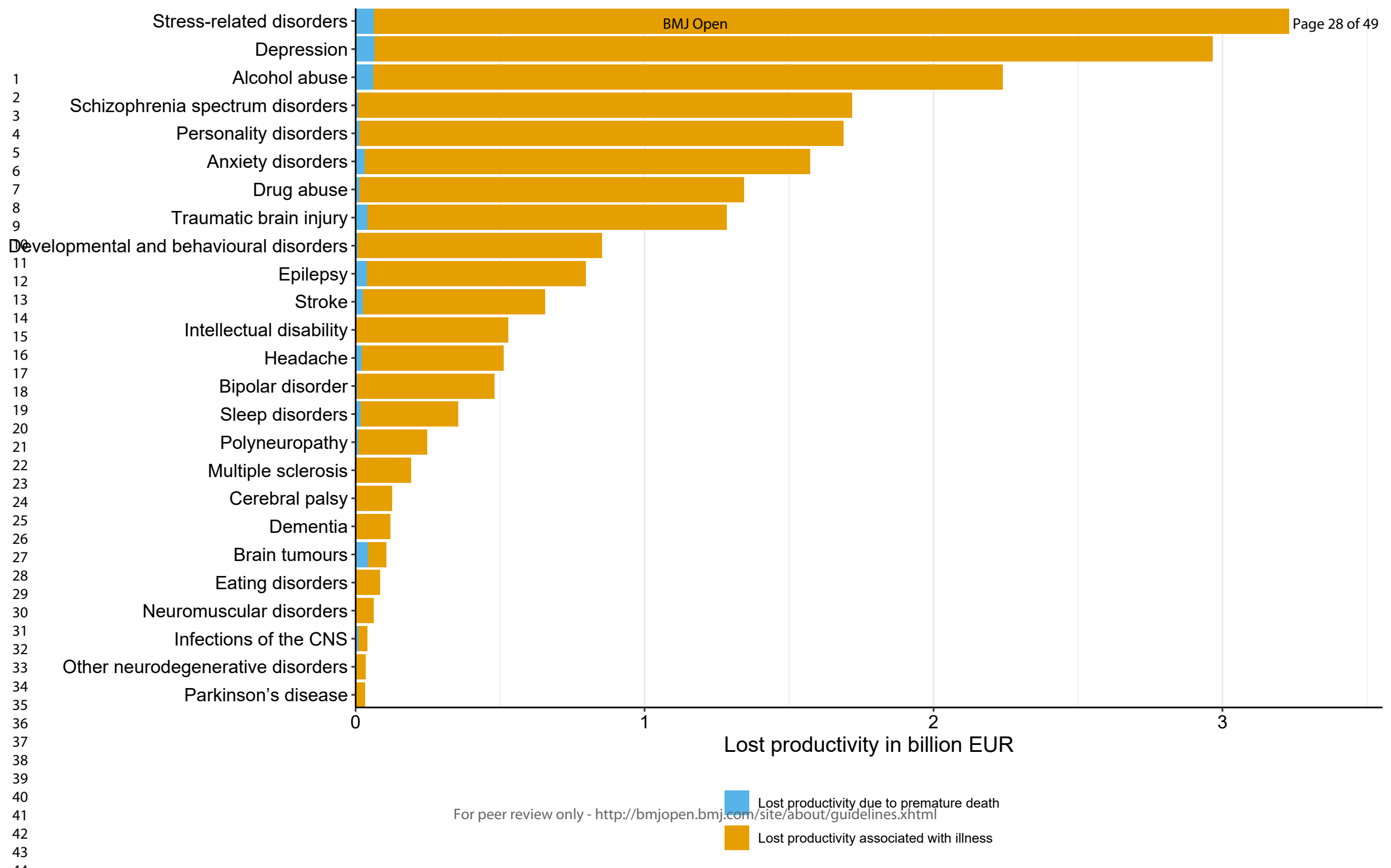


Brain disorder	Patient group - Deaths (%)	Comparison group - Deaths (%)	Adjusted hazard ratio (95% CI)
Any brain disorder	29 639 (7·8)	70 837 (1·9)	4·7 (4·7-4·8)
Other neurodegenerative disorders	409 (28·0)	317 (2·2)	15·3 (13·2-17·7)
Brain tumours	2 287 (24·5)	2 072 (2·2)	13·2 (12·4-14·0)
Anxiety disorders	7 319 (13·8)	4 786 (0·9)	12·8 (12·4-13·3)
Cerebral palsy	146 (6·8)	149 (0·7)	8·8 (6·9-11·2)
Intellectual disability	180 (2·2)	210 (0·3)	8·8 (7·2-10·7)
Alcohol abuse	3 629 (9·8)	4 591 (1·2)	7·4 (7·1-7·7)
Developmental and behavioural disorders	301 (0·6)	389 (0·1)	6·9 (5·9-8·0)
Infections of the CNS	755 (8·0)	1 101 (1·2)	6·8 (6·2-7·5)
Neuromuscular disorders	292 (9·6)	411 (1·3)	6·4 (5·5-7·4)
Stroke	14 045 (20·8)	30 249 (4·5)	5·6 (5·5-5·7)
Epilepsy	2 773 (13·1)	4 091 (1·9)	5·5 (5·2-5·8)
Drug abuse	505 (2·7)	775 (0·4)	5·5 (4·9-6·2)
Eating disorders	14 (0·2)	33 (0·1)	4·8 (2·5-9·1)
Multiple sclerosis	58 (1·7)	138 (0·4)	4·2 (3·1-5·7)
Depression	6 185 (7·9)	13 908 (1·8)	4·0 (3·9-4·2)
Schizophrenia spectrum disorders	593 (3·1)	1 633 (0·9)	3·6 (3·3-4·0)
Traumatic brain injury	3 847 (5·9)	11 084 (1·7)	3·6 (3·5-3·7)
Personality disorders	153 (0·7)	363 (0·2)	3·4 (2·8-4·2)
Bipolar disorder	269 (2·7)	718 (0·7)	3·3 (2·9-3·8)
Parkinson's disease	927 (14·3)	3 112 (4·8)	3·2 (2·9-3·4)
Stress-related disorders	1 241 (1·5)	3 441 (0·4)	3·0 (2·8-3·2)
Dementia	8 695 (20·3)	32 683 (7·6)	3·0 (2·9-3·0)
Sleep disorders	752 (2·4)	2 779 (0·9)	1·9 (1·7-2·0)
Polyneuropathy	1 066 (6·0)	4 772 (2·7)	1·7 (1·6-1·8)
Headache	207 (0·6)	1 553 (0·4)	1·1 (0·9-1·2)









APPENDIX 1 – DATA SOURCES

From the Danish Civil Registration System (DCRS), we obtained personal identification numbers (*i.e.*, CPR-numbers, a unique 10-digit number for every Danish citizen given at birth or immigration) to identify individuals across the nationwide registries in both the healthcare and socioeconomic systems. Also, the DCRS holds information on date of birth, sex, vital status, and place of living, of every person in Denmark.[1]

The Danish National Patient Registry (DNPR) holds information on all in- and outpatient hospital contacts since 1995, with details about date of admission and discharge, procedures and operations, and one or more discharge diagnoses.[2] Similarly, all contacts to psychiatric hospitals are recorded in the Danish Psychiatric Central Research Registry, which since 1995 has been included in the DNPR. The discharge diagnoses are recorded using the International Classification of Diseases, Tenth Revision (ICD-10).[3] For every hospital contact, the accumulated costs of the services provided are reimbursed to the hospital department using national reimbursement rates/tariffs based on average costs of the services. Diagnosis-related group (DRG) tariffs are used for inpatient contacts and Danish Ambulatory Grouping System (DAGS) tariffs for outpatient contacts.[4]

The Danish Health Service Registry (DHSR) contains information on services provided by health contractors in primary health care covered by the national health services during consultations, telephone consultations, and home visits. Services are recorded from a wide range of health contractors such as general practitioners, dentists, physiotherapists, chiropodists, chiropractors, psychologists, and other specialists. Every service recorded in the DHSR is accompanied with a corresponding tariff used when the counties reimburse services to the health contractor.[5]

The Danish National Prescription Registry includes nationwide data on all prescriptions filled at outpatient pharmacies since 1995, *e.g.*, drug type, number of packages, package size, and price. Since 2004, indication of prescriptions are recorded, but with missing indication in one third of prescriptions filled. Drug types are classified according to the Anatomical Therapeutic Chemical (ATC) classification system.[6]

Finally, Statistics Denmark hosts registries with information on every Danish resident on whether the person lives in an elderly home or nursery home, on exact time spent by public home help in private households (in hours), and on personal income before taxes.[7] Data on rehabilitation provided by municipalities were not available in any nationwide registry and therefore not included in our analyses.

