Long-term prognosis after central nervous system infections – population-based cohort studies from Denmark

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PREFACE

The work presented in this thesis was carried out during my employment as a research fellow at the Department of Infectious Diseases, Copenhagen University Hospital, Rigshospitalet.

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Casper Roed
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Studies included in this thesis

Study I Roed C, Omland LH, Engsig FN, Skinhøj P, Obel N. Long-Term Mortality in Patients Diagnosed with Meningococcal Disease: A Danish Nationwide Cohort Study. *PLoS One*. 2010;5(3): e9662.

Study II Roed C, Engsig FN, Omland LH, Skinhøj P, Obel N. Long-Term Mortality in Patients Diagnosed with Pneumococcal Meningitis: A Danish Nationwide Cohort Study. *Am J Epidemiol*. 2010;172(3):309-17.

Study III Roed C, Engsig FN, Omland LH, Skinhøj P, Obel N. Long-Term Mortality in Patients Diagnosed with *Listerial monocytogenes* Meningitis: A Danish Nationwide Cohort Study. *J Infect*. 2012;64(1):34-40.

Study IV Roed C, Engsig FN, Omland LH, Skinhøj P, Obel N. Long-Term Mortality in Children Diagnosed with *Haemophilus influenzae* Meningitis: A Danish Nationwide Cohort Study. *Pediatr Infect Dis J*. 2011;30(8); e147-54.

Study V Roed C, Omland LH, Skinhøj P, Rothman KJ, Sørensen HT, Obel N. Educational Achievement and Economic Self-sufficiency in Adults After Childhood Bacterial Meningitis. *JAMA*. 2013;309(16):1714-1721.

Study VI Roed C, Sørensen HT, Rothman KJ, Skinhøj P, Obel N. Employment and Disability Pension after Central Nervous System Infections. Under review.*
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CONTENTS

INTRODUCTION

In the developed world *Streptococcus pneumoniae* and *Neisseria meningitidis* constitute the two leading causes of bacterial meningitis in both children and adults. The third most common cause of bacterial meningitis in adults is due to *Listeria monocytogenes*, responsible for 4-8% of all reported cases.[1-3] Herpes simplex virus (HSV) type 2 and enteroviruses are the most frequent causative agents of viral meningitis, and HSV type 1 most frequently causes infectious encephalitis.[4-6]

Since the introduction of *Haemophilus influenzae* type b (Hib) conjugate vaccine for infants in the 1990s the incidence of bacterial meningitis in the developed world has declined by 55%.[2] A decade later the pneumococcal conjugate vaccine for infants was introduced, and a further decline in bacterial meningitis cases was observed.[7;8] As a result of the general childhood vaccination against these two pathogens, bacterial meningitis in the developed world has now predominantly become a disease of adults rather than of children.[9]

Herd immunity has further been provided by lower carriage rates in children vaccinated with Hib and pneumococcal conjugate vaccines. A reduction in invasive Hib disease was observed in unvaccinated children following the introduction of Hib conjugate vaccine and likewise following the introduction of pneumococcal conjugate vaccine a correlated decline was observed in adult cases of invasive pneumococcal disease caused by the 7 conjugate vaccine serotypes.[7-12]

Overall, the most common causes of infectious meningitis are viral and less often bacterial.[13] An observation that has only been strengthened after introducing the Hib- and pneumococcal conjugate vaccines.[9;12] Among more than 3,000 children and adolescents who presented at emergency departments in the United States between 2001 and 2004 with cerebrospinal fluid pleocytosis and who had not received antibiotic treatment prior to lumbar puncture, 4% had bacterial meningitis and 96% had aseptic meningitis.[13] It is important to keep in mind that this primarily applies to the developed world. On a global scale *S. pneumoniae* and Hib still take a horrendous toll being responsible for as many child deaths as HIV, malaria and tuberculosis combined.[14-16]

The general public may not be aware that high-risk behaviours like cigarette smoking and alcohol abuse are also linked to invasive bacterial disease with *N. meningitidis* or *S. pneumoniae*.[17-21] The cyclical nature of meningococcal disease with peaks and troughs every five-seven years is no longer seen in the United States, where the annual incidences have stayed historically low since the last peak of disease in the late 1990s.[22] After this a remarkable 60% decrease in the incidence of meningococcal disease was observed even before implementation of the quadrivalent meningococcal conjugate vaccine (serogroups A, C, Y and W-135) in 2005 in the United States.[23] Similarly in Denmark, though there has been no general recommendation for the use of meningococcal vaccine, the incidence of meningococcal disease has declined over the last 15 years

as well.[24] It is plausible that the reduction in smoking prevalence observed from the 1990s through 2000 reaching a level of 20% among adults in the United States,[25] may have contributed to this decreased incidence of meningococcal disease. The Royal College of Physicians 2010 report *Passive smoking and children* estimated that passive smoking by children accounted for 22% of the paediatric bacterial meningitis cases in the United Kingdom.[17] Whether or not the decline in the incidence of meningococcal disease proves to be permanent, the importance of behavioural risk factors for the disease should no longer be underestimated.

Despite advances in antibiotic therapy and modern intensive care bacterial meningitis is still associated with high case fatality rates and substantial morbidity, particularly when caused by *S. pneumoniae*.[26;27] In a recent study of bacterial meningitis from the United States the overall adult case fatality rate was reported to be 16%; 9% among patients 18-34 years of age and 23% among those > 65 years of age.[3] In patients with pneumococcal meningitis the case fatality rate was 18% while it was 10% in patients with meningococcal meningitis. The case fatality rate among the paediatric cases was 7%, and it was also higher for children with pneumococcal meningitis (9%) than with meningococcal meningitis (4%). The acute mortality associated with viral meningitis is low whereas it is 8-14% after herpes simplex encephalitis.[4;5;28;29]

Survivors of CNS infections are at risk of developing severe neurological sequelae.[1;4;26;27;30] Among the survivors the proportion that recover their previous work capacity is not fully known, but is an important indicator of complete rehabilitation.[31;32] Sequelae of bacterial meningitis include hearing loss, epilepsy, cognitive impairment and hydrocephalus. Well-described sequelae of herpes simplex encephalitis include severe memory impairment, personality change, aphasia and epilepsy.[33-36] The acquired brain damage is caused by a combination of the invading pathogen and the host inflammatory response. Neuronal necrosis may arise due to inflammation, infarction, haemorrhage or intractable seizures.[37] Important insights into the triggers and mechanisms of neuronal injury in bacterial meningitis have been obtained by studying animal models, exploring the host inflammatory response.[38-41] It has been described that impairment in learning and memory capacity after pneumococcal meningitis is likely to be explained by hippocampal apoptosis observed in pneumococcal meningitis models.[42;43] Antibiotics are not effective in controlling the increased intracranial pressure if cerebral oedema occurs, which is why dexamethasone therapy has been implemented as adjunctive treatment of acute bacterial meningitis.[40] In a recent review of randomised controlled trials of corticosteroids for acute bacterial meningitis neurological sequelae were reduced by corticosteroids, but overall mortality was not.[44] Animal models and retrospective studies indicate that patients contracting herpes simplex encephalitis may benefit from adjunctive treatment with dexamethasone and a European multicentre trial is currently being conducted. [45]

This thesis attempts to describe the long-term prognosis of common CNS infections in a developed country, and aims to bring new insights into the burden of these diseases and the importance of preventing them.

OBJECTIVES

The aim of this PhD study was to describe *long-term mortality* in bacterial meningitis, *functioning in adult life* after bacterial meningitis in childhood, and *work capacity* after bacterial meningitis, viral meningitis or herpes simplex encephalitis in adults.

The specific objectives of the study were to explore:

Study I Long-term mortality in children and adults diagnosed with meningococcal disease.

Study II Long-term mortality in children and adults diagnosed with pneumococcal meningitis.

Study III Long-term mortality in adults diagnosed with listeria meningitis.

Study IV Long-term mortality in children diagnosed with *Haemophilus influenzae* meningitis.

Study V Educational achievement and economic self-sufficiency in adults diagnosed with meningococcal, pneumococcal, or *Haemophilus influenzae* meningitis in childhood.

Study VI Work capacity in terms of employment and disability pension after meningococcal, pneumococcal, viral meningitis, or herpes simplex encephalitis in adults.

MATERIALS

DATA SOURCES

The population-based cohort studies were carried out by linking the following national registries.

The Danish Civil Registration System is a national register from 1968 and was originally established for administrative purposes, in particular to ease taxation at source and performance of population censuses.[46] All individuals alive and living in Denmark in the year of 1968 were included, and thereafter every live born child and new inhabitant have been registered electronically.[47] From 1972 everyone alive and living in Greenland has been included in the registration. Denmark, Greenland and the Faroe Islands collectively make up the Kingdom of Denmark, however only individuals living in Denmark and Greenland are included in the register. As of June 17, 2014 a total of 9,541,544 persons had been included.[48]

When an individual is recorded in the Danish Civil Registration System a unique personal identification number called the CPR (Central Person Registration) number is assigned. The CPR number includes ten digits and follows the individual forever. In case of misuse of an identity or if a person changes sex a new CPR number will be assigned, however one time used, the same CPR number will not be assigned to any other individual in the future. Almost all Danish administrative and medical registers use the CPR number making the linkage between the registers possible.[46-48]

The Danish Civil Registration System is updated on a daily basis and includes information on the individual's sex, date of birth, date of immigration, whether he or she has emigrated or disappeared and date of death. Furthermore, it includes the CPR number of the individual's parents and spouse along with the date of marriage. Complete information on maternal identity exists for everyone born in Denmark after 1960, and also paternal identification for everyone born after 1970. Siblings are identified by individuals with the same mother and twins by siblings born the same day. The information on siblings is complete since 1953.[47;48]

The data quality of the Danish Civil Registration System is considered to be very high, due to the fact that national registration of all residents is required by law and that the information is used for administrative purposes hereby being validated continuously.[47] Furthermore, two other important factors that contribute to the high quality of the register are a positive public attitude towards the practical use of the CPR number and confidence in that the extensive recording by the authorities will not result in privacy breaches. In 2004 it was made possible for Danish citizens to access their own data by use of a digital signature through the register's web page instead of having to send a request by mail.[46;47]

During the last two decades the CPR number has proven to be an invaluable tool in epidemiologic research in Denmark.[49;50] The CPR number makes possible to link data from more than 50 national clinical databases,[51] with information recorded in the Danish Civil Registration System,[47] in the national health registers, such as the Danish National Patient Register, the Danish Medical Birth Registry, the Danish Register of Causes of Death, the Danish Cancer Registry, the Danish National Prescription Registry and the Danish National Pathology Registry.[52-57] Also information in the national socio-economic registers hosted by Statistics Denmark can be retrieved using this unique personal identificator.[58;59] In 2012 the Danish National Biobank was inaugurated, consisting of a physical biobank and the Biobank Registry, designed to be linked with information from existing national registers with a hope to gain new knowledge on genetic and environmental determinants leading to disease.[60]

Furthermore, for each study of interest a population-based comparison cohort matched by age and sex to index cases, as well as siblings and parents of all study participants, can be identified from the Danish Civil Registration System by the use of the CPR number.[48]

The Danish National Patient Register is a national register that covers a large proportion of healthcare activities in Denmark.[57] The register is publicly financed and was established in 1977 under the Danish National Board of Health and offers a unique possibility to conduct medical and public health research.[61]

The Danish name of the register is Landspatientregisteret. Several English translations are in use, among others, the Danish National Registry of Patients, the Danish National Hospital Register, National Patient Registry, Hospital Discharge Registry, the Hospital Discharge Register for in-patients, Danish National Health Registry.

The first public hospital in Denmark opened in 1757 and was devoted to "the poor and suffering without means and fortune for treatment".[62] Since the establishment of the modern Danish welfare state in the 1950s the government has provided tax-supported health care free of charge to all inhabitants.[63] The original purpose of the Danish National Patient Register was to acquire national data on hospital activity.[61]

Through the years the register has increasingly been used for health care planning and research, therefore several studies exploring the validity and coverage of the diagnoses in the Danish National Patient Register have been undertaken. High positive predictive values and high coverage have been found for neurological discharge diagnoses such as epilepsy, stroke and febrile seizures,[64-66] but also for meningococcal meningitis.[67;68] Data quality of several cardiopulmonary discharge diagnoses such as paediatric and adult asthma, pulmonary embolism, pleural empyema, infant respiratory distress syndrome, acute coronary syndrome, and acute myocardial infarction has likewise been found to be high.[69-75] Other diagnoses, such as deep venous thrombosis appeared to be of only moderate validity when given as a discharge diagnosis in hospital wards and non-valid when given in emergency departments.[72] Discharge diagnoses of liver cirrhosis, diverticular disease and diabetes mellitus are highly valid and complete.[76-78] The register is likewise a valuable data source for studies of patients with discharge diagnoses of haematological malignancy and anemia caused by bleeding,[79;80] whereas a diagnosis of vitamin B12 deficiency anemia should be used with caution.[81] Specialized registries like the Staphylococcal Database or the Medical Birth Register increasingly use the Danish National Patient Register as a source register.[61]

Originally the register covered all somatic hospital admissions and has gradually been expanded to cover all psychiatric hospital admissions, outpatient activities including emergency room contacts and patients followed in outpatient clinics.[61] Data in the Danish National Patient Register are divided into administrative and clinical data.[82] The administrative data include patient's CPR number, municipality of residence, date of inpatient admission and discharge, hospital department, type of medical speciality, date of first and last visit to a hospital outpatient clinic and number of visits to a hospital outpatient clinic. The clinical data include discharge diagnoses coded

by the attending physician, surgical procedures coded by the surgeon, and medical conditions diagnosed in hospital outpatient clinics coded by the outpatient physician.[82] A medical secretary enters the given information which is electronically transmitted to the Danish National Patient Register. The diagnostic information in the register has been coded according to the *International Classification of Diseases*, using initially the 8th (ICD-8) revision until the end of 1993, and the 10th (ICD-10) revision thereafter.[57]

The Danish Register of Causes of Death is a national register and contains information from all Danish death certificates since 1943.[83]

The recording in the Danish Register of Causes of Death includes the deceased person's CPR number and underlying cause of death as well as the contributory causes (immediate event leading to the death and other contributing conditions leading to the death). Information on circumstances of death, on whether it was judged to be a natural death due to age or disease, an accident, violence or suicide is included. Also, data on date and place of death, sex, age, address, municipality of residence of the individual and whether or not an autopsy was performed are likewise recorded.[54;84]

The causes of death are chosen and registered by the medical doctor who verifies the death. The medical doctor would either be the deceased person's general practitioner, a physician from an emergency service, an attending physician in case of death during a hospital admission, or a medical officer when a medico-legal autopsy is performed.[54]

The medical staff of the National Board of Health used to receive the death certificate, interpret the information and choose in their opinion the most correct underlying cause of death to be recorded. Since 2007, death certificates are submitted electronically to the National Board of Health. This allows the direct transfer of data to the Danish Register of Causes of Death with an accelerated updating of death statistics; however the quality of the data on underlying cause of death now solely relies upon the notification by the individual physicians. Causes of death are coded according to the Danish version of the ICD-8 revision from 1972 until the end of 1993 and the ICD-10 revision from 1994 and onwards.[54;84]

The Danish Medical Birth Registry is a national register and contains data on all hospital and home births in the country since 1973. The data are extracted from birth certificates completed by midwives who attend all births and from the Danish National Patient Register.[56;85]

More than 50 perinatal variables are recorded in the Birth Registry, such as new-born's CPR number, date of birth, mode of delivery, Apgar scores, results of blood gases from the scalp vein and umbilical cord, birth weight, length and head circumference, gestational age and number of

malformations. Information on complications during pregnancy, labour and delivery as well as maternal age, height, weight, medical conditions and smoking status is likewise included.[85]

The Danish Cancer Registry is a national register and contains information on incident cancers diagnosed in Danish Citizens since 1943.[53] The register was founded as a nationwide research register. A small fee was paid for each notification and reporting was voluntary until 1987, where the Danish National Board of Health made reporting mandatory.[86]

The data available include patient's CPR number, personal characteristics and tumour characteristics, such as diagnosis, TNM classification for stage (T=tumour size, N=presence of regional lymph nodes, and M=presence of distant metastases), topography, morphology and date at time of diagnosis. The cases of cancer are coded according to the ICD 7th revision until 1977 and the ICD-10 diagnosis from 1978. Topography and morphology are coded according to the International Classification of Diseases for Oncology 3rd revision from 1978.[53] Since 2004 notification to the register has been performed electronically, linking with histology data from the Danish National Pathology Registry. The proportion of histologically verified tumours in the register is 89% and the coverage is considered to be high.[53;87]

The Attainment Register is a national register established in 1974 and administered by Statistics Denmark.[59;88] The register contains the highest educational achievement obtained by all Danish citizens in each calendar year. The primary source is the Student Register, which collects information from all educational institutions in the country, from elementary schools to universities.[89] Information on the individual's CPR number, date of entrance and exit, and completed levels of education is provided yearly from the educational institutions to the Student Register. Secondary sources of information are registers collecting data from part-time educational programs and from educational programs outside Denmark whose credits are formally transferred to a Danish educational institution. [59;88]

The validity of the data in the Attainment Register is high with a reported misclassification of less than 3%.[59] The coverage is likewise high; in 2013, 96% of the population aged 15-69 years had information on highest educational achievement.[90]

The Personal Income Statistics is a national register administered by Statistics Denmark.[58;91] The register contains data on income and has been updated annually since 1980. The primary source of data stems from the Salary Information Register and the Central Taxpayers' Register.[91] Personal Income Statistics contains information on the individual's CPR number, personal income, gross income, taxable income, tax and more than a hundred further variables provided by employers, banks and municipalities to the tax authorities according to Danish law. Personal income includes all types of income, except income from wealth, and the validity of the income data is generally

high. However undeclared work and faulty tax reports to the authorities result in an underestimation of the real income figure.[91]

The Employment Classification Module is a national register administered by Statistics Denmark.[92] The register contains data on employment and has been updated annually since 1980. An individual is registered as employed, when his or her main income in a full calendar year stems from (1) business profit from a company owned by the individual or the individual's spouse or (2) employment with a specified minimum income. This minimum income is specified by Statistics Denmark and is equivalent to the mean yearly income for Danish trainees and is adjusted by the Consumer Price Index. In the register the employment parameter is recorded in the variable BESKST (until December 31, 2001) and BESKST02 (from January 1, 2002).

Since January 1, 1994 the module has included complete nationwide data on whether an individual in Denmark received disability pension in a given calendar year, recorded in the variable SOCIO (until December 31, 2001) and SOCIO2 (from January 1, 2002). Information on the reason why disability pension was granted can be obtained by linkage with the Register on Judgments Regarding Disability Pension hosted by the National Social Appeals Board.[93]

STUDY POPULATION

Cohort of patients with CNS infection

Patients diagnosed in the period 1977 to 2008 with the following CNS infections were identified in the Danish National Patient Register; meningococcal meningitis, pneumococcal meningitis, listeria meningitis, *Haemophilus influenzae* meningitis, viral meningitis and herpes simplex encephalitis (see Appendix 1 for ICD-8 and ICD-10 codes). The criteria of being born in Denmark and not diagnosed with any other CNS infections (Appendix 1) before the diagnosis of meningitis or encephalitis had to be meet. Patients were excluded from the studies if they died, emigrated, or were lost to follow-up within the first year after their CNS infection diagnosis.

General population comparison cohort

We constructed a general population comparison cohort of individually matched persons identified from the Danish Civil Registration System.

For each patient with CNS infection, all Danish citizens meeting the following criteria were identified: (1) had the same birth date and sex as the patient, (2) were residing in Denmark and not diagnosed with a CNS infection at time of the corresponding patient's diagnosis; and (3) alive and living in Denmark one year after the corresponding patient's diagnosis date for CNS infection. From this population, we randomly chose four individuals to be included in the general population comparison cohort. The number of individuals chosen for each listeria meningitis patient was set to nine, due to a small number of listeria meningitis patients.

Sibling and parent cohorts
Siblings and parents of patients and members of the general population comparison cohort were identified from the Danish Civil Registration System.

DATA ON STUDY POPULATION

Information was obtained in the same way for all individuals:

Data on *birth, sex, date of immigration/emigration, loss to follow-up, and date of death* were provided by the Danish Civil Registration System.
Data on *inpatient admissions and hospital outpatient services* were provided by the Danish National Patient Register.
Data on *underlying cause of death* were provided by the Danish Register of Causes of Death.
Data on *birth weight, gestational age at birth and 5-minute Apgar score* were provided by the Danish Medical Birth Registry.
Data on *cancer diagnoses* were provided by the Danish Cancer Registry.
Data on *highest educational achievement* were provided by the Attainment Register.
Data on *employment status and receipt of disability pension* were provided by the Employment Classification Module.
Data on *personal income* were provided by the Personal Income Statistics.

STUDY DESIGNS

All of the performed studies were population-based cohort studies. In the studies of long-term mortality after bacterial meningitis (study I-IV) the primary outcome was time from study inclusion to death. The secondary outcome was time from study inclusion to cause-specific death.

In the study of functioning in adult life after bacterial meningitis in childhood (study V) the main outcome was cumulative incidence of educational achievements and economic self-sufficiency and differences between patient and comparison cohorts in cumulative incidence of these study outcomes at age 35 years.

In the study of working capacity in adults after bacterial meningitis, viral meningitis or herpes simplex encephalitis (study VI) the main outcomes were differences in proportions of individuals employed, in personal income for those employed, and in the proportions of individuals receiving disability pension between patient and comparison cohorts. Comparisons were made two years before the time of CNS infection, at the time of CNS infection and two and five years after CNS infection.

STATISTICAL ANALYSES

Observation time in the studies of long-term mortality

The observation time was calculated from date of study inclusion (one year after meningitis diagnosis) to the date of death, emigration, loss to follow-up, or January 1, 2008, whichever came first. The date of study inclusion for the members of the general population comparison cohort was the same as for the patient to whom they were matched.

Kaplan-Meier survival analyses

Kaplan-Meier analyses were used to construct survival curves.

Regression analyses

Cox regression and Poisson regression analyses were used to estimate unadjusted and adjusted mortality rate ratios (MRR) and their respective 95% confidence intervals (CI). Schoenfeld plots confirmed that the proportional hazard assumptions were fulfilled when Cox regression was used.

Cumulative incidence function

Cumulative incidence with 95% CIs of specific causes of death, of educational achievements and economic self-sufficiency were computed taking into account losses due to death, emigration and loss to follow-up as competing risks.[94]

STATISTICAL SOFTWARE

SPSS Statistics version 19 (IBM Inc., Chicago, Il, USA), Stata version 8.0 (Stata Corporation, College Station, Texas, USA) and R software, version 2.13.2 were used for data analysis.

ETHICS

The studies were approved by the Danish Data Protection Agency (record no. 2008-41-2467). Ethics approval and individual consent are not required by Danish legislation governing this type of registry study.

RESULTS

STUDY I

Characteristics of the study population

A total of 4,909 patients diagnosed with meningococcal disease in the period 1977 to 2007 and who were alive one year after diagnosis were included in the study. Among them, 3,297 patients were diagnosed with meningococcal meningitis, 1,211 with acute meningococcaemia, 23 with

chronic meningococcaemia, 11 with Watherhouse Friderichesen syndrome and 367 with meningococcal disease of other specified conditions. Individuals diagnosed before the age of 15 years made up 62% of the whole patient population. From the general population 19,636 individuals were included, individually matched on age and sex to patients (4:1). In the sibling cohort 8,126 siblings of meningococcal disease patients and 31,140 siblings of the members of the population comparison cohort were included.

All-cause mortality

In the observation period 321 (6.4%) meningococcal disease patients and 985 (5.0%) members of the population comparison cohort died. The overall MRR for meningococcal disease patients was 1.27 (95% CI, 1.12-1.45), adjusted MRR 1.21 (95% CI, 1.06-1.37). Stratified by type of meningococcal disease, the MRR for meningococcal meningitis patients was 1.30 (95% CI, 1.13-1.52) and 1.19 (95% CI, 0.89-1.59) for patients with acute meningococcaemia. The results indicated a slightly increased long-term mortality in siblings of meningococcal disease patients compared with siblings of the population comparison cohort, MRR of 1.17 (95% CI, 0.92-1.48).

Cause-specific mortality

Meningococcal disease was associated with increased risk of death due to nervous system diseases, MRR 3.57 (95% CI, 1.82-7.00). We did not observe any increased risk of death due to infections, neoplasms or cardiovascular diseases in patients with meningococcal disease compared with members of the population comparison cohort.

STUDY II

Characteristics of the study population

A total of 2,131 patients diagnosed with pneumococcal meningitis in the period 1977 to 2007 and who were alive one year after diagnosis were included in the study. From the general population 8,524 individuals were included, individually matched on age and sex to patients (4:1).

All-cause mortality

During the observation period 584 (27.4%) pneumococcal meningitis patients and 1,739 (20.4%) members of the population comparison cohort died. The patients were at increased risk of death throughout the study period. The MRR of pneumococcal meningitis patients compared with members of the population comparison cohort in 20-year age intervals revealed an eight-fold increased long-term mortality in the age category 0-<20 years to a 1.5-fold increased mortality in those aged 60-<80 years.

Cause-specific mortality

Pneumococcal meningitis was associated with an increased risk of death due to nervous system diseases, digestive system diseases and neoplasms. The risk of death due to nervous system

diseases was three times higher than for the general population. During follow-up, 32 patients with pneumococcal meningitis died from neurological causes, of whom five patients died from pneumococcal meningitis with a median of 5.8 years from the initial episode. Seven patients died of acquired hydrocephalus, and four died from sequelae of inflammatory diseases of the CNS. In the patients with pneumococcal meningitis the risks of death due to oropharyngeal cancer and malignant blood disorders were more than three and five times higher than for the general population. A subanalysis revealed the 10-year risk of death due to multiple myeloma to be 2.9% (95% CI, 1.4%-5.3%) for pneumococcal meningitis patients above 50 years of age compared with 0.1% (95% CI, 0.0%-0.2%) for the corresponding members of the population comparison cohort. Only six of 23 of the patients who died of multiple myeloma were diagnosed with the disorder prior to hospitalization for pneumococcal meningitis.

STUDY III

Characteristics of the study population

A total of 114 patients diagnosed with listeria meningitis above 16 years of age in the period 1977 to 2007 and who were alive one year after diagnosis were included in the study. From the general population 1,026 individuals were included, individually matched on age and sex to patients (9:1). The median age at diagnosis of listeria meningitis was 61.7 years (IQR, 49.9-72.7 years).

All-cause mortality

In the observation period 57 (50.0%) listeria meningitis patients and 400 (39.0%) members of the population comparison cohort died. The risk of death was two-fold increased for the patients the first five years of follow-up, thereafter the risk of death declined to that of the general population.

Cause-specific mortality

In the same period the MRR for death with an underlying cause of cancer was 3.85 (95%, 1.93-7.69) for listeria meningitis patients compared with members of the population comparison cohort. Of listeria meningitis patients older than 50 years of age and not diagnosed with cancer before the meningitis episode 18.9% (95% CI, 10.3%-29.5%) were diagnosed with cancer at five years of follow-up compared with 7.9% (95% CI: 5.9%-10.2%) of the members of the population comparison cohort.

STUDY IV

Characteristics of the study population

A total of 1,242 children diagnosed with *H. influenzae* meningitis under five years of age, in the period 1977-1996, and who were alive one year after diagnosis were included in the study. From the general population 7,452 individuals were included, individually matched on age and sex to patients (6:1).

All-cause mortality

The MRR for children diagnosed with *H. influenzae* meningitis was 1.08 (95% CI, 0.57-2.05), adjusted MRR 0.97 (95% CI, 0.5-1.89). No increased mortality due to infections, respiratory diseases or cancer was observed.

Morbidity

The risk of inpatient admission and of requiring hospital outpatient services for children who had *H. influenzae* meningitis was increased during the first 15 years of follow-up, mainly explained by increased morbidity caused by epilepsy, cerebral plasy and hearing loss.

STUDY V

Characteristics of the study population

A total of 2,784 children diagnosed with meningococcal (n=1,338), pneumococcal (n=455) or *H. influenzae* (n=991) meningitis under 12 years of age, in the period 1977-2007, born between 1975 and 1997, and alive and living in Denmark at 13 years of age were included in the study. From the general population 11,136 individuals were included, individually matched on age and sex to patients (4:1). In the sibling and parent cohorts a total of 14,147 full siblings and 27,601 parents of meningitis patients and members of the population comparison cohort were included.

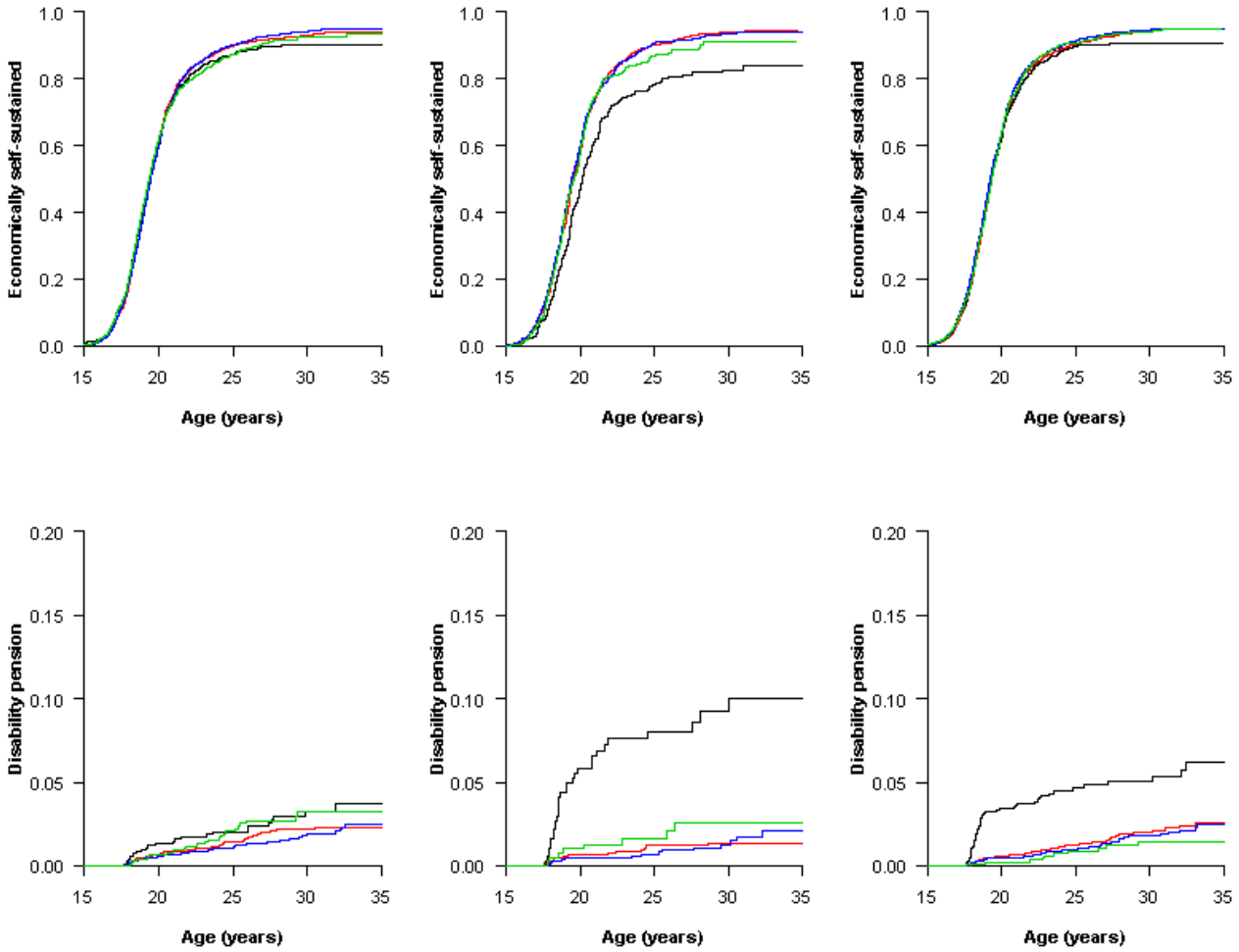
Educational achievement

By age 35 years, among adults with a history of childhood meningococcal, pneumococcal, and *H. influenzae* meningitis, an estimated 11.0% (95% CI, 7.3%-14.7%), 10.2% (95% CI, 3.8%-16.6%), and 5.5% (95% CI, 1.9%-9.1%) fewer, respectively, had completed high school and 7.9% (95% CI, 1.6%-14.2%), 8.9% (95% CI, 0.6%-17.2%), and 6.5% (95% CI, 1.4%-11.6%) fewer had attained a higher education compared with members of the population comparison cohort. Siblings and parents of meningococcal meningitis patients also had lower educational achievements, while educational achievements of siblings and parents of pneumococcal and *H. influenzae* meningitis patients did not differ substantially from those in the general population.

Economic self-sufficiency

By age 35 years, 3.8% (95% CI, 1.1%-6.5%), 10.6% (95% CI, 5.1%-16.1%), and 4.3% (95% CI, 2.0%-6.6%) fewer meningococcal, pneumococcal, and *H. influenzae* meningitis patients were economically self-sufficient and 1.5% (95% CI, -0.2% to 3.2%), 8.7% (95% CI, 5.0%-12.4%), and 3.7% (95% CI, 1.6%-5.8%) more received disability pension compared with members from the population comparison cohort (figure 1).

Figure 1. Cumulative incidence of having been economically self-sustained for a year and of receiving disability pension in the meningococcal, pneumococcal and *H. influenzae* meningitis patients (black), members of the population comparison cohort (red), full siblings of patients (green) and siblings of members of the population comparison cohort (blue).



STUDY VI

Characteristics of the study population

A total of 2,552 patients diagnosed with meningococcal (n=451), pneumococcal (n=553), viral (n=1433) meningitis and herpes simplex encephalitis (115) between 20 and 55 years of age, in the period 1980-2007, and who were alive one year after diagnosis were included in the study. From the general population 10,208 individuals were included, individually matched on age and sex to patients (4:1). In the sibling cohort 1,748 siblings of patients and 6,989 siblings of the members of the population comparison cohort were included.

Employment

Among meningococcal meningitis patients, 10.1% fewer (95% CI: 5.5%-14.7%) were employed two years before their diagnosis, compared with members of the comparison cohort. No substantial change in this disparity was observed after diagnosis of this CNS infection.

Among pneumococcal meningitis patients, 11.5% fewer (95% CI: 7.3%-15.7%) were employed two years before their diagnosis, compared with members of the comparison cohort. This disparity increased markedly post-diagnosis, with 19.7% fewer (95% CI: 14.8%-24.6%) pneumococcal meningitis patients employed five years after their diagnosis, compared with the comparison cohort. Similar results were found after restricting the analysis to individuals who had been employed and who had not received disability pension in the two years before pneumococcal meningitis. This was also the case when we excluded individuals who, before their episode of pneumococcal meningitis, had been diagnosed with comorbidity or with diseases that are known to be associated with work incapacity.

No substantial difference in employment was observed during the study period for viral meningitis patients compared with members of the comparison cohort.

Among herpes simplex encephalitis patients, 4.8% fewer (95% CI: -3.4%-13.0%) were employed two years before their diagnosis date, compared with members of the comparison cohort. This disparity increased markedly by five years after the diagnosis date, with 21.0% fewer (95% CI: 9.5%-32.6%) herpes simplex encephalitis patients employed.

Personal income

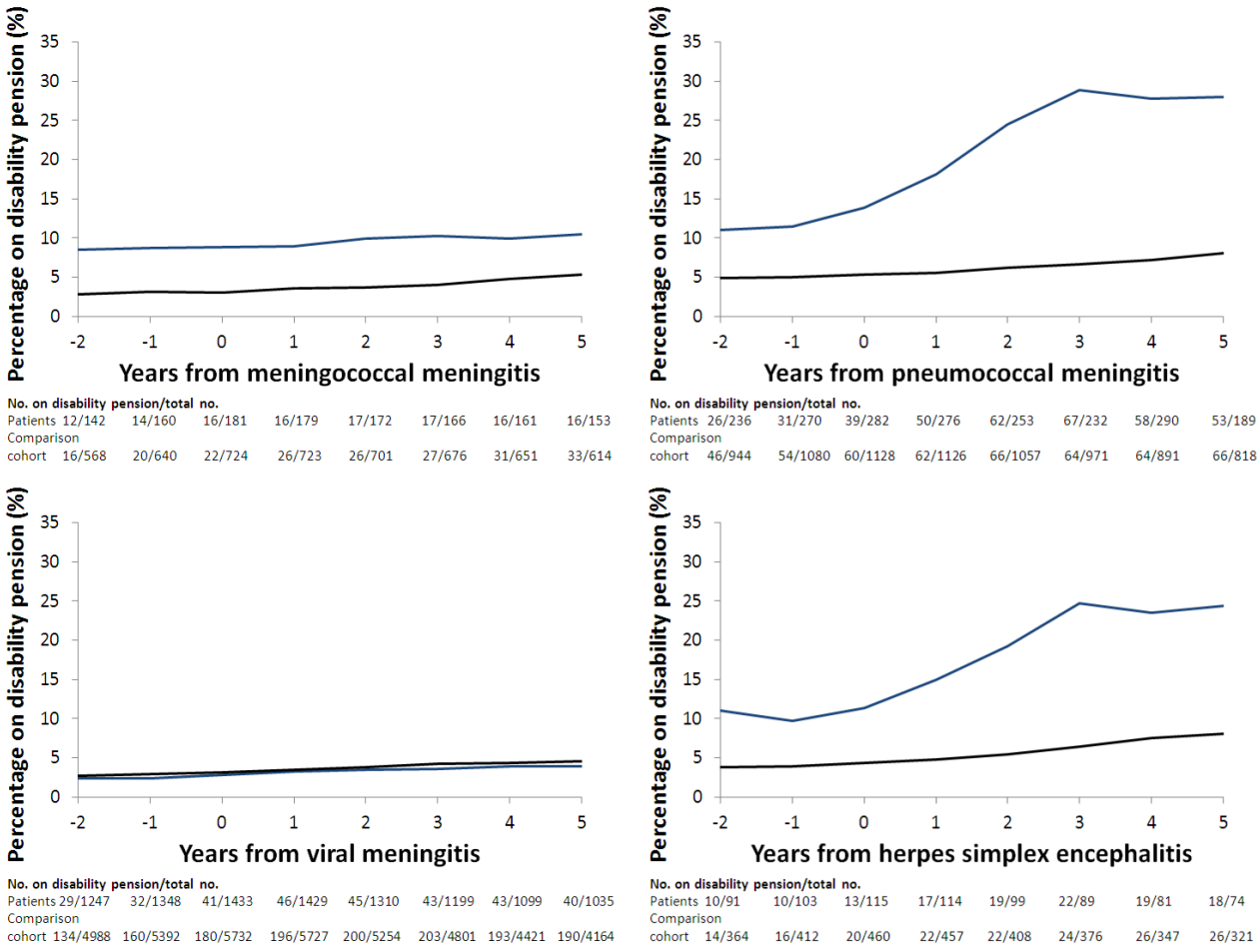
During the whole study period no substantial decrease in personal income was observed among employed meningococcal, pneumococcal or viral meningitis or herpes simplex encephalitis patients.

Disability pension

A higher proportion of meningococcal meningitis patients received disability pension compared with the comparison cohort throughout the study period. Little change in this difference was noted after the diagnosis (figure 2).

Two years before the diagnosis 6.1% (95% CI: 1.9%-10.4%) and 7.2% (95% CI: 0.3%-14.0%) more pneumococcal and herpes simplex encephalitis patients, respectively, received disability pension compared with members of their comparison cohorts. Five years after diagnosis 19.9% (95% CI: 13.4%-26.6%) and 16.2% (95% CI: 6.2%-26.3%) more patients with these two CNS infections received disability pension, compared with the comparison cohort. No substantial difference in receipt of disability pension was observed during the study period for viral meningitis patients compared with members of the comparison cohort.

Figure 2. Proportions receiving disability pension among meningococcal, pneumococcal, viral meningitis and herpes simplex encephalitis patients (blue line) diagnosed after 1994 and comparison cohorts (black line).



DISCUSSION

The research question posed was to which degree the most common CNS infections in a developed country are associated with long-lasting influence on health. The specific aims were to study long-term mortality after community-acquired bacterial meningitis in children and adults, to study educational achievement after bacterial meningitis in childhood and to study work capacity after bacterial meningitis, viral meningitis, or herpes simplex encephalitis in adults.

The hypothesis was that underlying conditions associated with the occurrence of CNS infections and neurological sequelae would likely appear to be main factors involved in observed increased long-term mortality and morbidity in this patient population. A sequela from meningitis has been defined by WHO Global Burden of Disease as a health state resulting from meningitis that impairs quality of life or activities of daily living.[95] Severe sequelae from meningitis include mental retardation with IQ<70, seizures, bilateral sensorineural hearing loss, spasticity or paresis of one or

more limbs, visual field loss and distinct pathological entity with any impairment to activities of daily living (i.e. hydrocephalus).[95]

Mortality and morbidity after bacterial meningitis

Our findings support this hypothesis, since a substantially increased long-term mortality was observed up to 30 years after patients were diagnosed with pneumococcal meningitis and up to five years after a diagnosis of listeria meningitis.[96;97] Similarly, in a recent population-based cohort study adult patients with tuberculous meningitis were shown to have a life-long increased risk of death compared with the general population.[98] By contrast, we only observed a slightly increased long-term mortality among meningococcal meningitis patients.