APPENDIX 2 – CODE BOOKS

ICD-10 and ATC codes

In the main analyses, brain disorders were defined by the "Included diagnosis codes" excluding the codes in "Excluded diagnosis codes". In the sensitivity analyses, brain disorders were defined by either "Included diagnosis codes" excluding the codes in "Excluded diagnosis codes" or by filled prescriptions including "Included ATC codes". For The Anatomical Therapeutic Chemical (ATC) codes, if any indication codes are given, only prescriptions with those ATC and indication codes were used. Diagnosis codes are given as International Classification of Diseases, Tenth Revision (ICD-10) codes. For both ICD-10 and ATC codes, all subcodes were included.

Brain disorder	Included diagnosis codes	Excluded diagnosis codes	Included ATC codes	Included indication codes
Any brain disorder				
Alcohol abuse	F10 E244 G312 G621 G721 I426 K292 K70 K852 K860 Q860	F100	V03AA N07BB	
Anxiety disorders	F40 F41 F42		N06A	371 830 163
Bipolar disorder	F30 F31		N05AN01	
Brain tumours	C70 C71 C72 D32 D33 D42 D43			
Cerebral palsy	G80			
Dementia	F00 F01 F02 F03 G30 G310B G311 G318 G319		N06D	330 331 329 838
Depression	F32 F33		N06A	168 270
Developmental and behavioural disorders	F84 F9	F99		
Drug abuse	F1	F10 F17	N07BC01 N07BC51	
Eating disorders	F500 F501 F502 F503			
Epilepsy	G40			
Headache	G43 G44		N02C	56 269 153
Infections of the central nervous system	G0 A17 A321 A327 A390 A521 A522 A523 A692 A83 A84 A85 A87 A89 B003 B004 B010 B011 B020 B021 B582 B451 B375	G08 G09		
Intellectual disability	F7 Q90 Q992			
Multiple sclerosis	G35			
Neuromuscular disorders	G70 G71 G72 G73			
Other neurodegenerative disorders	G10 G11 G122G G13 G14	G130 G139		
Parkinson's disease	G20 G23		N04BA N04BB N04BD N04BX	
Personality disorders	F60			
Polyneuropathy	G60 G61 G62 G63 G64 G130			
Schizophrenia spectrum disorders	F2			
Sleep disorders	F51 G470 G471 G473 G474		N05CF01 N05CH01	372 165 166 373 170
Stress-related disorders	F43			
Stroke	I60 I61 I63 I64	I608		
Traumatic brain injury	S020 S021 S027 S029 S06			

Charlson Comorbidity Index (CCI)

The codes included were used to identify comorbidity in persons with brain disorders and their comparisons. Persons were considered having the specific type of comorbidity when having at least one of the listed discharge diagnosis codes (including all subcodes) recorded in the Danish National Patient Registry up to 10 years before index date.

CCI disease	Included ICD-8 and ICD-10 diagnosis codes
Myocardial infarction	410 DI21 DI22 DI23
Congestive heart failure	42709 42710 42711 42719 42899 78249 DI50 DI110 DI130 DI132
Peripheral vascular disease	440 441 442 443 444 445 DI70 DI71 DI72 DI73 DI74 DI77
Cerebrovascular disease	430 431 432 433 434 435 436 437 438 DI6 DG45 DG46
Dementia	29009 2901 29309 DF00 DF01 DF02 DF03 DF051 DG30
Chronic pulmonary disease	490 491 492 493 515 516 517 518 DJ40 DJ41 DJ42 DJ43 DJ44 DJ45 DJ46 DJ47 DJ60 DJ61 DJ62 DJ63 DJ64 DJ65 DJ66 DJ67 DJ684 DJ701 DJ703 DJ841 DJ920 DJ961 DJ982 DJ983
Connective tissue disease	712 716 734 446 13599 DM05 DM06 DM08 DM09 DM30 DM31 DM32 DM33 DM34 DM35 DM36 DD86
Ulcer disease	53091 53098 531 532 533 534 DK221 DK25 DK26 DK27 DK28
Mild liver disease	571 57301 57304 DB18 DK700 DK701 DK702 DK703 DK709 DK71 DK73 DK74 DK760
Diabetes without end-organ damage	24900 24906 24907 24909 25000 25006 25007 25009 DE100 DE101 DE109 DE110 DE111 DE119
Hemiplegia	344 DG81 DG82
Moderate to severe renal disease	403 404 580 581 582 583 584 59009 59319 7531 792 DI12 DI13 DN00 DN01 DN02 DN03 DN04 DN05 DN07 DN11 DN14 DN17 DN18 DN19 DQ61
Diabetes with end-organ damage	24901 24902 24903 24904 24905 24908 25001 25002 25003 25004 25005 25008 DE102 DE103 DE104 DE105 DE106 DE107 DE108 DE112 DE113 DE114 DE115 DE116 DE117 DE118
Solid cancer tumour	14 15 16 17 18 190 191 192 193 194 DC0 DC1 DC2 DC3 DC4 DC5 DC6 DC70 DC71 DC72 DC73 DC74 DC75
Leukaemia	204 205 206 207 DC91 DC92 DC93 DC94 DC95
Lymphoma	200 201 202 203 27559 DC81 DC82 DC83 DC84 DC85 DC88 DC90 DC96
Moderate to severe liver disease	07000 07002 07004 07006 07008 57300 4560 DB150 DB160 DB162 DB190 DK704 DK72 DK766 DI85
Metastatic solid tumour	195 196 197 198 199 DC76 DC77 DC78 DC79 DC80
AIDS	07983 DB21 DB22 DB23 DB24

Supplementary tables

Suppl. Table 1. Characteristics of patients with prevalent disorders in Denmark in 2015 sorted in alphabetical order.

	Prevalent cohorts: 2015					
Disease group	Persons, N	Men, N (%)	Age, median (Q1-Q3)	CCI: 0, N (%)	CCI: 1-2, N (%)	CCI: +3, N (%)
Any brain disorder	1,075,081	536,462 (49.9)	46.0 (27.5-63.6)	788,948 (73.4)	222,453 (20.7)	63,680 (5.9)
Alcohol abuse	101,066	67,376 (66.7)	56.5 (46.2-65.8)	59,961 (59.3)	28,397 (28.1)	12,708 (12.6)
Anxiety disorders	96,943	33,768 (34.8)	41.2 (28.8-54.3)	78,009 (80.5)	15,181 (15.7)	3,753 (3.9)
Bipolar disorder	23,364	9,366 (40.1)	52.4 (39.3-64.9)	17,127 (73.3)	4,851 (20.8)	1,386 (5.9)
Brain tumours	14,953	6,101 (40.8)	62.6 (48.6-71.9)	8,718 (58.3)	4,339 (29.0)	1,896 (12.7)
Cerebral palsy	9,083	5,093 (56.1)	22.3 (14.1-37.0)	6,516 (71.7)	2,092 (23.0)	475 (5.2)
Dementia	40,037	15,645 (39.1)	81.7 (73.9-87.5)	8,340 (20.8)	22,655 (56.6)	9,042 (22.6)
Depression	180,886	64,191 (35.5)	49.0 (35.6-64.1)	130,862 (72.3)	38,342 (21.2)	11,682 (6.5)
Developmental and behavioural disorders	103,157	68,589 (66.5)	19.6 (14.2-26.0)	94,745 (91.8)	7,841 (7.6)	571 (0.6)
Drug abuse	50,066	32,295 (64.5)	38.6 (28.4-50.8)	38,657 (77.2)	9,180 (18.3)	2,229 (4.5)
Eating disorders	15,936	750 (4.7)	29.5 (23.0-36.9)	14,484 (90.9)	1,332 (8.4)	120 (0.8)
Epilepsy	72,205	37,047 (51.3)	43.5 (24.8-62.1)	51,701 (71.6)	15,562 (21.6)	4,942 (6.8)
Headache	96,252	32,218 (33.5)	45.4 (31.2-57.6)	75,439 (78.4)	17,566 (18.3)	3,247 (3.4)
Infections of the central nervous system	26,829	14,069 (52.4)	43.1 (22.9-61.5)	20,740 (77.3)	4,709 (17.6)	1,380 (5.1)
Intellectual disability	27,605	16,087 (58.3)	25.4 (17.1-45.1)	23,577 (85.4)	3,501 (12.7)	527 (1.9)
Multiple sclerosis	14,264	4,431 (31.1)	52.6 (42.9-62.7)	11,206 (78.6)	2,559 (17.9)	499 (3.5)
Neuromuscular disorders	7,080	3,649 (51.5)	51.4 (33.3-66.5)	4,427 (62.5)	1,992 (28.1)	661 (9.3)
Other neurodegenerative disorders	2,192	1,143 (52.1)	59.9 (46.2-70.5)	1,381 (63.0)	622 (28.4)	189 (8.6)
Parkinson's disease	8,942	5,083 (56.8)	75.3 (68.4-81.4)	4,430 (49.5)	3,323 (37.2)	1,189 (13.3)
Personality disorders	71,334	24,517 (34.4)	39.9 (30.6-51.0)	58,516 (82.0)	10,824 (15.2)	1,994 (2.8)
Polyneuropathy	32,710	18,918 (57.8)	66.7 (55.0-75.8)	15,900 (48.6)	11,139 (34.1)	5,671 (17.3)
Schizophrenia spectrum disorders	61,346	32,637 (53.2)	45.1 (32.1-57.7)	48,640 (79.3)	10,276 (16.8)	2,430 (4.0)
Sleep disorders	61,666	45,042 (73.0)	55.9 (43.0-66.2)	41,909 (68.0)	15,223 (24.7)	4,534 (7.4)
Stress-related disorders	196,291	77,494 (39.5)	42.3 (29.3-54.1)	158,789 (80.9)	31,138 (15.9)	6,364 (3.2)
Stroke	120,065	64,067 (53.4)	71.0 (61.1-79.9)	23,651 (19.7)	70,389 (58.6)	26,025 (21.7)
Traumatic brain injury	249,348	142,776 (57.3)	34.9 (22.1-53.4)	207,314 (83.1)	34,162 (13.7)	7,872 (3.2)

Abbreviations: Q, quartile; CCI, Charlson Comorbidity Index.

Suppl. Table 2. Characteristics of patients with incident brain disorders in Denmark during 2011-2015 sorted in alphabetical order.

	Incident cohorts: 2011-2015					
Disease group	Persons, N	Men, N (%)	Age, median (Q1-Q3)	CCI: 0, N (%)	CCI: 1-2, N (%)	CCI: +3, N (%)
Any brain disorder	381,759	187,780 (49.2)	46.6 (21.5-68.9)	295,560 (77.4)	64,746 (17.0)	21,453 (5.6)
Alcohol abuse	37,032	25,251 (68.2)	55.8 (42.7-66.8)	25,797 (69.7)	8,347 (22.5)	2,888 (7.8)
Anxiety disorders	53,350	20,013 (37.5)	35.8 (22.3-56.5)	39,034 (73.2)	8,480 (15.9)	5,836 (10.9)
Bipolar disorder	9,838	4,074 (41.4)	40.8 (28.5-55.0)	7,951 (80.8)	1,500 (15.2)	387 (3.9)
Brain tumours	9,336	4,199 (45.0)	64.1 (50.7-72.9)	6,044 (64.7)	2,227 (23.9)	1,065 (11.4)
Cerebral palsy	2,145	1,199 (55.9)	13.7 (3.1-54.3)	1,371 (63.9)	582 (27.1)	192 (9.0)
Dementia	42,798	17,454 (40.8)	81.8 (75.4-87.0)	21,015 (49.1)	15,686 (36.7)	6,097 (14.2)
Depression	78,926	29,379 (37.2)	45.4 (27.9-66.8)	56,768 (71.9)	15,445 (19.6)	6,713 (8.5)
Developmental and behavioural disorders	48,562	29,864 (61.5)	14.1 (8.6-21.9)	43,747 (90.1)	4,445 (9.2)	370 (0.8)
Drug abuse	18,843	12,469 (66.2)	26.9 (20.7-42.3)	15,944 (84.6)	2,322 (12.3)	577 (3.1)
Eating disorders	6,011	321 (5.3)	19.7 (16.0-24.9)	5,683 (94.5)	307 (5.1)	21 (0.3)
Epilepsy	21,255	11,301 (53.2)	53.2 (21.1-70.6)	12,057 (56.7)	6,319 (29.7)	2,879 (13.5)
Headache	35,180	11,547 (32.8)	37.6 (23.4-50.4)	29,066 (82.6)	5,292 (15.0)	822 (2.3)
Infections of the central nervous system	9,501	4,922 (51.8)	44.6 (21.9-64.2)	7,086 (74.6)	1,727 (18.2)	688 (7.2)
Intellectual disability	8,166	4,692 (57.5)	17.3 (9.9-34.8)	7,035 (86.1)	994 (12.2)	137 (1.7)
Multiple sclerosis	3,345	1,070 (32.0)	41.7 (31.9-52.0)	2,833 (84.7)	449 (13.4)	63 (1.9)
Neuromuscular disorders	3,062	1,596 (52.1)	52.8 (32.9-67.8)	1,950 (63.7)	803 (26.2)	309 (10.1)
Other neurodegenerative disorders	1,464	777 (53.1)	65.3 (53.1-73.2)	904 (61.7)	425 (29.0)	135 (9.2)
Parkinson's disease	6,478	3,883 (59.9)	75.5 (68.9-81.4)	3,459 (53.4)	2,236 (34.5)	783 (12.1)
Personality disorders	21,556	6,762 (31.4)	27.2 (21.3-38.6)	19,265 (89.4)	2,030 (9.4)	261 (1.2)
Polyneuropathy	17,925	10,755 (60.0)	65.9 (54.5-75.0)	8,825 (49.2)	6,108 (34.1)	2,992 (16.7)
Schizophrenia spectrum disorders	19,316	10,219 (52.9)	29.7 (21.1-48.9)	16,209 (83.9)	2,483 (12.9)	624 (3.2)
Sleep disorders	31,316	21,769 (69.5)	51.9 (38.5-62.7)	21,974 (70.2)	7,086 (22.6)	2,256 (7.2)
Stress-related disorders	80,953	34,110 (42.1)	34.5 (20.5-48.5)	68,431 (84.5)	10,356 (12.8)	2,166 (2.7)
Stroke	67,539	35,308 (52.3)	71.8 (61.1-81.3)	37,862 (56.1)	21,220 (31.4)	8,457 (12.5)
Traumatic brain injury	64,931	35,456 (54.6)	34.3 (15.7-63.4)	50,924 (78.4)	10,610 (16.3)	3,397 (5.2)

Abbreviations: Q, quartile; CCI, Charlson Comorbidity Index.

Suppl. Table 3. Occurrence of hospital-diagnosed brain disorders in the Danish population including incidence during 2011-2015 and prevalence in 2015 sorted in alphabetical order.

Disease group	Prevalent cohorts: 2015		Incident cohorts: 2011-2015	
	Prevalence, N (%)	Prevalence per 100,000 persons (95% CI)	Incidence, N	Incidence rate per 100,000 person-years (95% CI)
Any brain disorder	1,075,081 (18.9)	18,879 (18,844-18,915)	381,759	1,349 (1,345-1,353)
Alcohol abuse	101,066 (1.8)	1,775 (1,764-1,786)	37,032	131 (130-132)
Anxiety disorders	96,943 (1.7)	1,702 (1,692-1,713)	53,350	189 (187-190)
Bipolar disorder	23,364 (0.4)	410 (405-416)	9,838	35 (34-35)
Brain tumours	14,953 (0.3)	263 (258-267)	9,336	33 (32-34)
Cerebral palsy	9,083 (0.2)	160 (156-163)	2,145	8 (7-8)
Dementia	40,037 (0.7)	703 (696-710)	42,798	151 (150-153)
Depression	180,886 (3.2)	3,176 (3,162-3,191)	78,926	279 (277-281)
Developmental and behavioural disorders	103,157 (1.8)	1,812 (1,800-1,823)	48,562	172 (170-173)
Drug abuse	50,066 (0.9)	879 (872-887)	18,843	67 (66-68)
Eating disorders	15,936 (0.3)	280 (276-284)	6,011	21 (21-22)
Epilepsy	72,205 (1.3)	1,268 (1,259-1,277)	21,255	75 (74-76)
Headache	96,252 (1.7)	1,690 (1,680-1,701)	35,180	124 (123-126)
Infections of the central nervous system	26,829 (0.5)	471 (466-477)	9,501	34 (33-34)
Intellectual disability	27,605 (0.5)	485 (479-491)	8,166	29 (28-29)
Multiple sclerosis	14,264 (0.3)	250 (246-255)	3,345	12 (11-12)
Neuromuscular disorders	7,080 (0.1)	124 (121-127)	3,062	11 (10-11)
Other neurodegenerative disorders	2,192 (0.0)	38 (37-40)	1,464	5 (5-5)
Parkinson's disease	8,942 (0.2)	157 (154-160)	6,478	23 (22-23)
Personality disorders	71,334 (1.3)	1,253 (1,244-1,262)	21,556	76 (75-77)
Polyneuropathy	32,710 (0.6)	574 (568-581)	17,925	63 (62-64)
Schizophrenia spectrum disorders	61,346 (1.1)	1,077 (1,069-1,086)	19,316	68 (67-69)
Sleep disorders	61,666 (1.1)	1,083 (1,074-1,091)	31,316	111 (109-112)
Stress-related disorders	196,291 (3.4)	3,447 (3,432-3,462)	80,953	286 (284-288)
Stroke	120,065 (2.1)	2,108 (2,097-2,120)	67,539	239 (237-240)
Traumatic brain injury	249,348 (4.4)	4,379 (4,362-4,396)	64,931	229 (228-231)

Abbreviations: CI, confidence interval.