Chronic diseases, low socioeconomic status and high-risk behaviours such as smoking and alcohol abuse are known conditions associated with pneumococcal, listeria and tuberculous meningitis and subsequent neurological sequelae are well-documented.[99-103] Meningococcal meningitis differs from other types of bacterial meningitis in both epidemiological and clinical characteristics. In particular, this is a highly contagious disease that mainly affects individuals who are healthy.[3;104-106] This is reflected by the capability of the disease to cause outbreaks with an estimated 500-800 fold increased risk of disease in family members of patients with meningococcal disease, if antimicrobial chemoprophylaxis is not provided.[107] Individuals with properdin deficiency and late C component deficiencies are known to be highly susceptible to infection caused by *N. meningitidis*, however where meningococcal disease is epidemic or endemic the prevalence of these complement deficiencies is low among individuals with a first time infection.[108-111] Though anatomical or functional asplenia and HIV infection appear to be independent risk factors for meningococcal disease, the associations are much less compelling than for invasive pneumococcal disease.[21;22;112] Furthermore, disabling sequelae after meningococcal meningitis are described to be milder than after pneumococcal or *H. influenzae* meningitis,[27;30] which altogether is consistent with the findings in our study of a slightly increased long-term mortality in this patient population.[113]

In a Dutch study from 1996, which included patients from a population that is likely to resemble our study population, 415 survivors of meningococcal meningitis were included and 35 (8%) recovered with one or more sequelae.[105] The two most frequently reported sequelae were loss of hearing (4%) and scars after skin necrosis (3%), whereas conditions such as hydrocephalus, cerebral atrophy or mental retardation were reported in only three patients (0.7%) and epilepsy in one (0.2%) patient. The highest proportion of sequelae (14%) was found among patients with both meningitis and septicaemia, whereas it was 7% among the patients with only meningitis.[114] In our study we were not able to stratify patients into either meningitis or mixed meningococcal disease groups. Differences in outcomes according to serogroups A, B, C, Y or W135 meningococci have been described; meningococcal disease caused by group C is reported to be associated with

greater physical sequelae compared with group B.[115] An exceptionally high virulence of group C compared with group B was observed in 471 cases of meningococcal disease in Quebec, Canada.[116] The authors reported permanent reduced kidney function in three survivors, where one received a kidney transplant, all of whom had meningococcal disease caused by group C. In our study, we observed an increased risk of death due to genitourinary diseases, but were not able to stratify by serogroup. However, the observed excess mortality was mainly due to nervous system diseases, and no increased risk of death due to infectious diseases, cancer, cardiovascular, respiratory or rheumatological diseases was observed.[113] In a large Danish study of 2,984 patients with meningococcal disease caused by group B, no association was observed between the occurrence of meningococcal infection and the development of autoimmune diseases up to 31 years after the infection, thus supporting our findings of no increased risk of death due to rheumatological diseases in this patient population.[117]

The apparent effect of pneumococcal meningitis on increased long-term mortality in our study may partly be attributable to confounding, in terms of pre-existing comorbidity in pneumococcal meningitis patients.[96] Confounding, the mixing of effects, is a central issue for observational study design. A confounder must be imbalanced between the exposed group and the comparison group and have three properties; 1) a confounder must be associated with the exposure, 2) a confounder must be associated with the outcome, and 3) a confounder must not be an effect of the exposure.[118] A means to controlling confounding is stratification by the potential confounders, if they are recognized and measured.[118] The highest incidences of invasive pneumococcal disease are seen in immunocompromised patients with solid cancer, haematological malignancy or HIV carrying an approximately 23-48 times increased risk of disease compared with healthy adults.[103] Alcohol abuse is associated with an 11 times increased risk whereas persons with diabetes, chronic lung disease or cardiovascular disease have a 3-6 fold increased risk of invasive pneumococcal disease compared with healthy adults. Multiple chronic conditions seem to have a cumulative effect on the risk of invasive pneumococcal disease.[103] Among otherwise healthy adults under 65 years of age, cigarette smoking is the strongest independent risk factor for invasive pneumococcal disease with an estimated population attributable fraction to cigarette smoking of approximately 50%.[20]

Brain damage caused by CNS infections can be either focal or global.[37] Focal brain damage occurs primarily from the infective organism invading the brain parenchyma and generating areas of ischaemia which cause neuronal necrosis. Diffuse brain damage is usually of secondary pathophysiological origin and may be hypoxic, inflammatory or seizure-related.[37] Pneumococcal meningitis is more severe than meningococcal or *H. influenzae* meningitis with higher rates of acute complications and sequelae.[27;30;119;120] These observations are supported by experimental animal models.[39;41;42] Secondly, seizures in adults with bacterial meningitis are more likely to occur in cases of infection with *S. pneumoniae*.[121] Cerebral infarction has been shown to be particularly common in pneumococcal meningitis, reported to occur in up to 17-36% of patients, while only in

5-9% of patients with meningococcal meningitis and 20-28% of patients with meningitis of other bacterial aetiologies.[122;123] Likewise, cerebral haemorrhage was observed in 16 of 576 pneumococcal meningitis patients whereas in none of 96 patients with meningococcal meningitis.[124] A recent review of studies published on pneumococcal meningitis survivors in high-income countries between 1991 and 2009 reported a pooled prevalence of seizures to be 7%, hearing loss 21%, spasticity or paresis 9%, visual impairment 2% and hydrocephalus 7%.[125]

In a large Danish study from 2009 on invasive pneumococcal disease, specific pneumococcal serotypes were shown to be strongly associated with increased short-term mortality in 15,029 bacteremia patients, whereas no substantial differences were found in short-term mortality among 2,248 meningitis patients when stratified by pneumococcal serotype.[126]

Therefore, with the above mentioned risk factors for pneumococcal meningitis and the proportion of neurological sequelae in mind, one might expect to observe an increased long-term mortality in adult pneumococcal meningitis patients both due to predisposing chronic diseases and neurological sequelae. Another way to describe this logic matter would be that the apparent effect of pneumococcal meningitis on the increased long-term mortality in our study is expected partly to be attributable to confounding due to predisposing chronic diseases. When stratifying by cause-specific death, we found a three times increased risk of death due to nervous system diseases, a three times increased risk of death due to liver diseases and a five times increased risk due to haematological malignancies.[96] The latter observation was mainly due to a 20-times increased mortality from multiple myeloma. This finding was consistent with earlier observations of a substantially increased incidence rate ratio for a subsequent diagnosis of multiple myeloma in pneumococcal meningitis patients older than 40 years of age.[127] Presumably these patients already housed an unrecognised haematological malignancy at the time of diagnosis of pneumococcal meningitis making them prone to an invasive bacterial infection by *S. pneumoniae*. Screening of multiple myeloma in elderly pneumococcal meningitis survivors without obvious risk factors for pneumococcal meningitis other than age might be worth considering, partly in terms of the survival improvement of multiple myeloma seen over the last decade but most importantly because of the severe prognosis when diagnosed in an advanced stage.[128]

In our study the risk of death from liver diseases in pneumococcal meningitis patients was increased and more than half of these deaths were alcohol related.[96] Likewise, the risk of dying from oropharyngeal cancer was increased among patients with pneumococcal meningitis. This observation is in line with previously described strong associations of alcohol abuse and smoking with both pneumococcal meningitis and oropharyngeal cancer.[103;129-131] The synergism between tobacco and alcohol on the increased risk of oropharyngeal cancer was described as early as the 1970s, as well as estimates that 80% of all cancers of the head and neck were related to the use of tobacco.[132-135] However, in our study we were not able to stratify by alcohol abuse or cigarette smoking.

The clinical characteristics of the listeria meningitis patients in our study were similar to those with pneumococcal meningitis, as they also had a higher proportion of prevalent cancers at the time of diagnosis compared with the general population.[97] One third of the known cancer diagnoses in the listeria meningitis patients proved to be of haematological origin. Cancer is a main risk factor for listeria meningitis and patients with haematological malignancy have been found to carry the highest risk of invasive listeriosis.[136] Both the risk of being diagnosed with cancer after listeria meningitis and the risk of death due to cancer were increased in listeria meningitis patients compared with the general population.[97] Predisposing malignancy even appeared to be the main factor responsible for the increased long-term mortality after listeria meningitis, as we did not observe an increased risk of other causes of death. Still, in the cause-specific death analyses only data on underlying cause of death was considered and therefore conditions contributing to death, such as alcohol abuse, were not accounted for.

Pneumococcal meningitis in childhood was associated with increased long-term mortality, mainly due to nervous system diseases.[96] Children with meningococcal meningitis revealed a slightly increased long-term mortality compared with the general population, whereas no increased long-term mortality was found among children diagnosed with *H. influenzae* meningitis.[113;137] These observations are consistent with reports of children with pneumococcal meningitis carrying a higher risk of disabling sequelae than children with meningococcal or *H. influenzae* meningitis.[37;138] In a study on cerebral infarction in perinatal and childhood meningitis the most frequent causative pathogens were *S. pneumoniae* and *Salmonella* spp., accounting for 57% of infarction episodes.[139] An extensive review and meta-analysis on global and regional risk of disabling sequelae of bacterial meningitis in childhood reported a median risk of developing at least one severe sequela of 25% in patients with pneumococcal meningitis, 10% in *H. influenzae* meningitis and 7% in meningococcal meningitis patients.[30] Evidently, disparities in risk were revealed between high-income and low-income countries. The risk of at least one severe sequela from meningitis caused by one of the three pathogens was 9% in the European region and it was almost three times higher in the African and Southeast Asian region.

The overall risk of disabling neurological sequelae in survivors of bacterial meningitis in childhood stratified by pathogens is of particular interest because infants and small children are not exposed to alcohol consumption. One study on neuropsychological sequelae of bacterial meningitis reported no substantial differences between otherwise healthy pneumococcal and meningococcal meningitis patients without evidence of alcohol abuse.[140] Even though the study was underpowered by only including 16 patients in each subgroup and without considering known clinical predictors for an unfavourable outcome, the authors sustain that unmeasured confounding from alcohol abuse might have caused an overestimation of neuropsychological sequelae from bacterial meningitis in general. Our observations are not concordant with the above-mentioned findings, but also in the literature pneumococcal meningitis has repeatedly been

associated with a higher degree of disabling neurological sequelae compared with meningococcal and *H. influenzae* meningitis.[27;30;119;141]

A recent study on sequelae from pneumococcal meningitis in childhood with a median follow-up of 6 years reported partial or profound hearing impairment in 14% of patients and 1% of controls. Patients had a lower full scale IQ, verbal IQ, and numeracy compared with controls, who were siblings or neighbours of same age.[142] A favourable prognosis was found for the majority of children who were treated for meningitis caused by *H. influenzae* type b before the implementation of the Hib conjugate vaccine.[143] Sensorineural hearing loss was observed in 11% of the patients, seizures in 2% and mental retardation and hemiplegia in 1%. These findings are in accordance with our observations revealing no increased long-term mortality in children with *H. influenzae* meningitis, but an increased morbidity caused by hearing loss, epilepsy and cerebral palsy.[137] Four years after serogroup B meningococcal disease, 90% of 245 children showed no sign of major sequelae, but stratification by meningitis or septicaemia was not performed.[144] Sensorineural hearing loss was observed in 5% of meningococcal disease patients and <1% of the controls.

Adult functioning after childhood bacterial meningitis

Learning, memory and behavioural difficulties are well-described among survivors of childhood bacterial meningitis.[144-147] Previously, the longest follow-up of children with bacterial meningitis on educational achievements was reported in a study from the UK in 2007.[148] A total of 461 children who had bacterial meningitis in infancy in 1985-87 were followed until the end of primary school. Although loss to follow-up was high, the results included only 27% of the original study cohort published in 2001.[138;148] The authors found that more than a quarter of the patients failed to pass their secondary education at 16 years of age compared with 7% of the controls. The study did not take socioeconomic confounding into account, since it recruited age- and sex-matched controls from the panels of the same practitioner. Among patients who attended special schools, 31% had had meningitis due to *H. influenzae* and 22% due to *Escherichia coli*. No further stratification by bacterial aetiology was reported.[148]

In our study, episodes of meningococcal, pneumococcal or *H. influenzae* meningitis in childhood were all associated with lower educational achievement and economic self-sufficiency in adult life.[141] The observed association proved to be particularly relevant for pneumococcal and *H. influenzae* meningitis patients, whereas for meningococcal meningitis patients the lower educational achievement appeared to be family-related. Both siblings and parents of meningococcal meningitis patients presented lower educational levels compared with the general population. In contrast, siblings and parents of children who had had pneumococcal and *H. influenzae* meningitis attained similar levels of education as the general population. Altogether

these findings indicate that the lower level of education achieved among pneumococcal and *H. influenzae* meningitis patients is related to neurocognitive deficits induced by the meningitis episode.

Low birth weight and prematurity are well-established risk factors for adolescent learning difficulties[149-151] and have been shown to be associated with an increased risk of meningococcal disease in childhood.[152] Still, we found almost the same results after excluding individuals with low birth weight and prematurity from our analyses.

The risk of meningococcal disease in childhood is associated with unfavourable socioeconomic circumstances, and a clear dose-response effect with the number of cigarettes smoked at home and occurrence of meningococcal disease in children has been reported.[153;154] This socioeconomic pattern of meningococcal disease is consistent with our findings of lower levels of education among siblings and parents of meningococcal meningitis patients compared with the general population.[141]

Functioning after bacterial meningitis, viral meningitis or herpes simplex encephalitis in adults

In a Dutch study from 2002 on cognitive impairment in adults with good recovery after bacterial meningitis, neuropsychological evaluation was performed at 6-24 months after discharge.[27] The study subjects were patients aged between 16-65 years who were expected to be able to resume their daily life as before the episode of *N. meningitidis* or *S. pneumoniae* meningitis. At the time of neuropsychological evaluation a cognitive disorder was diagnosed in 27% of pneumococcal meningitis patients, in 4% of meningococcal patients and in 4% of controls who were recruited from partners, siblings and close friends. The main cognitive impairment in meningitis patients was loss of cognitive speed.[27]

The findings in our study of decreased employment and increased need of disability pension five years after pneumococcal meningitis among patients 20 to 55 years of age compared with the general population are in accordance with the above described study findings and with our observations of lower levels of educational achievement and self-sufficiency among childhood survivors of pneumococcal meningitis.[27;141;155] This further indicates that these findings might be related to neurocognitive deficits induced by a pneumococcal meningitis episode.

Adjunctive treatment with dexamethasone is associated with a beneficial effect on neurological sequelae of bacterial meningitis (RR 0.64, 95% CI: 0.48-0.85) and has been routine therapy in patients with suspected meningitis since 2004.[44;156] We did not have data on adjunctive treatment with dexamethasone and therefore could not perform stratified analyses by receipt of

corticosteroids. However, only a small proportion of the patients with bacterial meningitis included in our last two studies may have received adjunctive treatment with dexamethasone because study inclusion was during the period 1977-2007 for children and 1980-2008 for adults with bacterial meningitis.

Increased incidences of meningococcal disease observed in areas of social deprivation are consistent with our data revealing 10% fewer employed meningococcal meningitis patients two years before their diagnosis than in the general population with no substantial change in this disparity five years after the diagnosis.[155;157] Supported by the Dutch investigations and our own findings on adult functioning after meningococcal meningitis in childhood, the observation indicates that possible long-term neurocognitive deficits induced by a meningococcal meningitis episode are mild.[27;141]

Viral meningitis is considered to have the lowest risk of neurological sequelae among the CNS infections we studied, however retrospective studies indicated that cognitive impairment may follow the acute course of viral meningitis.[158] A follow-up study on 24 patients with viral meningitis, where none had focal morphological lesions on brain magnetic resonance imagining or any foci in electroencephalography, revealed mild cognitive impairments by neuropsychological testing 25±12 months after the acute stage.[159] The patients performed worse in cognitive speed and visual memory compared with controls matched for age, sex and years of education. All patients except for two worked again in their former profession at follow-up. Likewise, a cohort study of 59 viral meningitis patients reported that learning and memory functions of the patients were affected, nevertheless none in that cohort had to retire as a consequence of the viral meningitis episode.[140] In line with these findings we found that viral meningitis had no substantial impact on employment or receipt of disability pension five years after diagnosis. The personal income for the patients who were employed after the viral meningitis episode was similar to that of the general population, which indicates that the working capacity of the working part of the patients did not decrease.[155]

Profound memory impairment, personality changes, aphasia, and epilepsy are well-described sequelae of herpes simplex encephalitis.[34-36] The patients with herpes simplex encephalitis in our study were included during the period 1994-2008. The calendar periods are of particular relevance because the prognosis for herpes simplex encephalitis patients was dramatically improved by the introduction of antiviral treatment with aciclovir in the 1980s. Untreated, the case fatality rate among these patients exceeded 70% and the majority of survivors presented with severe neurological sequelae.[160] Aciclovir decreased the case fatality rate to 10-20%, with 27% of aciclovir-treated survivors reported to have no neuropsychological impairment, 59% to have mild, and 14% to have moderate to severe neuropsychological impairment after an average of three years of follow-up.[33] These reports on - however still severe - sequelae are in line with our findings of lower employment, lower personal income and increased receipt of disability pension in herpes

simplex encephalitis patients five years after discharge compared with the general population. In conclusion the impact of CNS infections on employment and on the need for disability pension appeared substantial in survivors of pneumococcal meningitis and herpes simplex encephalitis, but not for meningococcal or viral meningitis patients.[155]

It is important to underline that we conducted matched historic cohort studies from which causal relationship cannot be concluded. The associations revealed in such observational studies are more likely to reflect causality if sources of bias in terms of selection bias, information bias and confounding have been carefully considered and accounted for. Furthermore, a causal criterion is temporality; there must be agreement in time between exposure and outcome.[118]

Limitations

We relied on register-based discharge diagnoses given by attending physicians over a 30 year period. These diagnoses may be inaccurate and thereby have introduced selection bias in our studies. However, the registration of meningococcal meningitis in the Danish National Patient Register has been shown to be highly sensitive and specific,[24;161] making it reasonable to assume similarly high sensitivities and specificities for the other CNS infections.

There is likewise a risk of information bias in our studies relying on register-based data on causes of death, educational achievement and employment. However this information was obtained from the same data sources for the whole study population and therefore any misclassification would be non-differential.[118]

Due to the nature of our study with an inclusion period of 30 years and inclusion of patients with CNS infections diagnosed at all hospitals in Denmark, we did not have access to clinical and laboratory data or CNS imaging results obtained during the hospitalizations. Therefore we were not able to control for known predictors of unfavourable outcomes in terms of low Glasgow coma scale score and focal neurological deficits on admission, low cerebrospinal fluid leucocyte counts or intracranial and systemic complications.[1;162] In Denmark the currently recommended antibiotic treatment for suspected bacterial meningitis is combined treatment with ceftriaxone and ampicillin or penicillin combined with dexamethasone.[163] Data on time of initiation of antibiotic treatment - given prior to admission or with a potential delay - would have been extremely valuable.

We were not able to control for confounding from smoking including passive smoking or alcohol consumption.

Our findings on long-term mortality and functioning in adult life after bacterial meningitis in childhood are specific for a developed country. Children in developing countries are much more

vulnerable to neurological sequelae because of insufficient medical resources. A mere hearing loss can be devastating for a child living in a resource-limited setting with a low chance of proper education.

Reflections on reducing the burden of CNS infections

In the 20th century the advances in treatment and prevention of CNS infections were huge. From an invariably fatal disease, bacterial meningitis became a treatable condition with the discovery of antisera and antibiotics.[164;165] Vaccines against tuberculosis, polio, measles, tetanus, rabies and Japanese encephalitis were developed and widely distributed. Had it not been for human conflicts, vaccination would probably have eradicated polio by now.[166] The incidence of malaria has decreased profoundly worldwide. The discovery of antiretroviral drugs prevented millions of people living with HIV from falling sick from neuroinfections. Antiviral treatment with aciclovir changed the prognosis of the rare but devastating condition of herpes simplex encephalitis. In the developed world, general vaccination against Hib virtually brought about elimination of what was once the most common cause of childhood bacterial meningitis. A similar control of the now most prevalent bacterial aetiology of meningitis in children – *S. pneumoniae* meningitis - with the polyvalent pneumococcal conjugate vaccine is in progress. However, even with a strengthened vaccination policy in patients with comorbid conditions, vaccinations cannot stand alone as a preventive effort against invasive bacterial disease in a world with an alarming increase in the incidence of non-communicable diseases and emergence of multidrug-resistant bacteria. Non-communicable diseases predispose to infections. Thus a continuous awareness of the need of diminishing risks to health such as cigarette smoking, harmful alcohol use and physical inactivity is of utmost importance.[17;20;129;131;167-176]

Summary

The overall purpose was to explore the long-term prognosis after some of the most common CNS infections in Denmark, a developed country. The specific aims were to study long-term mortality after community-acquired bacterial meningitis, due to *Neisseria meningitidis, Streptococcus pneumoniae, Listeria monocytogenes* and *Haemophilus influenzae*. Furthermore, the objectives were to study educational achievement and economic self-sufficiency in adult life after bacterial meningitis in childhood and likewise employment and receipt of disability pension after bacterial meningitis, viral meningitis or herpes simplex encephalitis in adults. The hypothesis was that long-term mortality and morbidity after CNS infection would likely be associated with both underlying predisposing conditions and neurological sequelae of the disease.

The studies were population-based cohort studies and carried out by linking national registries. All Danish patients diagnosed with the above mentioned CNS infections from 1977 through 2007 and alive one year after diagnosis were identified from the Danish National Patient Register. Comparison cohorts from the same population individually matched on age and sex, and alive at study inclusion, were identified, as were siblings and parents of all study participants. Data on vital status, morbidity, cause of death, and socio-economic status were retrieved from the Danish Civil Registration System, the Danish National Patient Register, the Danish Medical Birth Registry, the Danish Cancer Registry, the Danish Register of Causes of Death, the Attainment Register, the Personal Income Statistics and the Employment Classification Module. Kaplan-Meier analyses were used to construct survival curves and Cox and Poisson regression analyses to estimate mortality rate ratios. Cumulative incidence function was used to estimate risks of specific causes of death, educational achievement and economic self-sufficiency taking into account competing risks.

A substantially increased long-term mortality was observed up to 30 years after patients were diagnosed with pneumococcal meningitis and up to five years after a diagnosis of listeria meningitis. By contrast, only a small life-long increased risk of death was found among meningococcal meningitis patients, mainly from death due to nervous system diseases. No increased long-term mortality was revealed in children with *H. influenzae* meningitis. In the pneumococcal meningitis patients the increased risk of death stemmed from both nervous system diseases and from predisposing chronic diseases. Predisposing malignancy appeared to be the main factor responsible for the increased long-term mortality after listeria meningitis. These findings are in accordance with pneumococcal and listeria meningitis known to be associated with chronic diseases whereas meningococcal meningitis mainly affects healthy individuals and less often causes severe sequelae.

Lower levels of educational achievement and self-sufficiency among childhood survivors of pneumococcal meningitis, as well as decreased employment and increased need of disability pension after pneumococcal meningitis in adults were observed compared with the general population. These findings might be related to long-term neurocognitive deficits induced by the pneumococcal meningitis episode. The association of lower educational achievement after meningococcal meningitis in childhood appeared to be family-related as both siblings and parents of meningococcal meningitis patients presented lower educational levels compared with the general population. Furthermore, no substantial impact of meningococcal meningitis or viral meningitis on employment or need for disability pension was observed. In contrast, profound memory impairment, personality change, aphasia and epilepsy are well-described sequelae of herpes simplex encephalitis and this disease was associated with substantially decreased employment and increased need of disability pension.

Dansk resumé (summary in Danish)

Det overordnede mål med det foreliggende studie har været at bestemme langtidsprognosen efter nogle af de hyppigste optrædende CNS infektioner i Danmark. Det specifikke mål har været at bestemme langtidsmortaliteten efter samfundserhvervet bakteriel meningitis, forårsaget af *Neisseria meningitidis, Streptococcus pneumoniae, Listeria monocytogenes* og *Haemophilus influenzae*. Yderligere har det været målet at belyse uddannelsesniveau og grad af selvforsørgelse hos voksne efter bakteriel meningitis i bardommen. Analogt hermed er der hos voksne foretaget vurdering af beskæftigelsesgrad samt behov for førtidspension efter henholdsvis bakteriel meningitis, viral meningitis og herpes simplex encephalitis. Studiets hypotese har været, at såvel langtidsmortalitet som morbiditet efter CNS infektion er associeret dels med underliggende prædisponerende forhold og dels med neurologiske sequelae efter infektionen.

De populationsbaserede kohortestudier blev udført ved at sammenkøre data fra danske nationale registre. Alle danske patienter, som var diagnosticeret med ovennævnte CNS infektioner fra 1977 til 2007 og som var i live et år efter diagnosen, blev identificeret fra Landspatientregisteret. En kontrolpopulation matched på køn samt alder og vitalstatus på patientens diagnosedato blev identificeret fra CPR-registeret. Ligeledes blev såvel søskende som forældre til alle patienter samt kontrolpersoner identificeret fra CPR-registeret. Data vedrørende vitalstatus, morbiditet, dødsårsag og socioøkonomisk status blev udtrukket fra følgende registre: CPR-registeret, Landspatientregisteret, Det Danske Fødselsregister, Cancerregisteret, Dødsårsagsregisteret og Danmarks Statistiks socioøkonomiske registre. Til bestemmelse af overlevelsen anvendtes Kaplan-Meier overlevelseskurver, og til estimering af mortalitetsrateratioer som mål for relativ risiko for død blev Cox og Poisson regressionsanalyser benyttet. Kumuleret incidensfunktion blev anvendt til at estimere risiko for årsagsspecifik død, uddannelsesniveau samt selvforsørgelse, idet der blev taget højde for competing risks.

Hos patienter med pneumokokmeningitis påvistes en betydelig øget dødelighed i op til 30 år efter infektionen, og hos patienter med listeriameningitis var dødeligheden betydeligt øget i op til 5 år. I modsætning hertil, blev der kun fundet en mindre øget dødelighed hos patienter med meningokokmeningitis, hovedsageligt grundet død på grund af neurologiske sygdomme. Hos børn med *H. influenzae* meningitis påvistes ingen forøget langtidsmortalitet. Den øgede dødelighed hos patienterne med pneumokokmeningitis stammede fra såvel neurologiske sygdomme som fra prædisponerende kroniske sygdomme. Prædisponerende malign sygdom afslørede sig som hovedansvarlig for den forøgede langtidsmortalitet efter listeriameningitis. Disse fund er forenelige med, at pneumokokmeningitis og listeriameningitis er kendt for at være associerede med kroniske sygdomme, hvorimod meningokokmeningitis hovedsageligt rammer raske individer og mindre hyppigt forårsager svære sequelae.

Sammenlignet med baggrundsbefolkningen blev der hos voksne, som havde overlevet pneumokokmeningitis som børn, fundet lavere opnået uddannelsesniveau og lavere grad af selvforsørgelse. Ligeledes fandtes efter pneumokokmeningitis hos voksne såvel nedsat beskæftigelse som øget behov for førtidspension. Disse fund kunne være relaterede til kognitive deficit forårsaget af pneumokokmeningitisepisoden. Associationen mellem lavere opnået uddannelsesniveau som voksen og meningokokmeningitis pådraget i barndommen, fremstod derimod at være familierelateret. Det viste sig nemlig at både søskende og forældre til de af patienterne, der i barndommen havde haft meningokokmeningitis, begge havde lavere uddannelsesniveau sammenlignet med baggrundsbefolkningen. Endvidere syntes hverken meningokokmeningitis eller viral meningitis at påvirke beskæftigelsesgrad eller behov for førtidspension. Efter herpes simplex encephalitis ses hyppigt sequelae i form af svært hukommelsestab, personlighedsforandring, afasi og epilepsi, og netop denne neuroinfektion fandtes associeret med efterfølgende betydelig nedsat beskæftigelse og øget behov for førtidspension.

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Appendix

Infections of the central nervous system were identified using the following ICD-8 codes for the years 1977-1993:

- Meningococcal meningitis: code 036.09
- H. *influenzae* meningitis: code 320.09
- Pneumococcal meningitis: code 320.19
- Streptococcal meningitis: code 320.80
- Meningitis per organismos alios specificatos: code 320.89
- Listeria meningitis: code 027.01
- Meningococcal infection: code 036.00-036.99
- Aseptic meningitis due to enterovirus: codes 045.00-045.99
- Varicella meningitis/encephalitis: codes 052.01
- Zoster meningitis/encephalitis: code 053.02
- Herpesviral meningitis/encephalitis: code 054.03

Infections of the central nervous system were identified using the following ICD-10 codes for the years 1994-2007:

- Meningococcal meningitis: code A39.0
- *H. influenzae* meningitis: code G00.0
- Pneumococcal meningitis: code G00.1
- Streptococcal meningitis: code G00.2
- Staphylococcal meningitis: code G00.3
- Other bacterial meningitis: code G00.8
- Bacterial meningitis, unspecified: code G00.9
- Listeria meningitis and meningoencephalitis: code A32.1
- Meningococcal infection: codes A39.0-A39.9
- Unspecified viral encephalitis: code A86
- Enteroviral meningitis: code A87.0
- Adenoviral meningitis: code A87.1
- Lymphocytic choriomeningitis: code A87.2
- Other viral meningitis: code A87.8
- Viral meningitis, unspecified: code A87.9
- Herpesviral meningitis: code B00.3
- Herpesviral encephalitis: code B00.4
- Varicella meningitis: code B01.0
- Varicella encephalitis: code B01.1
- Zoster encephalitis: code B02.0
- Zoster meningitis: code B02.1
- Zoster with other nervous system involvement: code B02.2

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Long-Term Mortality in Patients Diagnosed with Meningococcal Disease: A Danish Nationwide Cohort Study

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Abstract

Background: In contrast to the case fatality rate of patients diagnosed with meningococcal disease (MD) the long-term mortality in these patients is poorly documented.

Methodology/Principal Findings: We performed a nationwide, population-based cohort study including all Danish patients diagnosed with MD from 1977 through 2006 and alive one year after diagnosis. Data was retrieved from the Danish National Hospital Register, the Danish Civil Registration System and the Danish Register of Causes of Death. For each patient four age- and gender-matched individuals were identified from the population cohort. The siblings of the MD patients and of the individuals from the population cohort were identified. We constructed Kaplan-Meier survival curves and used Cox regression analysis, cumulative incidence function and subdistribution hazard regression to estimate mortality rate ratios (MRR) and analyze causes of death. We identified 4,909 MD patients, 19,636 individuals from the population cohort, 8,126 siblings of MD patients and 31,140 siblings of the individuals from the population cohort. The overall MRR for MD patients was 1.27 (95% confidence interval (CI), 1.12–1.45), adjusted MRR, 1.21 (95% CI, 1.06–1.37). MD was associated with increased risk of death due to nervous system diseases (MRR 3.57 (95% CI, 1.82–7.00). No increased mortality due to infections, neoplasms or cardiovascular diseases was observed. The MRR for siblings of MD patients compared with siblings of the individuals from the population cohort was 1.17 (95% CI, 0.92–1.48).

Conclusions: Patients surviving the acute phase of MD have increased long-term mortality, but the excess risk of death is small and stems mainly from nervous system diseases.

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Introduction

The case-fatality rate of meningococcal disease (MD) is well documented and reported to be approximately 10% in the developed world and substantially higher in non-industrialized countries [1–3]. In contrast, long-term mortality in this patient population is poorly documented [4].

A recent study from Bristol indicated that the incidence of MD was increased in areas of social deprivation [5]. Therefore studies are needed, not only to establish whether MD patients suffer from increased long-term mortality, but also to address to what extent this potentially increased mortality could be explained by family related risk factors.

We performed a nationwide, population-based cohort study to determine whether patients surviving the first year after a MD diagnosis have increased mortality compared with an age- and gender-matched population cohort. Further, we determined the specific causes of death. As a measure of unaccounted for confounders, we estimated the mortality in siblings of MD patients compared with siblings of individuals from the population cohort.

Methods

Ethics Statement

The study was approved by the Danish Data Protection Agency. The data was deidentified and anonymised at source.

Setting

The population of Denmark on January 1, 2008, was 5.5 million inhabitants [6]. Over the last decades there has been a declining incidence rate of MD in Denmark (1987: 5.8/100,000, 1997: 4.5/100,000 and 2007: 1.4/100,000) [7,8].

Data Sources

We used the unique 10-digit Central Person Registration number (CPR number), assigned to all Danish citizens at birth or immigration to track individuals in the following registers and to avoid multiple registrations.

The Danish National Hospital Register was initiated in 1977 and contains information on all patients discharged from Danish

hospitals. Records for each inpatient admission include CPR number, hospital department, dates of admission and discharge diagnosis coded according to the International Classification of Diseases 8th (ICD-8) and 10th (ICD-10) revision [9]. From this register, we extracted date of MD diagnosis, along with data on inpatient admissions prior to MD diagnosis.

The Danish Civil Registration System was established in 1963 and contains demographic data and vital status of all Danish citizens [10]. We extracted data on birth, gender, date of immigration and emigration, loss to follow-up, date of death and identity of siblings.

The Danish Register of Causes of Death contains information from all Danish death certificates since 1943 and is complete through 2006. Causes of death are coded according to ICD-8 and ICD-10, and registered as primary (immediate cause of death), secondary or tertiary cause of death [11]. From this register we extracted specific causes of death as recorded as the primary cause of death.

Study Population

MD patients: From the Danish National Hospital Register, we identified all patients who were registered during the period January 1, 1977, to December 31, 2006, for the first time with a diagnosis of MD, ICD-8 codes: 036.09–036.99 and ICD-10 codes: A39.0–A39.9. Patients were excluded in case they died, emigrated or were lost to follow-up within the first year after the diagnosis of MD, and in case they were diagnosed with other neuroinfections (as specified in Appendixes S1) prior to MD, did not live in Denmark at the date of the MD diagnosis or were born outside Denmark. The index date of these individuals was defined as one year after the date of first MD diagnosis.

Population cohort: From the Danish Civil Registration System we identified four individuals for each MD patient matched on gender and date of birth, all of whom were born in Denmark, alive and living in Denmark at the index date of the corresponding MD patient.

Cohort of siblings: From the Danish Civil Registration System, we identified all registered full and half-siblings for both MD patients and individuals from the population cohort. Siblings born before January 1, 1952 were excluded in order to reduce selection bias, as only a small fraction of individuals born before 1952 had siblings registered in the Danish Civil Registration System, but thereafter the registration is more than 98% complete [12].

Outcome

The primary study outcome was time from index date to death. The secondary outcome was time from index date to date of specific cause of death. The specific causes of death were categorized by ICD codes as listed in Appendixes S1.

Statistical Analysis

Time was calculated from index date to date of death, emigration, loss to follow-up or January 1, 2008, which ever came first. In the analyses of cause specific mortality time was censored at January 1, 2007, as the Danish Register of Causes of Death was complete through 2006. Kaplan-Meier analyses were used to construct survival curves. Cox regression analyses were used to estimate mortality rate ratios (MRR) adjusted for calendar periods and for inpatient admission in the period of two years prior to the date of MD diagnosis. Calendar periods for the date of MD diagnosis were introduced as design variables grouped in the three time periods 1977–1986, 1987–1996, and 1997–2006. We adjusted for inpatient admissions during the two years prior to the date of MD diagnosis using (a) the total number of inpatient days as a continous variable and (b) a series of 18 indicator variables for the primary discharge diagnoses, as listed in Appendixes S1.

We assessed the proportional hazards assumption with plots and tests that were based on smoothed scaled Schoenfeld residuals and cumulative residuals. We stratified calculations of overall mortality by gender, age at diagnosis (0-<15, 15-<30, 30-<60 and 60 years or older) and type of MD (meningococcal meningitis or acute meningococcemia as primary diagnosis). We further calculated MRRs for the first 15 years after index date and for the period 16–30 years after the index date. A sub-analysis calculating the MRRs was performed, in which patients diagnosed with nervous system or genitourinary diseases in the first year after the MD diagnosis were excluded.

In a robustness analysis, using a Cox regression model, adjusted for age and gender we included only patients who had not been admitted to hospital in the period of two years prior to the date of MD diagnosis.

We computed the cumulative incidence of specific causes of death, taking into account that these were competing risks and used competing risks regression to estimate cumulative incidence of specific causes of death [13,14].

We assessed the long-term mortality of the siblings in accordance with a previous study [12]. For siblings, time was calculated from one year of age of the sibling (to exclude peri- and postnatal mortality) or index date of the corresponding study participant, which ever came last, until date of death, emigration, loss to follow-up or January 1, 2008. MRR was calculated for siblings of MD patients compared with siblings of individuals from the population cohort and adjusted for calendar periods (design variable), age (design variable grouped in the age-intervals 1-<15, 15-<30, 30-<60 and 60 years or older at index date) and gender. As only siblings born after January 1, 1952 were included in these analyses, we calculated the MRR for MD patients compared with individuals from the population cohort born after January 1, 1952 for comparison. SPSS version 15.0 (SPSS Inc., Chicago, Il, USA) and R software, version 2.8.1 were used for data analysis.

Results

Baseline Characteristics

We identified 5,356 patients diagnosed with MD in the period 1977–2006. Within the first year of diagnosis of MD, 445 (8.3%) patients died, one emigrated and one was lost to follow-up leaving a total of 4,909 patients and 19,636 individuals from the population cohort in the study. 62% of the patients included in the study were diagnosed before they were 15 years of age. During the period of two years preceding the date of MD diagnosis the MD patients had a significantly higher admission rate for e.g. infectious diseases, neoplasms and nervous system diseases (Table 1).

8,126 siblings (5,338 full siblings (65.7%)) of MD patients and 31,140 siblings (22,181 full siblings (71.2%)) of individuals from the population cohort were available for analysis. The median age of the siblings of MD patients at index date was 8.9 years (IQR 0.6–16.9) and 8.7 years (IQR 1.3–16.9) in the siblings of the individuals from the population cohort. 4,239 (52.2%) of the siblings of the MD patients were males compared to 16,079 (51.6%) of the siblings of the individuals from the population cohort.

All-Cause Mortality

312 (6.4%) MD patients and 985 (5.0%) individuals from the population cohort died in the observation period (Table 2). Figure 1 presents Kaplan-Meier survival curves for MD patients and

Table 1. Characteristics of meningococcal disease (MD) patients and individuals from the population cohort.

	Patients with MD*	Individuals from the population cohort*	P-value
Number of study participants	4,909	19,636	
Males	2,661 (54.2)	10,644 (54.2)	
Age, median (years, IQR)	8.9 (2.3–17.8)	8.9 (2.3–17.8)	
Age at MD diagnosis			
0–14 years	3,070 (62.5)	12,280 (62.5)	
15–29 years	1,106 (22.5)	4,424 (22.5)	
30–59 years	473 (9.6)	1,892 (9.6)	
60+ years	260 (5.3)	1,040 (5.3)	
Primary diagnosis			
Meningococcal meningitis	3,297 (67.2)		
Acute meningococcaemia	1,211 (24.7)		
Chronic meningococcaemia	23 (0.5)		
Waterhouse Friderichsen syndrome	11 (0.2)		
Other specified conditions	367 (7.5)		
Calender period at MD diagnosis			
1977–1986	1,513 (30.8)	6,052 (30.8)	
1987–1996	2,089 (42.6)	8,356 (42.6)	
1997–2006	1,307 (26.6)	5,228 (26.6)	
Observation time (years)	73,058	293,585	
Emigration during study period	114 (2.3)	538 (2.7)	
Lost to follow-up during study period	2 (0.04)	5 (0.03)	
Number of study subjects with inpatient admission in the period of two years prior to the date of MD diagnosis	1,753 (35.7)	6,462 (32.9)	<0.001
Patients admitted with the following diagnosis-categories in the period of two years prior to the date of MD diagnosis			
Infectious diseases	109 (2.2)	242 (1.2)	<0.001
Neoplasms	34 (0.7)	90 (0.5)	0.04
Blood/immune diseases	11 (0.2)	22 (0.1)	0.06
Endocrine diseases	27 (0.6)	78 (0.4)	0.14
Mental disease/drug abuse	19 (0.4)	46 (0.2)	0.06
Nervous system diseases	36 (0.7)	74 (0.4)	0.001
Diseases of the sensory organs	56 (1.1)	182 (0.9)	0.17
Cardiovascular diseases	33 (0.7)	104 (0.5)	0.23
Respiratory diseases	215 (4.4)	677 (3.4)	0.002
Digestive system diseases	99 (2.0)	304 (1.5)	0.02
Skin diseases	29 (0.6)	67 (0.3)	0.01
Rheumatological diseases	51 (1.0)	126 (0.6)	0.003
Genitourinary diseases	51 (1.0)	199 (1.0)	0.87
Neonatal and congenital diseases.	158 (3.2)	397 (2.0)	<0.001
Pregnancy related diseases	29 (0.6)	155 (0.8)	0.15
Injury, poisoning and external causes of morbidity	158 (3.2)	475 (2.4)	0.002
Abnormal findings not classified otherwise	153 (3.1)	388 (2.0)	<0.001
Contacts with health services not classified above	1,049 (21.4)	4,267 (21.7)	0.58

*If not stated otherwise data is number and percentage of MD patients or individuals from the population cohort.

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corresponding individuals from the population cohort. The MRR for patients with MD was 1.27 (95% CI, 1.12–1.45), adjusted MRR 1.21 (95% CI, 1.06–1.37) (Table 2). MD patients were at increased risk of death throughout the study period and we saw no major difference in MRR between genders (Figure 1 and Table 2). The impact of MD on long-term mortality was seen in all age groups, but was only statistically significant in those diagnosed with MD after 30 years of age. In a sub-analysis in which only patients and individuals from the population cohort with no inpatient admissions in the period of two years prior to the date of MD diagnosis were included, the MRR was 1.20 (95% CI, 1.03–1.40), adjusted MRR 1.28 (95% CI, 1.10–1.49). In a sub-analysis in which patients diagnosed with

Table 2. Mortality rate ratios (MRR) for MD patients compared to individuals from the population cohort.

Characteristics	Unadjusted MRR (95% CI)	Adjusted* MRR (95% CI)	MD patients who died during the study period, N	Individuals from the population cohort who died during the study period, N
Meningococcal disease (MD), all types	1.27 (1.12–1.45)	1.21 (1.06–1.37)	312	985
Gender				
Female	1.28 (1.09–1.52)	1.22 (1.03–1.44)	180	564
Male	1.26 (1.04–1.53)	1.19 (0.98–1.45)	132	421
Age of patient at MD diagnosis				
0-<15 years	1.52 (0.97–2.36)	1.38 (0.88–2.16)	27	71
15-<30 years	1.24 (0.75–2.04)	1.29 (0.78–2.14)	20	65
30-<60 years	1.48 (1.17–1.88)	1.35 (1.06–1.73)	92	260
60 years or older	1.28 (1.08–1.52)	1.22 (1.02–1.45)	173	589
Type of MD				
1 Meningococcal meningitis	1.30 (1.13–1.52)	1.31 (1.13–1.52)	229	706
2 Acute meningococcaemia	1.19 (0.89–1.59)	1.11 (0.82–1.50)	58	195
Time period after MD diagnosis				
1-<16 years	1.29 (1.12–1.50)	1.28 (1.09–1.50)	242	752
16–30 years	1.27 (1.12–1.45)	1.20 (0.97–1.67)	70	233

*Adjusted for calendar periods and for inpatient admission prior to MD.

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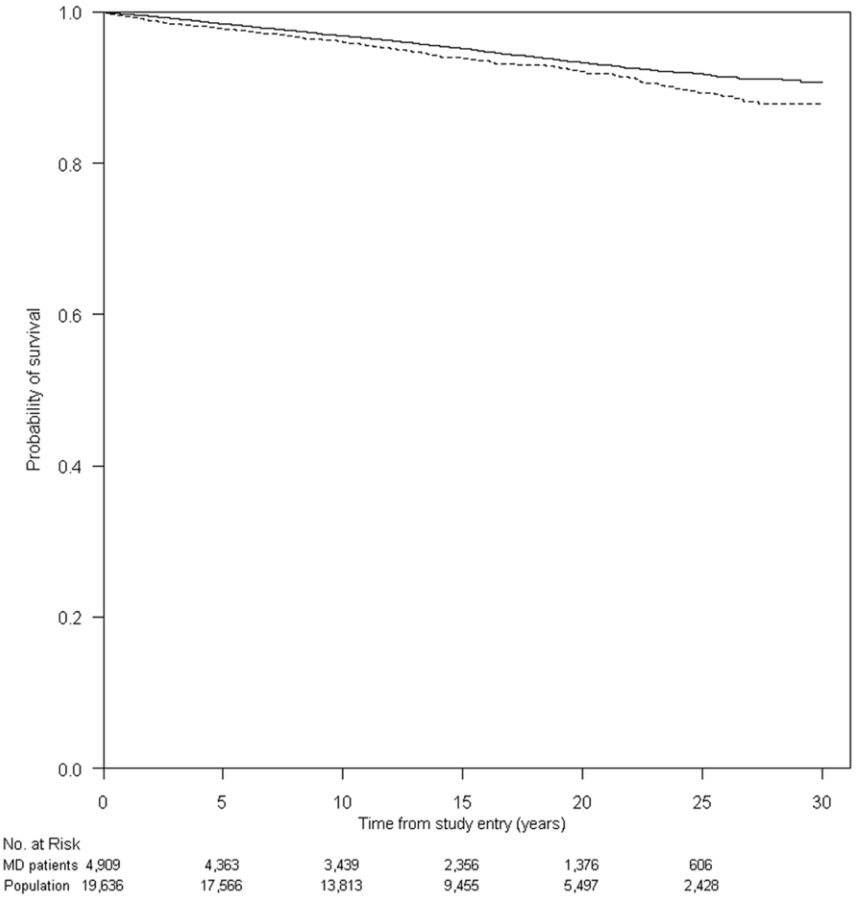

Figure 1. Kaplan-Meier survival curves of patients with meningococcal disease (MD) (dotted line) and individuals from the population cohort (full line).