Suppl. Table 4. Actual and attributable costs in total and per person in persons with prevalent brain disorders in 2015, and incident brain disorders during 2011-2015 sorted in alphabetical order and stratified by cost components.

		Prevalent cohort - 2015				Incident cohort - 2011-2015
Brain disorder	Cost component	Actual costs in 2015 (EUR)	Actual costs per person in 2015 (EUR)	Attributable costs in 2015 (EUR)	Attributable costs per person in 2015 (EUR)	Attributable costs per person in the first year after diagnosis (EUR)
Any brain disorder	Primary sector	488,168,143	460	191,774,339	181	175
	Secondary sector - Outpatient	1,491,081,458	1,406	743,338,257	701	2,702
	Secondary sector - Inpatient	2,522,910,114	2,379	1,638,312,025	1,545	8,457
	Filled prescriptions	533,852,195	503	319,922,005	302	211
	Home care	700,068,647	660	529,492,180	499	489
	Nursing home / sheltered accommodation	2,138,655,226	2,017	1,786,588,544	1,685	749
	Total cost (excl. lost productivity)	7,874,735,782	7,426	5,209,427,352	4,912	12,783
Alcohol abuse	Primary sector	43,832,697	444	10,708,496	109	164
	Secondary sector - Outpatient	182,619,411	1,851	90,265,391	915	2,318
	Secondary sector - Inpatient	509,785,016	5,166	396,078,314	4,014	14,252
	Filled prescriptions	70,574,116	715	41,364,956	419	329
	Home care	86,902,799	881	69,319,977	703	686
	Nursing home / sheltered accommodation	272,375,227	2,760	235,944,141	2,391	1,019
	Total cost (excl. lost productivity)	1,166,089,265	11,817	843,681,275	8,550	18,768
Anxiety disorders	Primary sector	46,880,525	488	17,760,012	185	270
	Secondary sector - Outpatient	186,143,973	1,939	112,251,855	1,169	4,937
	Secondary sector - Inpatient	304,572,473	3,172	220,690,805	2,298	8,872
	Filled prescriptions	58,721,973	612	38,187,658	398	502
	Home care	32,889,132	343	20,728,003	216	359
	Nursing home / sheltered accommodation	93,491,816	974	63,280,196	659	368
	Total cost (excl. lost productivity)	722,699,890	7,527	472,898,530	4,925	15,308
Bipolar disorder	Primary sector	12,927,768	561	4,802,917	209	227
	Secondary sector - Outpatient	68,871,491	2,990	47,030,959	2,042	6,368
	Secondary sector - Inpatient	147,299,161	6,395	120,588,736	5,235	17,468
	Filled prescriptions	23,251,036	1,009	16,487,361	716	755
	Home care	17,966,005	780	12,684,093	551	299
	Nursing home / sheltered accommodation	65,937,773	2,863	52,520,523	2,280	680
	Total cost (excl. lost productivity)	336,253,233	14,598	254,114,589	11,032	25,797
Brain tumours	Primary sector	9,283,859	640	3,508,912	242	223
	Secondary sector - Outpatient	42,180,950	2,910	26,480,502	1,827	12,604

		Prevalent cohort - 2015				Incident cohort - 2011-2015
Brain disorder	Cost component	Actual costs in 2015 (EUR)	Actual costs per person in 2015 (EUR)	Attributable costs in 2015 (EUR)	Attributable costs per person in 2015 (EUR)	Attributable costs per person in the first year after diagnosis (EUR)
	Secondary sector - Inpatient	57,321,123	3,954	36,118,409	2,492	29,223
	Filled prescriptions	8,861,608	611	3,527,159	243	295
	Home care	16,473,487	1,136	10,430,046	720	901
	Nursing home / sheltered accommodation	31,261,211	2,157	14,864,894	1,025	302
	Total cost (excl. lost productivity)	165,382,238	11,409	94,929,922	6,549	43,548
Cerebral palsy	Primary sector	13,167,622	1,462	11,318,548	1,256	960
	Secondary sector - Outpatient	11,430,545	1,269	6,723,166	746	2,731
	Secondary sector - Inpatient	27,487,812	3,051	21,438,091	2,380	11,838
	Filled prescriptions	6,630,687	736	5,437,246	604	567
	Home care	13,763,599	1,528	13,328,070	1,479	2,111
	Nursing home / sheltered accommodation	11,864,848	1,317	10,870,651	1,207	3,193
	Total cost (excl. lost productivity)	84,345,114	9,363	69,115,771	7,672	21,400
Dementia	Primary sector	24,098,562	667	4,596,178	127	137
	Secondary sector - Outpatient	43,138,878	1,193	-5,214,136	-144	1,567
	Secondary sector - Inpatient	140,689,111	3,891	46,270,459	1,280	6,237
	Filled prescriptions	35,544,655	983	14,366,512	397	458
	Home care	148,296,718	4,102	85,823,645	2,374	3,175
	Nursing home / sheltered accommodation	1,079,664,024	29,862	933,749,795	25,826	10,891
	Total cost (excl. lost productivity)	1,471,431,949	40,698	1,079,592,452	29,860	22,465
Depression	Primary sector	95,893,225	539	34,953,943	196	294
	Secondary sector - Outpatient	353,092,962	1,983	198,404,020	1,115	4,415
	Secondary sector - Inpatient	632,094,332	3,551	437,349,885	2,457	11,336
	Filled prescriptions	123,586,689	694	75,514,229	424	447
	Home care	147,797,688	830	94,735,383	532	817
	Nursing home / sheltered accommodation	510,771,406	2,869	367,705,421	2,066	1,275
	Total cost (excl. lost productivity)	1,863,236,302	10,466	1,208,662,881	6,789	18,584
Developmental and behavioural disorders	Primary sector	27,337,787	266	10,369,345	101	104
	Secondary sector - Outpatient	116,363,305	1,130	75,097,169	729	3,890
	Secondary sector - Inpatient	236,746,401	2,299	190,215,735	1,847	5,695
	Filled prescriptions	53,648,059	521	45,268,384	440	477
	Home care	5,642,767	55	4,450,425	43	28
	Nursing home / sheltered accommodation	11,467,658	111	8,904,950	86	39

		Prevalent cohort - 2015				Incident cohort - 2011-2015
Brain disorder	Cost component	Actual costs in 2015 (EUR)	Actual costs per person in 2015 (EUR)	Attributable costs in 2015 (EUR)	Attributable costs per person in 2015 (EUR)	Attributable costs per person in the first year after diagnosis (EUR)
	Total cost (excl. lost productivity)	451,205,976	4,382	334,306,007	3,247	10,235
Drug abuse	Primary sector	18,789,575	379	6,103,985	123	173
	Secondary sector - Outpatient	104,455,802	2,110	71,938,513	1,453	3,539
	Secondary sector - Inpatient	294,331,957	5,944	257,849,075	5,207	14,939
	Filled prescriptions	39,585,700	799	30,697,450	620	525
	Home care	21,420,415	433	17,004,322	343	320
	Nursing home / sheltered accommodation	55,090,031	1,113	44,708,406	903	324
	Total cost (excl. lost productivity)	533,673,480	10,778	428,301,752	8,650	19,820
Eating disorders	Primary sector	6,954,226	438	2,231,551	141	112
	Secondary sector - Outpatient	41,617,887	2,621	30,089,653	1,895	8,660
	Secondary sector - Inpatient	78,974,413	4,973	66,777,164	4,205	21,099
	Filled prescriptions	5,121,915	323	2,656,004	167	108
	Home care	1,027,908	65	768,275	48	40
	Nursing home / sheltered accommodation	1,702,989	107	1,282,483	81	65
	Total cost (excl. lost productivity)	135,399,338	8,526	103,805,130	6,536	30,084
Epilepsy	Primary sector	41,173,985	580	19,904,667	280	350
	Secondary sector - Outpatient	108,270,760	1,524	51,399,429	723	3,615
	Secondary sector - Inpatient	236,872,420	3,334	162,384,494	2,286	13,573
	Filled prescriptions	56,830,263	800	39,757,000	560	539
	Home care	71,643,564	1,008	57,009,489	802	1,439
	Nursing home / sheltered accommodation	186,490,441	2,625	148,199,767	2,086	3,600
	Total cost (excl. lost productivity)	701,281,434	9,871	478,654,845	6,737	23,117
Headache	Primary sector	45,555,311	475	15,231,927	159	213
	Secondary sector - Outpatient	133,513,223	1,393	53,710,708	560	1,579
	Secondary sector - Inpatient	165,735,926	1,729	72,915,060	761	2,660
	Filled prescriptions	41,304,678	431	18,445,725	192	144
	Home care	18,540,020	193	5,347,719	56	24
	Nursing home / sheltered accommodation	38,547,780	402	7,238,248	76	-2
	Total cost (excl. lost productivity)	443,196,937	4,625	172,889,385	1,804	4,618
Infections of the central nervous system	Primary sector	11,203,340	421	3,297,607	124	168
	Secondary sector - Outpatient	33,558,808	1,262	12,417,210	467	2,276
	Secondary sector - Inpatient	53,806,027	2,023	25,888,210	974	19,530
	Filled prescriptions	9,714,465	365	3,292,758	124	181

		Prevalent cohort - 2015				Incident cohort - 2011-2015
Brain disorder	Cost component	Actual costs in 2015 (EUR)	Actual costs per person in 2015 (EUR)	Attributable costs in 2015 (EUR)	Attributable costs per person in 2015 (EUR)	Attributable costs per person in the first year after diagnosis (EUR)
	Home care	12,811,201	482	7,584,973	285	563
	Nursing home / sheltered accommodation	27,418,463	1,031	14,310,372	538	461
	Total cost (excl. lost productivity)	148,512,305	5,585	66,791,130	2,512	23,180
Intellectual disability	Primary sector	15,988,512	583	9,893,121	361	278
	Secondary sector - Outpatient	33,228,973	1,213	17,182,705	627	3,055
	Secondary sector - Inpatient	102,644,232	3,746	84,346,003	3,078	9,397
	Filled prescriptions	21,583,017	788	17,432,722	636	538
	Home care	13,976,239	510	12,449,542	454	393
	Nursing home / sheltered accommodation	32,339,423	1,180	29,128,690	1,063	598
	Total cost (excl. lost productivity)	219,760,396	8,020	170,432,783	6,220	14,258
Multiple sclerosis	Primary sector	21,206,010	1,503	16,200,681	1,148	583
	Secondary sector - Outpatient	40,714,728	2,885	27,233,358	1,930	10,465
	Secondary sector - Inpatient	43,448,943	3,079	27,817,864	1,971	4,925
	Filled prescriptions	9,720,026	689	5,629,372	399	189
	Home care	51,880,624	3,676	49,746,582	3,525	644
	Nursing home / sheltered accommodation	31,328,567	2,220	27,272,490	1,933	335
	Total cost (excl. lost productivity)	198,298,897	14,051	153,900,347	10,905	17,140
Neuromuscular disorders	Primary sector	6,282,164	901	3,972,937	570	353
	Secondary sector - Outpatient	14,433,119	2,071	8,172,495	1,172	3,211
	Secondary sector - Inpatient	29,246,940	4,196	20,898,189	2,998	16,132
	Filled prescriptions	4,437,530	637	2,451,542	352	389
	Home care	8,986,447	1,289	7,194,501	1,032	544
	Nursing home / sheltered accommodation	8,955,012	1,285	4,625,467	664	147
	Total cost (excl. lost productivity)	72,341,211	10,378	47,315,130	6,788	20,777
Other neurodegenerative disorders	Primary sector	3,467,634	1,660	2,695,799	1,290	1,214
	Secondary sector - Outpatient	3,744,735	1,792	1,557,828	746	2,623
	Secondary sector - Inpatient	12,458,820	5,963	9,519,636	4,556	18,250
	Filled prescriptions	2,025,361	969	1,312,465	628	1,152
	Home care	9,972,538	4,773	9,295,614	4,449	5,491
	Nursing home / sheltered accommodation	15,620,797	7,476	13,965,869	6,684	3,904
	Total cost (excl. lost productivity)	47,289,884	22,634	38,347,211	18,354	32,634
Parkinson's disease	Primary sector	14,860,564	1,776	10,688,805	1,278	910

		Prevalent cohort - 2015				Incident cohort - 2011-2015
Brain disorder	Cost component	Actual costs in 2015 (EUR)	Actual costs per person in 2015 (EUR)	Attributable costs in 2015 (EUR)	Attributable costs per person in 2015 (EUR)	Attributable costs per person in the first year after diagnosis (EUR)
	Secondary sector - Outpatient	17,312,390	2,069	5,323,437	636	2,069
	Secondary sector - Inpatient	46,402,317	5,546	27,109,682	3,240	8,711
	Filled prescriptions	27,652,172	3,305	23,257,252	2,780	1,178
	Home care	45,766,641	5,470	38,139,915	4,559	3,594
	Nursing home / sheltered accommodation	118,302,501	14,140	96,210,216	11,499	5,067
	Total cost (excl. lost productivity)	270,296,586	32,307	200,729,307	23,992	21,530
Personality disorders	Primary sector	33,726,394	475	12,370,687	174	180
	Secondary sector - Outpatient	161,704,804	2,280	108,438,891	1,529	5,307
	Secondary sector - Inpatient	294,012,210	4,145	237,084,594	3,342	10,946
	Filled prescriptions	47,982,591	676	33,993,717	479	391
	Home care	18,267,898	258	13,204,541	186	60
	Nursing home / sheltered accommodation	50,162,995	707	39,971,083	563	175
	Total cost (excl. lost productivity)	605,856,892	8,541	445,063,513	6,274	17,058
Polyneuropathy	Primary sector	22,995,926	721	9,555,562	300	324
	Secondary sector - Outpatient	84,279,793	2,643	47,316,582	1,484	3,465
	Secondary sector - Inpatient	144,827,869	4,542	88,462,288	2,775	8,416
	Filled prescriptions	30,234,724	948	16,995,029	533	569
	Home care	53,022,119	1,663	35,217,614	1,105	773
	Nursing home / sheltered accommodation	92,592,235	2,904	40,739,401	1,278	-89
	Total cost (excl. lost productivity)	427,952,666	13,423	238,286,476	7,474	13,458
Schizophrenia spectrum disorders	Primary sector	25,870,906	427	7,901,500	130	130
	Secondary sector - Outpatient	184,183,351	3,039	138,302,570	2,282	7,692
	Secondary sector - Inpatient	471,018,165	7,773	418,546,262	6,907	28,598
	Filled prescriptions	60,736,022	1,002	47,173,595	778	584
	Home care	40,669,756	671	31,640,056	522	328
	Nursing home / sheltered accommodation	144,768,784	2,389	123,117,720	2,032	1,259
	Total cost (excl. lost productivity)	927,246,985	15,302	766,681,703	12,652	38,591
Sleep disorders	Primary sector	31,353,798	512	11,799,623	193	238
	Secondary sector - Outpatient	98,914,079	1,616	41,921,108	685	2,096
	Secondary sector - Inpatient	145,942,944	2,385	69,035,777	1,128	3,396
	Filled prescriptions	41,479,250	678	23,820,309	389	394
	Home care	20,461,339	334	9,184,546	150	217