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nervous system or genitourinary diseases in the first year after the MD diagnosis were excluded the MRR was 1.21 (95% CI, 1.06–1.39) adjusted MRR 1.16 (95% CI, 1.01–1.34).

The MRR for siblings of MD patients compared with siblings of the individuals from the population cohort was 1.17 (95% CI, 0.92–1.48), adjusted MRR 1.15 (95% CI, 0.90–1.46). In a sub-analysis including only full siblings we found a MRR of 1.14 (95% CI, 0.83–1.55), adjusted MRR 1.11 (95% CI, 0.81–1.51). Of interest, one sibling of an individual from the population cohort died from MD compared to none of the siblings of the MD patients (data not shown). For comparison we did an analysis in which we only included MD patients and individuals from the population cohort born after January 1, 1952, and found a MRR for the MD patients of 1.51 (95% CI, 1.11–2.07), adjusted MRR 1.44 (95% CI, 1.06–1.97).

Cause Specific Mortality

MD was associated with a statistically significant increased risk of death due to nervous system, genitourinary and digestive system diseases (Table 3 and Figure 2). An analysis of the individual causes of death due to nervous system and genitourinary diseases did not reveal any particular pattern (data not shown). The increased risk of death due to digestive system diseases was exclusively seen in patients diagnosed with MD after 30 years of age (data not shown). Further 8 of the 20 patients who died from digestive system diseases were diagnosed with alcohol abuse (Appendixes S1) at or before death compared with 9 of the 38 patients in the control group.

MD patients were not at increased risk of death due to infections, neoplasms or cardiovascular diseases (Table 3 and Figure 2).

Discussion

In this nationwide, population-based cohort study we found a slightly increased long-term mortality up to 30 years after patients were diagnosed with MD. The MD patients had increased risk of death due to nervous system, genitourinary and digestive system diseases of which the latter was associated with a diagnosis of alcohol abuse. We presume that the small excess mortality mainly stems from long-term sequelae and confounding.

The major strengths of the present study are its large sample size, the population-based design and the extensive and complete follow-up. The unique Danish Civil Registration System enabled us to identify a large control cohort of individuals well matched in terms of gender, age, and country of birth. Through the Danish national registers we had access to complete data on date of death, comorbidity, and causes of death and importantly, this data was obtained from the same data sources for both cohorts. The registers further allowed us to track all siblings of the study subjects.

Considering the limitations of the study we relied on register-based discharge diagnoses. Thereby the study population comprised MD patients irrespective of whether the diagnosis was confirmed by microbiological tests or exclusively based on clinical criteria. Although discharge diagnoses in general may not be entirely accurate, the registration of MD in the Danish National Hospital Register has been shown to be substantially valid [8,15,16]. Pre-hospital antibiotic treatment is mainly administered to the most severe MD cases [17], and may lead to decreased sensitivity of the microbiological tests performed after hospitalization. Thus, inclusion of only bacteriologically verified cases would most likely have biased the estimates of long-term mortality by exclusion of the most severe MD cases. Also, from the patient's point of view, the main interest is the long-term prognosis according to the discharge diagnosis. We therefore believe that our study, not only adds to the understanding of the medical aspects of MD, but also is of considerable relevance to the patients, who are diagnosed with MD and have a natural interest in knowing their long-term prognosis.

Table 3. Mortality rate ratios (MRR) for cause specific death in MD patients compared to individuals from the population cohort.

Causes of death*	Unadjusted MRR(95% CI)	Adjusted** MRR(95% CI)	Number of MD patients who died from the specific causes of death during the study period***	Number of individuals from the population cohort who died from the specific causes of death during the study period***
Infectious diseases	1.61(0.50–5.12)	1.67(0.52–5.35)	4	10
Neoplasms	1.04(0.79–1.38)	1.00(0.75–1.33)	61	235
Blood/Immune diseases	0.80(0.09–6.87)	0.53(0.06–5.07)	1	5
Endocrine diseases	1.57(0.73–3.40)	1.53(0.70–3.37)	9	23
Mental disease/drug abuse	1.13(0.54–2.37)	1.00(0.47–2.14)	9	32
Nervous system diseases	3.57(1.82–7.00)	3.15(1.59–6.23)	16	18
Cardiovascular diseases	1.09(0.85–1.38)	1.00(0.78–1.28)	84	311
Respiratory diseases	1.15(0.74–1.77)	1.09(0.70–1.70)	26	91
Digestive system diseases	2.06(1.20–3.53)	1.99(1.16–3.43)	20	39
Rheumatological diseases	2.41(0.58–10.09)	1.79(0.36–9.03)	3	5
Genitourinary diseases	5.02(1.35–18.70)	6.26(1.58–24.81)	5	4
Neonatal and congenital diseases	1.61(0.50–5.12)	1.12(0.34–3.70)	4	10
Injury and poisoning	1.32(0.86–2.03)	1.30(0.85–2.01)	28	85
Ill-defined causes	1.63(0.93–2.86)	1.65(0.94–2.90)	17	42
Unknown cause of death	0.62(0.14–2.74)	0.65(0.15–2.87)	2	13

*No causes of death due to diseases of the sensory organs, skin diseases or pregnancy related diseases were observed in the study population.

**Adjusted for calendar periods and for inpatient admission prior to MD.

***The Danish Register of Causes of Death was complete through 2006. In 2007, 23 MD patients and 62 individuals from the population cohort died and these deaths were not included in the analysis of causes of death.

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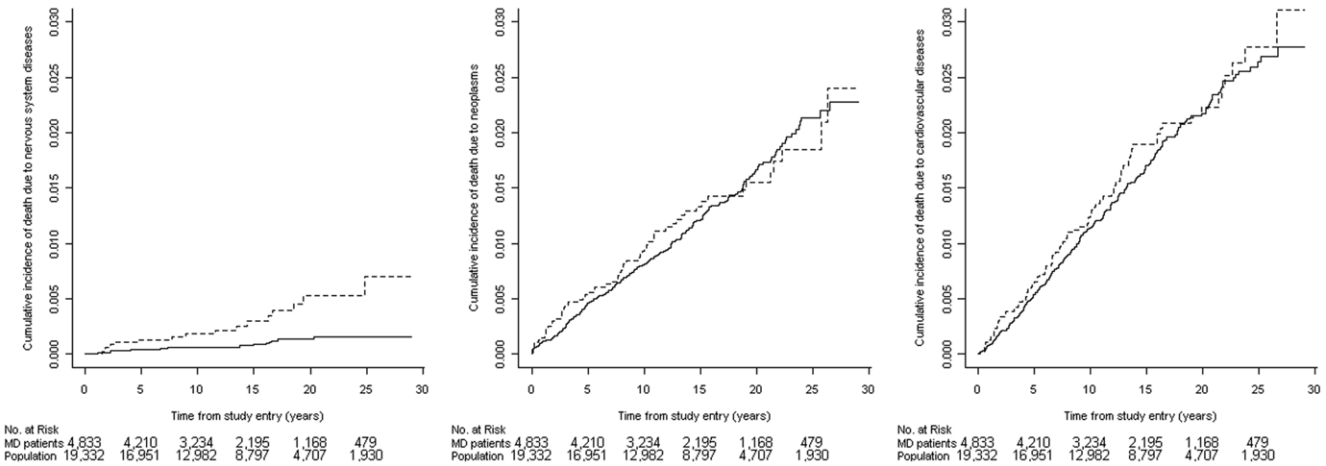

Figure 2. Cumulative incidences of death due to nervous system diseases, neoplasms and cardiovascular diseases for MD patients (dotted line) and individuals from the population cohort (full line). As the Danish Register of Causes of Death was only complete through 2006, patients with an index date in 2007 were not included in these analyses.
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Due to the nature of our study with an inclusion period of 30 years and inclusion of MD patients diagnosed at all hospitals in Denmark, we did not have access to clinical and paraclinical data obtained during the hospitalizations. Our data thereby does not allow identification of clinical predictors of long-term mortality or information on neurologic sequelae in the MD patients. Also, we were not able to control for confounding from smoking including passive smoking, alcohol consumption, educational level, socio-economic status or crowding.

Cases of MD are often categorized into septicaemia (approximately 30% in outbreaks), meningitis (10%) and mixed disease (60%) [18]. The Danish National Hospital Register allows one primary diagnosis and patients diagnosed with mixed MD are primarily registered as meningococcal meningitis. In accordance with this practice, we observed a somewhat higher proportion of patients registered primarily with meningitis (67%).

We observed a slightly increased long-term mortality in the MD patients in all age groups. To our knowledge only one previous study has examined the long-term mortality in MD patients [4]. The authors found an increased risk of death during the first four years following diagnosis of bacterial meningitis, whereas the risk of death declined to that of the background population from the fifth year of discharge. The study, however, only included 356 MD patients, had substantially shorter follow-up and pre-existing comorbidity was not accounted for.

We find it unlikely that comorbidity diagnosed prior to MD explains our findings, as the analysis, which only included patients not hospitalized prior to their MD diagnosis demonstrated essentially the same increased mortality as found for the complete MD study population. We were however only able to adjust for comorbidity in case it led to hospitalization and these analyses are probably hampered by unmeasured and residual confounding.

We observed an increased risk of death due to nervous system diseases, which is probably a consequence of the neurologic sequelae known to occur after MD [7], though the pre-existing higher admission rate for nervous system diseases before the diagnosis of MD may also have lead to increased risk of neurologic death. Nervous system diseases are known to lead to urological complications and we presume, that the increased risk of death due to genitourinary diseases could be related to this phenomenon, or to persistent kidney damage after MD sepsis-associated acute renal failure [19]. Exclusion of the patients diagnosed with nervous system or genitourinary diseases in the first year after the MD diagnosis reduced the estimated MRR, which further indicates that the increased mortality in the MD patients partly stems from sequelae in these organ systems. Several of the patients, who died from digestive system diseases, were diagnosed with alcohol abuse. Whether this was due to an increased risk of MD in alcoholics or an increased risk of alcohol abuse after MD could not be established in the actual study.

Some inherited immune deficiencies predispose to MD, but the prevalence of these conditions among patients with MD is low [1,20]. Likewise we did not observe any increased risk of death due to infections in the MD population. However, not all infections cause death and the fact that the MD patients had more inpatient admission for infectious diseases in the two years prior to the diagnosis of MD than the population cohort keeps the possibility of a specific immune defect open.

A point of interest revealed in our study was a trend towards a slightly increased long-term mortality in siblings of MD patients, although these associations were not statistically significant. Factors other than the pathogenicity of the MD infection per se likely contribute to the increased long-term mortality in MD patients. In the present study we could not determine whether these factors are of a genetic or environmental nature.

We conclude that patients diagnosed with MD have an increased long-term mortality, but the excess mortality is small. The MD population has no increased risk of death due to infections, neoplasms or cardiovascular diseases, but suffers from increased mortality mainly due to nervous system diseases. With the actual findings, patients treated for meningococcal disease can be reassured that their long-term mortality differs only slightly from that of the general population.

Supporting Information

Appendixes S1
Found at: doi:10.1371/journal.pone.0009662.s001 (0.02 MB DOC)

Author Contributions

Conceived and designed the experiments: CR LHO FNE PS NO. Performed the experiments: CR LHO FNE PS NO. Analyzed the data:

CR LHO FNE PS NO. Contributed reagents/materials/analysis tools: CR LHO FNE PS NO. Wrote the paper: CR LHO FNE PS NO.

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Original Contribution

Long-Term Mortality in Patients Diagnosed With Pneumococcal Meningitis: A Danish Nationwide Cohort Study

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The objective of the study was to determine the long-term mortality and the causes of death in patients diagnosed with pneumococcal meningitis. The authors performed a nationwide, population-based cohort study including all Danish patients diagnosed with pneumococcal meningitis from 1977 through 2006 and alive 1 year after diagnosis. Data were retrieved from medical databases in Denmark. The absolute and relative risks of all-cause and cause-specific death were analyzed by using Kaplan-Meier survival curves, Poisson regression analysis, Cox regression analysis, and cumulative incidence functions. The authors identified 2,131 pneumococcal meningitis patients and an age- and gender-matched, population-based cohort of 8,524 individuals. Compared with the background population, the pneumococcal meningitis patients had an increased long-term mortality varying from an 8-fold increased mortality in the age category 0–<20 years to a 1.5-fold increased mortality in those aged 60–<80 years. The increased risk of death stemmed from neoplasms, liver diseases, and nervous system diseases. The excess mortality due to neoplasms stemmed mainly from a 5-fold increased risk of death due to hematologic neoplasms. To improve survival in patients surviving the acute phase of pneumococcal meningitis, physicians should meticulously screen this patient population for neurologic sequelae and comorbidity predisposing to the disease.

cause of death; cohort studies; meningitis, pneumococcal; mortality; multiple myeloma

Abbreviations: CI, confidence interval; ICD, *International Classification of Diseases*.

Streptococcus pneumoniae and *Neisseria meningitidis* are the main infectious agents causing bacterial meningitis in Western countries (1). Currently, almost half of the cases of community-acquired bacterial meningitis in Denmark are caused by *S. pneumoniae* (2). The main risk factors for pneumococcal meningitis are age (<2 years and >65 years), immunodeficiencies, chronic illnesses, neoplasms, smoking, and alcohol abuse (3–5). Despite antibiotic therapy, adjunctive dexamethasone treatment, and modern intensive care facilities, the case fatality rate of acute pneumococcal meningitis in adults remains high (14%–30%) (6–9), and several studies have reported high rates of neurologic sequelae in adult survivors (30%–41%) (8, 9).

The long-term mortality in patients surviving pneumococcal meningitis is poorly documented and described in only 1 previous study (10). In this study that included 162 pneumococcal meningitis patients, an increased risk of death during the first 4 years following diagnosis of bacterial meningitis was found, whereas the risk of death declined to that of the background population from the fifth year of discharge.

We performed a nationwide cohort study to determine whether patients surviving the first year after pneumococcal meningitis have increased mortality compared with an age- and gender-matched population control cohort and if these patients were at increased risk of any specific causes of death.

MATERIALS AND METHODS

Setting

The population of Denmark on January 1, 2008, was 5.5 million inhabitants (11). In 2007, the incidence rate of

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Table 1. Characteristics of Pneumococcal Meningitis Patients and Population Controls, Denmark, 1977–2006

	Patients[a]			Population Controls[a]			*P* Value
	No.	%	Median (Interquartile Range)	No.	%	Median (Interquartile Range)	
Study participants	2,131			8,524			
Males	1,140	53.5		4,560	53.5		
Age, years, at diagnosis of pneumococcal meningitis[b]			44.3 (2.8–62.8)			44.3 (2.8–62.8)	
Age at diagnosis of pneumococcal meningitis[b]							
0–<20 years	717	35.6		3,028	35.6		
20–<40 years	233	10.9		932	10.9		
40–<60 years	508	23.8		2,032	23.8		
60–<80 years	561	26.3		2,244	26.3		
≥80 years	72	3.3		288	3.3		
Calendar period at diagnosis of pneumococcal meningitis[b]							
1977–1986	641	30.1		2,564	30.1		
1987–1996	737	34.6		2,948	34.6		
1997–2006	753	35.3		3,012	35.3		
Observation time, years	24,563			105,620			
Emigration during study period	16	0.8		112	1.3		
Lost to follow-up during study period	1			2			
Study subjects with inpatient admission in the period 2 years prior to the date of pneumococcal meningitis diagnosis[b]	916	43.0		3.086	36.2		<0.001
Patients admitted with the following diagnostic categories in the period 2 years prior to the date of pneumococcal meningitis diagnosis							
Infectious diseases	39	1.8		80	0.9		<0.001
Neoplasms[c]	137	6.4		326	3.8		<0.001
Blood/immune diseases	22	1.0		16	0.2		<0.001
Endocrine diseases	28	1.3		68	0.8		0.024

Table continues

pneumococcal meningitis in Denmark was 1.9/100,000 (12). Throughout the study period, tax-paid health care has been provided and free of charge to all Danish citizens.

Data sources

We used the unique 10-digit Central Person Registration number assigned to all Danish citizens at birth or immigration to avoid multiple registrations and to track individuals in the following registers.

The Danish National Hospital Register was initiated in 1977 and contains information on all patients discharged from Danish nonpsychiatric hospitals. The records for each inpatient admission include the Central Person Registration number, hospital department, dates of admission, and discharge diagnosis as coded by the attending physician according to the *International Classification of Diseases* (ICD), Eighth Revision, until the end of 1993 and the ICD, Tenth Revision, thereafter. Discharge diagnoses are classified as 1 primary and up to 19 secondary discharge diagnoses (13). From this register, we extracted the date of pneumococcal meningitis diagnosis, along with data on inpatient admissions prior to the diagnosis of pneumococcal meningitis.

The Danish Civil Registration System is a national register established in 1967 that contains the demographic data and vital status of all Danish citizens (14). From this register, we extracted data on birth, gender, date of immigration and emigration, loss to follow-up, and date of death.

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Table 1. Continued

	Patients[a]			Population Controls[a]			*P* Value
	No.	%	Median (Interquartile Range)	No.	%	Median (Interquartile Range)	
Mental disease/drug abuse	6	0.3		28	0.3		0.73
Nervous system diseases	32	1.5		39	0.5		<0.001
Diseases of the sensory organs	44	2.1		66	0.8		<0.001
Cardiovascular diseases	62	2.9		230	2.7		0.59
Respiratory diseases	82	3.8		178	2.1		<0.001
Digestive system diseases	70	3.3		197	2.3		0.01
Skin diseases	11	0.5		32	0.4		0.36
Rheumatologic diseases	53	2.5		124	1.5		0.001
Genitourinary diseases	34	1.6		142	1.7		0.82
Neonatal and congenital diseases	59	2.8		143	1.7		0.001
Pregnancy-related diseases	22	1.0		77	0.9		0.58
Injury, poisoning, and external causes of morbidity	98	4.6		212	2.5		<0.001
Abnormal findings not classified otherwise	63	3.0		165	1.9		0.004
Contacts with health services not classified above	484	22.7		1,928	22.6		0.93

[a] If not stated otherwise, data are the number and percentage of pneumococcal meningitis patients or population controls.
[b] For population controls at the matching date (date of meningitis diagnosis in the corresponding pneumococcal meningitis patient).
[c] Admitted with a cancer diagnosis prior to the pneumococcal meningitis diagnosis.

The Danish Register of Causes of Death contains information from all Danish death certificates since 1943, and registration is currently complete through 2006. Causes of death are coded according to the Danish version of the ICD, Eighth Revision, from 1972 until the end of 1993 and the ICD, Tenth Revision, from 1994 through 2006. The causes of death are registered by the attending physician on the death certificate as primary (immediate cause of death), secondary, or tertiary and an underlying cause of death (15). From this register, we extracted the specific causes of death as recorded as the underlying cause of death.

The Danish Cancer Register is a population-based register and contains information on incident cancers diagnosed in Danish citizens since 1943 (16, 17). The cases of cancer are coded according to the ICD, Seventh Revision, for all years and according to the *International Classification of Diseases for Oncology* from 1978.

Study population

Pneumococcal meningitis patients. From the Danish National Hospital Register, we identified all patients who were registered during the period from January 1, 1977, to December 31, 2006, for the first time with a primary or secondary diagnosis of pneumococcal meningitis (ICD, Eighth Revision, code 320.19 or ICD, Tenth Revision, code G00.1). Patients were excluded when they died, emigrated, or were lost to follow-up within the first year after the diagnosis of pneumococcal meningitis and when they were diagnosed with other infections of the central nervous system (as specified in Web Appendix 1) prior to pneumococcal meningitis, did not live in Denmark at the date of the pneumococcal meningitis diagnosis, or were born outside Denmark. (Web Appendix information is supplementary to the text and can be found on the *Journal*'s website (http://aje.oxfordjournals.org/).) The index date of these individuals was defined as 1 year after the date of first pneumococcal meningitis diagnosis.

Population control cohort. From the Danish Civil Registration System, we identified 4 population controls for each pneumococcal meningitis patient matched on gender and date of birth, who were born in Denmark, alive, and living in Denmark at the index date of the corresponding pneumococcal meningitis patient.

Outcome

The primary study outcome was time from the index date to death. The secondary outcome was time from the index date to the date of specific underlying cause of death as registered in the Danish Register of Causes of Death. The

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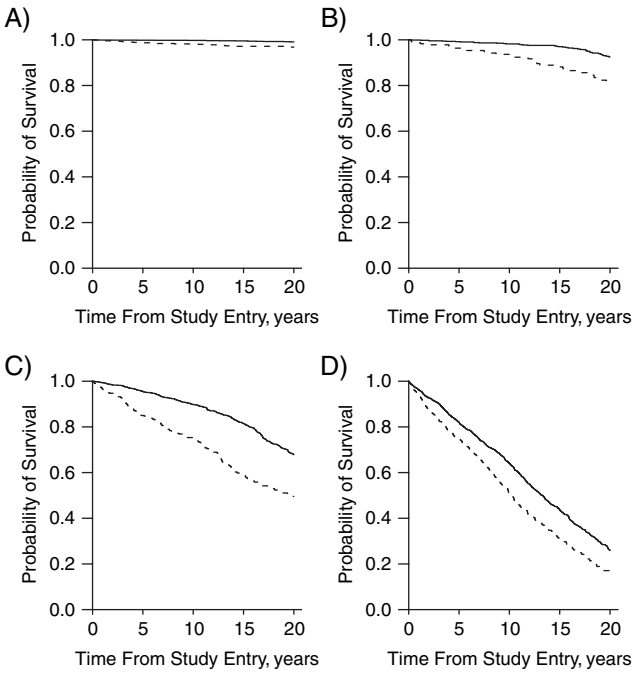

Figure 1. Kaplan-Meier survival curves of patients with pneumococcal meningitis (dashed line) and population controls (solid line), Denmark, 1977–2006. Age at diagnosis: 0–<20 years (A), 20–<40 years (B), 40–<60 years (C), and 60–<80 years (D).

specific underlying causes of death were categorized by ICD codes as listed in Web Appendix 2.

Statistical analysis

Time was calculated from the index date to the date of death, emigration, loss to follow-up, or January 1, 2008, whichever came first. In the analyses of cause-specific mortality, time was censored at January 1, 2007, as the Danish Register of Causes of Death was complete only through 2006. Kaplan-Meier analyses were used to construct survival curves. Poisson regression analysis was used to estimate mortality rate ratios in categories defined by age (0–<20, 20–<40, 40–<60, 60–<80, and 80 years of age or older) and follow-up time (in 10-year intervals). As the mortality rate ratio estimates for the follow-up times 10–<20 and 20–<30 years after the index date were not substantially different, we report only 1 follow-up estimate for the 10–<30 year period. The estimates were adjusted for calendar periods (introduced as design variables grouped in the 3 time periods 1977–1986, 1987–1996, and 1997–2006), days of inpatient admissions (number of inpatient admissions in the 2 years prior to pneumococcal meningitis diagnosis, continuous variable), diagnosis other than cancer registered in the Danish National Hospital Register in the 2 years prior to the date of pneumococcal meningitis diagnosis (grouped in 18 ICD categories as listed in Web Appendix 3 and introduced as design variables), and previous diagnosis of cancer (any cancer diagnosis vs. no previous diagnosis of cancer). We computed the cumulative incidence of specific causes of death, taking into account that these were competing risks (18). Cox regression analysis was used to calculate mortality rate ratios for specific causes of death adjusted for calendar periods, inpatient admission prior to diagnosis of pneumococcal meningitis, and previous cancer diagnoses as described above. Schoenfeld plots confirmed that the proportional hazard assumptions were fulfilled.

We repeated the Poisson regression analyses restricting the study sample to patients (and corresponding population controls) with pneumococcal meningitis as the primary diagnosis. We also repeated the Poisson regression analyses in a study sample excluding patients who had been admitted to a nonpsychiatric hospital within a period of 2 years prior to the date of pneumococcal meningitis diagnosis or were diagnosed with cancer at any time prior to pneumococcal meningitis diagnosis. These analyses were further adjusted for gender and age at diagnosis.

The study was approved by the Danish Data Protection Agency. SPSS, version 15.0, software (SPSS, Inc., Chicago, Illinois), STATA, version 8.0, software (Stata Corporation, College Station, Texas), and R software, version 2.8.1, were used for data analysis.

RESULTS

Characteristics of the study population

We identified 2,848 patients diagnosed with pneumococcal meningitis in the period 1977–2006. Within the first year of diagnosis of pneumococcal meningitis, 716 (25.1%) patients died, 1 emigrated, and none was lost to follow-up, leaving a total of 2,131 patients (1,976 patients (92.7%) with a primary diagnosis and 155 patients (7.3%) with a secondary diagnosis of pneumococcal meningitis) and 8,524 population controls in the study (Table 1). The median age of patients included in the study at diagnosis of pneumococcal meningitis was 44.3 years (interquartile range, 2.8–62.8 years), and 53.5% were males; 30.1% of the patients had pneumococcal meningitis in the period 1977–1986, 34.6% from 1987–1996, and 35.3% from 1997–2006. More pneumococcal meningitis patients than population controls had been admitted to a hospital in the period of 2 years prior to the date of pneumococcal meningitis diagnosis (43.0% vs. 36.2%). During the same period, pneumococcal meningitis patients were diagnosed with the majority of the diagnosis categories more frequently than population controls (Table 1).

All-cause mortality

A total of 584 (27.4%) pneumococcal meningitis patients and 1,739 (20.4%) population controls died in the observation period. Figure 1 presents Kaplan-Meier survival curves for pneumococcal meningitis patients and corresponding population controls in 20-year age intervals. Pneumococcal meningitis patients were at increased risk of death throughout the study period. We saw no major change in the mortality rate ratio between genders in the subanalysis including only patients with pneumococcal meningitis registered as

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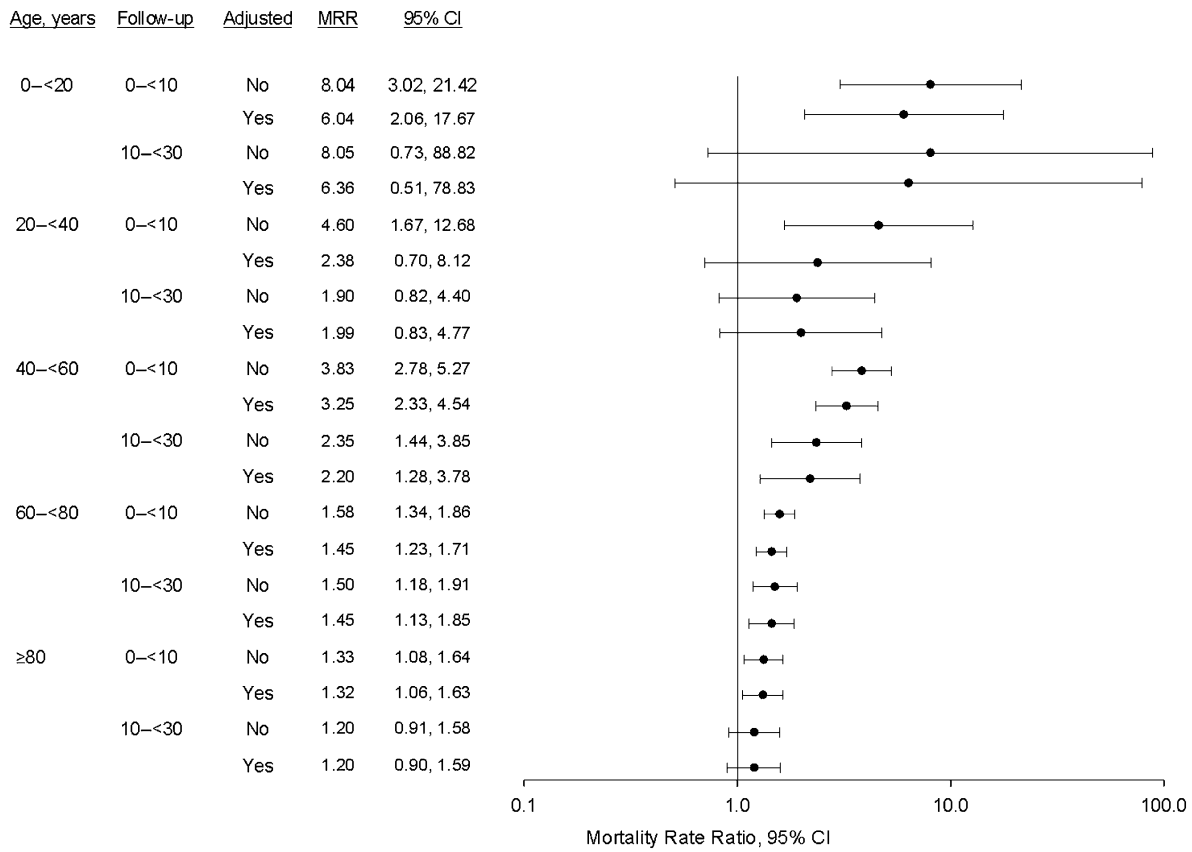

Figure 2. Unadjusted and adjusted mortality rate ratios for patients with pneumococcal meningitis compared with population controls, Denmark, 1977–2006. Adjusted for inpatient admission prior to pneumococcal meningitis. CI, confidence interval; MRR, mortality rate ratio.

the primary diagnosis or in the subanalysis in which individuals were excluded if they had either been hospitalized in the 2-year period prior to meningitis diagnosis, or were diagnosed with cancer prior to the meningitis episode (data not shown). The impact of pneumococcal meningitis on the relative risk of death was highest in the youngest age categories with a more than 8-fold increased long-term mortality in the age category 0–<20 years (Figure 2). The absolute increase in mortality was highest in those diagnosed with pneumococcal meningitis after 20 years of age (Figure 1).

Cause-specific mortality

Pneumococcal meningitis was associated with an increased risk of death due to neoplasms, digestive system diseases, and nervous system diseases (Table 2; Figure 3).

The risks of death due to neoplasms of the oropharynx and hematologic neoplasms were more than 3 and 5 times higher, respectively, in the pneumococcal meningitis patients (Table 2).

The risks of death due to multiple myeloma and chronic lymphatic leukemia were especially increased in the patients with pneumococcal meningitis. The 10-year risk of death due to multiple myeloma was 2.9% (95% confidence interval (CI): 1.4, 5.3) in patients diagnosed with pneumococcal meningitis after the age of 50 years compared with 0.1% (95% CI: 0.0, 0.2) in population controls (Figure 4). Of the patients who died of multiple myeloma, only 6 of 23 were diagnosed with the disease prior to hospitalization for pneumococcal meningitis. In contrast, 6 of 8 patients were diagnosed with chronic lymphatic leukemia prior to the pneumococcal meningitis diagnosis.

The increased risk of death due to digestive system diseases was seen exclusively in patients diagnosed with pneumococcal meningitis after 30 years of age, except from 1 individual who had pneumococcal meningitis as an infant and died from a peptic ulcer perforation at the age of 25 years. The increased risk of death in this group was observed exclusively for deaths related to liver diseases. In both cohorts, the majority of liver-related deaths were alcohol related (9 of 16 and 10 of 15, respectively).

We observed a trend toward an increased risk of death due to cardiovascular and respiratory diseases, although these associations were not statistically significant (Table 2).

During follow-up, 32 patients with pneumococcal meningitis died from neurologic causes, of whom 5 patients died from pneumococcal meningitis with a median of 5.8 years from the initial episode. Seven patients died of unspecified bacterial meningitis, 7 died of acquired hydrocephalus, and 4 died from sequelae of inflammatory diseases of the central nervous system.

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Table 2. Mortality Rate Ratios for Cause-specific Death in Pneumococcal Meningitis Patients Compared With Population Controls, Denmark, 1977–2006

Causes of Death[a]	Unadjusted MRR	95% CI	Adjusted[a] MRR	95% CI	No. of Pneumococcal Meningitis Patients Who Died From the Specific Cause[b]	No. of Population Controls Who Died From the Specific Cause[b]
Infectious diseases	2.33	0.93, 5.84	2.43	0.95, 6.18	7	13
Neoplasms	1.62	1.35, 1.94	1.62	1.35, 1.95	158	419
Oropharynx	3.53	1.08, 11.58	3.88	1.18, 12.74	5	6
Digestive organs	1.30	0.89, 1.89	1.24	0.84, 1.82	35	116
Respiratory and intrathoracic organs	1.25	0.83, 1.90	1.33	0.88, 2.02	29	99
Breast	1.38	0.65, 2.92	1.34	0.62, 2.87	9	28
Female genital organs	1.15	0.50, 2.64	1.25	0.54, 2.91	7	26
Male genital organs	1.05	0.46, 2.39	1.11	0.48, 2.54	7	29
Urinary tract	1.13	0.46, 2.78	1.13	0.45, 2.81	6	23
Hematologic neoplasms	5.16	3.21, 8.29	5.18	3.20, 8.38	38	31
Multiple myeloma	19.34	7.35, 50.88	20.71	7.81, 54.90	23	5
Chronic lymphatic leukemia	6.59	2.16, 20.14	6.99	2.27, 21.58	8	5
Endocrine diseases	1.51	0.85, 2.66	1.23	0.67, 2.26	16	46
Mental disease/drug abuse	1.11	0.57, 2.15	0.99	0.50, 1.95	11	43
Nervous system diseases	3.81	2.37, 6.13	3.58	2.20, 5.82	32	36
Inflammatory diseases of the central nervous system					17	0
Cardiovascular diseases	1.17	0.99, 1.38	1.10	0.92, 1.30	171	629
Respiratory diseases	1.24	0.91, 1.71	1.32	0.96, 1.83	51	152
Digestive system diseases	2.42	1.61, 3.63	1.92	1.25, 2.95	36	64
Gastrointestinal tract diseases	1.67	0.95, 2.92	1.29	0.72, 2.30	17	44
Liver diseases	4.53	2.24, 9.16	3.46	1.64, 7.33	16	15
Diseases of gallbladder, biliary tract, and pancreas	2.59	0.62, 10.82	2.76	0.66, 11.60	3	5
Genitourinary diseases	1.62	0.63, 4.14	1.49	0.56, 3.96	6	16
Injury and poisoning	1.25	0.78, 2.01	1.12	0.69, 1.83	22	75
Ill-defined causes	1.34	0.86, 2.07	1.11	0.70, 1.76	26	84

Abbreviations: CI, confidence interval; MRR, mortality rate ratio.

[a] Adjusted for calendar periods and for inpatient admission prior to pneumococcal meningitis.

[b] The Danish Register of Causes of Death was complete through 2006. In 2007, 35 pneumococcal meningitis patients and 134 population controls died, and these deaths were not included in the analysis of causes of death.

Only 20 deaths were observed in the patients diagnosed with meningitis before the age of 20 years, of which 6 deaths were due to nervous system diseases (adjusted mortality rate ratio = 8.28, 95% CI: 1.56, 44.00). Because of the small number of deaths, we were not able to further stratify the causes of death in this age group.

DISCUSSION

In this nationwide, population-based cohort study, we found a substantially increased mortality up to 30 years after patients were diagnosed with pneumococcal meningitis. The pneumococcal meningitis patients had an increased risk of death due to neoplasms, liver diseases, and nervous system diseases. To our knowledge, this is the first study to describe the long-term mortality in pneumococcal meningitis patients on a nationwide scale.

Strengths

The major strengths of the study are its large sample size, the population-based design, and the complete follow-up. The unique Danish Civil Registration System enabled us to identify a large population control cohort of individuals well matched in terms of gender, age, and country of birth. Through the Danish national registers, we had access to

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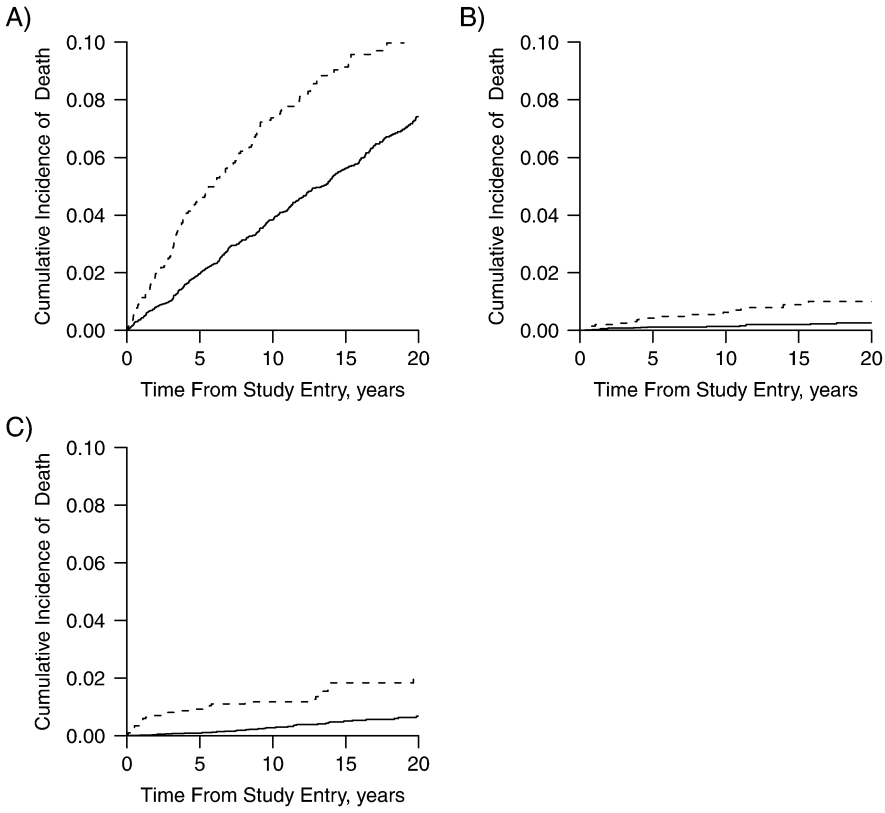

Figure 3. Cumulative incidences of death due to neoplasms (A), liver diseases (B), and nervous system diseases (C) for pneumococcal meningitis patients (dashed line) and population controls (solid line), Denmark, 1977–2006. As the Danish Register of Causes of Death was complete only through 2006, follow-up was terminated at January 1, 2007, and patients with an index date in 2007 were not included in these analyses.

complete data on date of death, comorbidity, cancer diagnosis, and causes of death and, importantly, these data were obtained from the same data sources for both cohorts.

Limitations

We relied on register-based discharge diagnoses that may not be accurate. However, the registration of meningococcal meningitis in the Danish National Hospital Register has been shown to be substantially valid (19), and a similar high sensitivity for the pneumococcal meningitis diagnoses can be assumed. In addition, the number of pneumococcal meningitis patients retrieved from the Danish National Hospital Register was consistent with the annual surveillance reports of pneumococcal meningitis from the Statens Serum Institut (20). From the patient's point of view, the main interest is the long-term prognosis according to the discharge diagnosis. We therefore believe that our study not only adds to the understanding of the medical aspects of pneumococcal meningitis but also is of considerable relevance to the patients, who are diagnosed with pneumococcal meningitis and have a natural interest in knowing their long-term prognosis.

Because of the nature of our study with an inclusion period of 30 years and inclusion of pneumococcal meningitis patients diagnosed at all hospitals in Denmark, we did not have access to clinical and paraclinical data obtained during the hospitalizations. Our data thereby do not allow identification of clinical predictors of long-term mortality or information on neurologic sequelae in the pneumococcal meningitis patients. We also were not able to control for confounding from smoking, alcohol consumption, educational level, or socioeconomic status.

Discussion of our own results and the literature

In the only previous study addressing the long-term prognosis in pneumococcal meningitis patients, Kjersem et al. (10) found an increased risk of death during the first 4 years following diagnosis of bacterial meningitis. The risk of death declined to that of the background population from the fifth year after the meningitis episode. Of the 875 meningitis patients included, only 162 cases were due to pneumococcal meningitis, the follow-up was short, and preexisting comorbidity was not accounted for.

Initiating this study, we hypothesized that some of the risk factors leading to pneumococcal meningitis (e.g., chronic illness, neoplasms, smoking, and alcohol abuse) (3, 21, 22) and neurologic sequelae from the disease were likely

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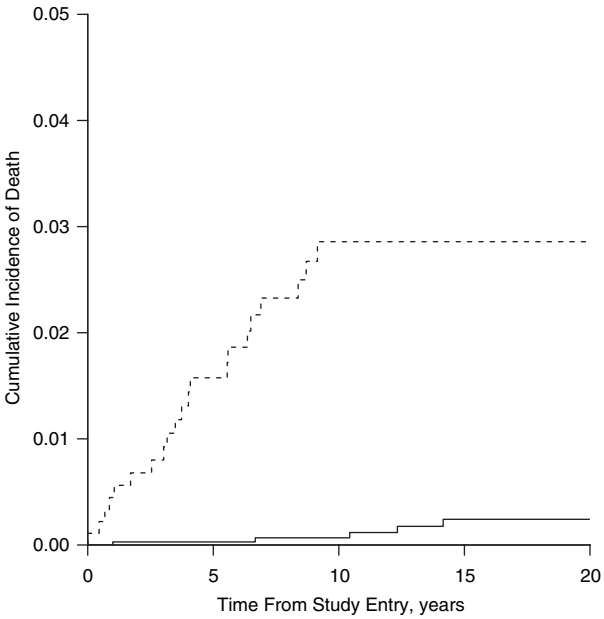

Figure 4. Cumulative incidence of death due to multiple myeloma for patients diagnosed with pneumococcal meningitis after the age of 50 years (dashed line) and population controls (solid line), Denmark, 1977–2006. As the Danish Register of Causes of Death was complete only through 2006, follow-up was terminated at January 1, 2007, and patients with an index date in 2007 were not included in these analyses.

to explain an increased long-term mortality in this patient population. Our data supported this hypothesis.

First, patients diagnosed with pneumococcal meningitis had an increased mortality from neoplasms and a higher proportion of prevalent neoplasms at study inclusion than the population controls. Of interest, the pneumococcal meningitis patients were 5 times more likely to die from hematologic neoplasms, mainly due to a 20 times increased mortality from multiple myeloma. In accordance with our study, Gregersen et al. (23) demonstrated a standardized incidence rate ratio for a subsequent diagnosis of multiple myeloma of 83.2 (95% CI: 22.6, 214.8) in 77 patients older than 40 years of age diagnosed with pneumococcal meningitis. Presumably, the patients at the time of diagnosis of pneumococcal meningitis already housed an unrecognized hematologic neoplasm making them prone to invasive bacterial infection. With an approximately 3% 10-year risk of death from multiple myeloma, it may be cost-effective to screen the pneumococcal meningitis patient population above 50 years systematically for this malignant disease. We also observed an increased risk of death from neoplasms of the oropharynx and presume that this observation stems from an increased risk of pneumococcal meningitis in patients in whom the anatomy in the region of close proximity to the central nervous system has been changed by a tumor.

A second support for our hypothesis was the finding of an increased risk of death due to diseases of the liver. Although we did not have access to data on alcohol consumption, more than half of these deaths were registered as alcohol related. The increased risk of death from liver diseases in the pneumococcal meningitis patients therefore most likely stems from an association with alcohol abuse.

Nevertheless, the analysis, excluding individuals hospitalized in the 2 years prior to meningitis diagnosis or diagnosed with neoplasms, demonstrated essentially the same increased mortality as found for the complete study population. We were, however, only able to adjust for comorbidity in case it led to hospitalization, and these analyses are probably hampered by unmeasured and residual confounding.

A final support of our hypothesis is our observation of increased long-term mortality due to nervous system diseases, of which several died from known sequelae to pneumococcal meningitis as, for example, hydrocephalus. In accordance with this observation, several studies have demonstrated that patients surviving pneumococcal meningitis have a high risk of suffering from neurologic sequelae (8). In the first nationwide cohort study to address the long-term mortality in survivors of meningococcal meningitis, our group likewise observed a higher risk of death due to nervous system diseases in these patients (24).