		Prevalent cohort - 2015				Incident cohort - 2011-2015
Brain disorder	Cost component	Actual costs in 2015 (EUR)	Actual costs per person in 2015 (EUR)	Attributable costs in 2015 (EUR)	Attributable costs per person in 2015 (EUR)	Attributable costs per person in the first year after diagnosis (EUR)
	Nursing home / sheltered accommodation	31,784,606	519	6,941,740	113	45
	Total cost (excl. lost productivity)	369,936,015	6,045	162,703,103	2,659	6,386
Stress-related disorders	Primary sector	86,677,745	444	29,534,278	151	251
	Secondary sector - Outpatient	334,672,975	1,716	190,005,389	974	3,344
	Secondary sector - Inpatient	594,516,328	3,048	435,161,116	2,231	8,650
	Filled prescriptions	94,996,342	487	55,121,881	283	263
	Home care	52,036,361	267	33,412,202	171	132
	Nursing home / sheltered accommodation	136,104,200	698	94,380,524	484	302
	Total cost (excl. lost productivity)	1,299,003,951	6,660	837,615,391	4,295	12,942
Stroke	Primary sector	87,618,648	759	36,193,449	313	275
	Secondary sector - Outpatient	200,887,719	1,740	56,107,195	486	1,741
	Secondary sector - Inpatient	462,612,656	4,006	236,363,400	2,047	24,956
	Filled prescriptions	92,706,631	803	39,925,529	346	356
	Home care	262,819,364	2,276	179,189,377	1,552	1,443
	Nursing home / sheltered accommodation	710,435,792	6,152	461,833,282	4,000	1,882
	Total cost (excl. lost productivity)	1,817,080,811	15,736	1,009,612,232	8,743	30,654
Traumatic brain injury	Primary sector	83,545,461	338	18,644,498	75	140
	Secondary sector - Outpatient	239,309,856	968	69,116,574	280	707
	Secondary sector - Inpatient	428,225,272	1,732	212,472,590	859	7,836
	Filled prescriptions	75,591,648	306	26,356,451	107	117
	Home care	92,933,811	376	50,946,346	206	438
	Nursing home / sheltered accommodation	277,317,019	1,122	163,141,079	660	950
	Total cost (excl. lost productivity)	1,196,923,068	4,841	540,677,538	2,187	10,188

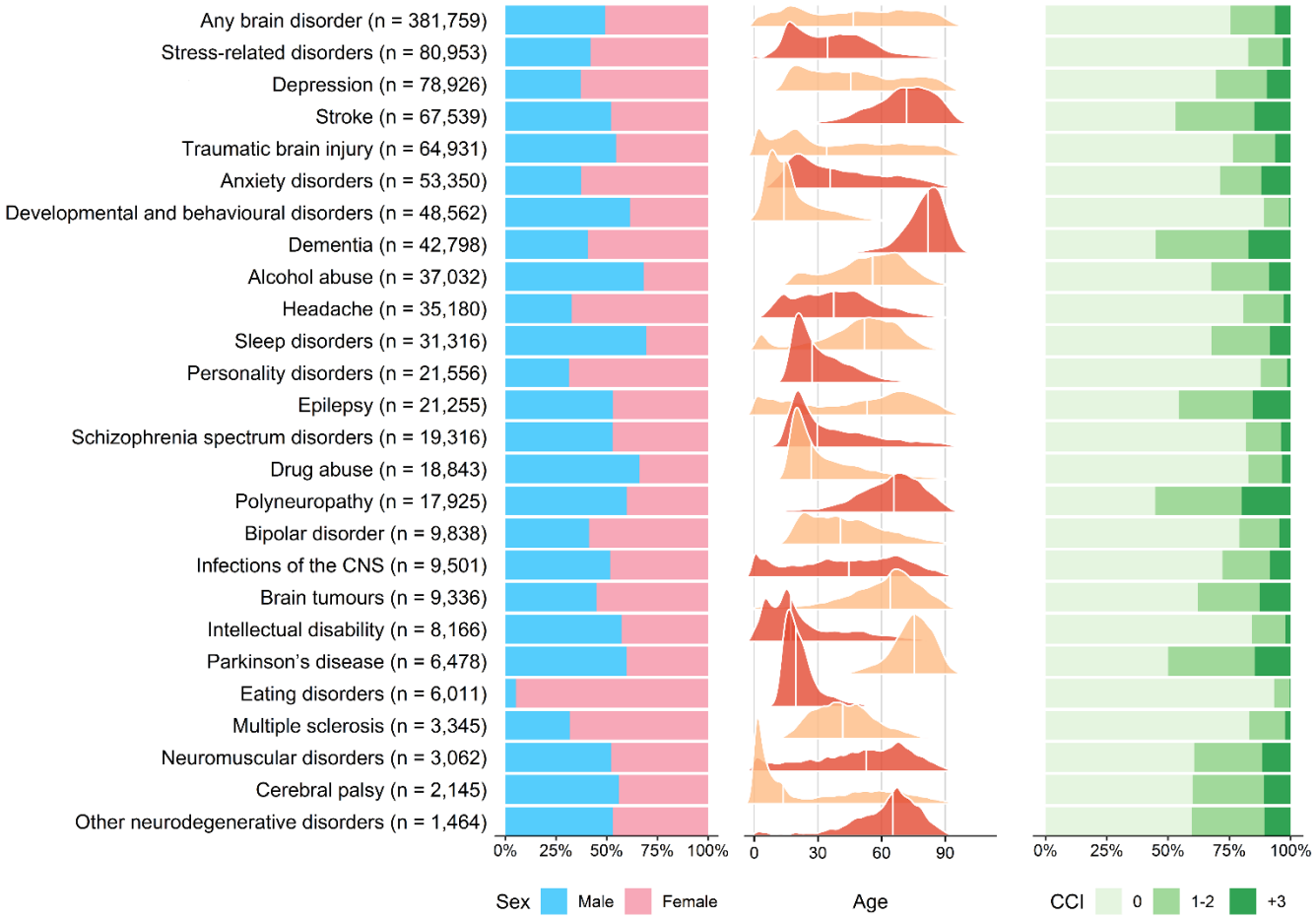
Abbreviations: EUR, Euro.

Suppl. Table 5. Lost productivity in persons with prevalent brain disorders in Denmark in 2015, and incident brain disorders in Denmark during 2011-2015.

	Lost productivity associated with illness			Lost productivity due to premature death		
Brain disorder	Attributable lost production in 2015 (EUR)	Attributable lost production per person in 2015 (EUR)	Attributable lost production per person in the year after diagnosis (EUR)	Attributable lost production among patients who died in 2015 (EUR)	Attributable lost production per person among patients who died in 2015 (EUR)	Attributable lost production per person among patients who died within one year after diagnosis (EUR)
Any brain disorder	10,871,306,597	15,471	11,501	310,599,261	66,595	176,821
Alcohol abuse	2,177,095,714	30,509	26,454	60,885,257	30,519	83,486
Anxiety disorders	1,540,715,518	19,281	19,717	32,197,400	59,515	145,515
Bipolar disorder	474,459,456	27,521	25,383	6,136,984	37,883	136,861
Brain tumours	62,414,375	8,259	15,068	44,062,492	174,851	205,107
Cerebral palsy	126,484,627	24,291	31,767	487,951	7,999	55,995
Dementia	118,974,339	32,436	28,305	1,408,193	8,140	28,505
Depression	2,900,683,027	21,708	20,838	64,470,952	63,706	162,215
Developmental and behavioural disorders	845,403,290	14,455	22,423	6,886,963	47,171	96,899
Drug abuse	1,330,382,612	29,742	24,512	14,271,378	22,908	67,596
Eating disorders	83,103,235	5,798	6,941	1,407,442	54,132	25,604
Epilepsy	757,818,260	16,449	18,764	39,647,665	61,469	167,731
Headache	490,757,570	6,493	6,165	21,177,971	101,330	174,465
Infections of the central nervous system	30,214,014	1,814	2,093	9,137,033	103,830	152,402
Intellectual disability	528,043,228	29,465	30,237	278,285	1,457	9,078
Multiple sclerosis	189,128,371	16,804	9,354	1,721,160	15,367	142,356
Neuromuscular disorders	61,263,234	14,022	9,262	1,733,127	36,875	106,274
Other neurodegenerative disorders	31,346,429	27,716	21,953	3,829,300	55,497	134,409
Parkinson's disease	32,248,038	22,662	14,259	3,565	105	49,396
Personality disorders	1,675,321,683	25,663	22,217	13,071,803	34,858	105,239
Polyneuropathy	238,332,654	16,662	16,701	8,543,728	29,873	78,341
Schizophrenia spectrum disorders	1,707,738,198	33,710	26,581	9,960,281	17,173	90,396
Sleep disorders	336,760,666	8,691	8,554	18,811,390	79,373	133,551
Stress-related disorders	3,167,569,516	19,310	19,520	63,414,446	69,917	175,773
Stroke	630,213,779	16,502	14,382	25,874,307	39,085	140,923
Traumatic brain injury	1,241,809,744	7,179	7,245	41,136,013	48,739	121,008

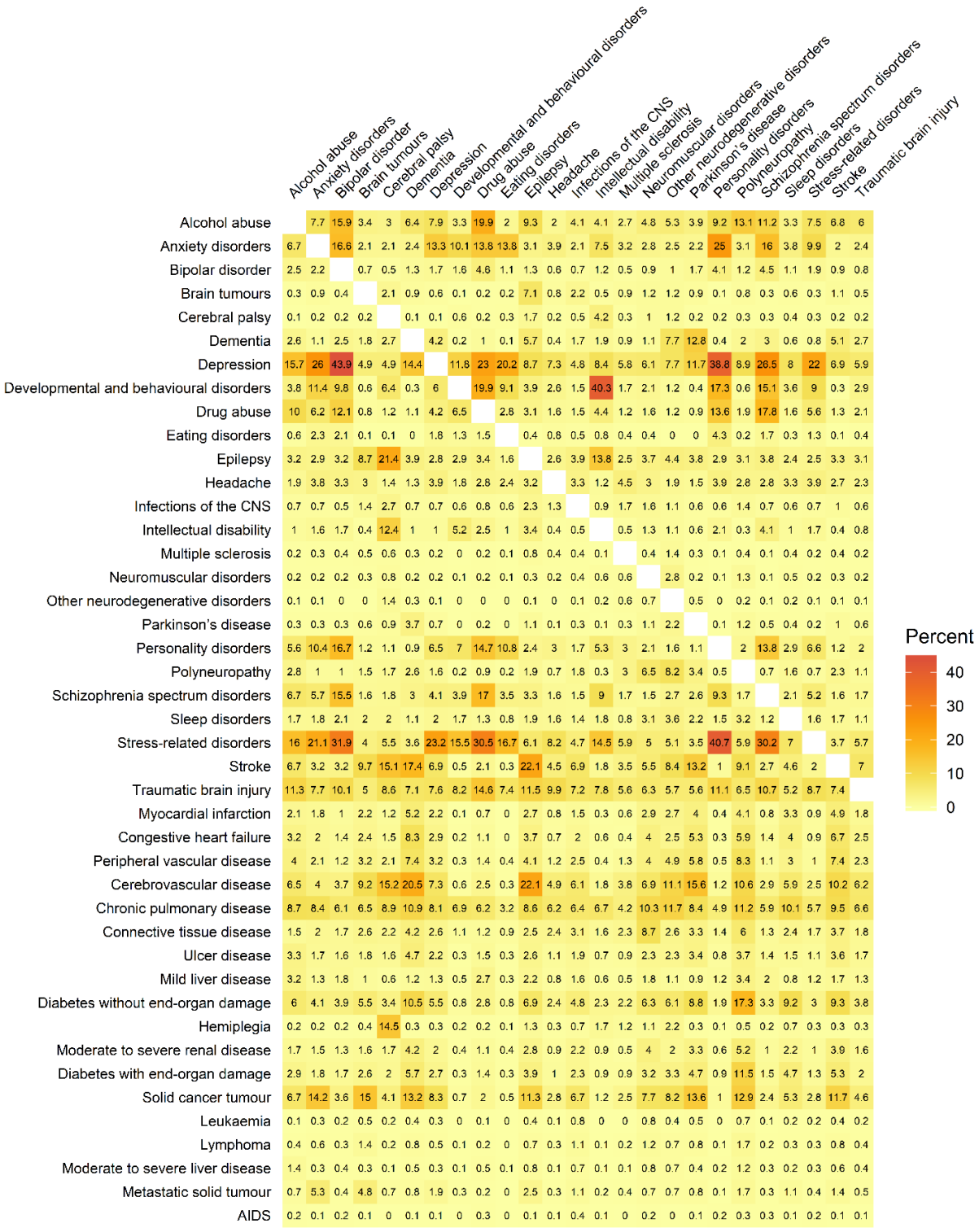
Abbreviations: EUR, Euro.

Supplementary figures



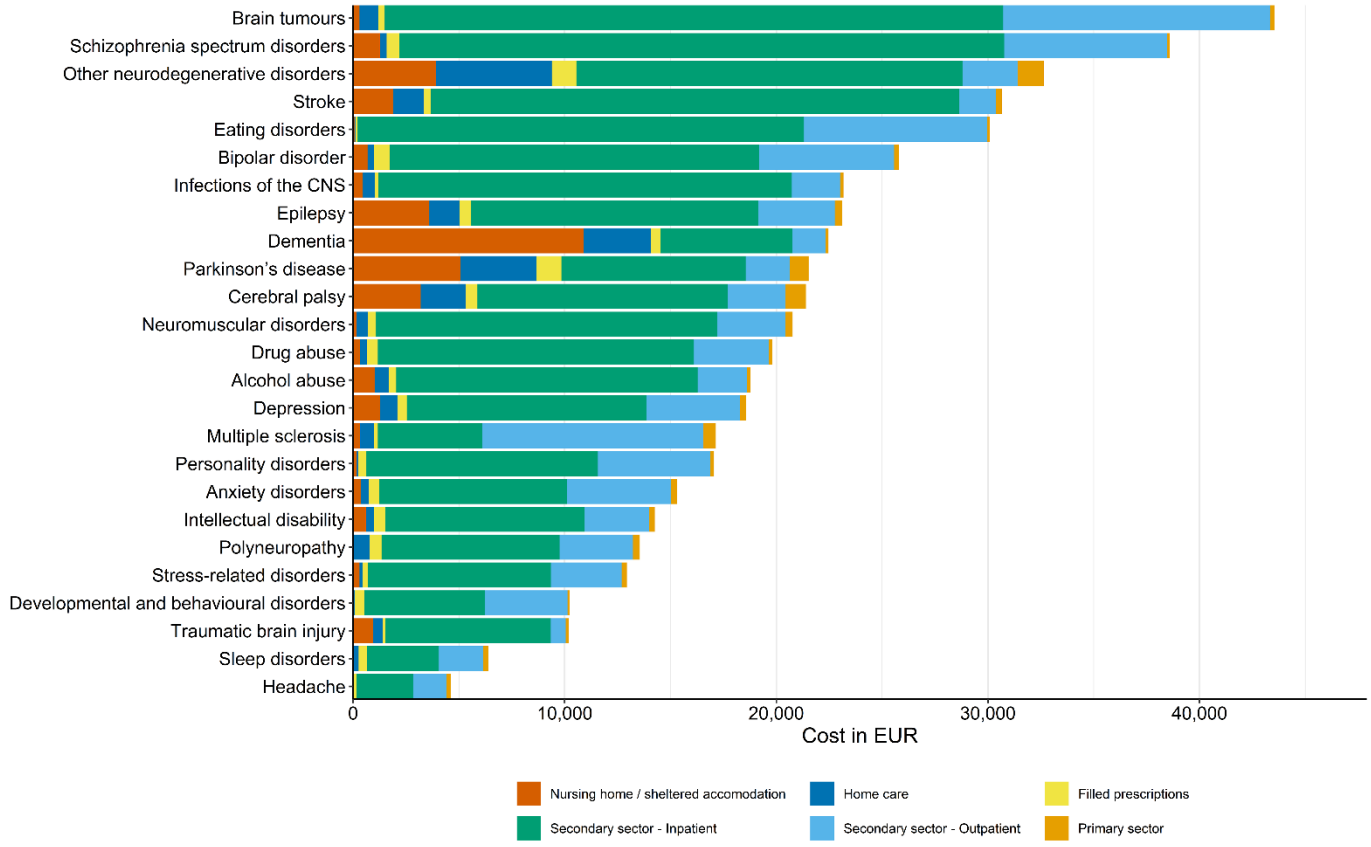
Suppl. Figure 1. Characteristics of patients with incident brain disorders in Denmark during 2011-2015 sorted from highest to lowest incidence (the white line in the age distribution represents the median age in each cohort).