In summary, patients diagnosed with pneumococcal meningitis have a substantially increased long-term mortality, mainly due to neoplasms (primarily hematologic neoplasms), liver diseases, and nervous system diseases. We presume that the increased risk stems from neurologic sequelae and comorbidity predisposing to pneumococcal meningitis, but not recognized prior to the primary meningitis episode. To improve survival in patients surviving the acute phase of pneumococcal meningitis, physicians should meticulously examine this patient population for neurologic sequelae and screen for comorbidity predisposing to the disease.

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Conflict of interest: none declared.

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Long-term mortality in patients diagnosed with *Listeria monocytogenes* meningitis: A Danish nationwide cohort study

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Meningitis;
Listeria;
Mortality

Summary *Objectives:* To determine the long-term mortality, the causes of death and the incidence of cancer in listeria meningitis patients.
Methods: Nationwide, population-based cohort study including all adult patients diagnosed with listeria meningitis from 1977 to 2006 and alive 1 year after diagnosis, and an age-and gender-matched, population control cohort. Kaplan—Meier tables, Cox regression analysis and cumulative incidence function were used as outcome analyses.
Results: We identified 114 listeria meningitis patients and 1026 population controls. The adjusted mortality rate ratio (MRR) for listeria meningitis patients the first 5 years of follow-up was 2.35(95% confidence interval (CI) 1.60—3.45) thereafter the MRR was 0.93(95% CI: 0.56—1.55). Listeria meningitis patients had an increased risk of death due to cancer the first 5 years of follow-up, and in the same period patients above 50 years of age had a 2-fold increased risk of being diagnosed with cancer, thereafter the risks declined to that of the background population.
Conclusions: The long-term mortality in adult patients diagnosed with listeria meningitis was increased the first 5 years of follow-up, mainly due to death from cancer, thereafter the mortality did not differ from the background population. To improve survival this patient population should be meticulously screened for predisposing conditions, mainly underlying malignant diseases.
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Introduction

The third most common cause of acute bacterial meningitis in Western World countries is *Listeria monocytogenes*, responsible for 4–12% of all reported cases.[1–3] The main risk factors for listeria meningitis are age (<1 year and >50 years), cancers (primarily hematologic cancers), immunodeficiencies, chronic illnesses, and alcohol abuse.[4–6] The case fatality rate of listeria meningitis in adults remains high (17–27%),[5,7] and important neurologic sequelae in adult survivors have been reported.[7] A comprehensive study on the long-term mortality in patients diagnosed with listeria meningitis has not been published previously. Therefore, we performed a nationwide, population-based cohort study to determine whether adult patients surviving the first year after listeria meningitis have increased long-term mortality compared with an age- and gender-matched, population control cohort and if these patients are at increased risk of any specific causes of death. As malignant diseases are main risk factors for listeria meningitis we estimated the risk of being diagnosed with cancer in the period after the listeria meningitis episode.

Materials and methods

Setting

The population of Denmark on December 31, 2007, was 5.5 million inhabitants.[8] In 2007, the incidence rate of listeria meningitis in Denmark was 0.13/100 000.[9] Throughout the study period, tax-paid health care has been provided free of charge to all Danish citizens.

Data sources

We used the unique 10-digit Central Person Registration number (CPR number), assigned to all Danish citizens at birth or immigration to avoid multiple registrations and to track individuals in the following registers:

The Danish National Hospital Register contains information on all patients discharged from Danish somatic hospitals since 1977. In 1995 the registry was expanded to also include psychiatric admissions. The records for each inpatient admission include the CPR number, hospital department, dates of admission, and discharge diagnosis as coded by the attending physician according to the *International Classification of Diseases* 8th (ICD-8) revision, until the end of 1993, and 10th (ICD-10) revision thereafter. Discharge diagnoses are classified as 1 primary and up to 19 secondary discharge diagnoses.[10] From this register, we extracted the date of listeria meningitis diagnosis, along with data on inpatient admissions prior to the diagnosis of listeria meningitis.

The Danish Civil Registration System is a national register established in 1967 that contains the demographic data and vital status of all Danish citizens.[11] From this register, we extracted data on birth, gender, date of immigration and emigration, loss to follow-up, and date of death.

The Danish Register of Causes of Death contains information from all Danish death certificates since 1943, and registration is currently complete through 2008. Causes of death are coded according to the Danish version of the ICD-8 revision, from 1972 until the end of 1993 and the ICD-10 revision, from 1994 through 2008. The causes of death are registered by the attending physician on the death certificate as primary (immediate cause of death), secondary, or tertiary and an underlying cause of death.[12] From this register, we extracted the specific causes of death as recorded as the underlying cause of death. The specific causes of death were categorized by ICD codes as listed in Appendix 1.

The Danish Cancer Register is a population-based register and contains information on incident cancers diagnosed in Danish citizens since 1943.[13,14] From 1943 to 1978 the cases of cancer are coded according to the *International Classification of Diseases* 7th (ICD-7) revision and from 1978 and onwards in accordance with ICD-10. From this register we extracted the cancer diagnoses and the date of cancer diagnoses in the study population.

Study population

Listeria meningitis patients

From the Danish National Hospital Register, we identified all patients who were registered during the period from January 1, 1977, to December 31, 2006, for the first time with a primary or secondary diagnosis of listeria meningitis (ICD-8 revision, code: 027.01) or listeria meningitis and meningoencephalitis (ICD-10 revision, code: A32.1). Patients were excluded if they 1) died, emigrated, or were lost to follow-up within the first year after the diagnosis of listeria meningitis, 2) were <16 years of age at diagnosis of listeria meningitis, 3) were diagnosed with other infections of the central nervous system (as specified in Appendix 2) prior to listeria meningitis, 4) did not live in Denmark at the date of the listeria meningitis diagnosis, or 5) were born outside Denmark. The index date of these individuals was defined as 1 year after the date of first listeria meningitis diagnosis.

Population control cohort

From the Danish Civil Registration System we identified 9 population controls for each listeria meningitis patient matched on gender and date of birth, who were born in Denmark, alive, and living in Denmark at the index date of the corresponding listeria meningitis patient.

Comorbidity

A modified Charlson Comorbidity Index (CCI) score derived from diagnoses registered in the Danish National Hospital Register and from cancer diagnoses registered in the Danish Cancer Register prior to the date of listeria meningitis was calculated. The CCI assigns a score from 1 to 6 to a range of diseases with the sum of the individual scores serving as a measure of the study population's overall comorbidity at the time of listeria meningitis diagnosis. Three levels of comorbidity were defined: none (CCI score = 0), low (CCI score = 1 and 2) and high (CCI score $\geq$ 3).[15,16]

Outcomes

The primary study outcome was time from the index date to death. The secondary study outcomes were 1) time from

the index date to specific causes of death and 2) time from the index date to first cancer diagnosis (Appendix 3).

Statistical analysis

For listeria meningitis patients and population controls time was calculated from the index date to the date of death (primary study outcome), to the date of specific cause of death (secondary study outcome), to the date of first cancer diagnosis (secondary study outcome), emigration, loss to follow-up, or January 1, 2008, whichever came first. Kaplan–Meier analyses were used to construct survival curves. A modified CCI score was calculated and diagnoses 2 years prior to index date (grouped in 18 categories as listed in Appendix 4) were assessed.

Cox regression analyses were used to estimate mortality rate ratios (MRR) in categories defined by age at diagnosis (16 to $<$50 and $\geq$50 years), as age $>$ 50 years has been shown to be a main risk factor for listeria meningitis,[4] and by follow-up time (the first 5 years and 6–30 years after the index date). We chose to divide the follow-up time in the 2 above mentioned intervals as the Kaplan–Meier survival curve for the whole listeria meningitis patient population demonstrated a marked increase in mortality in the first 5 years compared with the remaining part of follow-up. We used plots of Schoenfeld residuals to determine whether hazard ratios were constant within the follow up periods. The MRRs were adjusted for modified CCI score (introduced as design variables) and calendar periods (introduced as design variables grouped in the 3 time periods 1977–1986, 1987–1996, and 1997–2006).

We repeated the Cox regression analyses in a study sample excluding individuals with a cancer diagnosis prior to the listeria meningitis episode.

Cox regression analysis was used to calculate MRR for specific underlying causes of death adjusted for CCI score and calendar time as described above. To investigate whether potentially undiagnosed cancers are unmasked in the period after the listeria meningitis diagnosis we used data from the Danish Cancer Register to compute the cumulative incidence of cancer diagnoses in the first 20 years from index date, excluding individuals with a cancer diagnosis prior to the listeria meningitis episode.

The study was approved by the Danish Data Protection Agency. SPSS version 15.0 (SPSS Inc., Chicago, Il, USA) and *R* software, version 2.13.0 were used for data analysis.

Results

Characteristics of the study population

We identified 183 patients above 16 years of age diagnosed with listeria meningitis in the period 1977–2006. Within the first year following a diagnosis of listeria meningitis, 69(37.7%) patients died, none emigrated or was lost to follow-up, leaving 114 patients and 1026 population controls in the study (Table 1). The median age at diagnosis of listeria meningitis was 61.7 years (interquartile range [IQR], 49.9–72.7 years), 57.0% were males; 29.8% of the patients had listeria meningitis in the period 1977–1986, 38.6% from 1987 to 1996, and 31.6% from 1997 to 2006. During the study period, the listeria meningitis patients accumulated 993 person years of observation (PYR) and the population controls 10 434 PYR. Listeria meningitis patients had more comorbidities than population controls. In the period of 2 years prior to the date of listeria meningitis diagnosis the patients were diagnosed more frequently with infectious diseases, cancers, endocrine, nervous system, respiratory and digestive system diseases compared with the population controls (Table 1). Of the cancers diagnosed in patients prior to the date of listeria meningitis diagnosis 6 were hematologic and 12 non-hematologic cancers.

All-cause mortality

A total of 57(50.0%) listeria meningitis patients and 400(39.0%) population controls died during follow-up. The listeria meningitis patients had a 2-fold increased risk of death the first 5 years from index date compared with population controls (Figs. 1 and 2 and Table 2), whereas the risk of death declined to that of the population controls from the fifth year after index date. For the complete patient population we saw no major changes in MRR between genders or in the sub-analysis in which individuals with a prior diagnosis of cancer were excluded.

Cause specific mortality

Listeria meningitis was associated with a 3-fold increased risk of death due to cancer the first 5 years of follow-up. We observed no increased risk of death due to cardiovascular or respiratory diseases (Table 3). The number of deaths due to infectious diseases (2 patients and 1 population control) and nervous system diseases (2 patients and 5 population controls) during follow-up were not sufficient to calculate meaningful cause-specific MRRs for these categories.

Risk of cancer diagnosis

21 listeria meningitis patients compared with 156 population controls were diagnosed with cancer during the first 20 years of follow-up from index date (6 gastrointestinal, 5 skin, 2 lung, 2 renal, 3 prostate, 1 breast cancer, 1 nasopharyngeal and 1 with a metastatic cancer to the bones). Only 1 of the listeria meningitis patients below the age of 50 years at time of diagnosis developed a cancer during follow-up. Of the listeria meningitis patients $\geq$ 50 years of age at diagnosis and not diagnosed with cancer before listeria meningitis diagnosis 5.9%(95% CI: 1.9%–13.2%) compared with 2.1%(95% CI: 1.2%–3.4%) of the population controls were diagnosed with cancer the first year of follow-up, 18.9%(95% CI: 10.3%–29.5%) compared with 7.9%(95% CI: 5.9%–10.2%) at 5 years of follow-up, and 26.6%(95% CI: 15.9%–38.4%) compared with 20.7(95% CI: 17.3%–24.3%) at 15 years of follow-up.

Discussion

In this nationwide, population-based cohort study, we found a substantially increased mortality the first 5 years of follow-up in adult listeria meningitis patients alive 1 year

after diagnosis compared with the background population. The increased mortality stemmed mainly from death due to cancer. Patients above 50 years of age had a 2-fold increased risk of being diagnosed with cancer in the first 5 years of follow-up.

The major strengths of the study are the population-based design and the long and complete follow-up. The unique Danish Civil Registration System enabled us to identify a large population control cohort of individuals well matched in terms of gender, age, and country of birth. Through the Danish national registers we had access to complete data on date of death, causes of death and cancer diagnoses and importantly, these data were obtained from the same data sources for both cohorts.

The study is based on all possible Danish cases over a 30 year period, and to our knowledge it is the largest ever published cohort study what concerns number of patients with listeria meningitis and person years of follow-up. Nevertheless, there were only 114 listeria meningitis patients included in the analyses resulting in small numbers for some of the outcomes of interest, particular in the age-stratified and the cause-specific death analyses. We relied on register-based discharge diagnoses that may not be accurate. However, the registration of meningococcal meningitis in the Danish National Hospital Register has been shown to be substantially valid,[17] and a similar high sensitivity for the listeria meningitis diagnoses can be assumed. In addition, the number of listeria meningitis patients retrieved from the Danish National Hospital Register was consistent with the annual number of cases reported to the Danish Reference Center for Listeriosis, Statens Serum Institut, Copenhagen, Denmark.[18] From the

Table 1 Characteristics of listeria meningitis patients and population controls, Denmark, 1977–2006.

	Patients[a]	Population controls[a]	*P*-value
Number of study participants	114	1026	
Males	65(57.0)	585(57.0)	
Age, median (years, IQR) at diagnosis of listeria meningitis	61.7(49.7–72.7)	61.7(49.7–72.7)	
Age at diagnosis of listeria meningitis			
16 to <30 years	9(7.9)	81(7.9)	
30 to <50 years	20(17.5)	180(17.5)	
≥50 years	85(74.6)	765(74.6)	
Calendar period at diagnosis of listeria meningitis			
1977–1986	34(29.8)	306(29.8)	
1987–1996	44(38.6)	396(38.6)	
1997–2006	36(31.6)	324(31.6)	
Observation time (person-years)	993	10 434	
Emigration during study period	0	4(0.4)	
Lost to follow-up during study period	0	0	
Modified Charlson Comorbidity Index			<0.001
None (score: 0)	80(70.2)	837(81.6)	
Low (score: 1 and 2)	23(20.2)	164(16.0)	
High (score: ≥3)	11(9.6)	25(2.4)	
Number of study subjects with inpatient admission in the period of 2 years prior to the date of listeria meningitis diagnosis	41(36.0)	202(19.7)	<0.001
Patients admitted with the following diagnostic categories in the period of 2 years prior to the date of listeria meningitis diagnosis			
Infectious diseases	4(3.5)	1(0.1)	< 0.001
Cancers	18(15.8)	72(7.0)	0.001
Blood/immune diseases	1(0.9)	4(0.4)	0.56
Endocrine diseases	4(3.5)	5(0.5)	0.001
Mental disease/drug abuse	0	2(0.2)	0.64
Nervous system diseases	3(2.6)	6(0.6)	0.02
Diseases of the sensory organs	0	9(0.9)	0.32
Cardiovascular diseases	9(7.9)	53(5.2)	0.22
Respiratory diseases	6(5.3)	17(1.7)	0.01
Digestive system diseases	9(7.9)	36(3.5)	0.02
Skin diseases	1(0.9)	1(0.1)	0.06
Rheumatologic diseases	5(4.4)	19(1.9)	0.07
Genitourinary diseases	3(2.6)	23(2.2)	0.79
Pregnancy and related diseases	1(0.9)	11(1.1)	0.85

[a] If not stated otherwise data are the number and percentage of listeria meningitis patients or population controls.

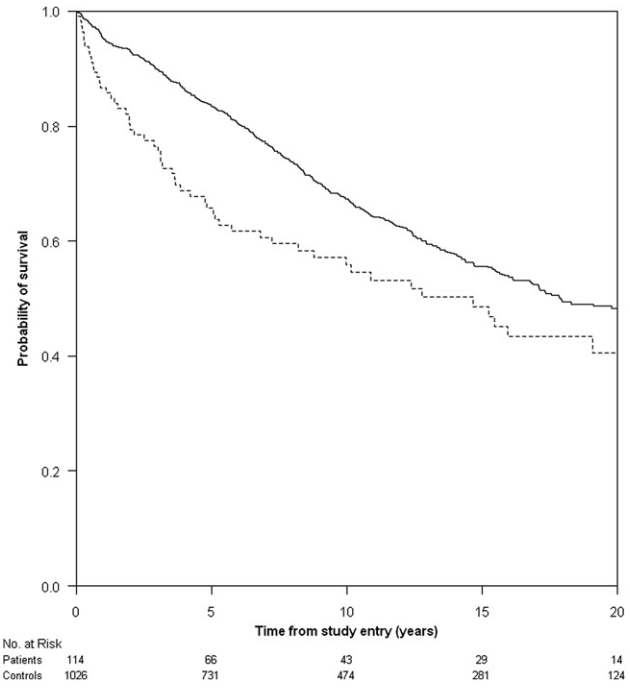

Figure 1 Kaplan—Meier survival curves of patients with listeria meningitis (dashed line) and population controls (solid line), Denmark, 1977—2006.

patient's point of view, the main interest is the long-term prognosis according to the discharge diagnosis. We therefore believe that our study not only adds to the understanding of the medical aspects of listeria meningitis, but also is of considerable relevance to the patients, who are diagnosed with listeria meningitis and have a natural interest in knowing their long-term prognosis. We did not have access to clinical and paraclinical data obtained during the hospitalizations. Our data thereby do not allow identification of clinical predictors of long-term mortality or information on neurologic sequelae in the listeria meningitis patients. Further, we were not able to control for confounding from smoking, alcohol consumption, educational level or socioeconomic status.

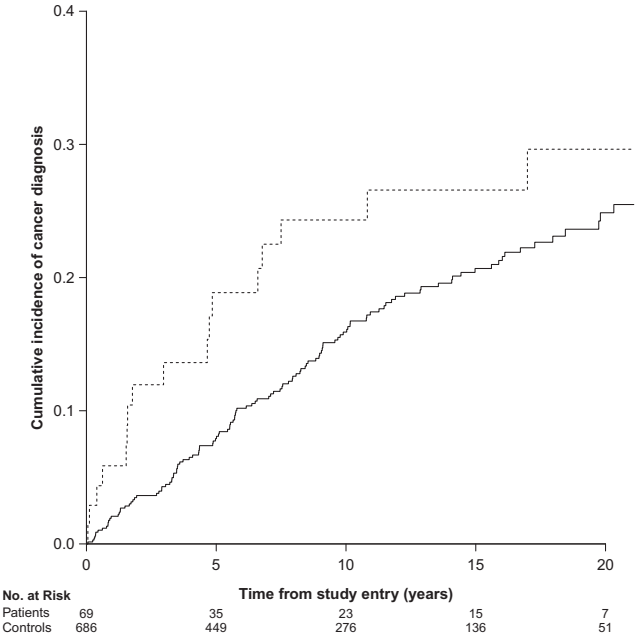

Figure 2 Cumulated incidence of cancer diagnosis after index date in patients above 50 years at diagnosis of listeria meningitis (dashed line) and population controls (solid line), Denmark, 1977—2006.

Initiating the study, we hypothesized, that adult patients surviving listeria meningitis had an increased long-term mortality due to predisposing conditions (e.g. cancers, chronic diseases and alcohol abuse) reported to be present in 30—60% of patients[6,7,19,20] and due to neurologic sequelae from the disease. Our data partly supported this hypothesis as we observed an increased long-term mortality in the listeria meningitis patients, but only in the first 5 years of observation. From 5 years follow-up the survival for listeria meningitis patients was equivalent to that of the background population.

The long-term mortality in patients surviving listeria meningitis is poorly described in the literature. Kjersem et al. found an increased risk of death during the first 4 years following diagnosis of bacterial meningitis, whereas the risk of death declined to that of the background population from the fifth year of discharge.[21] However only 9 out of the 875 meningitis cases were due to *Listeria monocytogenes*, the follow-up was short, and pre-existing comorbidity was not accounted for. In a study of 36 adult patients treated for listeria meningitis from 1983 to 2006 75% of the patients were reported alive at 5 years follow-up. [20] In a case report on 4 previously healthy adults with listeria meningitis none died nor developed diseases associated with immunosuppression after a follow-up of 2—6 years.[22]

Several parts of our analyses help explain the increased mortality the first 5 years from study inclusion in listerial meningitis patients: First, listerial meningitis patients had a higher proportion of prevalent cancers at time of study inclusion. Second, the 5 year risk of a cancer diagnosis during follow-up was increased in patients compared with controls. Presumably, theses patients at the time of diagnosis of listerial meningitis already housed an unrecognized malignancy making them prone to an invasive bacterial infection by *L. monocytogenes*. Third, the risk of death due to cancer was increased in patients compared with controls. Of cancer patients, the ones with hematologic malignancies are found to carry the highest risk of invasive listeriosis,[5,23] supporting our findings of one third of the patients with a known diagnosis of cancer at time of listeria meningitis to be of hematologic origin. Further, as we did not observe an increased risk of other causes of death, our study demonstrates that predisposing malignancy is probably the main factor responsible for the increased long-term mortality following listeria meningitis. However only data on the underlying cause of death was considered in the cause-specific death analyses and conditions contributing to the death not listed as underlying cause (e.g. alcohol abuse) would not be captured.

We have previously demonstrated that pneumococcal meningitis patients have substantially increased long-term mortality due to cancer, primarily of hematologic origin, whereas meningococcal meningitis patients do not carry any increased risk of death due to cancer.[24,25]

Table 2 Mortality rate ratios (MRR) for listeria meningitis patients compared with population controls, Denmark, 1977–2006.

Characteristics	MRR (95% CI) for the first 5 years from index date	Adjusted[a] MRR (95% CI) for the first 5 years from index date	MRR (95% CI) 5 years from index date and onwards	Adjusted[a] MRR (95% CI) 5 years from index date and onwards	Number of patients who died during the 2 study periods	Number of population controls who died during the 2 study periods
Listeria meningitis	2.63(1.80–3.82)	2.35(1.60–3.45)	0.97(0.59–1.61)	0.93(0.56–1.55)	37 + 20	155 + 245
Gender						
Female	2.59(1.46–4.60)	2.30(1.27–4.15)	1.02(0.46–2.27)	0.96(0.42–2.16)	16 + 9	55 + 98
Male	2.65(1.62–4.36)	2.46(1.47–4.11)	0.95(0.49–1.81)	0.93(0.48–1.79)	21 + 11	100 + 147
Age at diagnosis of listeria meningitis						
16 to <50 years	3.00(0.31–28.84)	1.23(0.10–15.04)	1.34(0.30–6.00)	1.35(0.28–15.04)	1 + 2	4 + 16
> 50 years	2.62(1.79–3.83)	2.37(1.61–3.50)	0.94(0.55–1.60)	0.90(0.52–1.54)	36 + 18	151 + 229
No cancer diagnosis before listeria meningitis	2.25(1.44–3.53)	2.20(1.39–3.47)	0.86(0.50–1.48)	0.83(0.48–1.44)	25 + 17	109 + 227

Abbreviations: CI, confidence interval; MRR, mortality rate ratio.
[a] Adjusted for modified Charlson comorbidity index score and calendar periods.

Table 3 Mortality rate ratios (MRR) for cause-specific death in listeria meningitis patients compared with population controls, Denmark, 1977–2006.

Characteristics	MRR (95% CI) for the first 5 years from index date	Adjusted[a] MRR (95% CI) for the first 5 years from index date	MRR (95% CI) 5 years from index date and onwards	Adjusted[a] MRR (95% CI) 5 years from index date and onwards	Number of patients who died during the 2 study periods	Number of population controls who died during the 2 study periods
Cancer	3.85(1.93–7.69)	3.09(1.49–6.38)	0.61(0.22–2.45)	0.66(0.19–2.23)	12 + 3	39 + 51
Cardiovascular diseases	1.94(0.96–3.88)	1.77(0.85–3.68)	1.04(0.48–2.26)	0.96(0.43–2.15)	10 + 9	60 + 116
Respiratory diseases	1.41(0.31–6.45)	1.35(0.25–7.19)	1.40(0.44–4.44)	1.52(0.41–5.60)	2 + 4	13 + 30

The categories of causes of death were omitted if less than 5 deaths occurred in the listeria meningitis patient population.
Abbreviations: CI, confidence interval; MRR, mortality rate ratio.
[a] Adjusted for modified Charlson comorbidity index score and calendar periods.

Conclusion

We conclude that patients diagnosed with listeria meningitis have an increased 5 year risk of death from follow-up, mainly due to cancer, thereafter their mortality does not differ from the background population. For listeria meningitis patients ≥50 years of age the 5 year risk of being diagnosed with cancer is doubled compared with the background population. To improve survival in patients surviving the acute phase of listeria meningitis, this patient population should be meticulously screened for predisposing conditions, mainly underlying malignant diseases.

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Appendix 1

The 18 categories of specific underlying causes of death were specified by ICD-8 revision, codes for the years 1977–1993 and ICD-10 revision, codes from 1994 to 2006. For infectious diseases, the codes were 000–134.99/A00-B99; cancer 140–209/C00-C96; blood/immune diseases 280–289.99/D50-D89; endocrine diseases 240–279.09/E00-E90; mental diseases/drug abuse 290–315/F00-F99; nervous system diseases 320–358.09/G00-G99; diseases of the sensory organs 360–389.99/H00-H59; cardiovascular diseases 390–458.99/I00-I99; respiratory diseases 460–519.99/J00-J99; digestive system diseases 520–577.99/K00-K93; skin diseases 680–709.99/L00-L99; rheumatological diseases 710–738.09/M00-M99; genitourinary diseases 580–629.99/N00-N99; neonatal/congenital disorders 740–779.99/P00-Q99; pregnancy related diseases

630—678.09/O00-O99; injury/poisoning 800—999/S00-T98,V,W,X,Y; ill-defined causes 780—796.99/R00-R99 and no cause of death reported.

Appendix 2

Infections of the central nervous system were defined by the following ICD-8 revision, codes for the years 1977—1993. For bacterial meningits the codes were 320.00—320.99; Listeria meningits 027.01; Meningococcal infection 036.00—036.99; Aseptic meningitis due to enterovirus 045.00—045.99; Varicella meningitis/encephalitis 052.01; Zoster meningitis/encephalitis 053.02 and Herpesviral meningitis/encephalitis 054.03.

Infections of the central nervous system were defined by the following ICD-10 revision, codes for the years 1994—2007. For inflammatory diseases of the central nervous system the codes were G00.0-G01.9; Listeria meningitis and meningoencephalitis A32.1; Meningococcal infection A39.0-A39.9; Unspecified viral encephalitis A86; Enteroviral meningitis A87.0; Adenoviral meningitis A87.1; Lymphocytic choriomeningitis A87.2; Other viral meningitis A87.8; Viral meningitis, unspecified A87.9; Herpesviral meningitis B00.3; Herpesviral encephalitis B00.4; Varicella meningitis B01.0; Varicella encephalitis B01.1; Zoster encephalitis B02.0; Zoster meningitis B02.1; Zoster with other nervous system involvement B02.2.

Appendix 3

Cancer diagnoses obtained from the Danish Cancer Register were defined by the following ICD-7 revision, codes: 140—207 and ICD-10 revision, codes: C00-C97.

Appendix 4

The 18 categories of primary discharge diagnoses were specified by ICD-8 revision, codes for the years 1977—1993 and ICD-10 revision, codes from 1994 to 2007 obtained from The Danish National Hospital Register for inpatient admissions in the 2 years prior to listeria meningitis. For infectious diseases, the codes were 000—134.99/A00-B99; cancer 140—209/C00-C96; blood/immune diseases 280—289.99/D50-D89; endocrine diseases 240—279.09/E00-E90; mental diseases/drug abuse 290—315/F00-F99; nervous system diseases 320—358.09/G00-G99; diseases of the sensory organs 360—389.99/H00-H59; cardiovascular diseases 390—458.99/I00-I99; respiratory diseases 460—519.99/J00-J99; digestive system diseases 520—577.99/K00-K93; skin diseases 680—709.99/L00-L99; rheumatological diseases 710—738.09/M00-M99; genitourinary diseases 580—629.99/N00-N99; neonatal/congenital disorders 740—779.99/P00-Q99; pregnancy related diseases 630—678.09/O00-O99; injury/poisoning 800—999/S00-T98,V,W,X,Y; abnormal findings not classified otherwise 780—796.99/R00-R99 and contacts with health services not classified above Y00-Y95.

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Long-term Mortality in Children Diagnosed With *Haemophilus influenzae* Meningitis

A Danish Nationwide Cohort Study

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Background: The long-term mortality in children diagnosed with *Haemophilus influenzae* meningitis is poorly documented.

Methods: We performed a nationwide, population-based cohort study including all Danish children diagnosed at the age between 0 and <5 years with *H. influenzae* meningitis from 1977 through 1996 and who were alive 1 year after diagnosis. Data were retrieved from medical databases in Denmark. For each *H. influenzae* meningitis patient, 6 age- and gender-matched population controls were indentified. We constructed Kaplan-Meier survival curves and used Cox regression analysis to estimate mortality rate ratios (MRR) and analyze causes of death. The risk of inpatient admission and of requiring hospital outpatient services during follow-up was calculated.

Results: We identified 1242 *H. influenzae* meningitis patients and 7452 population controls, with a median follow-up time of 21.3 years. The MRR for patients with *H. influenzae* meningitis was 1.08 (95% confidence interval, 0.57–2.05), adjusted MRR was 0.97 (95% confidence interval, 0.50–1.89). No increased mortality due to infections, respiratory diseases, or cancer was observed. The overall risk of inpatient admission and of requiring hospital outpatient services for the *H. influenzae* meningitis patients was increased the first 15 years of follow-up, mainly due to the nervous system diseases and ear diseases, thereafter the risk decreased to that of the population controls.

Conclusions: In a developed country, children younger than 5 years surviving the acute phase of *H. influenzae* meningitis have no increased long-term mortality and only moderately increased morbidity.

Key Words: cause of death, cohort study, *Haemophilus influenzae*, meningitis, long-term mortality

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Although the majority of children diagnosed with *Haemophilus influenzae* meningitis are spared from long-term sequelae, these include such serious disabilities as hearing loss, mental retardation, speech/language disorder, motor abnormalities, and seizures.[1,2] To our knowledge, no comprehensive study on the long-term mortality in children diagnosed with *H. influenzae* meningitis has been published previously. We therefore performed a nationwide, population-based cohort study to determine whether children aged 0 to <5 years and who survived the first year after an episode of *H. influenzae* meningitis had increased long-term overall and cause-specific mortality compared with an age- and gender-matched population control cohort. As a measure for morbidity, we calculated the degree of inpatient admissions and hospital outpatient services during the study period for *H. influenzae* meningitis patients compared with the population controls.

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MATERIALS AND METHODS

Setting

The population of Denmark was 4.9 million inhabitants until December 31, 1996.[3] The *H. influenzae* type b (Hib) conjugate vaccine was introduced into the Danish childhood vaccination program on June 1, 1993. Before the introduction of the conjugate vaccine, the incidence of *H. influenzae* meningitis in Denmark was 50 to 80 cases per year, compared with a yearly incidence of only 1 to 6 cases after the introduction of the vaccine.[4] Throughout the study period, tax-paid health care has been provided free of charge to all Danish citizens.

Data Sources

We used the unique 10-digit Central Person Registration number (CPR number), assigned to all Danish citizens at birth or immigration to avoid multiple registrations and to track individuals in the following registers.

The Danish National Hospital Register contains information on all patients discharged from Danish nonpsychiatric hospitals since January 1, 1977.[5] The records for each inpatient admission include the CPR number, type of specialty, dates of admission, and discharge diagnosis as coded by the attending physician according to the International Classification of Diseases 8th (ICD-8) revision, until the end of 1993, and 10th (ICD-10) revision thereafter. Discharge diagnoses are classified as 1 primary and up to 19 secondary discharge diagnoses. Medical care on an outpatient basis provided by Danish hospitals has been recorded in the register since January 1, 1986. The records for each hospital outpatient service include the CPR number, type of specialty, date of first and last visit to a hospital outpatient clinic, number of visits, and the medical condition coded by the outpatient physician according to the ICD-8 revision, until the end of 1993, and ICD-10 revision thereafter. From The Danish National Hospital Register, we extracted the date of *H. influenzae* meningitis diagnosis, along with data on inpatient admissions and hospital outpatient services.

The Danish Civil Registration System is a national register established in 1967 that contains the demographic data and vital status of all Danish citizens.[6] From this register, we extracted data on birth, gender, date of immigration and emigration, loss to follow-up, and date of death.

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The Danish Register of Causes of Death contains information from all Danish death certificates since 1943, and registration is currently complete through 2009.[7] Causes of death are coded according to the Danish version of the ICD-8 revision, from 1972 until the end of 1993 and the ICD-10 revision, from 1994 through 2009. The causes of death are registered by the attending physician on the death certificate as primary (immediate cause of death), secondary, or tertiary and an underlying cause of death. From this register, we extracted the specific causes of death as recorded as the underlying cause of death. The specific causes of death were categorized by ICD codes as listed in Appendix A.

Study Population

H. influenzae Meningitis Patients

From the Danish National Hospital Register, we identified all children who were registered during the period from January 1, 1977 to December 31, 1996, for the first time with a primary or secondary diagnosis of *H. influenzae* meningitis (ICD-8 code: 320.09 or ICD-10 code: G00.0) at the age between 0 and <5 years old. Information on *H. influenzae* serotype was not available in the register. Patients were excluded when they died, emigrated, or were lost to follow-up within the first year after the diagnosis of *H. influenzae* meningitis, and when they were diagnosed with other infections of the central nervous system (as specified in Appendix B) before *H. influenzae* meningitis, did not live in Denmark at the date of the *H. influenzae* meningitis diagnosis, or were born outside Denmark. The index date was defined as 1 year after the date of first *H. influenzae* meningitis diagnosis.

Population Control Cohort

From the Danish Civil Registration System, we identified 6 population controls for each *H. influenzae* meningitis patient matched on gender and date of birth, born in Denmark, alive, and living in Denmark at the index date of the corresponding *H. influenzae* meningitis patient.

Outcomes

The primary study outcome was time from the index date to death. The secondary outcome was time from the index date to the date of specific underlying cause of death. We further calculated the number of inpatient admissions and hospital outpatient services.

Statistical Analysis

Time was calculated from the index date to the date of death (primary study outcome), emigration, loss to follow-up, or January 1, 2008, whichever came first. Kaplan-Meier analyses were used to construct survival curves. Cox regression analyses were used to estimate mortality rate ratios (MRR) adjusted for calendar periods and for inpatient admission up to 2 years before the date of *H. influenzae* meningitis diagnosis. Calendar periods for the date of *H. influenzae* meningitis diagnosis were introduced as design variables grouped into the following 2 time periods: 1977 to 1986 and 1987 to 1996. We adjusted for inpatient admissions up to 2 years before the date of *H. influenzae* meningitis diagnosis using (*a*) the total number of inpatient days as a continuous variable and (*b*) a series of 18 design variables for the primary discharge diagnoses, as listed in Appendix C.

For both cohorts, the number of inpatient admissions, hospital outpatient services, and person-years at risk were calculated for the study periods 0 to <5, 5 to <10, 10 to <15, 15 to <20, and 20 to <25 years after the index date. Inpatient admission rates (number of inpatient admissions/100 person-years of follow-up) and hospital outpatient service rates (number of hospital outpatient services/100 person-years of follow-up) could hereby be calculated for both cohorts in the aforementioned 5-year study periods and for groups of primary discharge diagnosis categorized by medical specialty as described in Appendix C. Three of the 18 diagnostic groups (endocrine, nervous, and ear diseases) were further subcategorized as described in Appendix D. We calculated crude Poisson 95% confidence intervals (95% CIs) and relative risk comparing rates in the *H. influenzae* meningitis patients with that in the population controls.

The study was approved by the Danish Data Protection Agency. SPSS version 15.0 (SPSS Inc., Chicago, IL) and R software, version 2.11.1 were used for data analysis.

RESULTS

Characteristics of the Study Population

We identified 1281 patients diagnosed at the age of 0 to 5 years with *H. influenzae* meningitis in the period 1977 to 1996. Within the first year following a diagnosis of *H. influenzae* meningitis, 38 (3.0%) patients died, 1 emigrated, and none was lost to follow-up, leaving a total of 1242 patients and 7452 population controls in the study (Table 1), with a median follow-up time of 21.3 years (interquartile range [IQR], 17.0–25.8 years). The median age of patients included in the study at diagnosis of *H. influenzae* meningitis was 1.1 years (IQR, 0.7–1.8 years). In all, 53% were males; 58.9% of the patients had *H. influenzae* meningitis in the period 1977 to 1986 and 41.1% from 1987 to 1996. During the study period, the *H. influenzae* meningitis patients accumulated 26,409 person-years of observation and the population controls presented a total of 157,890 person-years of observation. Significantly more *H. influenzae* meningitis patients than population controls had been admitted to a hospital in a period of up to 2 years before the date of *H. influenzae* meningitis diagnosis (21.6% vs. 17.6%) mainly due to the infectious diseases and ear diseases (Table 1). Otitis media made up the majority of diagnoses in the category of ear diseases.

All-cause Mortality

A total of 11 (0.9%) *H. influenzae* meningitis patients of whom 4 were girls and 7 were boys and 61 (0.8%) population controls of whom 16 were girls and 45 were boys died during follow-up. Figure 1 presents Kaplan-Meier survival curves for *H. influenzae* meningitis patients and corresponding individuals from the population control cohort. The unadjusted MRR for patients with *H. influenzae* meningitis was 1.08 (95% CI, 0.57–2.05), adjusted MRR was 0.97 (95% CI, 0.50–1.89). No difference was observed between the genders (data not shown).

Cause-specific Mortality

An analysis of the individual causes of death revealed that only 2 deaths in the patient population were possibly linked with the *H. influenzae* meningitis episode, one due to status epilepticus and another due to sequelae of neuroinfection. Of the remaining deaths in the *H. influenzae* meningitis patients, 2 were caused by inherited nervous system disease, 2 by cancer, 3 by accidents, and 2 due to other conditions. *H. influenzae* meningitis patients were not at an increased risk of death caused by neither infectious diseases, cancer, respiratory nor rheumatologic diseases (data not shown).

Inpatient Admission

The relative risk of inpatient admission for the *H. influenzae* meningitis patients was significantly increased up to 15 years from index date, and thereafter the risk did not differ from that of the population controls (Table 2). When categorized according to primary discharge diagnosis, the relative risk of inpatient admission for nervous system diseases was significantly increased dur-

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TABLE 1. Characteristics of Children Having Had *Haemophilus influenzae* Meningitis and a Population Control Cohort, Denmark, 1977–1996

	Children Having Had *H. influenzae* Meningitis*	Population Control Cohort*	*P*
No. study participants	1242	7452	
Males	658 (53.0)	3948 (53.0)	
Age, median (yr, IQR) at diagnosis of *H. influenzae* meningitis	1.1 (0.7–1.8)	1.1 (0.7–1.8)	
Age at diagnosis of *H. influenzae* meningitis			
0–<1	526 (42.4)	3156 (42.4)	
1–<2	477 (38.4)	2862 (38.4)	
2–<3	143 (11.5)	858 (11.5)	
3–<4	63 (5.1)	378 (5.1)	
4–<5	33 (2.6)	198 (2.6)	
Calendar period at diagnosis			
1977–1986	731 (58.9)	4386 (58.9)	
1987–1996	511 (41.1)	3066 (41.1)	
Observation time (yr)	26,409	157,890	
Emigration during study period	28 (2.3)	264 (3.5)	
Lost to follow-up during study period	1 (0.1)	3 (0.04)	
No. study subjects with inpatient admission in the period of 2 yr prior to the date of *H. influenzae* meningitis diagnosis	268 (21.6)	1310 (17.6)	0.001
Patients admitted with the following diagnosis categories in the period of 2 yr prior to the date of *H. influenzae* meningitis diagnosis			
Infectious diseases	40 (3.2)	123 (1.7)	<0.001
Cancer	1 (0.1)	1 (0.0)	0.15
Blood/immune diseases	2 (0.2)	10 (0.1)	0.81
Endocrine diseases	6 (0.5)	46 (0.6)	0.57
Nervous system diseases	9 (0.7)	31 (0.4)	0.14
Eye diseases	1 (0.1)	15 (0.2)	0.36
Ear diseases	25 (2.0)	74 (1.0)	0.002
Otitis media	25 (2.0)	71 (1.0)	0.001
Respiratory diseases	57 (4.6)	340 (4.6)	0.97
Digestive system diseases	22 (1.8)	112 (1.5)	0.48
Skin diseases	7 (0.6)	36 (0.5)	0.71
Rheumatologic diseases	3 (0.2)	9 (0.1)	0.29
Genitourinary diseases	6 (0.5)	24 (0.3)	0.37
Neonatal and congenital diseases	69 (5.6)	394 (5.3)	0.70
Injury, poisoning, and external causes of morbidity	18 (1.4)	93 (1.2)	0.56

*If not stated otherwise data are number and percentage of patients or individuals from the population control cohort.
IQR indicates interquartile range.

ing the whole study period for the *H. influenzae* meningitis patients compared with the population controls. During 0 to <5 years from index date, the relative risk of inpatient admission for nervous system diseases was increased by a factor of 12, whereas the relative risk decreased to 2.03 (95% CI, 1.11–3.72) 20 to <25 years from index date. The inpatient admission rates were significantly increased for the *H. influenzae* meningitis patients in the following subcategories of the nervous system: epilepsies/seizure disorders and cerebral palsy and other paralytic syndromes (Table 2). The relative risk of inpatient admission for eye and ear diseases was increased during the first 10 years from index date. In the category of ear diseases a diagnosis of otitis media was the main reason for getting admitted. An increased relative risk of inpatient admission for endocrine diseases was mainly driven by inpatient admissions due to diabetes mellitus in the *H. influenzae* meningitis patients (data not shown).

Of interest, no increased relative risk of inpatient admission for infectious or respiratory diseases was observed in the *H. influenzae* meningitis patients.

Hospital Outpatient Service

The overall relative risk of requiring hospital outpatient services was only slightly increased for the *H. influenzae* meningitis patients compared with population controls the first 15 years from index date and thereafter decreased to that of the population controls (Table 3). The *H. influenzae* meningitis patients had significantly more hospital outpatient services due to nervous system diseases and ear diseases than the population controls. The predominating subcategories of the nervous system diseases leading to hospital outpatient services were epilepsies/seizure disorders and cerebral palsy and other paralytic syndromes (Table 3). The hospital outpatient services due to ear diseases were mainly caused by otitis media and hearing loss problems. No increased relative risk of requiring hospital outpatient services due to infectious or respiratory diseases was observed in the *H. influenzae* meningitis patients. The *H. influenzae* meningitis patients were not seen more often due to diabetes mellitus than population controls (data not shown).

DISCUSSION

In this nationwide, population-based cohort study, we found no increased long-mortality in children diagnosed with *H. influenzae* meningitis. However for the *H. influenzae* meningitis patients, the overall relative risk of inpatient admission and of requiring hospital outpatient services was increased during the first 15 years from index date. Especially, the relative risk of inpatient admission for nervous system diseases was increased during the whole study period.

The major strengths of the study are its large sample size, the population-based design, and the long and complete follow-up. The unique Danish Civil Registration System enabled us to identify a large population control cohort of individuals well matched in terms of gender, age, and country of birth. Through the Danish

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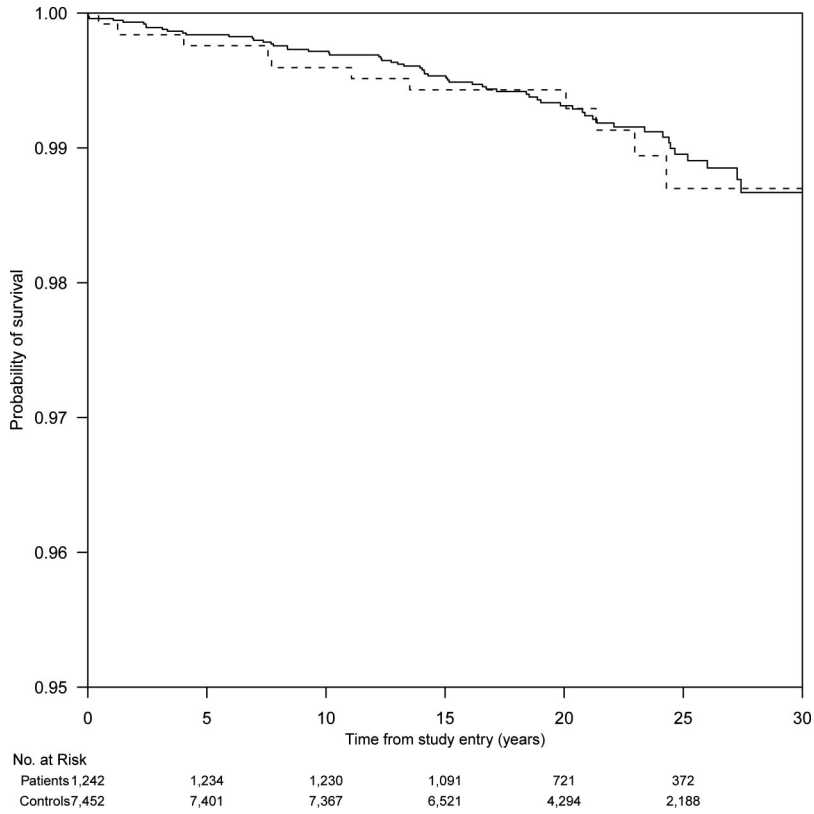

FIGURE 1. Kaplan-Meier survival curves of patients with *Haemophilus influenzae* meningitis (dashed line) and population controls (solid line), Denmark, 1977–1996.

national registers, we had access to complete data on date of death, causes of death, inpatient admissions, and hospital outpatient services and importantly, these data were obtained from the same data sources for both cohorts.

We relied on register-based discharge diagnoses that may not be accurate. However, the registration of meningococcal meningitis in the Danish National Hospital Register has been shown to be substantially valid,[8] and a similar high sensitivity for the *H. influenzae* meningitis diagnoses can be assumed. In addition, the number of *H. influenzae* meningitis patients retrieved from the Danish National Hospital Register was consistent with the numbers published on annual cases of *H. influenzae* meningitis in Denmark.[5,9] We did not have access to clinical and paraclinical data obtained during the inpatient admissions or outpatient visits. Our data thereby do not allow identification of clinical predictors of long-term mortality or information on neurologic sequelae in the *H. influenzae* meningitis patients. As the registries did not include information about serotype, we were not able to subcategorize the patients according to this factor. Further, we were not able to control for confounding from educational level or socioeconomic status.

In the first 10 years of the conjugate vaccine era in Denmark, from 1994 to 2005, there were 29 confirmed cases of *H. influenzae* meningitis in children; of whom, 16 cases (53%) were due to Hib and 14 cases (47%) were due to non-Hib.[9] In our study, we decided not to include the few patients diagnosed later than 1996 as we consider these children to be a selected population biased by uncertainty of vaccination status and possible immune deficiency.

Initiating the study, with the sequelae of *H. influenzae* meningitis in mind, we hypothesized that children treated for the disease were likely to have an increased long-term mortality. However, our study, as the only one to our knowledge on the subject, revealed no difference in long-term mortality compared with the background population. Of interest, neither children diagnosed with *H. influenzae* meningitis nor with meningococcal meningitis carry any increased long-term risk of death due to infections, rheumatologic diseases, or cancer.[10]

Before the *H. influenzae* meningitis episode, the patients had an increased inpatient admission rate mainly due to the infections in general and otitis media. Although a predisposition to infectious disease and otitis media may contribute to an increased risk of *H. influenzae* meningitis, the numbers are small and can only explain a minor proportion of the meningitis cases. An increased risk of inpatient admission and of requiring hospital outpatient services was observed in the *H. influenzae* meningitis patients up to 15 years after their initial meningitis episode. This was explained by increased morbidity in the *H. influenzae* meningitis population caused by nervous system and ear diseases, whereas an increased risk of further severe infections could not be registered. These observations are in accordance with the literature reporting lifelong disabilities such as hearing loss, cognitive delay (mental retardation and learning disability), motor abnormalities, and seizures to occur in 14% to 28% of children after *H. influenzae* meningitis.[1,11,12] Taylor et al reported persisting neurologic sequelae in 14 out of 97 children (14%) treated for Hib meningitis, with a mean follow-up of 8.1 years.[1] The majority of sequelae was due to sensorineural hearing loss

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TABLE 2. Inpatient Admission Rates for *Haemophilus influenzae* Meningitis Patients and Population Controls With Relative Risk Overall and Stratified on ICD Diagnoses

Periods	0–<5 yr From Index Date IR* (95% CI†)	RR† (95% CI)	5–<10 yr From Index Date IR (95% CI)	RR (95% CI)	10–<15 yr From Index Date IR (95% CI)	RR (95% CI)	15–<20 yr From Index Date IR (95% CI)	RR (95% CI)	20–<25 yr From Index Date IR (95% CI)	RR (95% CI)
All diagnoses										
Meningitis patients	13.99 (13.08–14.95)	1.52 (1.41–1.64)	8.99 (8.27–9.77)	1.38 (1.26–1.52)	9.53 (8.78–10.34)	1.21 (1.11–1.33)	12.92 (11.91–14.02)	1.03 (0.94–1.12)	17.04 (15.56–18.67)	0.99 (0.89–1.09)
Population controls	9.20 (8.89–9.51)		6.50 (6.24–6.76)		7.85 (7.56–8.14)		12.56 (12.14–12.99)		17.30 (16.67–17.95)	
Infectious disease										
Meningitis patients	0.82 (0.63–1.08)	1.59 (1.16–2.16)	0.34 (0.22–0.52)	1.18 (0.74–1.88)	0.30 (0.19–0.48)	1.11 (0.67–1.84)	0.40 (0.25–0.64)	1.04 (0.63–1.72)	0.33 (0.17–0.64)	0.94 (0.46–1.89)
Population controls	0.52 (0.45–0.60)		0.29 (0.24–0.35)		0.27 (0.22–0.33)		0.39 (0.32–0.47)		0.35 (0.27–0.46)	
Cancers										
Meningitis patients	0.78 (0.58–1.03)	1.40 (0.02–1.91)	0.08 (0.03–0.19)	0.21 (0.09–0.51)	1.32 (1.06–1.65)	3.43 (2.60–4.52)	0.38 (0.24–0.61)	0.71 (0.43–1.17)	0.04 (0.01–0.26)	0.09 (0.01–0.63)
Population controls	0.56 (0.48–0.64)		0.39 (0.33–0.46)		0.39 (0.33–0.46)		0.54 (0.46–0.63)		0.42 (0.33–0.53)	
Endocrine disease										
Meningitis patients	0.31 (0.20–0.48)	2.65 (1.55–4.55)	0.36 (0.24–0.54)	2.31 (1.41–3.78)	0.45 (0.31–0.66)	2.45 (1.56–3.83)	0.31 (0.19–0.53)	1.85 (1.02–3.38)	0.55 (0.33–0.92)	1.22 (0.70–2.13)
Population controls	0.12 (0.09–0.16)		0.15 (0.12–0.20)		0.18 (0.15–0.24)		0.17 (0.13–0.23)		0.45 (0.36–0.57)	
Nervous system disease										
Meningitis patients	2.34 (1.99–2.76)	12.43 (9.35–16.53)	1.46 (1.19–1.80)	8.17 (5.95–11.22)	0.97 (0.75–1.26)	3.82 (2.74–5.30)	0.92 (0.68–1.25)	4.01 (2.70–5.95)	0.52 (0.31–0.87)	2.03 (1.11–3.72)
Population controls	0.19 (0.15–0.24)		0.18 (0.14–0.23)		0.25 (0.21–0.31)		0.23 (0.18–0.29)		0.25 (0.19–0.35)	
Epilepsies/ seizure disorders										
Meningitis patients	1.02 (0.80–1.30)	8.79 (5.97–12.96)	0.71 (0.53–0.96)	6.43 (4.20–9.84)	0.47 (0.32–0.68)	3.29 (2.07–5.21)	0.67 (0.47–0.96)	5.59 (3.40–9.20)	0.40 (0.22–0.73)	2.61 (1.29–5.31)
Population controls	0.12 (0.09–0.16)		0.11 (0.08–0.15)		0.14 (0.11–0.19)		0.12 (0.08–0.17)		0.15 (0.10–0.23)	
Cerebral palsy and other paralytic syndromes										
Meningitis patients	0.21 (0.12–0.36)	4.59 (2.23–9.45)	0.36 (0.24–0.54)	13.18 (6.24–27.84)	0.35 (0.23–0.54)	8.38 (4.32–16.26)	0.18 (0.09–0.36)	3.67 (1.52–8.85)	0.07 (0.02–0.29)	—
Population controls	0.05 (0.03–0.07)		0.03 (0.01–0.05)		0.04 (0.03–0.07)		0.05 (0.03–0.08)		0	
Eye diseases										
Meningitis patients	0.31 (0.20–0.48)	1.73 (1.04–2.88)	0.19 (0.11–0.34)	2.00 (1.04–3.84)	0.03 (0.01–0.13)	0.80 (0.18–3.49)	0.18 (0.09–0.36)	3.18 (1.35–7.50)	0.07 (0.02–0.29)	0.99 (0.22–4.42)
Population controls	0.18 (0.14–0.23)		0.10 (0.07–0.14)		0.04 (0.03–0.07)		0.06 (0.03–0.09)		0.07 (0.04–0.13)	
Ear diseases										
Meningitis patients	1.03 (0.81–1.32)	3.00 (2.22–4.05)	0.60 (0.44–0.83)	3.36 (2.25–5.02)	0.12 (0.06–0.25)	1.02 (0.46–2.28)	0.04 (0.01–0.18)	0.66 (0.15–2.85)	0.11 (0.04–0.34)	1.62 (0.45–5.80)
Population controls	0.34 (0.29–0.41)		0.18 (0.14–0.23)		0.11 (0.08–0.16)		0.07 (0.04–0.11)		0.07 (0.04–0.12)	
Otitis media										
Meningitis patients	0.73 (0.54–0.97)	2.90 (2.03–4.14)	0.37 (0.25–0.56)	3.36 (2.02–5.60)	0.02 (0.00–0.12)	0.29 (0.04–2.12)	0.04 (0.01–0.18)	1.99 (0.40–9.85)	0.07 (0.02–0.29)	11.87 (1.08–130.96)
Population controls	0.25 (0.20–0.31)		0.11 (0.08–0.15)		0.06 (0.04–0.09)		0.02 (0.01–0.05)		0.01 (0.00–0.04)	
Respiratory disease										
Meningitis patients	2.93 (2.53–3.39)	1.20 (1.02–1.41)	0.91 (0.70–1.18)	1.08 (0.81–1.43)	0.77 (0.58–1.03)	0.90 (0.66–1.23)	0.83 (0.60–1.14)	1.02 (0.72–1.45)	0.74 (0.47–1.14)	1.45 (0.89–2.36)
Population controls	2.44 (2.28–2.60)		0.85 (0.76–0.94)		0.85 (0.76–0.95)		0.81 (0.71–0.93)		0.51 (0.41–0.63)	
Digestive system diseases										
Meningitis patients	0.84 (0.64–1.10)	1.24 (0.92–1.68)	0.65 (0.48–0.89)	1.10 (0.78–1.54)	0.59 (0.42–0.82)	0.80 (0.56–1.14)	0.94 (0.69–1.27)	1.03 (0.74–1.43)	1.25 (0.89–1.75)	0.96 (0.67–1.38)
Population controls	0.68 (0.60–0.77)		0.59 (0.52–0.67)		0.73 (0.65–0.82)		0.91 (0.80–1.03)		1.30 (1.14–1.49)	
Rheumatologic diseases										
Meningitis patients	0.10 (0.04–0.22)	0.68 (0.29–1.58)	0.08 (0.03–0.19)	0.42 (0.17–1.03)	0.55 (0.39–0.78)	1.54 (1.05–2.26)	0.67 (0.47–1.96)	1.14 (0.77–1.68)	0.48 (0.28–0.82)	0.65 (0.37–1.15)
Population controls	0.14 (0.11–0.19)		0.20 (0.15–0.25)		0.36 (0.30–0.43)		0.59 (0.50–0.69)		0.74 (0.62–0.88)	
Urinary tract disease										
Meningitis patients	0.52 (0.37–0.73)	1.12 (0.77–1.63)	0.29 (0.18–0.46)	0.83 (0.51–1.36)	0.35 (0.23–0.54)	0.86 (0.54–1.36)	0.45 (0.29–0.69)	0.64 (0.41–1.02)	1.03 (0.71–1.49)	1.50 (0.99–2.27)
Population Controls	0.46 (0.40–0.54)		0.35 (0.30–0.42)		0.41 (0.35–0.48)		0.69 (0.60–0.80)		0.69 (0.57–0.83)	
Pericongenital diseases										
Meningitis patients	0.70 (0.52–0.94)	1.20 (0.87–1.67)	0.70 (0.52–0.94)	1.29 (0.93–1.80)	0.37 (0.24–0.56)	1.34 (0.85–2.13)	0.18 (0.09–0.36)	1.06 (0.50–2.25)	0.22 (0.10–0.49)	1.62 (0.66–3.99)
Population Controls	0.58 (0.51–0.66)		0.54 (0.47–0.62)		0.27 (0.22–0.33)		0.17 (0.13–0.23)		0.14 (0.09–0.21)	
Trauma										
Meningitis patients	1.49 (1.21–1.82)	1.02 (0.82–1.28)	1.23 (0.99–1.54)	0.98 (0.77–1.25)	1.66 (1.36–2.02)	0.97 (0.78–1.20)	2.01 (1.64–2.48)	0.82 (0.66–1.02)	2.02 (1.55–2.64)	0.95 (0.72–1.27)
Population Controls	1.45 (1.34–1.58)		1.25 (1.15–1.37)		1.71 (1.58–1.85)		2.64 (2.27–2.65)		2.13 (1.91–2.36)	

*IR: Incidence rates (number of inpatient admissions/100 PYRS).

†RR: Relative risk (IR for *H. influenzae* meningitis patients/IR for population control).

CI indicates confidence interval; ICD, International Classification of Diseases.

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TABLE 3. Hospital Outpatient Service Rates for *Haemophilus influenzae* Meningitis Patients (Diagnosed January 1, 1986 and onwards) and Population Controls With Relative Risk Overall and Stratified on ICD Diagnoses

Periods	0–<5 yr From Index Date IR* (95% CI)	RR† (95% CI)	5–<10 yr From Index Date IR (95% CI)	RR (95% CI)	10–<15 yr From Index Date IR (95% CI)	RR (95% CI)	15–<20 yr From Index Date IR (95% CI)	RR (95% CI)	20–<25 yr From Index Date IR (95% CI)	RR (95% CI)
All diagnoses										
Meningitis patients	8.23 (7.25–9.35)	1.87 (1.62–2.17)	14.40 (13.08–15.85)	1.35 (1.21–1.50)	27.13 (25.24–29.17)	1.23 (1.14–1.33)	57.17 (53.06–61.60)	1.05 (0.97–1.14)	300.27 (247.77–363.90)	0.84 (0.69–1.04)
Population controls	4.39 (4.09–4.72)		10.70 (10.23–11.20)		22.04 (21.33–22.77)		54.50 (52.82–56.24)		355.71 (330.77–382.53)	
Infectious disease										
Meningitis patients	0.07 (0.02–0.28)	2.00 (0.40–9.93)	0	—	0.11 (0.04–0.34)	0.72 (0.22–2.38)	1.16 (0.69–1.96)	1.37 (0.76–2.44)	17.32 (7.78–38.56)	2.95 (1.11–7.86)
Population controls	0.03 (0.02–0.08)		0.06 (0.03–0.11)		0.15 (0.10–0.23)		0.85 (0.66–1.09)		5.87 (3.33–10.34)	
Cancers										
Meningitis patients	0.03 (0.00–0.25)	0.43 (0.06–3.27)	0.21 (0.09–0.46)	1.13 (0.47–2.69)	0.44 (0.25–0.78)	1.26 (0.68–2.35)	1.49 (0.94–2.37)	1.51 (0.90–2.53)	2.89 (0.41–20.50)	0.98 (0.12–8.17)
Population controls	0.08 (0.05–0.14)		0.18 (0.13–0.26)		0.35 (0.27–0.46)		0.99 (0.78–1.25)		2.94 (1.32–6.53)	
Endocrine disease										
Meningitis patients	0.21 (0.09–0.46)	1.39 (0.57–3.37)	0.35 (0.19–0.64)	1.50 (0.75–3.00)	0.59 (0.36–0.97)	1.78 (1.02–3.11)	0.58 (0.28–1.22)	0.60 (0.27–1.29)	2.89 (0.41–20.50)	0.28 (0.04–2.09)
Population controls	0.15 (0.10–0.22)		0.23 (0.17–0.31)		0.33 (0.26–0.44)		0.98 (0.77–1.23)		10.27 (6.70–15.76)	
Nervous system disease										
Meningitis patients	1.45 (1.07–1.97)	6.83 (4.39–10.62)	1.80 (1.37–2.37)	4.88 (3.39–7.04)	1.74 (1.31–2.32)	4.70 (3.21–6.88)	1.66 (1.07–2.57)	2.09 (1.26–3.48)	5.77 (1.44–23.09)	1.31 (0.28–6.07)
Population controls	0.21 (0.15–0.29)		0.37 (0.29–0.47)		0.37 (0.29–0.48)		0.79 (0.61–1.03)		4.40 (2.29–8.46)	
Epilepsies/seizure disorders										
Meningitis patients	0.48 (0.29–0.82)	6.48 (3.04–13.78)	0.83 (0.56–1.24)	4.97 (2.89–8.54)	0.59 (0.36–0.97)	3.00 (1.65–5.47)	1.08 (0.63–1.86)	3.10 (1.58–6.05)	5.77 (1.44–23.09)	2.36 (0.46–12.17)
Population controls	0.07 (0.04–0.13)		0.17 (0.12–0.24)		0.18 (0.14–0.28)		0.35 (0.24–0.52)		2.45 (1.02–5.88)	
Cerebral palsy and other paralytic syndromes										
Meningitis patients	0.59 (0.37–0.95)	8.52 (4.07–17.84)	0.69 (0.45–1.08)	8.01 (4.10–15.65)	0.74 (0.48–1.15)	8.00 (4.10–15.62)	0.17 (0.04–0.66)	1.49 (0.32–7.01)	0	—
Population controls	0.07 (0.04–0.12)		0.09 (0.05–0.14)		0.09 (0.06–0.15)		0.11 (0.06–0.22)		0	
Eye diseases										
Meningitis patients	0.38 (0.21–0.69)	3.31 (1.59–6.90)	0.52 (0.31–0.86)	2.82 (1.53–5.20)	0.41 (0.23–0.74)	1.65 (0.85–3.22)	0.83 (0.45–1.54)	1.49 (0.74–2.98)	0	—
Population controls	0.12 (0.07–0.18)		0.18 (0.13–0.26)		0.25 (0.18–0.34)		0.56 (0.41–0.76)		4.40 (2.29–8.46)	
Ear diseases										
Meningitis patients	1.35 (0.99–1.85)	6.17 (3.95–9.65)	1.94 (1.50–2.53)	3.36 (2.43–4.67)	1.30 (0.93–1.80)	2.47 (1.67–3.66)	1.16 (0.69–1.96)	2.25 (1.22–4.17)	11.55 (4.33–30.77)	11.80 (2.16–64.44)
Population controls	0.22 (0.16–0.30)		0.58 (0.47–0.70)		0.52 (0.42–65)		0.52 (0.37–0.71)		0.98 (0.24–3.91)	
Otitis media										
Meningitis patients	0.62 (0.39–0.99)	7.22 (3.64–14.32)	0.66 (0.42–1.03)	3.26 (1.87–5.70)	0.15 (0.06–0.39)	1.26 (0.43–3.71)	0.41 (0.17–1.00)	4.25 (1.35–13.40)	2.89 (0.41–20.50)	5.90 (0.37–94.35)
Population controls	0.09 (0.05–0.14)		0.20 (0.15–0.28)		0.12 (0.07–0.39)		0.10 (0.05–0.20)		0.49 (0.07–3.47)	
Hearing loss and acoustic neuritis in infectious diseases										
Meningitis patients	0.48 (0.29–0.82)	7.66 (3.48–16.86)	0.87 (0.59–1.28)	5.78 (3.34–10.00)	0.48 (0.28–0.83)	2.60 (1.36–4.98)	0.41 (0.17–1.00)	2.71 (0.94–7.79)	8.66 (2.79–26.86)	
Population controls	0.06 (0.04–0.11)		0.15 (0.10–0.22)		0.19 (0.13–0.26)		0.15 (0.08–0.28)		0	
Respiratory disease										
Meningitis patients	0.55 (0.34–0.90)	0.78 (0.46–1.32)	0.49 (0.29–0.82)	0.57 (0.33–0.98)	0.81 (0.54–1.24)	0.86 (0.55–1.34)	1.33 (0.81–2.17)	1.02 (0.60–1.74)	8.66 (2.79–26.86)	1.97 (0.53–7.27)
Population controls	0.71 (0.59–0.84)		0.85 (0.73–1.00)		0.95 (0.81–1.11)		1.30 (1.06–1.59)		4.40 (2.29–8.46)	
Digestive system diseases										
Meningitis patients	0.28 (0.14–0.55)	1.42 (0.66–3.06)	0.56 (0.34–0.91)	1.58 (0.91–2.73)	0.96 (0.66–1.41)	1.09 (0.72–1.66)	2.82 (2.02–3.95)	0.92 (0.64–1.31)	2.89 (0.41–20.50)	0.22 (0.03–1.61)
Population controls	0.20 (0.14–0.27)		0.35 (0.27–0.45)		0.88 (0.75–1.04)		3.08 (2.70–3.51)		13.21 (9.06–19.26)	
Rheumatologic diseases										
Meningitis patients	0.14 (0.05–0.37)	0.65 (0.23–1.82)	0.59 (0.37–0.95)	0.84 (0.50–1.39)	2.81 (2.25–3.52)	1.39 (1.08–1.78)	6.64 (5.33–8.26)	1.44 (1.13–1.84)	28.87 (15.53–53.66)	1.07 (0.55–2.10)
Population controls	0.21 (0.15–0.29)		0.70 (0.59–0.84)		2.03 (1.82–2.26)		4.60 (4.13–5.12)		26.91 (20.66–35.05)	
Urinary tract disease										
Meningitis patients	0.14 (0.05–0.37)	0.57 (0.21–1.60)	0.35 (0.19–0.64)	0.53 (0.28–1.01)	0.48 (0.28–0.83)	0.84 (0.47–1.50)	2.16 (1.47–3.17)	0.93 (0.61–1.40)	11.55 (4.33–30.77)	0.79 (0.28–2.23)
Population controls	0.24 (0.18–0.33)		0.66 (0.55–0.79)		0.57 (0.47–0.70)		2.33 (2.00–2.71)		14.68 (10.26–20.99)	
Pericongenital diseases										
Meningitis patients	0.73 (0.47–1.11)	1.91 (1.17–3.13)	0.83 (0.56–1.24)	1.04 (0.67–1.60)	1.15 (0.81–1.63)	1.75 (1.18–2.62)	0.66 (0.33–1.33)	1.08 (0.51–2.30)	2.89 (0.41–20.50)	0.84 (0.10–6.85)
Population controls	0.38 (0.30–0.48)		0.80 (0.68–0.95)		0.65 (0.54–0.79)		0.61 (0.46–0.82)		3.42 (1.63–7.18)	

(Continued)

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TABLE 3. *(Continued)*

Periods	0–<5 yr From Index Date IR* (95% CI)	RR† (95% CI)	5–<10 yr From Index Date IR (95% CI)	RR (95% CI)	10–<15 yr From Index Date IR (95% CI)	RR (95% CI)	15–<20 yr From Index Date IR (95% CI)	RR (95% CI)	20–<25 yr From Index Date IR (95% CI)	RR (95% CI)
Trauma										
Meningitis patients	0.90 (0.61–1.32)	1.20 (0.79–1.83)	2.43 (1.92–3.07)	1.09 (0.85–1.41)	4.00 (3.31–4.83)	1.04 (0.85–1.28)	5.23 (4.08–6.69)	0.85 (0.66–1.11)	20.21 (9.63–42.39)	0.66 (0.30–1.43)
Population controls	0.75 (0.63–0.89)		2.22 (2.01–2.46)		3.83 (3.54–4.15)		6.12 (5.57–6.72)		30.82 (24.08–39.46)	
Pregnancy										
Meningitis patients	0		0		0.15 (0.06–0.39)	1.04 (0.36–3.02)	0.83 (0.45–1.54)	0.45 (0.24–0.86)	8.66 (2.79–26.86)	0.38 (0.12–1.21)
Population controls	0		0		0.14 (0.09–0.21)		1.84 (1.55–2.18)		23.00 (17.28–30.61)	
Health status and contact with health services										
Meningitis patients	1.14 (0.81–1.61)	1.95 (1.31–2.88)	2.50 (1.98–3.15)	1.02 (0.79–1.31)	10.47 (9.32–11.77)	1.10 (0.97–1.25)	25.14 (22.46–28.14)	0.94 (0.83–1.06)	153.02 (116.91–200.30)	0.82 (0.62–1.09)
Population controls	0.59 (0.48–0.71)		2.45 (2.23–2.70)		9.51 (9.05–10.00)		26.80 (25.63–28.02)		186.42 (168.61–206.11)	

*IR: Incidence rates (number of hospital outpatient services/100 PYRS).
†RR: Relative risk (IR for *H. influenzae* meningitis patients/IR for population control).
CI indicates confidence interval; ICD, International Classification of Diseases.

(11 patients). Two cases of epilepsia and 1 case of mental retardation were diagnosed during follow-up. Only small differences in cognitive, academic, and behavioral skills were found by comparing the children treated for meningitis with their nearest siblings. The authors concluded that the consequences of disease were found to be less severe than once thought, and that the prognosis was favorable for the majority.[1]

It is important to stress that our results on the long-term mortality following *H. influenzae* meningitis only accounts for children in a high standard industrialized country, whereas children in low-income countries may be more vulnerable to any long-term neuropsychological sequelae. A mere hearing loss can be devastating for a child living in resource-limited settings, with low chance of a proper education and even the risk of being left alone. In a systematic review on sequelae due to bacterial meningitis among African children, including 9 studies with data on *H. influenzae* meningitis sequelae, the median risk of neuropsychological sequelae was 25% (IQR, 17%–28%) in survivors of *H. influenzae* meningitis.[13] In 2 studies from Gambia the postdischarge case fatality rates were 14% and 16% with a mean follow-up of 4.2 years and 8 months of confirmed *H. influenzae* meningitis.[14,15] Gambia was one of the 19 countries out of 46 countries in the World Health Organization African region that as of 2008 had included Hib conjugate vaccine in their national immunization program.[16]

CONCLUSION

We conclude that in a high-standard industrialized country children surviving with the acute phase of *H. influenzae* meningitis have no increased long-term mortality. They however have increased risk of inpatient admission and of requiring hospital outpatient services up to 16 years from the initial *H. influenzae* meningitis episode, mainly due to nervous system diseases and ear diseases.

APPENDIX A

The 18 categories of specific underlying causes of death were specified by the following ICD-8 codes for the years 1977 to 1993 and ICD-10 codes from 1994 to 2009: infectious diseases, 000–134.99/A00-B99.9; cancer, 140–239.99/C-D48.9; blood/immune diseases, 280–289.99/D50-D89.9; endocrine diseases, 240–279.09/E00-E90.9; mental diseases/drug abuse, 290–315/F00-F99.9; nervous system diseases, 320–358.09/G00-G99.8; eye diseases, 360–379.3/H00–59.9; ear diseases, 380–389.99/H60–95.9; cardiovascular diseases, 390–458.99/I00-I99.9; respiratory diseases, 460–519.99/J00-J99.8; digestive system diseases, 520–577.99/K00-K93.8; skin diseases, 680–709.99/L00-L99.8; rheumatologic diseases, 710–738.09/M00-M99.9; genitourinary diseases, 580–629.99/N00-N99.9; pregnancy, childbirth, and the puerperium, 630–678.09/O00-O99.8; neonatal/congenital disorders, 740–779.99/P00-Q99.9; injury/poisoning, 800–999/S00-T98.3,V,W,X,Y; and ill-defined causes and no cause of death reported, 780–796.99/R00-R99.9.

APPENDIX B

Infections of the central nervous system were defined by the following ICD-8 codes for the years 1977 to 1993: bacterial meningitis, 320.00–320.99; Listeria meningitis, 027.01; meningococcal infection, 036.00–036.99; aseptic meningitis due to enterovirus, 045.00–045.99; varicella meningitis/encephalitis, 052.01; zoster meningitis/encephalitis, 053.02; and Herpesviral meningitis/encephalitis, 054.03.

Infections of the central nervous system were defined by the following ICD-10 codes for the years 1994 to 2007: bacterial

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meningitis, G00.0-G01.9; Listeria meningitis and meningoencephalitis, A32.1; meningococcal infection, A39.0-A39.9; unspecified viral encephalitis, A86; enteroviral meningitis, A87.0; adenoviral meningitis, A87.1; lymphocytic choriomeningitis, A87.2; other viral meningitis, A87.8; viral meningitis, unspecified, A87.9; Herpesviral meningitis, B00.3; Herpesviral encephalitis, B00.4; varicella meningitis, B01.0; varicella encephalitis, B01.1; zoster encephalitis, B02.0; zoster meningitis, B02.1; and zoster with other nervous system involvement, B02.2.

APPENDIX C

The 18 categories of primary discharge diagnoses and hospital outpatient services were specified by the following ICD-8 codes for the years 1977 to 1993 and ICD-10 codes from 1994 to 2007: infectious diseases, 000–134.99/A00-B99.9; cancer, 140–239.99/C-D48.9; blood/immune diseases, 280–289.99/D50-D89.9; endocrine diseases, 240–279.09/E00-E90.9; mental diseases/drug abuse, 290–315/F00-F99.9; nervous system diseases, 320–358.09/G00-G99.8; eye diseases, 360–379.3/H00–59.9; ear diseases, 380–389.99/H60–95.9; cardiovascular diseases, 390–458.99/I00-I99.9; respiratory diseases, 460–519.99/J00-J99.8; digestive system diseases, 520–577.99/K00-K93.8; skin diseases, 680–709.99/L00-L99.8; rheumatologic diseases, 710–738.09/M00-M99.9; genitourinary diseases, 580–629.99/N00-N99.9; pregnancy, childbirth, and the puerperium, 630–678.09/O00-O99.8; neonatal/congenital disorders, 740–779.99/P00-Q99.9; injury/poisoning, 800–999/S00-T98.3,V,W,X,Y; and abnormal findings not elsewhere classified, 780–796.99/R00-R99.9.

APPENDIX D

Endocrine diseases were subcategorized into disorders of thyroid gland, 240–246.09/E00-E07.9; diabetes mellitus, 249–250.09/E10-E14.9; other disorders of glucose regulation and pancreatic internal secretion, 251–251.09/E15-E16.9; disorders of other endocrine glands, 252–258.99/E20-E35.8; nutritional disorders, 260–269.99/E40-E68.9; and metabolic disorders, 270–279.09/E70-E90.9.

Nervous system diseases were subcategorized into inflammatory diseases of the central nervous system, 320–324.09/G00–09.9; hereditary and degenerative diseases of the nervous system, 330–342.99/G10-G37.9; epilepsies/seizure disorders, 345–346.09/G40-G47.9; cerebral palsy and other paralytic syndromes, 343–344.99/G80-G83.9; and other disorders of the nervous system, 347–358.09/G50-G73.7, G90-G99.8.

Ear diseases were subcategorized into diseases of the external ear, 380–380.09/H60-H62.8; otitis media, 381–382.99/H65-H67.8; diseases of middle ear and mastoid except for otitis media, 383–383.99/H68-H75.8; diseases of inner ear, 384–386.99/H80-H83.9; hearing loss and acoustic neuritis in infectious diseases, 388–389.99/H90-H91.9, H94-H94.8; and other disorders of ear, 387–387.99/H92-H93.9, H95-H95.9.

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Educational Achievement and Economic Self-sufficiency in Adults After Childhood Bacterial Meningitis

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Importance To our knowledge, no previous study has examined functioning in adult life among persons who had bacterial meningitis in childhood.

Objective To study educational achievement and economic self-sufficiency in adults diagnosed as having bacterial meningitis in childhood.

Design, Setting, and Participants Nationwide population-based cohort study using national registries of Danish-born children diagnosed as having meningococcal, pneumococcal, or *Haemophilus influenzae* meningitis in the period 1977-2007 (n=2784 patients). Comparison cohorts from the same population individually matched on age and sex were identified, as were siblings of all study participants. End of study period was 2010.

Main Outcomes and Measures Cumulative incidences of completed vocational education, high school education, higher education, time to first full year of economic self-sufficiency, and receipt of disability pension and differences in these outcomes at age 35 years among meningitis patients, comparison cohorts, and siblings.

Results By age 35 years, among persons who had a history of childhood meningococcal (n=1338), pneumococcal (n=455), and *H influenzae* (n=991) meningitis, an estimated 11.0% (41.5% vs 52.5%; 95% CI, 7.3%-14.7%), 10.2% (42.6% vs 52.8%; 95% CI, 3.8%-16.6%), and 5.5% (47.7% vs 53.2%; 95% CI, 1.9%-9.1%) fewer persons, respectively, had completed high school and 7.9% (29.3% vs 37.2%; 95% CI, 1.6%-14.2%), 8.9% (28.1% vs 37.0%; 95% CI, 0.6%-17.2%), and 6.5% (33.5% vs 40.0%; 95% CI, 1.4%-11.6%) fewer had attained a higher education compared with individuals from the comparison cohort. Siblings of meningococcal meningitis patients also had lower educational achievements, while educational achievements of siblings of pneumococcal and *H influenzae* meningitis patients did not differ substantially from those in the general population. At end of follow-up, 3.8% (90.3% vs 94.1%; 95% CI, 1.1%-6.5%), 10.6% (84.0% vs 94.6%; 95% CI, 5.1%-16.1%), and 4.3% (90.6% vs 94.9%; 95% CI, 2.0%-6.6%) fewer meningococcal, pneumococcal, and *H influenzae* meningitis patients were economically self-sufficient and 1.5% (3.7% vs 2.3%; 95% CI, −0.2% to 3.2%), 8.7% (10.0% vs 1.3%; 95% CI, 5.0%-12.4%), and 3.7% (6.2% vs 2.5%; 95% CI, 1.6%-5.8%) more received disability pension compared with individuals from the comparison cohort.

Conclusions and Relevance In a Danish population, bacterial meningitis in childhood was associated with lower educational achievement and economic self-sufficiency in adult life. This association may apply particularly to pneumococcal and *H influenzae* meningitis, whereas for meningococcal meningitis the lower educational achievement may be family-related.

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SHORT- AND LONG-TERM MORTALITY in children diagnosed as having bacterial meningitis have been well described.[1-4] The infection may lead to brain damage due to inflammation, infarction, or seizures causing neuronal necrosis,[5] and survivors of childhood bacterial meningitis are at particular risk of hearing loss, seizure disorders, motor deficits, and cognitive impairment.[6] Learning disabilities are well documented as sequelae of the disease,[7] with implications for educational achievement in adolescence.[8]

To our knowledge, no previous study has examined functioning in adult life among persons diagnosed as having bacterial meningitis in childhood. We therefore aimed to estimate educational achievement and economic self-sufficiency among children surviving bacterial meningitis on a population-based, nationwide scale compared with the general population. To elucidate the potential association with family-related factors, we compared the outcomes of the patients with that of their siblings and further estimated the educational achievement of the parents of members of the patient and comparison cohorts.

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METHODS

We used 4 nationwide, population-based cohorts identified from Danish registries: (1) all patients who in the period 1977-2007 and before age 12 years had diagnoses of bacterial meningitis due to *Neisseria meningitidis, Streptococcus pneumoniae*, or *Haemophilus influenzae* and survived to age 13 years; (2) a comparison cohort from the general population individually matched on date of birth and sex; (3) full siblings of the meningitis patients; and (4) full siblings of persons in the population comparison cohort. The outcomes were time from age 13 years to (1) completion of vocational education, (2) completion of high school, (3) completion of higher education, (4) first full year of economic self-sufficiency from personal income, and (5) first year an individual received disability pension.

Cumulative incidence of these outcomes and differences between the cohorts in cumulative incidence at age 35 years were measured. The cumulative incidence curve by age summarizes the age-specific prevalences of the outcomes to age 35 years.

Setting

The population of Denmark younger than age 12 years was 893 650 on January 1, 1977, and 790 691 on January 1, 2010.[9] In the study period, *N meningitidis, S pneumoniae*, and *H influenzae* were the most frequent etiologies of bacterial meningitis in children, and more than 80% of bacterial meningitis cases in Denmark were due to these 3 bacteria.[10,11] During this period, tax-supported medical care and education were available to all Danish residents.

Data Sources

We used the unique 10-digit personal identification number (PIN) assigned to all Danish citizens at birth or immigration to avoid multiple registrations and to track individuals in the following registries, described in detail in eAppendix 1 (available at http://www.jama.com).

From the Danish National Registry of Patients (DNRP) we extracted the first date of any meningococcal, pneumococcal, or *H influenzae* meningitis diagnosis for each patient.[12] Study participants diagnosed as having intrauterine and birth asphyxia or chromosomal abnormalities (*International Statistical Classification of Diseases, 8th Revision* [*ICD-8*] and *10th Revision* [*ICD-10*] codes specified in eAppendix 2) were also identified from this registry.

From the Danish Civil Registration System, the population comparison cohort and siblings and parents of the patients and population comparison cohort members were identified.[13,14] From this registry, we also extracted data on birth, sex, date of immigration/emigration, loss to follow-up, and date of death of all study participants.

From the Danish Medical Birth Registry, we extracted information on birth weight, gestational age at birth, and 5-minute Apgar score.[15]

From the Danish Educational Attainment Registry, Statistics Denmark, we extracted data on the highest educational achievement obtained by the study population in each calendar year during the study period.[16,17] In total, 97% of the ethnic Danish population has nonmissing education information in the registry, with an estimated misclassification of 0% to 3%.[17]

From the Employment Classification Module, Statistics Denmark, we extracted the first date an individual was registered as economically self-sufficient from personal income and the first date an individual received disability pension.[18-20] In the registry, an individual is registered as economically self-sufficient when his or her main income for a full year stems from either business profit or employment (described in eAppendix 1).

The study was approved by the Danish Data Protection Agency. Ethics approval and individual consent are not required by Danish legislation governing this type of study.

Study Population

Cohort of Meningitis Patients. We used the DNRP to identify all patients who (1) were registered with a diagnosis of meningococcal, pneumococcal, or *H influenzae* meningitis (*ICD-8* and *ICD-10* codes specified in eAppendix 3) for the first time during the period January 1, 1977, to January 1, 2007 (January 1, 1997, for *H influenzae* meningitis patients); (2) had diagnoses before age 12 years (before age 5 years for *H influenzae* meningitis patients, as the majority of childhood *H influenzae* meningitis cases occur before age 5 years[21]); (3) were born in Denmark during the period January 1, 1975, to January 1, 1997 (January 1, 1990, for *H influenzae* meningitis patients); and (4) were not diagnosed as having any other neuroinfection (as specified in eAppendix 4) before diagnosis of bacterial meningitis. The *H influenzae* type b conjugate vaccine was introduced into the Danish childhood vaccination program on June 1, 1993.[22] Thus, we did not include *H influenzae* meningitis patients with diagnoses later than December 31, 1996, or born after January 1, 1990, as we consider them a selected population. The 7-valent conjugated pneumococcal vaccine was not introduced into the Danish childhood vaccination program until October 1, 2007,[23] and meningococcal vaccine has never been included. Patients were excluded from the study if they died, emigrated, or were lost to follow-up before age 13 years.

Population Comparison Cohort. Individuals in the population comparison cohorts were individually matched. From the Danish Civil Registration System, we identified for each meningitis patient all Danish citizens who were born on the same date and were the same sex as the patient and were alive and not diagnosed as having meningitis before age 13 years. From this population, we randomly chose 4 individuals for the comparison cohort.

Sibling Cohorts. To take into account potential confounding from family-related factors, we used the Danish Civil Registration System to identify all full siblings of both meningitis patients and individuals from the population comparison cohort who were born in the period January 1, 1975, to

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January 1, 1997 (January 1, 1990, for siblings of *H influenzae* meningitis patients and the corresponding comparison cohort) and alive and living in Denmark at age 13 years.

Parents of the Study Population. We used the Danish Civil Registration System to identify all parents of the meningitis patients and members of the population comparison cohort.

Study Outcome

We measured the time intervals from age 13 years to the first date the individual was registered (1) as having completed vocational education or training (eg, carpenter, dental technician, hairdresser); (2) as having completed high school education (completing the 12th school year); (3) as having completed higher education (obtaining a degree from an institution of higher education; eg, college or university); (4) as economically self-sufficient; and (5) as having received disability pension. In Denmark, completing high school is required for higher education but not for vocational education. In all cohorts, less than 2% had no information on educational achievements, and these individuals were classified in the analyses as having no education other than elementary school.

Statistical Analysis

Observation time was calculated from age 13 years to 1 of the above mentioned outcomes, death, emigration, loss to follow-up, age 35 years, or October 1, 2010, whichever came first. Because most people in Denmark finish their higher education between ages 25 and 30 years, we continued follow-up through age 35 years for each person. For meningitis patients, persons in the population comparison cohort, and siblings, we calculated cumulative incidence of the outcomes, taking into account losses due to death and emigration, and because all individuals were included starting at the same age (13 years), the cumulative incidence function also describes the age-specific prevalence rates.

We calculated the differences between the prevalences at age 35 years for patients vs members of the population comparison cohort, patients vs their siblings, and siblings of patients vs siblings of the comparison cohorts. The analyses were performed separately for patients with meningococcal, pneumococcal, and *H influenzae* meningitis and members of their respective population comparison cohorts and sibling cohorts. Two subanalyses were performed: (1) excluding all individuals in the study population diagnosed as having low birth weight, premature birth, intrauterine and birth asphyxia, a 5-minute Apgar score less than 7, and chromosomal abnormalities and (2) stratifying by birth before and after January 1, 1980.

In a cross-sectional analysis, the educational achievements of parents of meningitis patients and individuals in the population comparison cohort were assessed 1 year before the diagnosis date of bacterial meningitis in the patient population. SPSS, version 19 (IBM Inc), and R software, version 2.14.2, were used for data analysis.

RESULTS

We identified 2924 patients who met the inclusion criteria: 1391 patients with meningococcal meningitis, 496 with pneumococcal meningitis, and 1037 with *H influenzae* meningitis. Fifty-three patients (3.8%) with meningococcal meningitis, 41 (8.3%) with pneumococcal meningitis, and 39 (3.8%) with *H influenzae* meningitis had died, 6 had emigrated, and 1 was lost to follow-up before age 13 years, leaving a total of 2784 patients and 11 136 members of the population comparison cohort in the study (TABLE 1 and FIGURE 1).