Abbreviations: CNS, central nervous system; CCI, Charlson Comorbidity Index



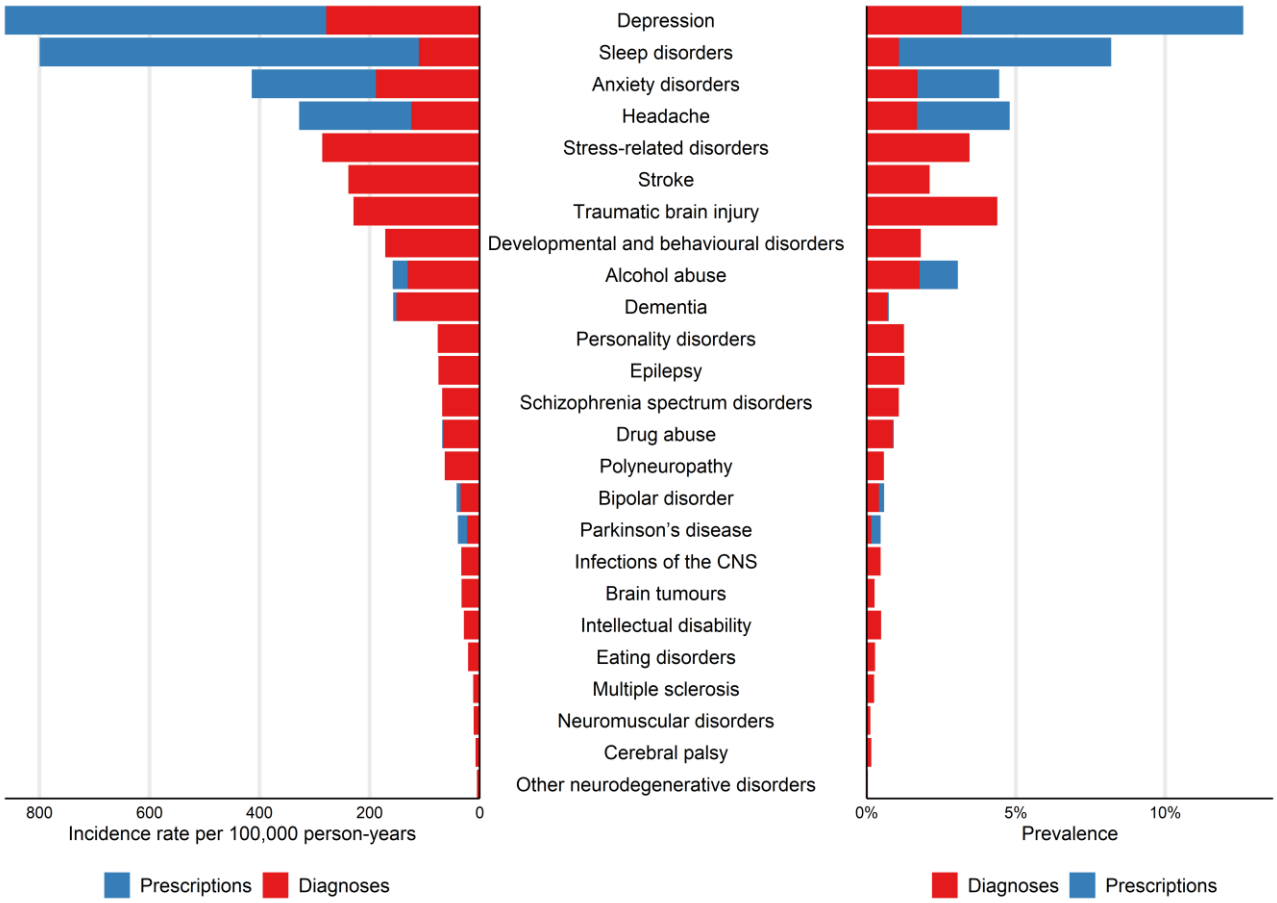
Suppl. Figure 2. Proportion of persons with incident brain disorders in the Danish population during 2011-2015 (columns), who had been diagnosed with comorbid brain or non-psychiatric disorders included in the Charlson Comorbidity Index up to 10 years before the index date of the brain disorder (rows).

Abbreviations: CNS, central nervous system



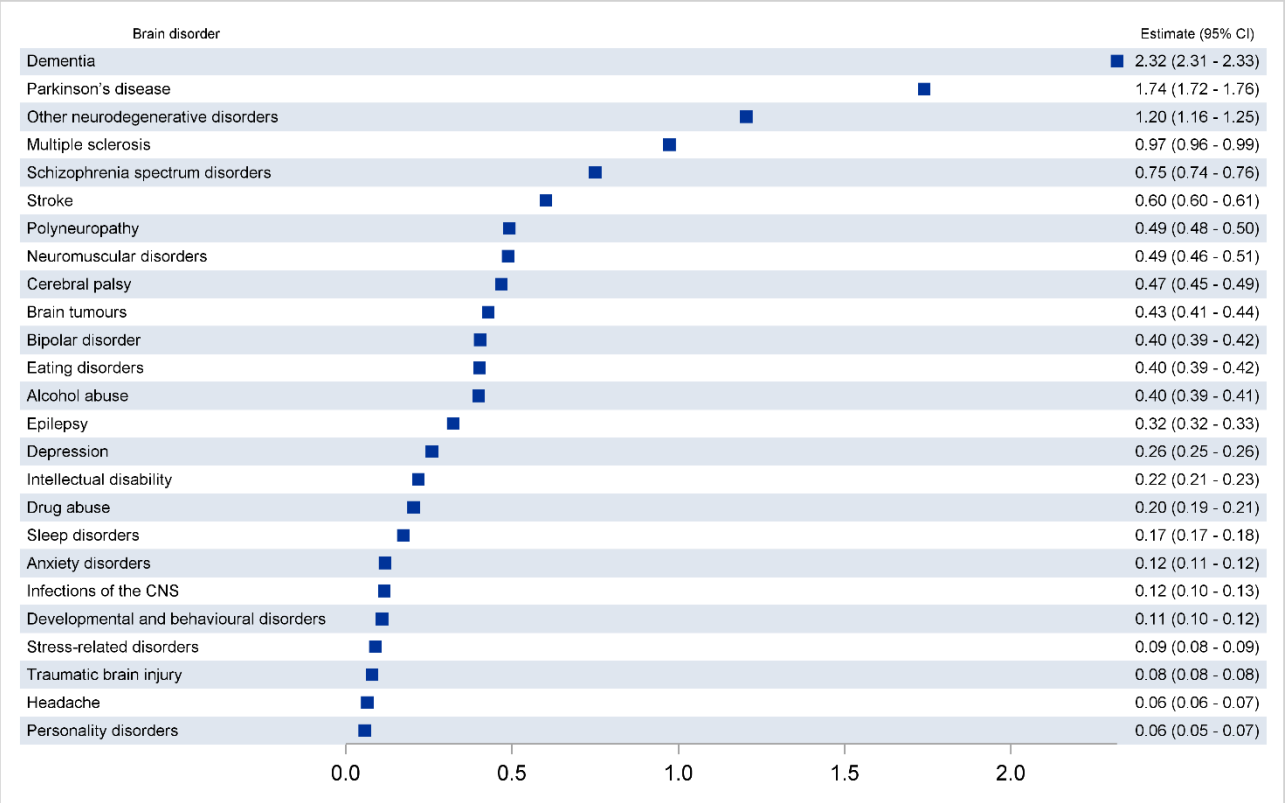
Suppl. Figure 3. Attributable direct costs per person during the first year after diagnosis in persons with incident brain disorders in Denmark during 2011-2015 (in 2015 prices) sorted from highest to lowest costs.

Abbreviations: CNS, central nervous system



Suppl. Figure 4. Occurrence of brain disorders in the Danish population including incidence during 2011-2015 and prevalence in 2015. Alcohol abuse, bipolar disorder, dementia, depression, drug abuse, headache, multiple sclerosis, Parkinson's disease, and sleep disorders were identified by either recorded hospital diagnoses or filled prescriptions of relevant medication, and all other brain disorders were identified by recorded hospital diagnoses.

Abbreviations: CNS, central nervous system



Suppl. Figure 5. Costs in €10,000 associated with each of 25 groups of brain disorders adjusted for comorbid brain disorders in persons with prevalent brain disorders in Denmark in 2015 (2015 prices).
Abbreviations: CI, confidence interval; CNS, central nervous system

Supplementary references

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7. Statistics Denmark. Documentation of statistics [cited 2019 12/12]. Available from: https://www.dst.dk/en/Statistik/dokumentation/documentationofstatistics accessed 12 Dec 2019.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	title page
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	page 3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	page 6
Objectives	3	State specific objectives, including any prespecified hypotheses	page 6
Methods			
Study design	4	Present key elements of study design early in the paper	page 7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	page 7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	page 7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	page 7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	page 8-9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	page 8-9 + Appendix 1
Bias	9	Describe any efforts to address potential sources of bias	page 10-11
Study size	10	Explain how the study size was arrived at	page 7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	page 8-9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	page 9-10
		(*b*) Describe any methods used to examine subgroups and interactions	page 9-10
		(*c*) Explain how missing data were addressed	NA
		(*d*) If applicable, explain how loss to follow-up was addressed	NA
		(*e*) Describe any sensitivity analyses	page 10
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	page 11
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	page 11+22
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) Summarise follow-up time (eg, average and total amount)	-
Outcome data	15*	Report numbers of outcome events or summary measures over time	page 11-12
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	page 12
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	page 13
Discussion			
Key results	18	Summarise key results with reference to study objectives	page 13-14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	page 14-15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	page 15-16
Generalisability	21	Discuss the generalisability (external validity) of the study results	page 15-16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	page 17

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.