Educational Achievement

Time to completion of vocational education, high school, and higher education are shown in FIGURE 2. Number of events in the study population and total observation time are shown in eTable 1. Among meningococcal meningitis patients, an estimated 11.0% fewer (41.5% vs 52.5%; 95% CI, 7.3%-14.7%) had completed high school and 7.9% fewer (29.3% vs 37.2%; 95% CI, 1.6%-14.2%) had obtained a higher education by age 35 years compared with members of the population comparison cohort (TABLE 2). The educational achievement of the meningococcal meningitis patients did not differ substantially from that of their siblings. Of note, by age 35 years an estimated 13.0% fewer siblings of meningococcal meningitis patients (41.1% vs 54.1%; 95% CI, 9.4%-16.6%) had completed high school and 4.6% fewer (32.9% vs 37.5%; 95% CI, −2.0% to 11.2%) had obtained a higher education than siblings of the population comparison cohort.

We observed no substantial difference between pneumococcal meningitis patients and members of the population comparison cohort in estimated proportions completing a vocational education at age 35 years (Figure 2 and Table 2). By age 35 years, an estimated 10.2% fewer (42.6% vs 52.8%; 95% CI, 3.8%-16.6%) and 8.9% fewer (28.1% vs 37.0%; 95% CI, 0.6%-17.2%) pneumococcal meningitis patients had completed high school and higher education compared with members of the population comparison cohort. A lower proportion of pneumococcal meningitis patients had completed high school and higher education compared with their siblings. In contrast, no substantial differences were observed between the 2 cohorts of siblings.

Among *H influenzae* meningitis patients, 5.5% fewer (47.7% vs 53.2%; 95% CI, 1.9%-9.1%) had completed high school and 6.5% fewer (33.5% vs 40.0%; 95% CI, 1.4%-11.6%) had completed higher education by age 35 years compared with members of the population comparison cohort; compared with their siblings, 5.5% fewer (47.7% vs 53.2%; 95% CI, 0.8%-10.2%) and 7.9% fewer (33.5% vs 41.4%; 95% CI, 1.4%-14.4%) had attained these education levels (Figure 2 and Table 2). No substantial differences in educational achievements were observed between the 2 cohorts of siblings.

One year before diagnosis of meningococcal meningitis, parents of the patients had lower educational achieve-

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ments than parents of members of the population comparison cohort (TABLE 3). The educational achievements of parents of pneumococcal and *H influenzae* meningitis patients did not differ substantially from those of the parents of members of the corresponding population comparison cohorts.

Economic Self-sufficiency and Disability Pension

At end of follow-up, an estimated 3.8% (90.3% vs 94.1%; 95% CI, 1.1%-6.5%), 10.6% (84.0% vs 94.6%; 95% CI, 5.1%-16.1%), and 4.3% (90.6% vs 94.9%; 95% CI, 2.0%-6.6%) fewer meningococcal, pneumococcal, and *H influenzae* meningitis patients had been economically self-sufficient compared with the individuals from the comparison cohort, and 1.5% (3.7% vs 2.3%; 95% CI, −0.2% to 3.2%), 8.7% (10.0% vs 1.3%; 95% CI, 5.0%-12.4%), and 3.7% (6.2% vs 2.5%; 95% CI, 1.6%-5.8%) more patients received disability pension (eFigure 1 and Table 2).

A subanalysis in which individuals diagnosed as having underlying neonatal conditions were excluded yielded almost the same estimates as obtained in the analyses including all study participants, except for the estimated prevalence of disability pension at age 35 years in pneumococcal meningitis patients, which was 6.1% (95% CI, 3.6%-9.6%) (eTable 2). We observed no substantial differences in risk estimates in patients born before and after January 1, 1980 (eFigure 2 and eFigure 3).

Table 1. Characteristics of Children Who Had Bacterial Meningitis at Age 0 to 12 Years, Members of the Population Comparison Cohort, and Siblings and Parents of These 2 Cohorts

Characteristics	Patients (n = 2784)	Population Comparison Cohort (n = 11 136)	Siblings of Patients (n = 2882)	Siblings of Population Comparison Cohort (n = 11 265)	Mothers of Patients (n = 2784)	Fathers of Patients (n = 2753)	Mothers of Population Comparison Cohort (n = 11 077)	Fathers of Population Comparison Cohort (n = 10 987)
Male, No. (%)	1542 (55.4)	6168 (55.4)	1567 (54.4)	6217 (55.2)				
Bacterial etiology, No.								
Meningococcal meningitis	1338	5352	1489	5846	1338	1319	5326	5288
Pneumococcal meningitis	455	1820	501	1974	455	452	1812	1794
Haemophilus influenzae meningitis	991	3964	892	3445	991	982	3939	3905
Age at time of patient diagnosis, median (IQR), y[a]								
Meningococcal meningitis	2.5 (1.0 to 5.0)	2.5 (1.0 to 5.0)	3.8 (−1.3 to 8.2)	3.7 (−1.2 to 7.5)	30.0 (25.8 to 34.5)	33.0 (28.6 to 38.2)	30.9 (27.1 to 34.9)	33.5 (29.6 to 38.0)
Pneumococcal meningitis	1.0 (0.6 to 2.2)	1.0 (0.6 to 2.2)	2.1 (−2.5 to 5.7)	2.8 (−2.3 to 5.8)	29.3 (26.0 to 32.8)	31.6 (28.4 to 35.5)	29.4 (25.9 to 33.0)	31.6 (28.2 to 36.0)
H influenzae meningitis	1.2 (0.7 to 1.9)	1.2 (0.7 to 1.9)	2.9 (−1.3 to 4.9)	2.2 (−2.0 to 5.1)	28.5 (25.4 to 31.5)	31.2 (28.0 to 34.4)	28.4 (25.1 to 31.9)	31.0 (27.7 to 34.8)
Calendar period at diagnosis of meningitis, No. (%)								
1977-1986	1417 (50.9)							
1987-1996	1146 (41.2)							
1997-2006	221 (7.9)							
Calendar period at birth, No. (%)								
1975-1979	725 (26.0)	2900 (26.0)	665 (23.1)	2605 (23.1)				
1980-1984	732 (26.3)	2928 (26.3)	791 (27.4)	3033 (26.9)				
1985-1989	781 (28.1)	3124 (28.1)	803 (27.9)	3197 (28.4)				
1990-1996	546 (19.6)	2184 (19.6)	623 (21.6)	2430 (21.6)				
Low birth weight (<2500 g), No. (%)	200 (7.2)	551 (4.9)	183 (6.3)	554 (4.9)				
Premature birth (<37 gestational wk), No. (%)	151 (5.4)	447 (4.0)	141 (4.9)	443 (3.9)				
5-min Apgar score <7 or intrauterine/birth asphyxia, No. (%)	161 (6.1)	545 (4.9)	110 (3.8)	524 (4.7)				
Chromosomal abnormalities, No. (%)	11 (0.4)	22 (0.2)	4 (0.1)	21 (0.2)				
Observation time, y								
Meningococcal meningitis	15 553	62 338	16 886	66 965				
Pneumococcal meningitis	5294	21 287	5666	22 667				
H influenzae meningitis	14 814	59 057	13 755	51 964				
Emigrated during study period, No. (%)	59 (2.1)	301 (2.7)	56 (1.9)	233 (2.1)				
Lost to follow-up during study period, No. (%)	0	4 (0.04)	1 (0.03)	2 (0.02)				
Died during study period, No. (%)	24 (0.9)	65 (0.6)	21 (0.7)	54 (0.5)				
Older siblings, No. (%)			1496 (51.9)	5645 (50.1)				
Younger siblings, No. (%)			1319 (45.8)	5368 (47.7)				
Twins, No. (%)			67 (2.3)	252 (2.2)				

[a] The negative numbers in sibling interquartile ranges (IQRs) appear because some siblings were not born yet at the time of the patients' diagnosis.

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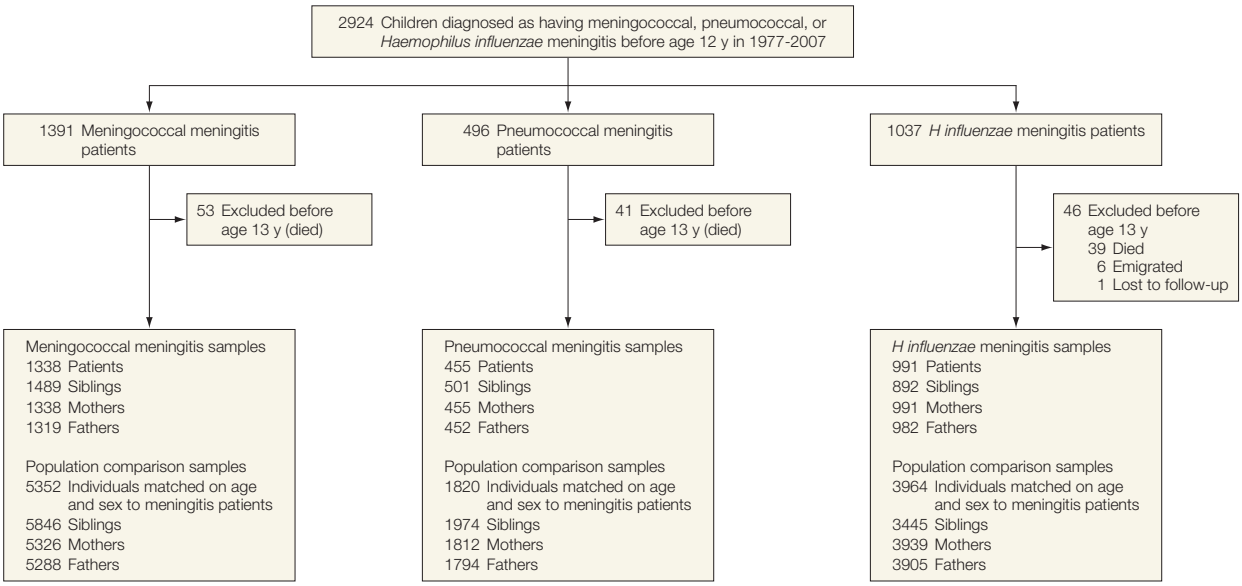
Figure 1. Summary of the Study Design



DISCUSSION

To our knowledge, this is the first study to describe on a national scale the achievements of adults who were diagnosed as having bacterial meningitis in childhood. In almost 3000 children, a diagnosis of meningococcal, pneumococcal, or *H influenzae* meningitis was associated with lower educational levels than in the general population. In contrast to siblings and parents of pneumococcal and *H influenzae* meningitis patients, siblings and parents of meningococcal meningitis patients also had lower educational achievements. In addition, the associations between childhood pneumococcal and *H influenzae* meningitis diagnoses and receiving disability pension suggest that these conditions affect functioning in adult life.

The meningococcal meningitis patients achieved educational levels comparable with that of their siblings, indicating that the lower level of education in these patients may stem from factors not directly related to the meningitis episode. Low birth weight and prematurity are well-established risk factors for adolescent learning difficulties[24-26] and have been shown to be associated with an increased risk of meningococcal disease in childhood.[27] Still, our results suggest that family-related factors are associated with the low educational achievements in the meningococcal meningitis cohort after excluding individuals diagnosed as having low birth weight and prematurity from the analyses. The lower level of education among parents of meningococcal meningitis patients further suggests that family-related factors are associated with the low educational achievements in this patient group.

In contrast, siblings of patients with pneumococcal meningitis and *H influenzae* meningitis achieved educational levels comparable with those of members of the population comparison cohort and their siblings. This finding implies that the lower level of education achieved among pneumococcal and *H influenzae* meningitis patients may stem from neurocognitive deficits induced by the meningitis episode. The observation of equivalent educational achievements among parents of pneumococcal and *H influenzae* meningitis patients and the parents of members of the population comparison cohort further supports the conclusion that educational deficits in these 2 meningitis groups are not attributable to family-related factors.

Learning, memory, and behavioral difficulties are well described among survivors of childhood bacterial meningitis[7,28-30] and have been shown to affect subsequent educational achievements in adolescents.[8] An English study reported that more than a quarter of 461 children who had bacterial meningitis in infancy in 1985-1987, compared with 6.6% of those who did not, failed all national examinations at age 16 years. Of the children who had had meningitis, 7.8% attended special schools compared with none in the comparison group. Because the study recruited age- and sex-matched controls from the panels of the same general practitioners, it did not take into account socioeconomic confounding. Among case patients who attended special schools, 31% had been infected with *H influenzae* and 22% had had meningitis due to *Escherichia coli*. No further stratification by bacterial etiology was reported.[8]

Children with pneumococcal meningitis are at higher risk of developing disabling sequelae than children with meningococcal meningitis and, to a lesser extent, those with *H influenzae* meningitis.[5,6] A recent study on sequelae following pneumococcal men-

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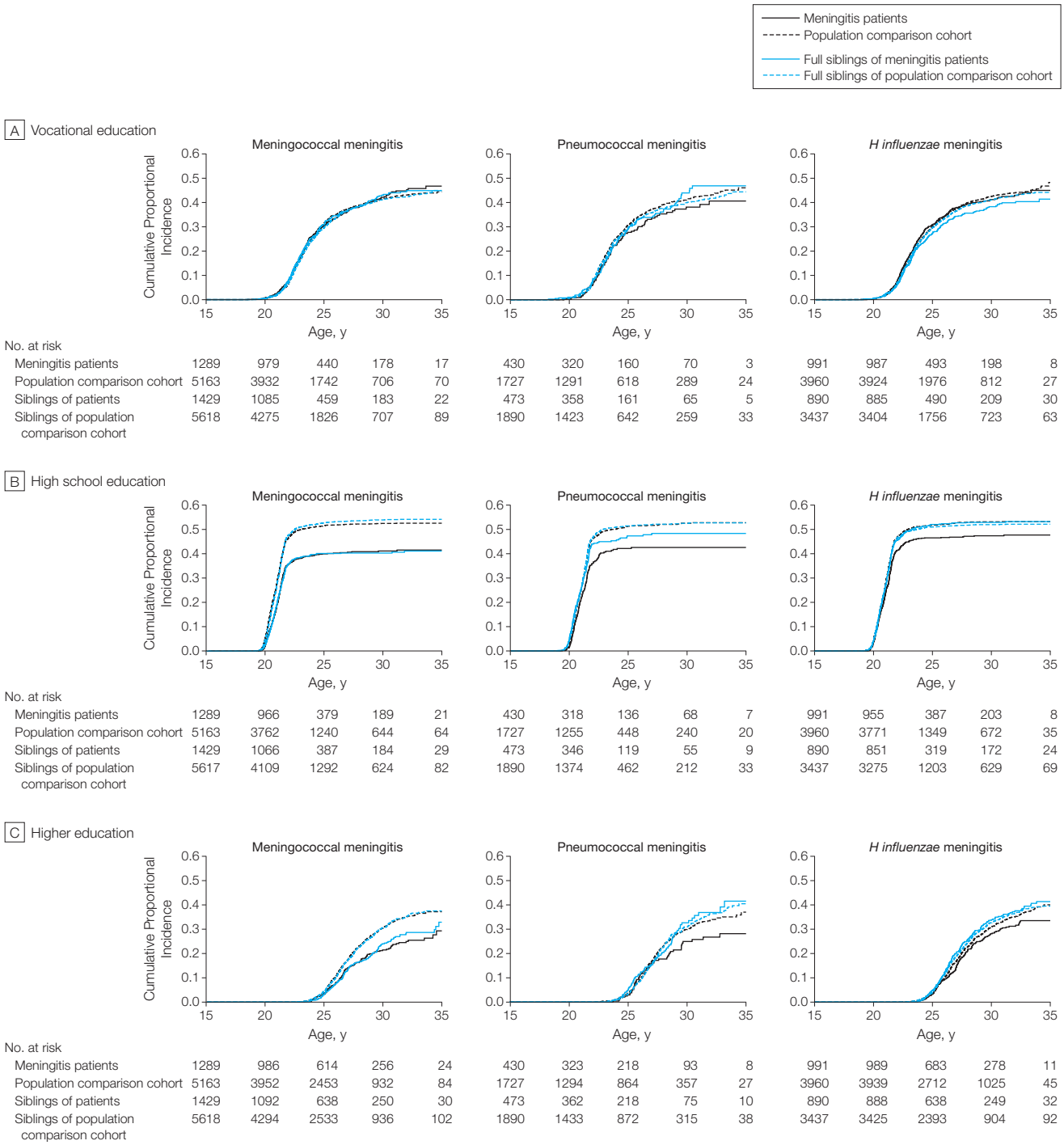
ingitis in childhood with a median follow-up of 6 years revealed lower full-scale IQ, verbal IQ, and numeracy in patients compared with controls, who were siblings or neighbors of the same age.[31] Learning and memory impairments following an episode of pneumococcal meningitis are likely explained by the virulence of the pneumococcus bacterium.[32]

Maternal smoking is associated with an increased risk of meningococcal disease.[33,34] As well, variation in meningococcal disease burden among geographic and socioeconomic subgroups has

Figure 2. Cumulative Incidence of Vocational Education, High School, and Higher Education



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been described, revealing an increased incidence of meningococcal disease in areas of social deprivation.[35,36] The socioeconomic pattern of meningococcal disease incidence accords with our finding of lower educational achievement among siblings and parents of meningococcal meningitis patients compared with the general population. Social deprivation in families of meningococcal meningitis patients thereby seems to be a strong predictor for their eventual lower educational status—even stronger than the meningococcal meningitis episode itself.

The major strengths of the present study are its large size, its population-based design, and its nearly complete and long-term follow-up. The Danish Civil Registration System enabled us to identify a large population-based comparison cohort well matched in terms of sex, age, and country of birth. To account for confounding from family-related factors, we identified siblings and parents of patients and members of the population comparison cohort. The Danish Educational Attainment Registry made it possible to obtain almost complete educational status at multiple points during a 30-year period and access to data on economic self-sufficiency and disability pension allowed us to determine whether the meningitis episodes were associated with adverse economic outcomes.

Possible study limitations include reliance on registry-based discharge diagnoses, which may be inaccurate and incomplete. However, the registration of meningococcal meningitis in the DNRP has been shown to be highly sensitive and specific,[37,38] making it rea-

Table 2. Estimated Prevalence at Age 35 Years of Vocational Education, High School, Higher Education, Economic Self-sufficiency, and Disability Pension Among Meningitis Patients, Members of the Population Comparison Cohorts, and Their Siblings

	Estimated Prevalence, %				Difference, % (95% CI)		
	Patients (n = 2784)	Population Comparison Cohort (n = 11 136)	Siblings of Patients (n = 2882)	Siblings of Population Comparison Cohort (n = 11 265)	Between Patients and Population Comparison Cohort	Between Patients and Siblings of Patients	Between Siblings of Patients and Siblings of Population Comparison Cohort
Meningococcal meningitis							
Vocational education	46.8	44.4	44.9	45.0	2.4 (−2.7 to 7.5)	1.9 (−4.2 to 8.0)	−0.1 (−4.7 to 4.5)
High school education	41.5	52.5	41.1	54.1	−11.0 (−14.7 to −7.3)	0.4 (−4.2 to 5.0)	−13.0 (−16.6 to −9.4)
Higher education	29.3	37.2	32.9	37.5	−7.9 (−14.2 to −1.6)	−3.6 (−12.1 to 4.9)	−4.6 (−11.2 to 2.0)
Economic self-sufficiency[a]	90.3	94.1	93.3	95.0	−3.8 (−6.5 to −1.1)	−3.0 (−6.5 to 0.5)	−1.7 (−4.5 to 1.1)
Disability pension	3.7	2.3	3.2	2.5	1.5 (−0.2 to 3.2)	0.5 (−1.6 to 2.6)	0.7 (−0.8 to 2.2)
Pneumococcal meningitis							
Vocational education	40.6	46.0	46.9	44.4	−5.4 (−13.5 to 2.7)	−6.3 (−16.3 to 3.7)	2.5 (−5.7 to 10.7)
High school education	42.6	52.8	48.4	52.7	−10.2 (−16.6 to −3.8)	−5.8 (−13.7 to 2.1)	−4.3 (−10.4 to 1.8)
Higher education	28.1	37.0	41.5	40.5	−8.9 (−17.2 to −0.6)	−13.4 (−25.1 to −1.7)	1.0 (−9.4 to 11.5)
Economic self-sufficiency[a]	84.0	94.6	91.0	94.2	−10.6 (−16.1 to −5.1)	−7.0 (−13.7 to −0.3)	−3.2 (−7.9 to 1.5)
Disability pension	10.0	1.3	2.6	2.1	8.7 (5.0 to 12.4)	7.4 (3.3 to 11.5)	0.5 (−1.7 to 2.8)
Haemophilus influenzae meningitis							
Vocational education	45.0	48.3	41.4	44.2	−3.3 (−9.0 to 2.4)	3.6 (−2.6 to 9.8)	−2.8 (−7.7 to 2.1)
High school education	47.7	53.2	53.2	52.1	−5.5 (−9.1 to −1.9)	−5.5 (−10.2 to −0.8)	1.1 (−2.8 to 5.0)
Higher education	33.5	40.0	41.4	39.5	−6.5 (−11.6 to −1.4)	−7.9 (−14.4 to −1.4)	1.9 (−3.6 to 7.4)
Economic self-sufficiency[a]	90.6	94.9	94.9	95.1	−4.3 (−6.6 to −2.0)	−4.3 (−7.1 to −1.5)	−0.2 (−2.3 to 1.9)
Disability pension	6.2	2.5	1.5	2.5	3.7 (1.6 to 5.8)	4.7 (2.5 to 6.9)	−1.0 (−2.2 to 0.2)

[a] As defined in Statistics Denmark. A detailed description is provided in eAppendix 1. The estimated rates of economic self-sufficiency are for age 34 years because of small numbers at risk after that age.

Table 3. Educational Status Among Parents of Study Participants 1 Year Before Date of Diagnosis of Meningitis in Patient Population

	Maternal Educational Status, %			Paternal Educational Status, %		
	Mothers of Patients (n = 2784)	Mothers of Population Comparison Cohort (n = 11 077)	Difference Between Mothers of Patients and Population Comparison Cohort, %	Fathers of Patients (n = 2753)	Fathers of Population Comparison Cohort (n = 10 987)	Difference Between Fathers of Patients and Population Comparison Cohort, %
Meningococcal meningitis						
Vocational education	28.8	33.9	−5.1 (−7.9 to −2.3)	44.6	47.8	−3.2 (-6.2 to −0.2)
Higher education	12.1	19.6	−7.5 (−9.5 to −5.5)	8.5	16.5	−8.0 (−9.8 to −6.2)
Pneumococcal meningitis						
Vocational education	34.7	34.3	0.4 (−4.5 to 5.3)	44.2	48.7	−4.5 (−9.6 to 0.6)
Higher education	18.2	19.1	−0.9 (−4.4 to 2.6)	15.5	16.1	−0.6 (−4.3 to 3.1)
Haemophilus influenzae meningitis						
Vocational education	31.4	30.1	1.3 (−1.9 to 4.5)	47.3	46.5	0.8 (−2.7 to 4.3)
Higher education	19.4	18.4	1.0 (−1.8 to 3.8)	16.1	16.4	−0.3 (−2.9 to 2.3)

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sonable to assume similar high sensitivities and specificities for the pneumococcal and *H influenzae* meningitis diagnoses. We did not have access to clinical and laboratory data obtained during hospitalizations. Furthermore, we were not able to access data on individual-level school grades, special educational needs, or number of failed examinations during the study period.

CONCLUSION

A diagnosis of meningococcal, pneumococcal, or *H influenzae* meningitis in childhood is associated with lower educational achievement and economic self-sufficiency in adult life. This association may apply particularly to pneumococcal and *H influenzae* meningitis, whereas for meningococcal meningitis the lower educational achievement may be family related. Our study suggests that children diagnosed as having pneumococcal or *H influenzae* meningitis may benefit from follow-up into adulthood to identify those who could potentially benefit from psychosocial support.

Author Contributions: Dr Roed had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Roed, Omland, Sorensen, Obel.
Acquisition of data: Roed.
Analysis and interpretation of data: All authors.
Drafting of the manuscript: Roed, Rothman, Obel.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Roed, Omland, Rothman, Obel.
Obtained funding: Roed, Obel.
Administrative, technical, or material support: Roed, Obel.
Study supervision: Roed, Omland, Skinhoj, Sorensen, Obel.
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Online-Only Material: The 4 eAppendixes, 2 eTables, and 3 eFigures are available at http://www.jama.com.

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Supplementary Online Content

Roed C, Omland LH, Skinhoj P, Rothman KJ, Sorensen HT, Obel N. Educational achievement and economic self-sufficiency in adults after childhood bacterial meningitis. *JAMA*. doi:10.1001/jama.2013.3792

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Appendix 1. Description of Registries

- The Danish National Registry of Patients (DNRP) contains information on all patients discharged from all Danish hospitals since 1977.[12] Records for each inpatient admission include the PIN number, hospital department, dates of admission, a primary and up to 19 secondary discharge diagnoses coded by the attending physician according to the *International Classification of Diseases* 8th (ICD-8) revision, until the end of 1993, and 10th (ICD-10) revision thereafter.
- The Danish Civil Registration System, a national registry established in 1968, contains demographic data and vital status for all Danish citizens.[13,14] Registration of siblings in the Danish Civil Registration System is more than 98% complete from 1952 onwards.
- The Danish Medical Birth Registry contains data on all births in the country since 1973.[15] The data in the Registry is extracted from birth certificates completed by midwives, who attend all births.
- The Danish Educational Attainment Registry, Statistics Denmark, a national registry established in 1974, is administered by Statistics Denmark.[16,17] The registry contains the highest educational achievement obtained by all Danish citizens in each calendar year. The primary source of registry data is the Integrated Student Registry, which collects data from all educational institutions in the country, from elementary schools to universities. Secondary sources are registries collecting data from part-time educational programs and from educational programs outside Denmark whose credits are formally transferred to a Danish educational institution.
- The Employment Classification Module (AKM), Statistics Denmark is a national registry administered by Statistics Denmark.[18-20] The registry contains data on employment and has been updated annually since 1980. In the registry an individual is registered as economically self-sufficient when his or her main income in a full calendar year stems from 1) business profit from a company owned by the individual or the individual's spouse or 2) employment with a specified minimum income. This minimum income is specified by Statistics Denmark and is equivalent to the mean yearly income for Danish trainees and is adjusted for consumer price index. The minimum

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income was 42 224 Danish kroner (7446 US Dollar) in 1998 and 49 138 Danish kroner (8621 US Dollar) in 2005. In the register this parameter is recorded in the parameters BESKST (until December 31, 2001) and BESKST02 (from January 1, 2002).[19] From January 1, 1994 the module also includes complete and nationwide data on whether a specified individual in Denmark in a calendar year received disability pension. [19]

Appendix 2. Diagnosis Codes for Intrauterine and Birth Asphyxia or Chromosomal Abnormalities

Intrauterine and birth asphyxia were identified using ICD-8 revision codes 776-776.9 and ICD-10 revision codes P20-21.9. Chromosomal abnormalities were identified using ICD-8 revision codes 759.3-759.5 and ICD-10 revision codes Q90-99.

Appendix 3. Diagnosis Codes for Meningococcal, Pneumococcal, Or *H influenzae* Meningitis

Meningococcal meningitis was identified using ICD-8 revision code 036.09 and ICD-10 revision code A39.0.

Pneumococcal meningitis was identified using ICD-8 revision code 320.19 and ICD-10 revision code G00.1.

H. influenzae meningitis was identified using ICD-8 revision code 320.09 and ICD-10 revision code G00.0.

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Appendix 4. Diagnosis Codes for Neuroinfections Other Than Bacterial Meningitis

Infections of the central nervous system were identified using the following ICD-8 revision codes for the years 1977-1993:

- Bacterial meningitis:codes 320.00-320.99
- Meningococcal meningitis: code 036.09
- Pneumococcal meningitis: code 320.19
- H. *influenzae* meningitis: code 320.09
- Listeria meningitis: code 027.01
- Meningococcal infection: code 036.00-036.99
- Aseptic meningitis due to enterovirus: codes 045.00-045.99
- Varicella meningitis/encephalitis: codes 052.01
- Zoster meningitis/encephalitis: code 053.02
- Herpesviral meningitis/encephalitis: code 054.03.

Infections of the central nervous system were identified using the following ICD-10 revision codes for the years 1994-2007:

- For inflammatory diseases of the central nervous system: codes G00.0-G01.9
- Meningococcal meningitis: code A39.0
- Pneumococcal meningitis: code G00.1
- *H. influenzae* meningitis: code G00.0
- Listeria meningitis and meningoencephalitis: code A32.1
- Meningococcal infection: codes A39.0-A39.9
- Unspecified viral encephalitis: code A86
- Enteroviral meningitis: code A87.0
- Adenoviral meningitis: code A87.1
- Lymphocytic choriomeningitis: code A87.2
- Other viral meningitis: code A87.8
- Viral meningitis, unspecified: code A87.9
- Herpesviral meningitis: code B00.3
- Herpesviral encephalitis: code B00.4
- Varicella meningitis: code B01.0
- Varicella encephalitis: code B01.1
- Zoster encephalitis: code B02.0
- Zoster meningitis: code B02.1
- Zoster with other nervous system involvement: code B02.2.

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eTable 1. Number of Events in the Study Population and Total Observation Time

	Events in patients	Total observation time for patients* (years)	Events in population comparison cohort	Total observation time for population comparison cohort* (years)	Events in full siblings of patients	Total observation time for full siblings of patients* (years)	Events in full siblings of population comparison cohort	Total observation time for full siblings of population comparison cohort* (years)
Meningococcal meningitis								
Vocational education	318	13,752	1,252	55,217	341	15,152	1,282	59,665
High school exam	379	13,046	1.961	49,545	409	14,286	2,144	53,545
Higher education	132	15,065	736	59,823	146	16,408	761	64,307
Economic self-sufficiency	861	8,051	3,510	32,047	957	8,903	3,799	34,974
Disability pension	27	15,398	71	61,918	26	16,728	65	66,578
Pneumococcal meningitis								
Vocational education	95	4,684	425	18,802	114	5,090	432	20,260
High school exam	128	4,422	628	16,857	162	4,617	705	18,226
Higher education	52	5,104	260	20,338	68	5,444	263	21,758
Economic self-sufficiency	255	3,058	1,146	10,801	311	3,054	1,269	11,813
Disability pension	30	5,055	16	21,193	8	5,618	17	22,586
H. influenzae meningitis								
Vocational education	335	12,820	1,355	51,378	286	12,041	1,160	45,162
High school exam	453	11,741	2,025	44,724	458	10,365	1,736	39,446
Higher education	184	14,187	825	56,124	217	12,983	765	49,249
Economic self-sufficiency	865	6,866	3,554	26,991	812	6,111	3,136	23,160
Disability pension	50	14,452	68	58,649	10	13,721	53	51,675

*to event or end of observation time

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eTable 2. Estimated Prevalence at Age 35 of Vocational Education, High School, Higher Education, Economic Self-sufficiency and Disability Pension Among Meningitis Patients, Members of the Population Comparison Cohorts, and Their Siblings Without Neonatal Morbidity*

	Patients*	Population comparison cohort**	Full siblings of patients**	Full siblings of population comparison cohort**	Difference between patients and population comparison cohort ***	Difference between patients and siblings of patients***	Difference between siblings of patients and siblings of population comparison cohort***
Meningococcal meningitis							
Vocational education	47.6	44.1	44.9	43.9	3.5 (-2.0, 9.0)	2.7 (-4.0, 9.4)	1.0 (-4.2, 6.2)
High school exam	43.1	53.5	42.3	55.6	-10.4 (-14.4, -6.4)	0.8 (-4.3, 5.9)	-13.3 (-17.4, -9.2)
Higher education	31.1	38.6	33.1	38.8	-7.5 (-14.3, -0.7)	-2.0 (-10.7, 6.7)	-5.7 (-12.3, 0.9)
Economic self-sufficiency §	91.1	94.5	95.2	95.6	-3.4 (-6.3, -0.5)	-4.1 (-8.0, -0.2)	-0.4 (-3.6, 2.8)
Disability pension	2.7	1.8	2.2	2.4	0.9 (-0.7, 2.5)	0.5 (-1.5, 2.5)	-0.2 (-1.7, 1.3)
Pneumococcal meningitis							
Vocational education	45.2	46.1	48.6	43.7	-0.9 (-9.8, 8.0)	-3.4 (-14.4, 7.6)	4.9 (-4.1, 13.9)
High school exam	43.9	53.2	49.9	53.8	-9.3 (-16.2, -2.4)	-6.0 (-14.7, 2.7)	-3.9 (-10.9, 3.1)
Higher education	28.5	38.2	40.9	40.6	-9.7 (-18.9, -0.5)	-12.4 (-25.1, 0.3)	0.3 (-11.1, 11.7)
Economic self-sufficiency §	88.4	94.7	91.6	94.5	-6.3 (-11.9, -0.7)	-3.2 (-10.0, 3.6)	-2.9 (-8.0, 2.2)
Disability pension	6.1	0.6	1.3	1.1	5.5 (2.4, 8.6)	4.8 (1.4, 8.2)	0.2 (-1.8, 2.2)
H. influenzae meningitis							
Vocational education	45.5	48.1	41.0	44.1	-2.6 (-8.6, 3.4)	4.5 (-2.1, 11.1)	-3.1 (-8.5, 2.3)
High school exam	48.1	53.0	53.7	52.6	-4.9 (-8.7, -1.1)	-5.6 (-10.6, -0.6)	1.1 (-3.1, 5.3)
Higher education	34.3	40.1	42.3	38.8	-5.8 (-11.2, -0.4)	-8.0 (-15.0, -1.0)	3.5 (-2.5, 9.5)
Economic self-sufficiency §	91.4	94.7	95.6	95.1	-3.3 (-5.7, -0.9)	-4.2 (-7.2, -1.2)	0.5 (-1.8, 2.8)
Disability pension	5.4	2.5	1.1	2.5	2.9 (0.7, 5.1)	4.3 (2.0, 6.6)	-1.4 (-2.7, -0.1)

* Low birth weight (<2500 g), premature birth (< 37 weeks of pregnancy), intrauterine and birth asphyxia or chromosomal abnormalities.
**Estimated prevalence of specified educational level (%)
*** Differences in estimated prevalence in the 2 populations (%) and 95% confidence interval
§ As defined in Statistics Denmark. For detailed description of the parameter see Appendix 1. The estimated rates for "economic self-sufficiency" are for age 34 due to small numbers at risk after that age.

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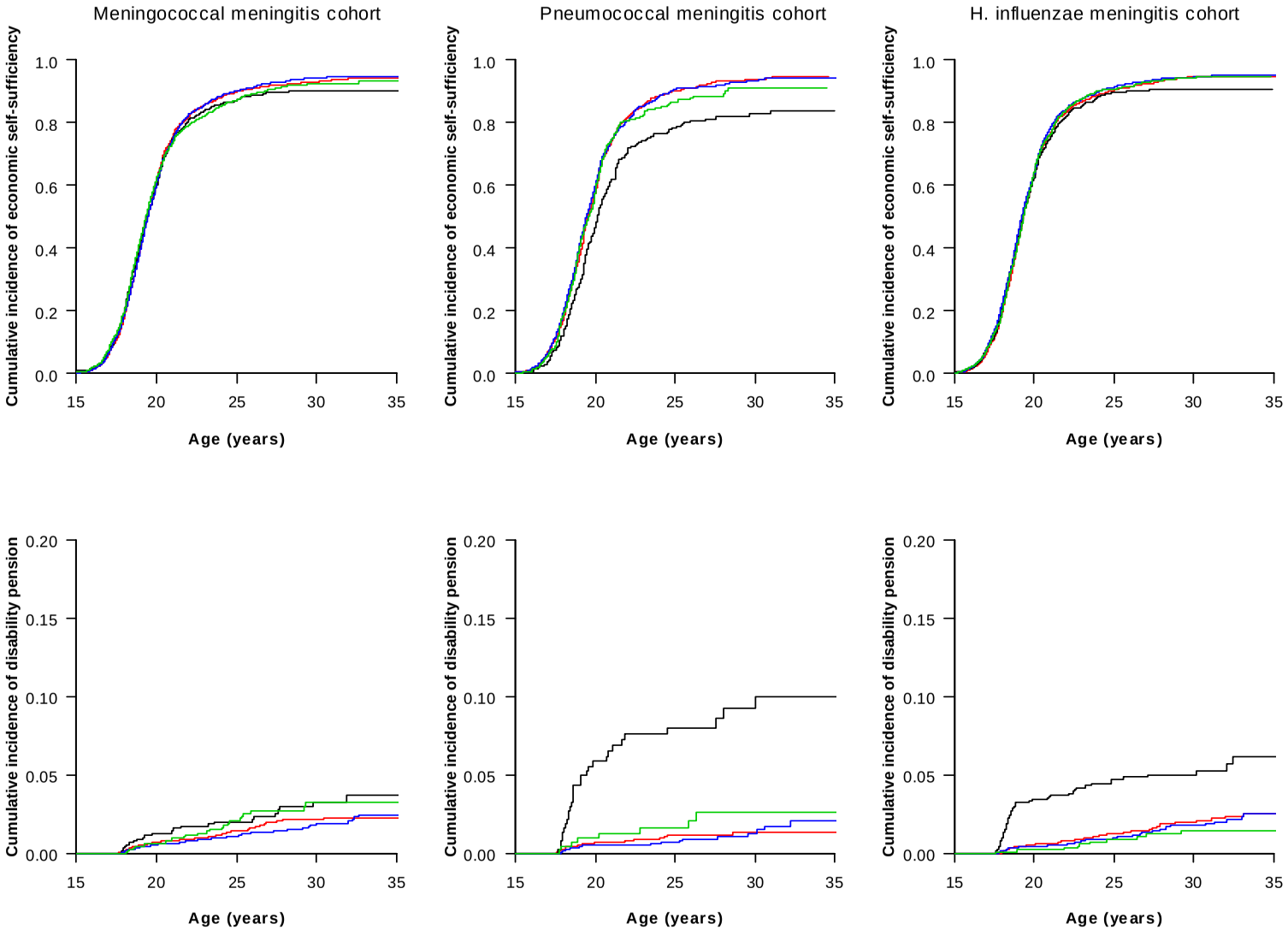
eFigure 1. Cumulative Incidence of Having Been Economically Self-sufficient for a Year and of Receiving Disability Pension in the Meningococcal, Pneumococcal and *H. influenzae* Meningitis Patients (Black), Members of the Population Comparison Cohort (Red), Full Siblings of Patients (Green) and Siblings of Members of the Population Comparison Cohort (Blue)



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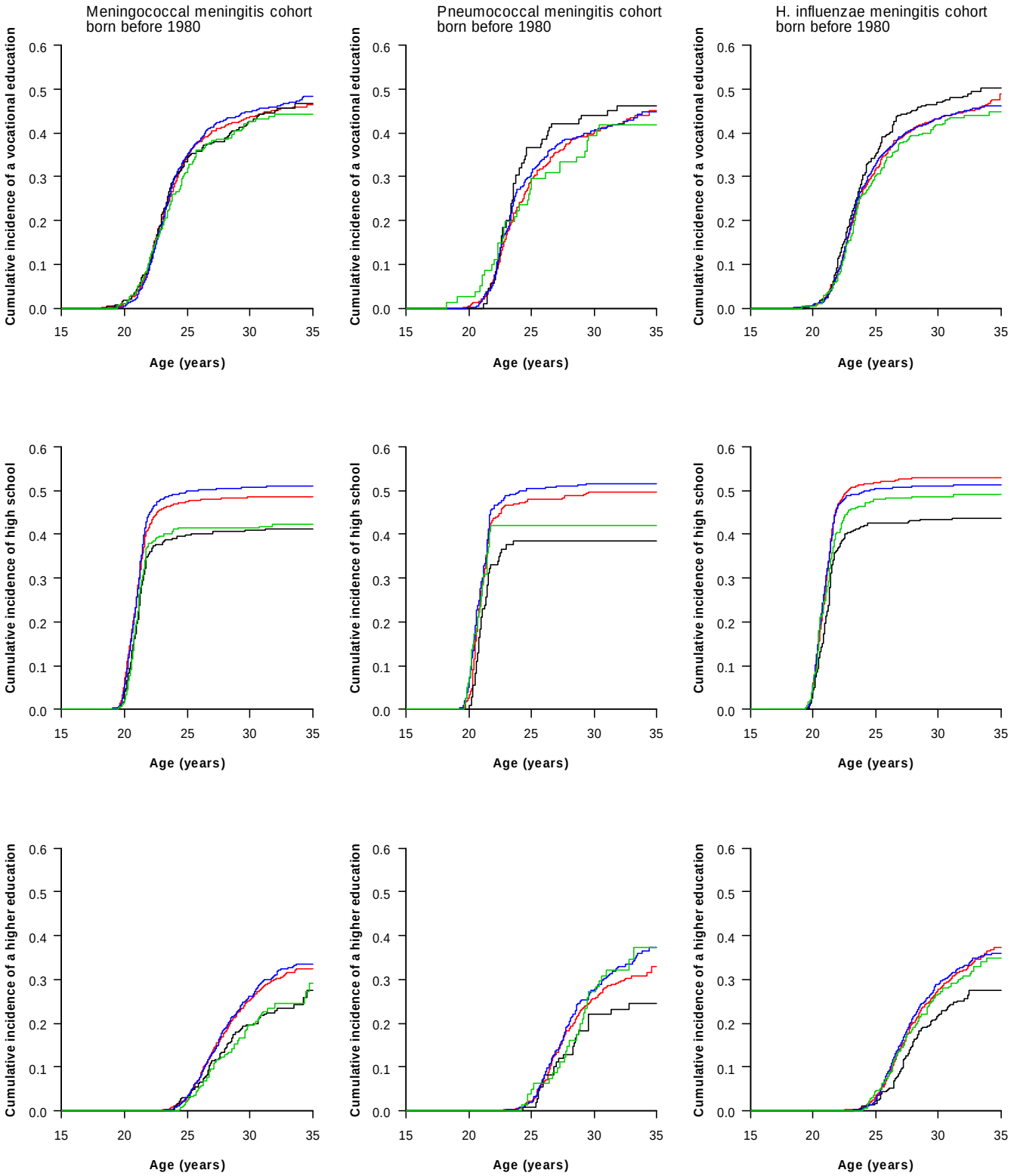
eFigure 2. Cumulative Incidence of Vocational Education, High School and Higher Education for Meningococcal, Pneumococcal and *H. influenzae* Meningitis Patients (Black), Members of the Population Comparison Cohort (Red), Full Siblings of Patients (Green) and Full Siblings of Members of the Population Comparison Cohort (Blue) Born Before 1980



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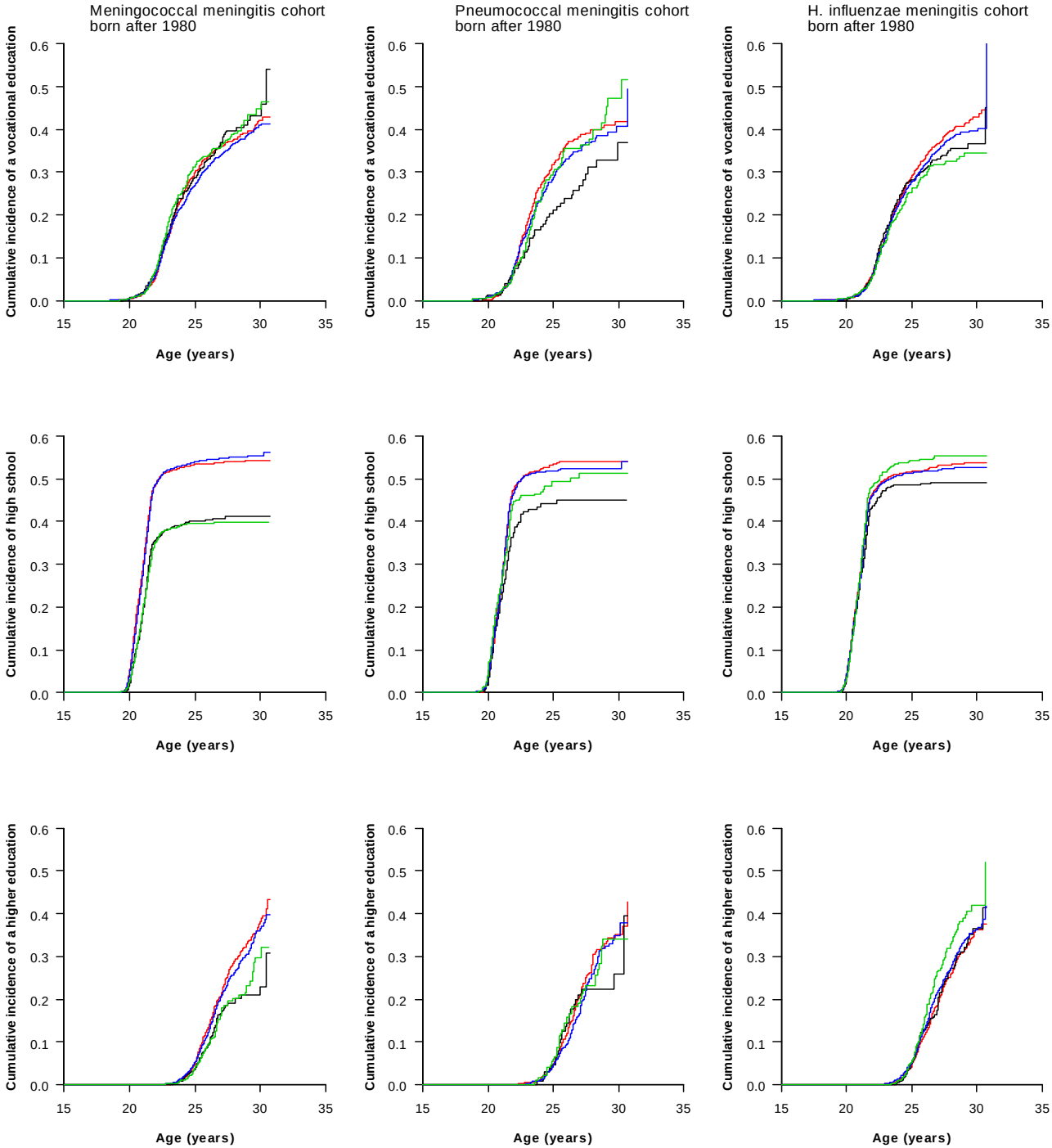
eFigure 3. Cumulative Incidence of Vocational Education, High School and Higher Education for Meningococcal, Pneumococcal and *H. influenzae* Meningitis Patients (Black), Members of the Population Comparison Cohort (Red), Full Siblings of Patients (Green) and Full Siblings of Members of the Population Comparison Cohort (Blue) Born After 1980



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Title
Employment and Disability Pension after Central Nervous System Infections in Adults

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Abstract

In this nationwide population-based cohort study using national registries, in the period 1980-2008, the aim was to study employment and receipt of disability pension after central nervous system infections. All patients diagnosed between 20 and 55 years of age with meningococcal (n=451), pneumococcal (n=553), or viral meningitis (n=1433) or herpes simplex encephalitis (n=115), who were alive 1 year after diagnosis, were identified. Comparison cohorts were drawn from the general population and the members were individually matched on age and sex to patients. The difference in proportions employed and on disability pension in meningococcal and viral meningitis patients vs. members of the comparison cohorts did not increase substantially during follow-up. Five years after diagnosis 19.7% (95% CI: 14.8%, 24.6%) fewer pneumococcal meningitis and 21.0% (95% CI: 9.5%, 32.6%) fewer herpes simplex encephalitis patients were employed and respectively 19.9% (95% CI: 13.4%, 26.6%) and 16.2% (95% CI: 6.2%, 26.3%) more received disability pension compared with members of the comparison cohorts. In conclusion, the impact of CNS infections on employment and on the need for disability pension appeared to be substantial in survivors of pneumococcal meningitis and herpes simplex encephalitis, but not for meningococcal meningitis or viral meningitis patients.

Key words

Disability pension, employment, herpes simplex encephalitis, meningococcal meningitis, pneumococcal meningitis, viral meningitis

Survivors of central nervous system (CNS) infections are at risk of developing disabling sequelae in terms of hearing loss, seizure disorder and cognitive impairment (1-7). Identification of those who may benefit from medical and vocational rehabilitation is an important public-health priority (8-9). Despite modern therapy the short-term mortality associated with CNS infections varies from low in viral meningitis, to 10% in meningococcal meningitis, 10-20% in herpes simplex encephalitis and 20-30% in pneumococcal meningitis (1,2,5-7). Among the survivors, the proportion that recover their previous work capacity is not known, but is an important indicator of complete rehabilitation, as is employment.

In this population-based cohort study employment, personal income for those employed and receipt of a disability pension in patients surviving bacterial meningitis, viral meningitis or herpes simplex encephalitis were determined annually for 5 years after CNS infection as well as for the 2 years before disease. We compared their experience with that of adults from the general population. We explored potential associations with family-related factors by measuring the same outcomes in the siblings of members of both cohorts.

METHODS

We identified the following 4 nationwide population-based cohorts using Danish registries: (1) all Danish patients diagnosed between ages 20-55 years with bacterial meningitis due to *Neisseria meningitidis* or *Streptococcus pneumoniae* during the period 1980-2008, or viral meningitis or herpes simplex encephalitis during the period 1994-2008, and alive 1 year after diagnosis; (2) a comparison cohort drawn from the general population whose members were individually matched with the patients on date of birth and sex; (3) full siblings of members of the patient cohort; and (4) full siblings of members of the comparison cohort.

The 4 cohorts were followed for 4 years, starting 1 year after CNS infection. The primary outcomes were proportions employed, personal income and proportions receiving disability pension.

Setting

As of January 2009, Denmark had an estimated population of 5.5 million. In the first quarter of 2009, 75.8% (2,749,000/3,627,869) of the population aged 15-64 years was employed, while 6.5% (236,244/3,627,869) received disability pension. In 2009 the mean monthly income for people above age 15 years was US $ 3,941 (10).

During the study period *N. meningitidis* and *S. pneumoniae* were the most frequent causative agents of bacterial meningitis (11). Herpes simplex virus (HSV) type 2 and enteroviruses were the most frequent causative agents of viral meningitis, and HSV type 1 most frequently caused infectious encephalitis (5-7). In Denmark pneumococcal vaccination is recommended for people at increased risk of invasive pneumococcal disease, while there is no general recommendation for use of the meningococcal vaccine (12). Throughout the study period, tax-supported medical care was provided free of charge to all Danish residents.

Data sources

We used the unique 10-digit personal identification number (PIN number) assigned to all Danish citizens at birth or upon immigration, in order to track individuals identified in the following registries and to avoid multiple registrations (see Appendix 1):

- The Danish National Registry of Patients (DNRP) covering all Danish hospitals was used to identify the first date of all meningococcal, pneumococcal, or viral meningitis or herpes

simplex encephalitis diagnoses for each patient. Further the DNRP provided data on inpatient admissions and hospital outpatient services (13).

- The Danish Civil Registration System was used to identify members of the general population comparison cohort and their siblings, as well as siblings of the patients. This registry also provided data on sex and date of birth, immigration/emigration, loss to follow-up, and death of all study participants (14).
- The Employment Classification Module (AKM), Statistics Denmark, provided data on the employment status of study participants in each calendar year during the study period. It also provided data on receipt of disability pension starting on January 1, 1994 (15, 16).
- Personal Income Statistics, administered by Statistics Denmark, provided data on personal income of the study participants in each calendar year during the study period (17).
- The Danish Educational Attainment Registry, also administered by Statistics Denmark, provided data on the highest educational level attained by all members of the study population as of the year when CNS infection was diagnosed among members of the patient cohort (18,19).

Study population

Cohort of patients with CNS infection. We used the DNRP to identify all patients meeting the following criteria: (1) diagnosed with meningococcal, pneumococcal, or viral meningitis, or herpes simplex encephalitis (see Appendix 2 for ICD-8 and ICD-10 codes) for the first time during the period January 1, 1980 (January 1, 1994 for viral meningitis and herpes simplex encephalitis patients) to January 1, 2008; (2) diagnosed with these infections between the ages of 20 and 55

years; (3) born in Denmark ; and (4) not diagnosed with any other CNS infections (as specified in Appendix 3) before the diagnosis of meningitis or encephalitis. Patients were excluded from the study if they died, emigrated, or were lost to follow-up within the first year after their diagnosis with a CNS infection. The date of study inclusion was 1 year after the diagnosis date of the CNS infection.

General population comparison cohort. We constructed comparison cohorts of individually matched persons identified from the Danish Civil Registration System. First we identified all Danish citizens meeting the following criteria: (1) had the same birth date and sex as the patient, (2) were residing in Denmark and not diagnosed with a CNS infection at time of the corresponding patient's diagnosis; and (3) alive and living in Denmark 1 year after the corresponding patient's diagnosis date for CNS infection. From this population, we randomly chose 4 individuals for the comparison cohort. Their date of study inclusion was 1 year after the diagnosis date of the matched CNS infection patient.

Sibling cohorts. To estimate the potential confounding from inherited or family-related life style risk factors we also estimated employment status, personal income and receipt of disability pension in full siblings of the patients and comparison cohort members. The siblings were identified from the Danish Civil Registration System. To limit differences in age siblings born 5 years before or later than their respective patient or comparison cohort member were excluded.

Comorbidity

A modified Charlson Comorbidity Index score derived from DNRP discharge diagnoses before time of CNS infection was used as a measurement of comorbidity (20). A score of 1, 2, 3 or 6 was

assigned to a range of comorbid conditions and 3 levels of comorbidity were defined; none (CCI score = 0), low (CCI score = 1-2) or high (CCI score > 3).

Cumulative incidence for common diseases associated with work disability was calculated 3 months before the CNS infection diagnosis date of members of all cohorts, based on discharge diagnoses and diagnoses given at hospital outpatient services (See Appendix 4 for diseases included in this category, references and ICD-8 and ICD-10 codes).

Study outcomes

Differences in proportions employed, in personal income for those employed and in proportions receiving disability pension were compared between the patient and comparison cohorts and similarly between the 2 sibling cohorts.

Less than 2% of the patients and members of the comparison cohorts and less than 3% of the siblings lacked annual information on employment status, personal income and receipt of disability pension. Persons without this information for a given calendar year were omitted from the analyses for that year.

Statistical analysis

Employment status, personal income for those employed and receipt of disability pension, were determined at time of CNS infection, and 1 and 2 years before, as well as annually for each year afterwards, which was the earliest of 5 years after CNS infection, the end of 2008, or the year before the person died, emigrated, or became lost to follow-up. The calendar year of CNS infection diagnosis was designated as year 0, and the following calendar years were given values relative to year 0.

We compared the proportions employed and the proportions receiving disability pension among patients vs. members of the comparison cohort, and among siblings of patients vs. siblings of members of the comparison cohorts. Comparisons were made 2 years before the time of CNS infection, at the time of CNS infection and 2 and 5 years after CNS infection. Separate analyses were performed for patients with meningococcal, pneumococcal, or viral meningitis or herpes simplex encephalitis and members of their comparison cohorts and sibling cohorts. We repeated the analyses restricting the study sample to individuals who had been employed and who had not received disability pension in the 2 years before CNS infection. We also repeated the analyses 1) in a study sample excluding individuals diagnosed before the time of CNS infection with a comorbid condition defined by the Charlson Comorbidity Index and 2) in a study sample excluding individuals diagnosed as having disease associated with work disability before the time of CNS infection.

To determine whether patients employed after the CNS infection had decreased work capacity, we calculated the mean monthly income for employed patients and compared with the income for employed members of their respective comparison cohorts. Comparisons were made 2 years before the time of CNS infection, at the time of CNS infection and 2 and 5 years after CNS infection. During the study period, mean monthly income was estimated in US $ in 2012 prices. This entailed deflating the mean monthly income by multiplying it by the Consumer Price Index of 2012 and dividing by the actual year's Price Index [21].

In a cross-sectional analysis, the educational status of members of all cohorts was assessed at the year of CNS infection.

SPSS Statistics version 19 (IBM Inc., Chicago, Il, USA) was used for data analysis.

Ethics

The study was approved by the Danish Data Protection Agency (record no. 2008-41-2467). Ethics approval and individual consent are not required by Danish legislation governing this type of registry study.

RESULTS

Descriptive data

Of the 2742 patients who met the inclusion criteria, 485 patients had meningococcal meningitis, 695 had pneumococcal meningitis, 1442 had viral meningitis, and 120 had herpes simplex encephalitis. Of these, 34 patients with meningococcal meningitis, 142 with pneumococcal meningitis, 8 with viral meningitis, and 4 with herpes simplex encephalitis died, 2 emigrated, and none was lost to follow up within the first year after CNS infection diagnosis, leaving a total of 2552 patients and 10,208 members of the comparison cohort in the study (Table 1 and Figure 1). During the study period 28 (1.1%) patients emigrated and none was lost to follow-up.

Employment

Proportions of the patients and members of the comparison cohort who were employed in the period 2 years before to 5 years after CNS infection diagnosis are shown in Table 2 and Figure 2. Among meningococcal meningitis patients, 10.1% fewer (71.8% vs 81.9%; 95% CI: 5.5%, 14.7%) were employed 2 years before their diagnosis date, compared with members of the comparison cohort. No substantial change in this disparity was observed after diagnosis of this CNS infection.

Among pneumococcal meningitis patients, 11.5% fewer (72.2% vs 83.7%; 95% CI: 7.3%, 15.7%) were employed 2 years before their diagnosis date, compared with members of the comparison cohort. This disparity increased markedly post-diagnosis, with 19.7% fewer (61.6% vs 81.3%; 95% CI: 14.8%, 24.6%) pneumococcal meningitis patients employed 5 years after their diagnosis date, compared with the comparison cohort.

Two years before diagnosis date 0.9% more (80.0% vs 79.1%; 95% CI: -1.3%, 3.3%) and 5 years after diagnosis date 1.3% fewer (83.1% vs 84.4%; 95% CI: -1.3%, 3.8%) viral meningitis patients were employed compared with members of the comparison cohort.

Among herpes simplex encephalitis patients, 4.8% fewer (78.3% vs 83.0%; 95% CI: -3.4%, 13.0%) were employed 2 years before their diagnosis date, compared with members of the comparison cohort. This disparity increased markedly by 5 years after the diagnosis date, with 21.0% fewer (62.2% vs 83.2%; 95% CI: 9.5%, 32.6%) herpes simplex encephalitis patients employed.

Personal income

During the whole study period no substantial decrease in personal income was observed among employed meningococcal, pneumococcal or viral meningitis or herpes simplex encephalitis patients (eTable 1, eFigure 1). Employed viral meningitis patients had a slightly higher income during the whole study period, compared with employed members of the comparison cohort.

Disability pension

A higher proportion of meningococcal meningitis patients received disability pension compared with the comparison cohort throughout the study period (Table 2, Figure 3). Little change in this difference was noted after the diagnosis date.

Two years before diagnosis date 6.1% (11.0% vs 4.9%; 95% CI: 1.9%, 10.4%) and 7.2% (11.0% vs 3.8%; 95% CI: 0.3%, 14.0%) more pneumococcal and herpes simplex encephalitis patients, respectively, received disability pension compared with members of their comparison cohorts. Five years after diagnosis 19.9% (28.0% vs 8.1%; 95% CI: 13.4%, 26.6%) and 16.2% (24.3% vs 8.1%; 95% CI: 6.2%, 26.3%) more patients with these 2 CNS infections received disability pension, compared with the comparison cohort.

Two years before diagnosis date 0.4% (2.3% vs 2.7%; 95% CI: -0.6%, 1.3%) and 5 years after 0.7% (3.9% vs 4.6%; 95% CI: -0.6%, 2.0%) fewer viral meningitis patients received disability pension compared with members of the comparison cohort.

Subanalysis

When individuals with a comorbid condition defined by the Charlson Comorbidity Index (Table 1) or with a disease associated with work incapacity (Table1) before CNS infection were excluded, we observed almost the same estimates as obtained in the analyses including all study participants (eTable 2,3, eFigure 2,3). This was also the case in the analysis restricting the study sample to individuals who had been employed and not having received disability pension in the 2 years before CNS infection (eTable 4, eFigure 4,5).

Sibling cohorts

No substantial differences in proportions employed or receipt of disability pension were observed between the cohorts of siblings of CNS infection patients and the siblings of the comparison cohorts (eTable 5). This finding held for all CNS infection cohorts.

DISCUSSION

We found that an episode of pneumococcal meningitis or herpes simplex encephalitis was associated with substantially decreased employment and increased need of disability pension. This did not seem to be the case for patients with meningococcal or viral meningitis. The personal income for the patients who were employed after the CNS infection episode was similar to that of the comparison cohorts from the general population, which indicates that the working capacity of the working part of the patients did not decrease.

Patients with meningococcal meningitis were less likely to be employed than members of the comparison cohort 2 years before the diagnosis date and this disparity remained throughout the study. This finding may reflect that decreased employment in the meningococcal meningitis patients stems from factors not directly related to the meningitis episode. This possibility is consistent with the known environmental risk factors for meningococcal disease, which include social deprivation and cigarette smoking (22-25). The observation that meningococcal meningitis patients did not have increased need of disability pension compared with the general population during follow-up implies that the possible long-term neurocognitive deficits induced by a meningococcal meningitis episode are mild. Investigations by van de Beek *et al*. on cognitive impairment after bacterial meningitis in adults, using almost the same age groups (16-65 years) as in our study, found that only 4% (1/25) of meningococcal meningitis patients suffered from cognitive disorders 6-24 months after the meningitis episode (26).

Compared with the general population, the pneumococcal meningitis patients had a substantially decreased employment rate and increased receipt of disability pension during follow-up. A similar finding held when we excluded individuals who, before their episode of pneumococcal meningitis,

had been diagnosed with diseases that are known to be associated with work incapacity. This finding is likely related to neurological sequelae induced by the infectious episode. Other risk factors, such as inapparent alcohol dependence, may have contributed to this association (27), but siblings of the patient and comparison cohorts had nearly equal levels of employment throughout the study period. It is well documented that pneumococcal meningitis patients are at higher risk of disabling sequelae than patients with meningococcal and *Haemophilus influenzae* meningitis (3). In the study cited above by van de Beek *et al*. 27% (7/26) of pneumococcal meningitis patients were found to suffer from cognitive disorders 6-24 months after the infection (26).

We found that a viral meningitis episode had no substantial impact on employment or receipt of disability pension. As well, the personal income for employed viral meningitis patients remained slightly higher than for employed comparison cohort members during the follow-up period, implying that the viral meningitis patients did not accept employment in less demanding jobs as a consequence of their illness. A cohort study of 59 viral meningitis patients reported that learning and memory functions of the patients were affected (28). Nevertheless, none of the patients in that cohort had to retire as a consequence of the viral meningitis episode.

In patients diagnosed with herpes simplex encephalitis, general and focal signs of brain parenchymal involvement are present, and thereby these patients differ clinically from patients with viral meningitis. Severe memory impairment, personality change, aphasia, and epilepsy are well described sequelae of herpes simplex encephalitis (29-31), with 27% (6/22) of acyclovir-treated survivors reported to have no neuropsychological impairment, 59% (13/22) to have mild, and 14% (3/22) to have moderate/severe neuropsychological impairment after an average of 3 years of follow-up (32). These severe sequelae accord with our findings of lower employment rate,

lower personal income and increased receipt of disability pension in herpes simplex encephalitis patients compared with the general population.

We relied on registry-based discharge diagnoses, which may be inaccurate. The registries maintained by Statistics Denmark provided access to almost complete annual data on employment status and personal income during 1980-2009 and complete annual data on disability pension during 1994-2009, allowing us to determine whether the CNS infections were associated with adverse socio-economic outcomes. However, the registration of meningococcal meningitis in the DNRP has been shown to be highly sensitive and specific (33, 34), making it reasonable to assume similarly high sensitivities and specificities for the other CNS infections. A limitation of the viral meningitis analyses was lack of stratification by viral aetiology. We also did not have access to clinical and laboratory data or CNS imagining results during hospitalizations. In conclusion, the impact of CNS infections on employment and on the need for disability pension appeared to be substantial in survivors of pneumococcal meningitis and herpes simplex encephalitis, but not for meningococcal or viral meningitis patients.

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Table 1. Characteristics of meningococcal, pneumococcal, or viral meningitis and herpes simplex encephalitis patients at age 20-55 years, members of the comparison cohorts, and siblings of these cohorts.

	Patients	Comparison cohorts	Siblings of patients	Siblings of members of the comparison cohorts
Characteristics, No.	2552	10,208	1748	6989
Male, No. (%)	1290 (50.5)	5160 (50.5)	894 (51.1)	3769 (53.9)
CNS infection etiology, No.				
Meningococcal meningitis	451	1804	258	965
Pneumococcal meningitis	553	2212	225	943
Viral meningitis	1433	5732	1192	4798
Herpes simplex encephalitis	115	460	73	283
Age at time of CNS infection, median (IQR) years				
Meningococcal meningitis	34.5 (24.6, 45.3)	34.5 (24.6, 45.3)	26.0 (22.1, 31.8)	25.8 (22.5, 32.7)
Pneumococcal meningitis	43.4 (33.9, 50.1)	43.4 (33.9, 50.1)	34.8 (27.0, 40.9)	34.7 (27.7, 41.7)
Viral meningitis	32.5 (27.9, 38.2)	32.5 (27.9, 38.2)	32.6 (27.9, 37.6)	32.3 (27.8, 37.1)
Herpes simplex encephalitis	39.8 (32.4, 47.8)	39.8 (32.4, 47.8)	36.3 (30.9, 42.7)	33.7 (28.4, 39.3)
Calendar period of CNS infection, No. (%)				
- 1980-1989	374 (14.7)			
- 1990-1999	994 (38.9)			
- 2000-2008	1184 (46.4)			
Higher education at time of CNS infection, No. (%)				
Meningococcal meningitis	57 (12.6)	222 (12.3)	21 (8.1)	96 (9.9)
Pneumococcal meningitis	66 (11.9)	331 (15.0)	36 (16.0)	161 (17.1)
Viral meningitis	249 (17.4)	1053 (18.4)	209 (17.5)	800 (16.7)

Herpes simplex encephalitis	20 (17.4)	104 (22.6)	14 (19.2)	67 (23.7)
Charlson comorbidity >= 1, at time of CNS infection, No. (%)				
Meningococcal meningitis	33 (7.3)	72 (4.0)	5 (1.9)	26 (2.7)
Pneumococcal meningitis	90 (16.3)	136 (6.1)	19 (8.4)	35 (3.7)
Viral meningitis	129 (9.0)	316 (5.5)	55 (4.6)	210 (4.4)
Herpes simplex encephalitis	10 (8.7)	31 (6.7)	5 (6.9)	19 (6.7)
Diagnosed with a disease associated with work incapacity at time of CNS infection, No. (%)				
Meningococcal meningitis	70 (15.5)	151 (8.4)	19 (7.4)	67 (6.9)
Pneumococcal meningitis	150 (27.1)	282 (12.8)	33 (14.7)	88 (9.3)
Viral meningitis	273 (19.1)	747 (13.0)	144 (12.1)	442 (9.2)
Herpes simplex encephalitis	28 (24.4)	69 (15.0)	7 (9.6)	30 (10.6)
Observation time, years				
Meningococcal meningitis	6892	28,993	3576	14,273
Pneumococcal meningitis	7098	31,454	2348	10,124
Viral meningitis	11,091	44,594	8121	32,567
Herpes simplex encephalitis	870	3705	455	1922
Emigrated during study period, No. (%)	28 (1.1)	121 (1.2)	56 (3.2)	211 (3.0)
Lost to follow-up during study period, No. (%)	0	3	0	3
Died during study period, No. (%)	223 (8.7)	396 (3.9)	68 (3.9)	243 (3.5)
Meningococcal meningitis	61 (13.5)	112 (6.2)	14 (5.4)	33 (3.4)
Pneumococcal meningitis	126 (22.8)	201 (9.1)	11 (4.9)	41 (4.3)
Viral meningitis	24 (1.7)	73 (1.3)	40 (3.4)	165 (3.4)
Herpes simplex encephalitis	12 (10.4)	10 (2.2)	3 (4.1)	4 (1.4)

Table 2. Proportions employed and receiving disability pensions among meningococcal, pneumococcal, or viral meningitis and herpes simplex encephalitis patients and members of the comparison cohorts.

	Patients	Comparison cohorts		Patients	Comparison cohorts	
	Proportions employed % (95% CI)		Difference % (95% CI) [a]	Proportions receiving disability pension % (95% CI) [b]		Difference % (95% CI) [c]
Meningococcal meningitis						
- 2 years before diagnosis	71.8 (67.4, 75.9)	81.9 (80.0, 83.7)	-10.1 (-14.7, -5.5)	8.5 (4.9, 14.2)	2.8 (1.7, 4.5)	5.7 (0,8, 10.5)
- Year of diagnosis	72.5 (68.4, 76.4)	82.4 (80.6, 84.1)	-9.9 (-14.4, -5.5)	8.8 (5.5, 13.9)	3.0 (2.0, 4.6)	5.8 (1.4, 10.2)
- 2 years after diagnosis	70.6 (66.2, 74.7)	82.6 (80.8, 84.3)	-12.0 (-16.6, -7.4)	9.9 (6.3, 15.3)	3.7 (2.5, 5.4)	6.2 (1.4, 10.9)
- 5 years after diagnosis	70.4 (65.8, 74.6)	81.7 (79.8, 83.5)	-11.3 (-16.1, -6.6)	10.5 (6.5, 16.3)	5.4 (3.9, 7.5)	5.1 (-0.1, 10.3)
Pneumococcal meningitis						
- 2 years before diagnosis	72.2 (68.1, 75.9)	83.7 (82.0, 85.2)	-11.5 (-15.7, -7.3)	11.0 (7.6, 15.7)	4.9 (3.7, 6.4)	6.1 (1.9, 10.4)
- Year of diagnosis	68.5 (64.6, 72.3)	84.3 (82.7, 85.8)	-15.8 (-19.9, -11.6)	13.8 (10.3, 18.4)	5.3 (4.2, 6.8)	8.5 (4.3, 12.8)
- 2 years after diagnosis	61.4 (57.1, 65.5)	83.3 (81.6, 84.8)	-21.9 (-26.4, -17.4)	24.5 (19.6, 30.2)	6.2 (4.9, 7.9)	18.3 (12.8, 23.8)
- 5 years after diagnosis	61.6 (56.9, 66.0)	81.3 (79.5, 83.0)	-19.7 (-24.6, -14.8)	28.0 (22.1, 34.8)	8.1 (6.4, 10.1)	19.9 (13.4, 26.6)
Viral meningitis						
- 2 years before diagnosis	80.0 (77.9, 82.0)	79.1 (78.0, 80.1)	0.9 (-1.3, 3.3)	2.3 (1.6, 3.3)	2.7 (2.3, 3.2)	-0.4 (-1.3, 0.6)
- Year of diagnosis	82.8 (80.7, 84.6)	82.0 (81.0, 83.0)	0.8 (-1.4, 3.0)	2.9 (2.1, 3.9)	3.1 (2.7, 3.6)	-0.2 (-1.3, 0.7)
- 2 years after diagnosis	82.0 (79.8, 84.0)	82.0 (81.0, 83.0)	0.0 (-2.4, 2.3)	3.4 (2.6, 4.6)	3.8 (3.3, 4.4)	-0.4 (-1.5, 0.8)
- 5 years after diagnosis	83.1 (80.7, 85.3)	84.4 (83.2, 85.4)	-1.3 (-3.8, 1.3)	3.9 (2.9, 5.2)	4.6 (4.0, 5.2)	-0.7 (-2.0, 0.6)
Herpes simplex encephalitis						
- 2 years before diagnosis	78.3 (69.9, 84.8)	83.0 (79.3, 86.2)	-4.7 (-13.0, 3.4)	11.0 (6.1, 19.1)	3.8 (2.3, 6.4)	7.2 (0.3, 14.0)
- Year of diagnosis	76.5 (68.8, 83.3)	85.7 (82.2, 88.6)	-9.2 (-17.4, -0.8)	11.3 (6.7, 18.4)	4.3 (2.8, 6.6)	7.0 (0.8, 13.1)
- 2 years after diagnosis	62.6 (52.8, 71.5)	85.5 (81.8, 88.6)	-22.9 (-29.5, -16.3)	19.2 (12.6, 28.0)	5.4 (3.6, 8.0)	13.8 (5.8, 21.8)
- 5 years after diagnosis	62.2 (50.8, 72.4)	83.2 (78.7, 86.9)	-21.0 (-32.6, -9.5)	24.3 (16.0, 35.2)	8.1 (5.6, 11.6)	16.2 (6.2, 26.3)

[a] Difference in proportions employed in the 2 populations (%) and 95% confidence interval.

[b] Percentage diagnosed after 1994 who were receiving disability pension.

[c] Difference in proportions receiving disability pension in the 2 populations (%) and 95% confidence interval

Figure 1. Summary of the Study Design.

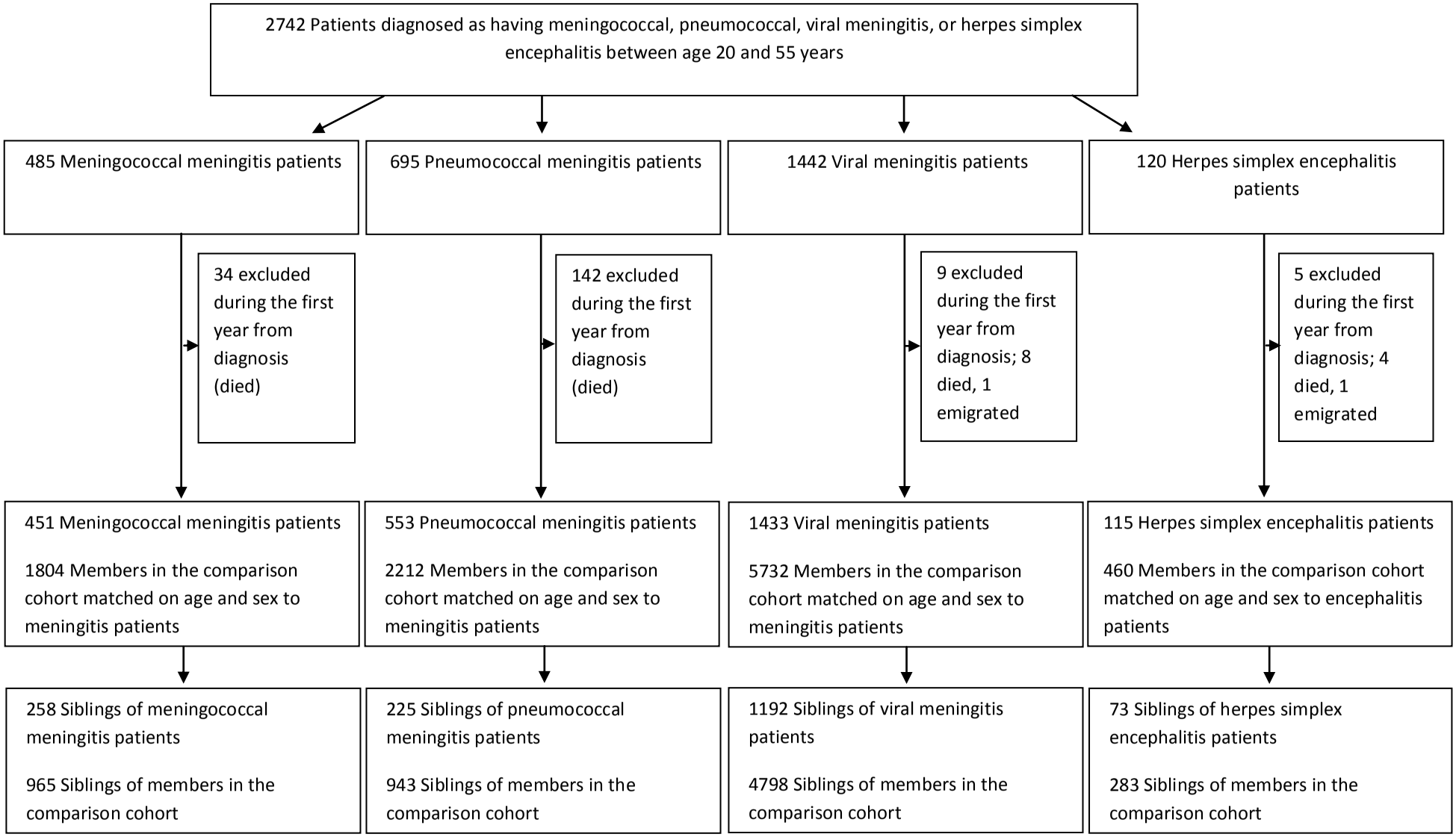
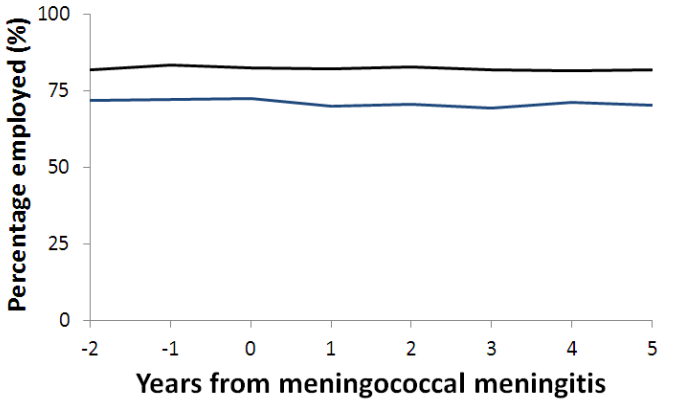
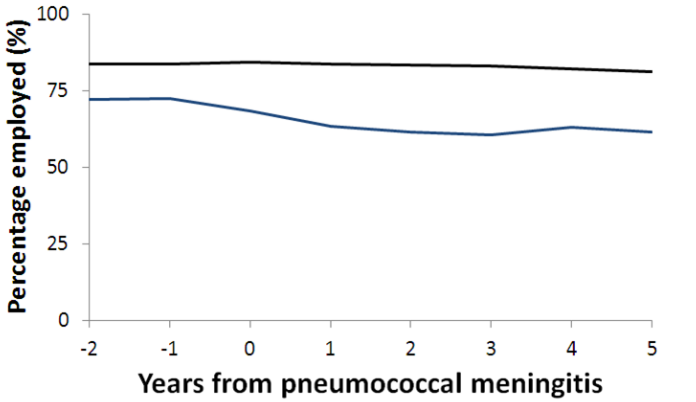


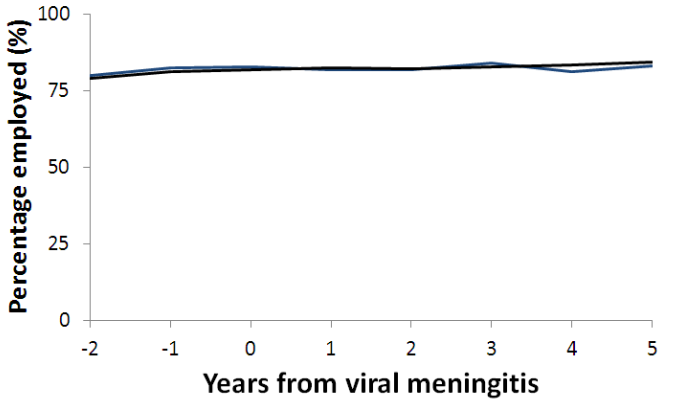
Figure 2. Proportions employed among meningococcal, pneumococcal, viral meningitis and herpes simplex encephalitis patients (blue line) and comparison cohorts (black line).



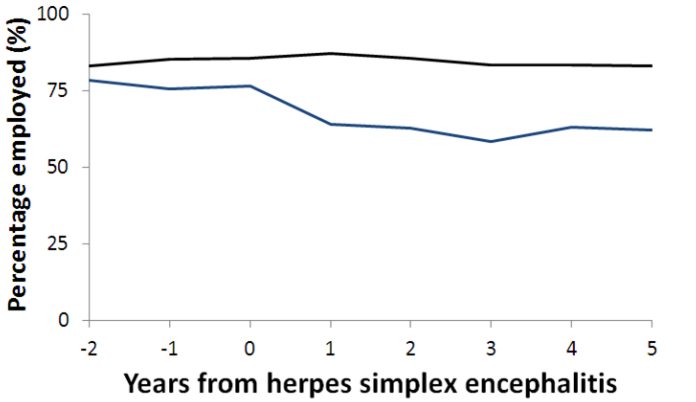
No. employed/total no.	-2	-1	0	1	2	3	4	5
Patients	306/426	314/436	327/451	314/448	310/439	299/431	301/423	290/412
Comparison cohort	1396/1704	1456/1744	1487/1804	1479/1802	1466/1774	1428/1745	1400/1715	1369/1675



No. employed/total no.	-2	-1	0	1	2	3	4	5
Patients	368/510	384/531	379/553	345/544	315/513	296/489	291/461	269/437
Comparison cohort	1707/2040	1780/2124	1865/2212	1844/2206	1776/2133	1702/2046	1607/1958	1528/1880

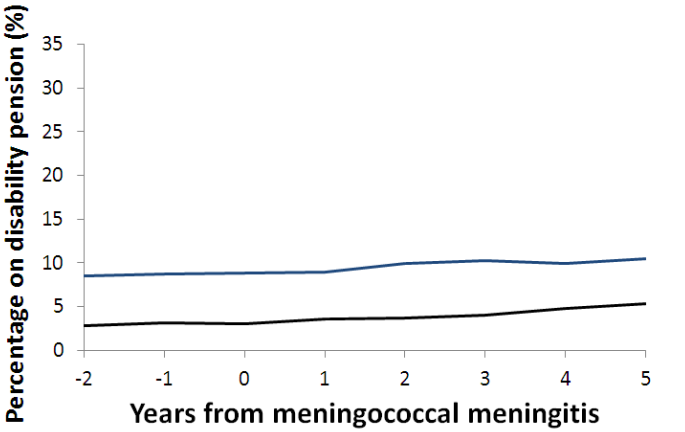


No. employed/total no.	-2	-1	0	1	2	3	4	5
Patients	1147/1433	1184/1433	1186/1433	1169/1429	1074/1310	1008/1199	892/1099	860/1035
Comparison cohort	4532/5732	4652/5732	4700/5732	4728/5727	4309/5254	3980/4801	3686/4421	3513/4164

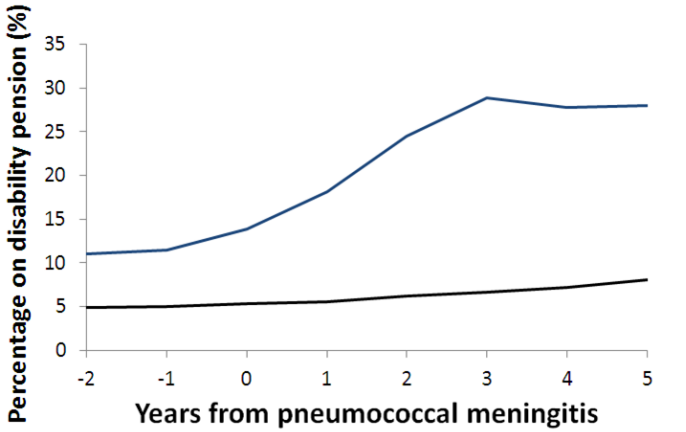


No. employed/total no.	-2	-1	0	1	2	3	4	5
Patients	90/115	87/115	88/115	73/114	62/99	52/89	51/81	46/74
Comparison cohort	382/460	393/460	394/460	399/457	349/408	314/376	290/347	267/321

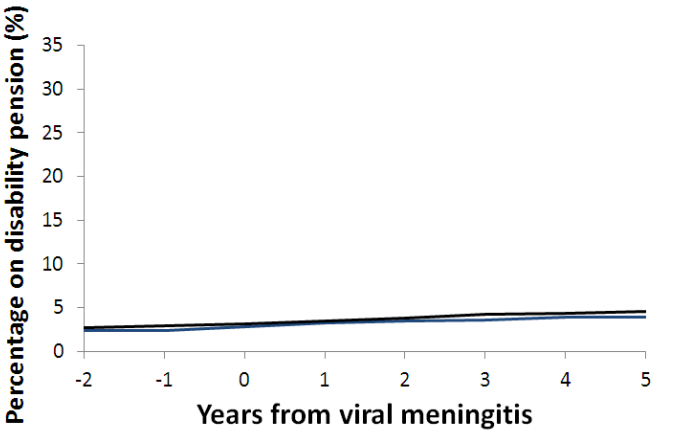
Figure 3. Proportions receiving disability pension among meningococcal, pneumococcal, viral meningitis and herpes simplex encephalitis patients (blue line) diagnosed after 1994 and comparison cohorts (black line).



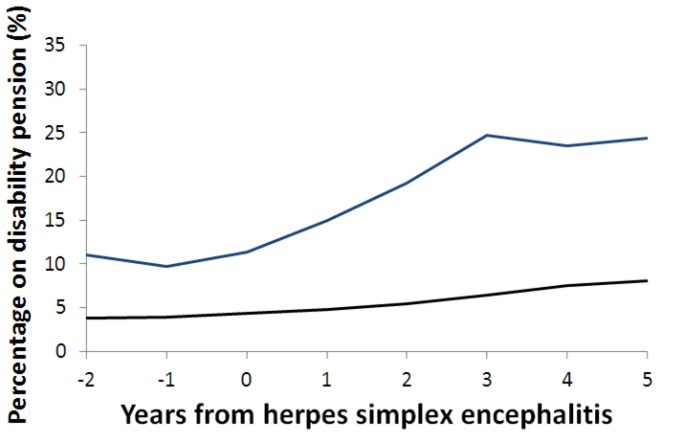
No. on disability pension/total no.								
Patients	12/142	14/160	16/181	16/179	17/172	17/166	16/161	16/153
Comparison cohort	16/568	20/640	22/724	26/723	26/701	27/676	31/651	33/614



No. on disability pension/total no.								
Patients	26/236	31/270	39/282	50/276	62/253	67/232	58/290	53/189
Comparison cohort	46/944	54/1080	60/1128	62/1126	66/1057	64/971	64/891	66/818



No. on disability pension/total no.								
Patients	29/1247	32/1348	41/1433	46/1429	45/1310	43/1199	43/1099	40/1035
Comparison cohort	134/4988	160/5392	180/5732	196/5727	200/5254	203/4801	193/4421	190/4164



No. on disability pension/total no.								
Patients	10/91	10/103	13/115	17/114	19/99	22/89	19/81	18/74
Comparison cohort	14/364	16/412	20/460	22/457	22/408	24/376	26/347	26/321

Appendices 1-4

References

eTable1. Personal income. Mean monthly income of employed meningococcal, pneumococcal, and viral meningitis and herpes simplex encephalitis patients, and of employed members of the comparison cohorts.

eTable2. Individuals without comorbid conditions defined by the Charlson Comorbidity Index before CNS infection. Proportions employed and receiving disability pension among meningococcal, pneumococcal, or viral meningitis and herpes simplex encephalitis patients and members of the comparison cohorts.

eTable3. Individuals not diagnosed with a disease associated with work incapacity* before CNS infection. Proportions employed and receiving disability pension among meningococcal, pneumococcal, or viral meningitis and herpes simplex encephalitis patients and members of the comparison cohorts.

eTable4. Individuals employed 2 years before CNS infection and not having received disability pension. Proportions employed and receiving disability pension among meningococcal, pneumococcal, or viral meningitis and herpes simplex encephalitis patients and members of the comparison cohorts.

eTable 5. Siblings. Proportions employed and receiving disability pension among siblings of meningococcal, pneumococcal, or viral meningitis and herpes simplex encephalitis patients and siblings of the comparison cohorts.

eFigure 1. Personal income. Mean monthly income in US Dollars in 2012 prices for employed meningococcal, pneumococcal, and viral meningitis and herpes simplex encephalitis patients (blue line) and employed members of the comparison cohorts (black line).

eFigure 2. Individuals not diagnosed with a disease associated with work incapacity* before CNS infection. Proportions employed among meningococcal, pneumococcal, viral meningitis and herpes simplex encephalitis patients (blue line) and members of the comparison cohorts (black line).

eFigure 3. Individuals not diagnosed with a disease associated with work incapacity* before CNS infection. Proportions receiving disability pension among meningococcal, pneumococcal, viral meningitis and herpes simplex encephalitis patients (blue line) diagnosed after 1994 and members of the comparison cohort (black line).

eFigure 4. Individuals employed 2 years before CNS infection and not having received disability pension. Proportions employed among meningococcal, pneumococcal, viral meningitis and herpes simplex encephalitis patients (blue line) and members of the comparison cohorts (black line).

eFigure 5. Individuals employed 2 years before CNS infection and not having received disability pension. Proportions receiving disability pension among meningococcal, pneumococcal, viral meningitis and herpes simplex encephalitis patients (blue line) diagnosed after 1994 and members of the comparison cohort (black line).

*defined in Appendix 4

Appendix 1
Description of registries:

- The Danish National Registry of Patients (DNRP) contains information on all patients discharged from all Danish hospitals since 1977.[1] Records for each inpatient admission include the PIN number, hospital department, dates of admission, a primary and up to 19 secondary discharge diagnoses coded by the attending physician according to the *International Classification of Diseases* 8th (ICD-8) revision until the end of 1993, and 10th (ICD-10) revision thereafter. Medical care on an outpatient basis provided by Danish hospitals has been recorded in the registry since 1986. The records for each hospital outpatient service include the PIN number, hospital department, date of first and last visit to a hospital outpatient clinic, number of visits, and the medical condition coded by the outpatient physician according to the ICD-8 revision, until the end of 1993, and ICD-10 revision thereafter.

- The Danish Civil Registration System, a national registry established in 1968, contains demographic data and vital status for all Danish citizens.[2] Registration of siblings in the Danish Civil Registration System is more than 98% complete from 1952 on.

- The Employment Classification Module (AKM) is a national registry maintained by Statistics Denmark.[3,4] The registry contains data on employment and has been updated annually since 1980. An individual is registered as employed in the AKM when his or her main income in a full calendar year stems from (1) business profit from a company owned by the individual or the individual's spouse or (2) employment with a specified minimum income. This minimum income is specified by Statistics Denmark and is equivalent to the mean yearly income for Danish trainees and is adjusted by the Consumer Price Index. The minimum income was 42 224 Danish kroner (US $ 7446) in 1998 and 49 138 Danish kroner (US $ 8621) in 2005. In the registry this parameter is recorded in the parameters BESKST (until December 31, 2001) and BESKST02 (from January 1, 2002).[3] Since January 1, 1994 the module also has included complete nationwide data on whether a specified individual in Denmark received a disability pension in a given calendar year, recorded in the parameters SOCIO (until December 31, 2001) and SOCIO2 (from January 1, 2002).[3]

- Personal Income Statistics is a national registry administered by Statistics Denmark.[5] The registry contains data on personal income and has been updated annually since 1980. Personal income includes all types of income except income from wealth. The primary source of registry data is the Central Customs and Tax Administration's Central Taxpayers' Register.[5]

- The Danish Educational Attainment Registry, a national registry established in 1974, is administered by Statistics Denmark.[6,7] The registry contains the highest educational achievement obtained by all Danish citizens in each calendar year. The primary source of registry data is the Integrated Student Registry, which collects data from all educational institutions in the country, from elementary schools to universities. Secondary sources are registries collecting data from part-time educational programs and from educational programs outside Denmark whose credits are formally transferred to a Danish educational institution.

Appendix 2

- Meningococcal meningitis was identified using ICD-8 code 036.09 and ICD-10 code A39.0
- Pneumococcal meningitis was identified using ICD-8 code 320.19 and ICD-10 code G00.1

- Viral meningitis was identified using ICD-10 code A87.9
- Herpes simplex encephalitis was identified using ICD-10 code B00.4

Appendix 3

Infections of the central nervous system were identified using the following ICD-8 codes for the years 1977-1993:

- Meningococcal meningitis: code 036.09
- H. *influenzae* meningitis: code 320.09
- Pneumococcal meningitis: code 320.19
- Streptococcal meningitis: code 320.80
- Meningitis per organismos alios specificatos: code 320.89
- Listeria meningitis: code 027.01
- Meningococcal infection: code 036.00-036.99
- Aseptic meningitis due to enterovirus: codes 045.00-045.99
- Varicella meningitis/encephalitis: codes 052.01
- Zoster meningitis/encephalitis: code 053.02
- Herpesviral meningitis/encephalitis: code 054.03

Infections of the central nervous system were identified using the following ICD-10 codes for the years 1994-2007:

- Meningococcal meningitis: code A39.0
- *H. influenzae* meningitis: code G00.0
- Pneumococcal meningitis: code G00.1
- Streptococcal meningitis: code G00.2
- Staphylococcal meningitis: code G00.3
- Other bacterial meningitis: code G00.8
- Bacterial meningitis, unspecified: code G00.9
- Listeria meningitis and meningoencephalitis: code A32.1
- Meningococcal infection: codes A39.0-A39.9
- Unspecified viral encephalitis: code A86
- Enteroviral meningitis: code A87.0
- Adenoviral meningitis: code A87.1
- Lymphocytic choriomeningitis: code A87.2
- Other viral meningitis: code A87.8
- Viral meningitis, unspecified: code A87.9
- Herpesviral meningitis: code B00.3
- Herpesviral encephalitis: code B00.4
- Varicella meningitis: code B01.0
- Varicella encephalitis: code B01.1
- Zoster encephalitis: code B02.0
- Zoster meningitis: code B02.1
- Zoster with other nervous system involvement: code B02.2

Appendix 4

Diseases associated with work incapacity [8-42] were identified using the following ICD-8 codes for the years 1977 / ICD-10 codes for the years 1994-2007:

- Human immunodeficiency virus: codes 079.83 / B20-B29.9, B24-B24.9
- Malignant neoplasms: codes 140-207.99 / C00-C97.9
- Diabetes mellitus with renal, ophthalmic, neurological and peripheral circulatory complications: codes 249.01-249.05, 249.08, 250.01-250.05, 250.08 / E10.2-E10.7, E11.2-E11.7, E12.2-E12.7, E13.2-E13.7, E14.2-E14.7
- Mental and behavioral disorders; mental disorders, schizophrenia, mood affective disorders, neurotic disorders, disorders of adult personality, mental retardation: codes 290.00-302.00, 303.00-306.00, 310.00-320.00 / F00-F50.9, F60-F63.9, F70-F79.0
- Diseases of the nervous system; degenerative diseases of the nervous system, episodic and paroxysmal disorders, polyneuropathies, paralytic syndromes: codes 330.00-360.00 / G10-G99.8
- Diseases of the circulatory system; myocardial infarction, heart failure, peripheral vascular disease, cerebrovascular disease: codes 410.00-410.99, 427.09, 427.10, 427.11, 427.19, 428.99, 430.00-438.99, 440.00-445.99, 782.49 / G45-G46.9, I11.0, I21.0-I23.9, I25.2, I42.5-I42.9, I43.0-I43.9, I50-I50.9, I60-I69.9, I70-I74.9, I77-I77.9, I79.0, I79.2
- Chronic diseases of the respiratory system; chronic lower respiratory diseases, lung diseases due to external agents, cystic fibrosis: codes 490.00-493.99, 515.00-518.99 / J40-J47.9, J60-J67.9, J68.4, J70.1, J70.3, I27.8, I27.9, E84-E84.9
- Gastrointestinal diseases; Crohn disease, ulcerative colitis, acute and chronic hepatitis B and C virus, liver diseases: codes 070.00, 070.02, 070.04, 070.06, 070.08, 456.00-456.09, 563.00-563.99, 571.00-571.99, 573.00, 573.01, 573.04 / B16-B18.9, I85.0, I85.9, I86.4, I88.2, K50-K51.9, K70-K77.8, Z94.4
- Diseases of the musculoskeletal system and connective tissue; inflammatory polyarthropathies, systemic connective tissue disorders, sarcoidosis, dorsopathies: codes 135.99, 712.00-712.99, 716.00-716.99, 725.00-727.00, 734.00-734.99, 446.00-446.99 / M05-M06.9, M30-M36.9, M40-M54.9, D86-D86.9
- Chronic kidney diseases; hypertensive renal disease, glomerular diseases, renal failure, care involving dialysis: codes 403.00-404.99, 580.00-584.99, 590.09, 593.19, 753.10-753.19, 792.00-792.99 / I12-I13.9, N00-N08.8, N17-N19.9, N25.0, Z49-Z49.2, Z94.0, Z99.2
- Alcohol abuse; codes 291.00-292.00, 571.09-571.11, 303.00-303.90 / F10-F11, G31.2, G62.1, G72.1, I42.6, K29.2, K70-K71, K85.2, K86.0, R78.0, T51-T51.9, Z72.1

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eTable1. Personal income. Mean monthly income for employed meningococcal, pneumococcal, or viral meningitis and herpes simplex encephalitis patients and for employed members of the comparison cohorts.

	Employed patients [a]	**Employed members of the comparison cohorts** [a]	Difference between employed patients and employed members of the comparison cohorts (95% CI) [b]
Meningococcal meningitis, mean monthly income, US $			
- 2 years before diagnosis	4317	4198	119 (-256, 494)
- Year of diagnosis	4425	4460	-35 (-416, 347)
- 2 years after diagnosis	4517	4663	-146 (-432, 140)
- 5 years after diagnosis	4828	4968	-140 (-481, 200)
Pneumococcal meningitis, mean monthly income, US $			
- 2 years before diagnosis	4625	5076	-451 (-753, -150)
- Year of diagnosis	4821	5166	-344 (-673, -16)
- 2 years after diagnosis	5268	5318	-50 (-455, 355)
- 5 years after diagnosis	5438	5364	74 (-552, 701)
Viral meningitis, mean monthly income, US $			
- 2 years before diagnosis	5105	4694	411 (84, 738)
- Year of diagnosis	5360	5009	350 (101, 600)
- 2 years after diagnosis	5713	5235	478 (177, 779)
- 5 years after diagnosis	5977	5594	383 (52, 714)
Herpes simplex encephalitis, mean monthly income, US $			
- 2 years before diagnosis	4866	5273	-407 (-984, 170)
- Year of diagnosis	5177	5496	-318 (-1001, 365)
- 2 years after diagnosis	5059	5579	-520 (-1152, 112)
- 5 years after diagnosis	5261	5910	-648 (-1460, 165)

[a] US dollars, in 2012 prices.

[b] Difference in mean income of the 2 populations and 95% confidence interval.

eTable2. Individuals without comorbid conditions defined by the Charlson Comorbidity Index before CNS infection. Proportions employed and receiving disability pension among meningococcal, pneumococcal, or viral meningitis and herpes simplex encephalitis patients and members of the comparison cohorts.

	Patients	**Comparison cohort**		**Patients**	**Comparison cohort**	
	Proportions employed % (95% CI)		Difference % (95% CI) [a]	Proportions receiving disability pension % (95% CI) [b]		Difference % (95% CI) [c]
Meningococcal meningitis						
- 2 years before diagnosis	72.8 (68.2, 77.0)	82.4 (80.5, 84.2)	-9.6 (-14.4, -4.8)	5.5 (2.7, 10.9)	2.5 (1.4, 4.2)	3.0 (-1.3, 7.3)
- Year of diagnosis	74.6 (70.3, 78.6)	83.0 (81.2, 84.7)	-8.4 (-12.9, -3.9)	6.6 (3.7, 11.5)	2.6 (1.7, 4.1)	4.0 (-0.1, 8.1)
- 2 years after diagnosis	72.5 (68.0, 76.6)	83.5 (81.6, 85.1)	-11.0 (-15.6, -6.3)	8.1 (4.8, 13.4)	3.2 (2.1, 4.8)	4.9 (0.4, 9.5)
- 5 years after diagnosis	72.0 (67.3, 76.2)	82.6 (80.7, 84.4)	-10.6 (-15.4, -5.8)	8.3 (4.8, 14.0)	4.8 (3.4, 6.9)	3.5 (-1.4, 8.4)
Pneumococcal meningitis						
- 2 years before diagnosis	74.1 (69.7, 78.0)	84.6 (83.0, 86.2)	-10.5 (-15.0, -6.1)	7.7 (4.7, 12.4)	3.6 (2.6, 5.1)	4.1 (0.1, 8.2)
- Year of diagnosis	71.3 (67.0-75.2)	85.5 (84.0-87.0)	-14.2 (-18.6, -9.9)	9.4 (6.3, 13.9)	3.9 (2.9, 5.3)	5.5 (1.6, 9.5)
- 2 years after diagnosis	64.3 (59.7, 68.7)	84.3 (82.6, 85.8)	-20.0 (-24.8, -15.2)	20.9 (15.9, 26.8)	5.1 (3.9, 6.6)	15.8 (10.2, 21.4)
- 5 years after diagnosis	64.2 (59.2, 68.9)	82.4 (80.5, 84.1)	-18.2 (-23.3, -13.0)	23.8 (17.9, 30.9)	6.8 (5.2, 8.8)	17.0 (10.3, 23.8)
Viral meningitis						
- 2 years before diagnosis	81.6 (79.4, 83.6)	79.7 (78.6, 80.7)	1.9 (-0.4, 4.3)	1.4 (0.9, 2.3)	2.1 (1.7, 2.5)	-0.7 (-1.5, 0.2)
- Year of diagnosis	84.0 (82.0, 85.9)	82.7 (81.7, 83.7)	1.3 (-0.8, 3.6)	1.8 (1.2, 2.7)	2.5 (2.1, 2.9)	-0.7 (-1.5, 0.2)
- 2 years after diagnosis	82.8 (80.5, 84.8)	82.6 (81.6, 83.7)	0.2 (-2.3, 2.5)	2.5 (1.8, 3.6)	3.1 (2.6, 3.6)	-0.6 (-1.6, 0.5)
- 5 years after diagnosis	83.1 (80.6, 85.4)	85.2 (84.1, 86.3)	-2.1 (-4.8, 0.5)	3.4 (2.4, 4.7)	3.8 (3.2, 4.4)	-0.4 (-1.7, 0.9)
Herpes simplex encephalitis						
- 2 years before diagnosis	79.0 (70.3, 85.7)	84.4 (80.6, 87.5)	-5.3 (-13.8, 3.1)	9.9 (5.1, 18.3)	3.3 (1.8, 5.8)	6.6 (-0.3, 13.5)
- Year of diagnosis	77.1 (68.2, 84.1)	86.9 (83.4, 89.4)	-9.8 (-18.4, -1.2)	9.5 (5.3, 16.6)	3.3 (2.0, 5.4)	6.2 (0.4, 12.2)
- 2 years after diagnosis	61.8 (51.4, 71.2)	86.4 (82.5, 89.4)	-24.6 (-35.0, -14.1)	18.0 (11.4, 27.2)	4.5 (2.8, 7.0)	13.5 (5.3, 21.7)
- 5 years after diagnosis	63.2 (51.4, 73.7)	83.9 (79.4, 87.6)	-20.7 (-32.6, -8.8)	23.5 (15.3, 34.9)	7.2 (4.8, 10.7)	16.3 (6.1, 26.6)

[a] Difference in proportions employed in the 2 populations (%) and 95% confidence interval.

[b] Percentage diagnosed after 1994 who were receiving disability pension.

[c] Difference in proportions receiving disability pension in the 2 populations (%) and 95% confidence interval.

eTable3. Individuals not diagnosed with a disease associated with work incapacity* before CNS infection. Proportions employed and receiving disability pension among meningococcal, pneumococcal, or viral meningitis and herpes simplex encephalitis patients and members of the comparison cohorts.*defined in Appendix 4

	Patients	**Comparison cohort**		**Patients**	**Comparison cohort**	
	Proportions employed % (95% CI)		Difference % (95% CI) [a]	Proportions receiving disability pension % (95% CI) [b]		Difference % (95% CI) [c]
Meningococcal meningitis						
- 2 years before diagnosis	77.2 (72.5, 81.2)	83.2 (81.3, 85.0)	-6.0 (-10.8, -1.4)	2.6 (0.9, 7.3)	1.4 (0.7, 2.9)	1.2 (-2.2, 4.5)
- Year of diagnosis	78.7 (74.4, 82.6)	84.1 (82.3, 85.8)	-5.4 (-9.8, -0.9)	3.3 (1.4, 7.5)	1.6 (0.9, 2.9)	1.7 (-1.5, 4.9)
- 2 years after diagnosis	76.3 (71.8, 80.4)	84.4 (82.6, 86.1)	-8.1 (-12.7, -3.4)	4.8 (2.3, 9.5)	1.9 (1.1, 3.4)	2.9 (-1.0, 6.6)
- 5 years after diagnosis	75.4 (70.7, 79.6)	83.5 (81.5, 85.2)	-8.1 (-12.9, -3.2)	6.0 (3.1, 11.4)	3.9 (2.6, 5.9)	2.1 (-2.3, 6.6)
Pneumococcal meningitis						
- 2 years before diagnosis	78.8 (74.4, 82.7)	85.4 (83.7, 87.0)	-6.6 (-11.0, -2.1)	5.8 (3.1, 10.7)	2.8 (1.8, 4.2)	3.0 (-1.0, 7.0)
- Year of diagnosis	74.4 (70.0-78.5)	86.9 (85.4-88.4)	-12.5 (-17.0, -8.0)	7.3 (4.4, 11.9)	3.0 (2.1, 4.4)	4.3 (0.4, 8.2)
- 2 years after diagnosis	67.4 (62.5, 71.9)	85.3 (83.6, 86.8)	-17.9 (-22.9, -13.0)	16.8 (11.9, 23.0)	4.0 (2.9, 5.6)	12.8 (7.0, 18.4)
- 5 years after diagnosis	66.9 (61.7, 71.7)	83.6 (81.8, 85.3)	-16.7 (-22.1, -11.5)	22.0 (16.0, 29.5)	5.7 (4.2, 7.7)	16.3 (9.3, 23.3)
Viral meningitis						
- 2 years before diagnosis	82.8 (80.6, 84.9)	80.8 (79.7, 81.9)	2.0 (-0.4, 4.5)	0.5 (0.2, 1.2)	1.3 (1.1, 1.7)	-0.8 (-1.4, -0.3)
- Year of diagnosis	85.7 (83.6, 87.6)	84.0 (83.0, 85.0)	1.7 (-0.5, 3.9)	0.8 (0.4, 1.5)	1.6 (1.3, 2.0)	-0.8 (-1.5, -0.2)
- 2 years after diagnosis	84.9 (82.6, 86.9)	83.9 (82.8, 84.9)	1.0 (-1.4, 3.4)	1.1 (0.7, 2.0)	2.0 (1.7, 2.5)	-0.9 (-1.7, -0.2)
- 5 years after diagnosis	84.9 (82.4, 87.2)	86.4 (85.2, 87.4)	-1.5 (-4.1, 1.2)	2.0 (1.3, 3.2)	2.8 (2.3, 3.4)	-0.8 (-1.9, 0.3)
Herpes simplex encephalitis						
- 2 years before diagnosis	81.6 (72.2, 88.4)	86.7 (83.0, 89.7)	-5.1 (-13.9, 3.7)	6.1 (2.4, 14.6)	2.0 (0.9, 4.3)	4.1 (-2.3, 10.4)
- Year of diagnosis	81.6 (72.2, 88.4)	89.0 (85.5, 91.7)	-7.4 (-16.1, 1.3)	5.7 (2.5, 12.8)	2.0 (1.0, 4.0)	3.7 (-1.7, 9.1)
- 2 years after diagnosis	65.0 (54.1, 74.6)	87.9 (84.1, 91.0)	-22.9 (-33.7, -12.1)	15.0 (8.8, 24.4)	2.9 (1.6, 5.2)	12.1 (4.1, 20.1)
- 5 years after diagnosis	61.3 (48.9, 72.4)	86.5 (82.0, 90.0)	-25.2 (-37.6, -12.8)	24.2 (15.2, 36.2)	5.3 (3.3, 8.6)	18.9 (8.0, 29.7)

[a] Difference in proportions employed in the 2 populations (%) and 95% confidence interval.

[b] Percentage diagnosed after 1994 who were receiving disability pension.

[c] Difference in proportions receiving disability pension in the 2 populations (%) and 95% confidence interval.

eTable4. Individuals employed 2 years before CNS infection and not having received disability pension. Proportions employed and receiving disability pension among meningococcal, pneumococcal, or viral meningitis and herpes simplex encephalitis patients and members of the comparison cohorts.

	Patients	**Comparison cohort**		**Patients**	**Comparison cohort**	
	Proportions employed % (95% CI)		Difference % (95% CI) [a]	Proportions receiving disability pension % (95% CI) [b]		Difference % (95% CI) [c]
Meningococcal meningitis						
- 2 years before diagnosis	100	100	0	0	0	0
- Year of diagnosis	92.8 (89.1, 95.3)	94.6 (93.2, 95.7)	-1.8 (-5.1, 1.6)	1.0 (0,2, 5,7)	0	1.0 (-1.7, 3.8)
- 2 years after diagnosis	87.5 (83.0, 90.9)	92.0 (90.4, 93.3)	-4.5 (-8.7, -0.3)	1.1 (0.2, 6.0)	0.5 (0.1, 1.7)	0.6 (-2.4, 3.6)
- 5 years after diagnosis	87.2 (82.5, 90.7)	90.1 (88.3, 91.7)	-2.9 (-7.4, 1.5)	2.5 (0.7, 8.7)	2.2 (1.1, 4.3)	0.3 (-4.0, 4.6)
Pneumococcal meningitis						
- 2 years before diagnosis	100	100	0	0	0	0
- Year of diagnosis	91.5 (88.1-94.0)	96.1 (95.1-97.0)	-4.6 (-7.7, -1.5)	5.8 (3.1, 10.7)	0.6 (0.1, 3.5)	5.2 (1.0, 9.4)
- 2 years after diagnosis	75.9 (71.0, 80.3)	93.5 (92.2, 94.6)	-17.6 (-22.4, -12.8)	13.9 (9.2, 20.5)	1.1 (0.6, 2.2)	12.8 (7.0, 18.5)
- 5 years after diagnosis	75.1 (69.7, 79.8)	89.6 (87.8, 91.1)	-14.5 (-19.8, -9.2)	21.3 (14.6, 29,9)	2.7 (1.6, 4.5)	18.6 (10.8, 26.4)
Viral meningitis						
- 2 years before diagnosis	100	100	0	0	0	0
- Year of diagnosis	95.6 (94.2, 96.7)	95.3 (94.6, 95.9)	0.3 (-1.1, 1.7)	0.1 (0.0, 0.6)	0.1 (0.0, 0.3)	0.0 (-0.4, 0.3)
- 2 years after diagnosis	92.2 (90.3, 93.7)	92.8 (92.0, 93.6)	-0.6 (-2.5, 1.2)	0.9 (0.5, 1.8)	0.4 (0.2, 0.7)	0.5 (-0.2, 1.2)
- 5 years after diagnosis	90.7 (88.5, 92.6)	92.8 (91.9, 93.7)	-2.1 (-4.3, 0.1)	1.8 (1.0, 3.1)	0.8 (0.5, 1.2)	1.0 (-0.1, 2.1)
Herpes simplex encephalitis						
- 2 years before diagnosis	100	100	0	0	0	0
- Year of diagnosis	97.6 (91.6, 99.3)	96.5 (94.1, 97.9)	1.1 (-3.2, 5.4)	1.5 (2.6, 7.9)	0	1.5 (-1.2, 4.1)
- 2 years after diagnosis	75.0 (63.9, 83.6)	94.8 (91.9, 96.8)	-19.8 (-30.0, -9.7)	12.1 (6.0, 22.9)	0.4 (0.1, 2.2)	11.7 (3.2, 20.2)
- 5 years after diagnosis	70.0 (57.5, 80.1)	91.8 (87.8, 94.6)	-21.8 (-33.6, -10.0)	23.9 (13.9, 37.9)	2.2 (0.9, 5.5)	21.7 (9.5, 33.9)

[a] Difference in proportions employed in the 2 populations (%) and 95% confidence interval.

[b] Percentage diagnosed after 1994 who were receiving disability pension.

[c] Difference in proportions receiving disability pension in the 2 populations (%) and 95% confidence interval.

eTable 5. Siblings. Proportions employed and receiving disability pension among siblings of meningococcal, pneumococcal, or viral meningitis and herpes simplex encephalitis patients and siblings of the comparison cohorts.

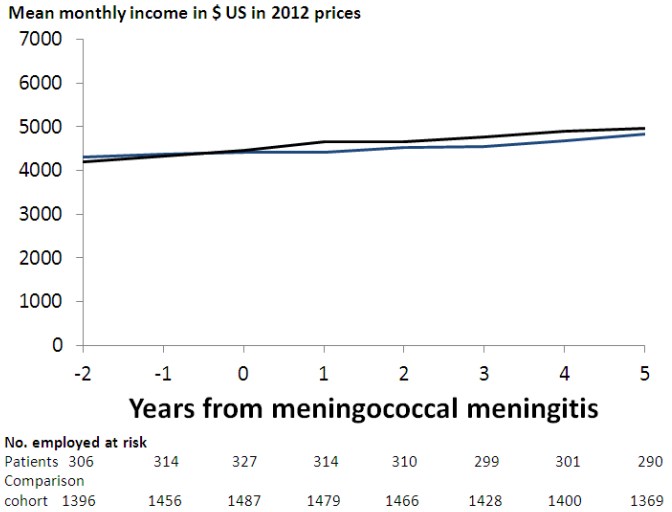
	Siblings of patients	**Siblings of comparison cohort**		**Siblings of patients**	**Siblings of comparison cohort**	
	Proportions employed % (95% CI)		Difference % (95% CI) [a]	Proportions receiving disability pension % (95% CI) [b]		Difference % (95% CI) [c]
Meningococcal meningitis						
- 2 years before diagnosis	62.9 (56.8, 68.9)	67.5 (64.5, 70.6)	-4.6 (-11.4, 2.1)	3.1 (1.1, 8.6)	2.3 (1.2, 4.4)	0.8 (-3.3, 4.9)
- Year of diagnosis	66.0 (60.1, 71.9)	75.4 (72.7, 78.2)	-9.4 (-15.9, -2.9)	3.3 (1.3, 8.2)	1.9 (0.9, 3.6)	1.4 (-2.3, 5.1)
- 2 years after diagnosis	76.2 (70.9, 81.6)	81.6 (79.1, 84.1)	-5.4 (-11.2, 0.5)	3.4 (1.4, 8.5)	2.2 (0.1, 4.1)	1.2 (-2.8, 5.4)
- 5 years after diagnosis	79.4 (74.0, 84.7)	81.6 (79.0, 84.1)	-2.2 (-8.2, 3.8)	1.1 (0.2, 5.9)	3.1 (1.7, 5.4)	-2.0 (-5.4, 1.4)
Pneumococcal meningitis						
- 2 years before diagnosis	80.6 (75.2, 86.0)	79.0 (76.3, 81.6)	1.6 (-4.4, 7.7)	7.3 (3.9, 13.2)	3.2 (2.0, 5.1)	4.1 (-0.8, 9.0)
- Year of diagnosis	82.1 (76.9-87.2)	81.1 (78.6-83.7)	1.0 (-4.8, 6.7)	6.9 (3.8, 12.3)	3.4 (2.2, 5.2)	3.5 (-1.0, 8.0)
- 2 years after diagnosis	85.8 (80.9, 90.7)	83.0 (80.5, 85.5)	2.8 (-2.7, 8.3)	7.0 (3.7, 12.7)	4.1 (2.7, 6.1)	2.9 (-1.9, 7.7)
- 5 years after diagnosis	81.6 (75.6, 87.5)	84.3 (81.5, 87.0)	-2.7 (-9.2, 3.9)	8.4 (4.3, 15.7)	4.8 (3.0, 7.4)	3.6 (-2.5, 9.8)
Viral meningitis						
- 2 years before diagnosis	78.4 (76.1, 80.8)	77.2 (76.0, 78.4)	1.2 (-1.4, 3.9)	2.5 (1.7, 3.7)	2.5 (2.1, 3.0)	0.0 (-1.0, 1.1)
- Year of diagnosis	81.8 (79.5, 84.0)	81.2 (80.1, 82.3)	0.6 (-2.0, 3.1)	2.7 (1.9, 3.9)	3.0 (2.5, 3.5)	-0.3 (-1.4, 0.9)
- 2 years after diagnosis	82.0 (79.7, 84.3)	83.1 (81.9, 84.2)	-1.1 (-3.7, 1.5)	3.4 (2.4, 4.6)	3.3 (2.8, 3.9)	0.1 (-1.2, 1.3)
- 5 years after diagnosis	86.0 (83.6, 88.4)	83.7 (82.5, 85.0)	2.3 (-0.4, 4.9)	3.4 (2.4, 4.8)	3.8 (3.2, 4.5)	-0.4 (-1.8, 0.9)
Herpes simplex encephalitis						
- 2 years before diagnosis	87.0 (79.0, 94.9)	79.0 (74.2, 83.9)	8.0 (-1.4, 17.2)	0	3.6 (1.8, 6.7)	-3.6 (-6.0, -1.1)
- Year of diagnosis	82.6 (73.7, 91.6)	82.0 (77.4, 86.6)	0.6 (-9.4, 10.7)	0	3.7 (2.0, 6.6)	-3.7 (-6.0, -1.4)
- 2 years after diagnosis	85.5 (76.7, 94.3)	86.2 (81.8, 90.6)	-0.7 (-10.5, 9.1)	3.2 (0.9, 11.0)	4.6 (2.6, 8.1)	-1.4 (-7.1, 4.4)
- 5 years after diagnosis	91.8 (84.2, 99.5)	84.6 (79.2, 89.9)	7.2 (-2.1, 16.6)	0	6.3 (3.6, 10.9)	-6.3 (-9.9, -2.6)

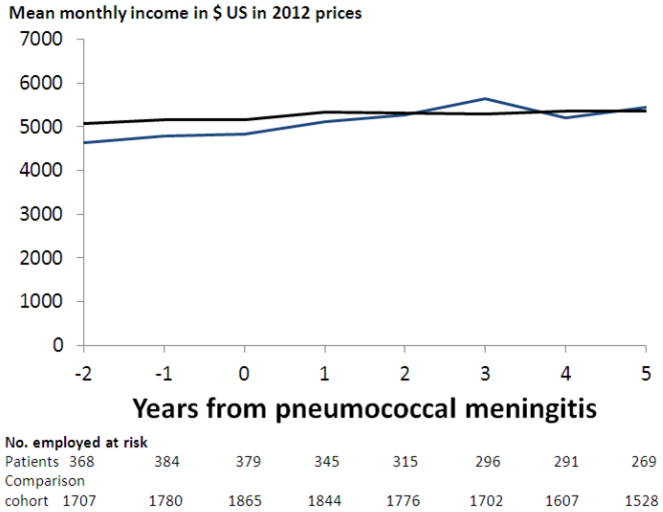
[a] Difference in proportions employed in the 2 populations (%) and 95% confidence interval.

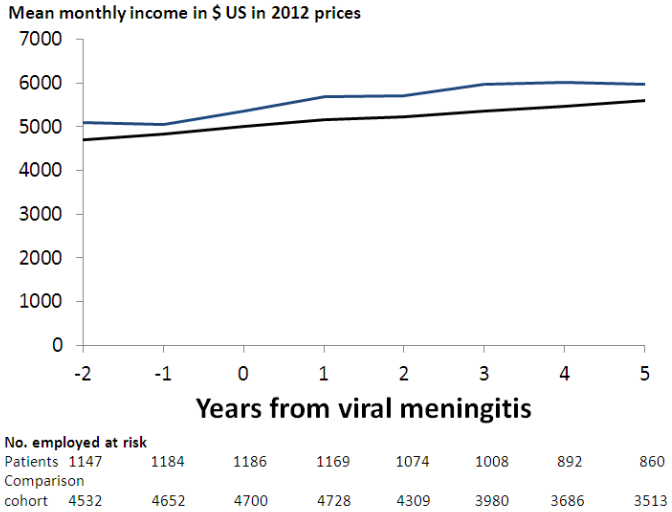
[b] Percentage diagnosed after 1994 who were receiving disability pension.

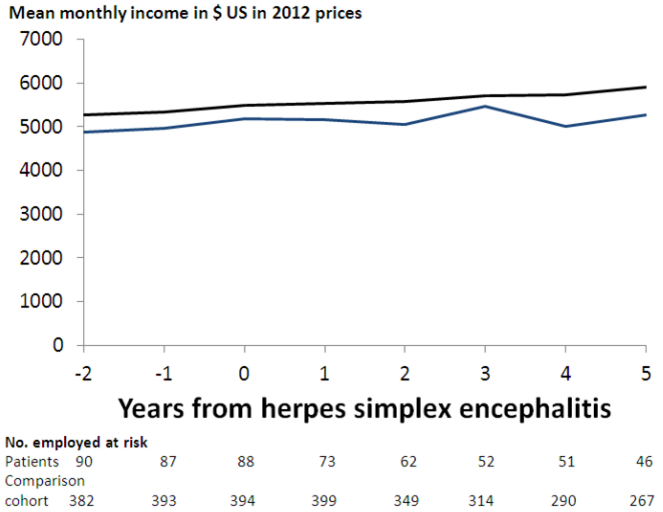
[c] Difference in proportions receiving disability pension in the 2 populations (%) and 95% confidence interval.

eFigure 1. Personal income. Mean monthly income in US Dollars in 2012 prices of employed meningococcal, pneumococcal, or viral meningitis and herpes simplex encephalitis patients (blue line) and employed members of the comparison cohorts (black line).

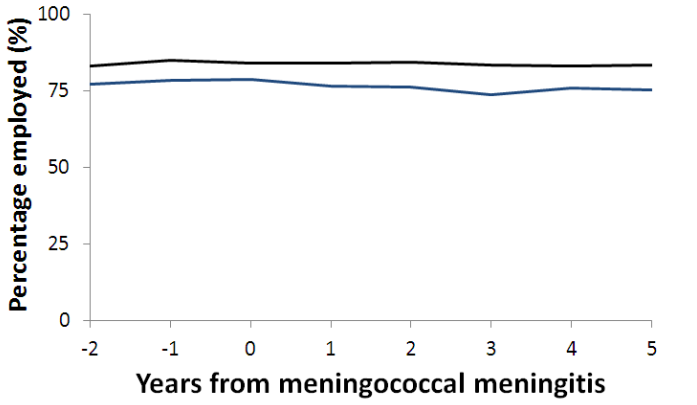




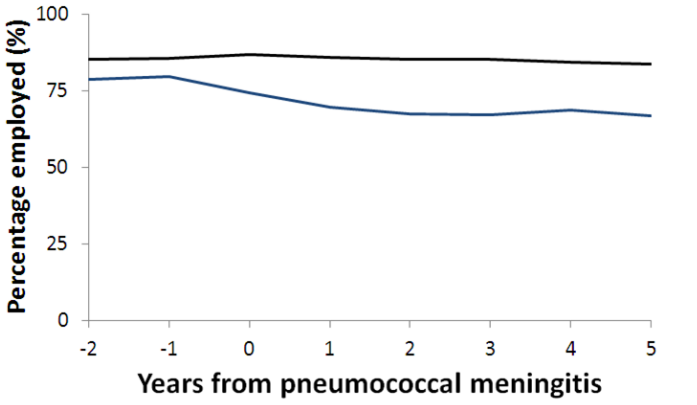




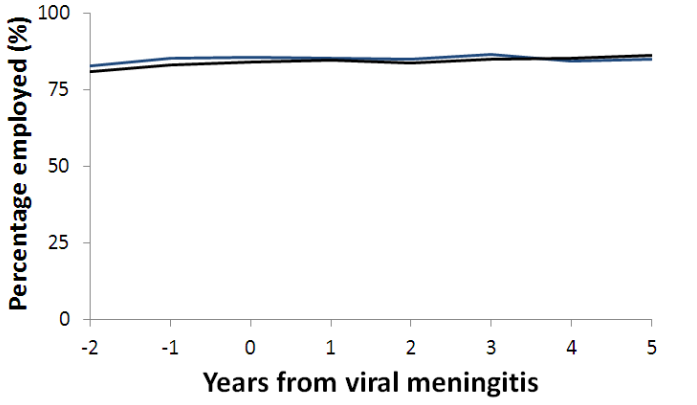
eFigure 2. Individuals not diagnosed with a disease associated with work incapacity* before CNS infection. Proportions employed among meningococcal, pneumococcal, or viral meningitis and herpes simplex encephalitis patients (blue line) and members of the comparison cohorts (black line). *defined in Appendix 4



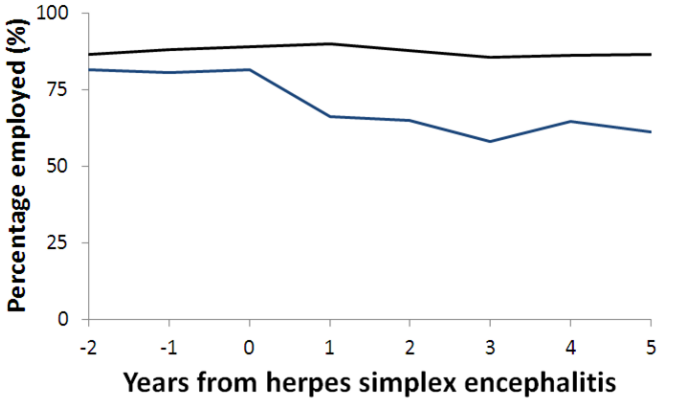
No. employed/total no.								
Patients	277/359	289/369	300/381	291/380	287/376	274/372	279/367	270/358
Comparison cohort	1296/1557	1356/1594	1390/1653	1385/1651	1375/1629	1338/1604	1311/1577	1287/1542



No. employed/total no.								
Patients	287/364	305/383	300/403	278/399	256/380	246/367	242/352	226/338
Comparison cohort	1506/1763	1581/1844	1678/1930	1655/1927	1596/1871	1538/1805	1465/1737	1405/1680

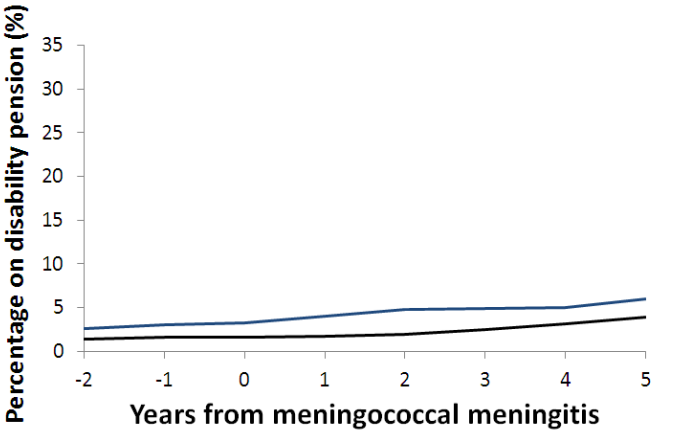


No. employed/total no.								
Patients	961/1160	988/1160	994/1160	986/1157	900/1060	844/975	759/900	726/855
Comparison cohort	4028/4985	4141/4985	4187/4985	4220/4982	3854/4595	3580/4216	3337/3910	3180/3682

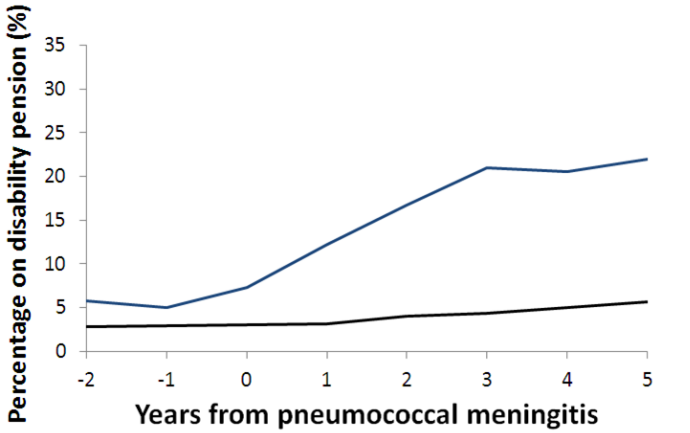


No. employed/ total no.								
Patients	71/87	70/87	71/87	57/86	52/80	43/74	44/68	38/62
Comparison cohort	339/391	344/391	348/391	350/389	306/348	277/323	261/303	244/282

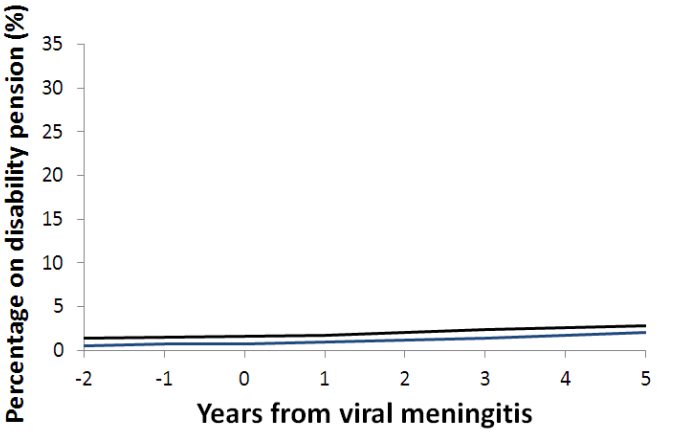
eFigure 3. Individuals not diagnosed with a disease associated with work incapacity* before CNS infection. Proportions receiving disability pension among meningococcal, pneumococcal, or viral meningitis and herpes simplex encephalitis patients (blue line) diagnosed after 1994 and members of the comparison cohort (black line). *defined in
Appendix 4



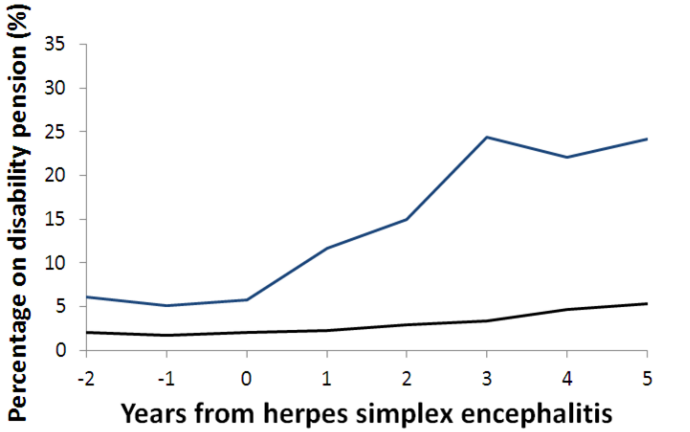
No. on disability pension/total no.								
Patients	3/116	4/133	5/152	6/151	7/147	7/143	7/140	8/133
Comparison cohort	7/489	9/554	10/635	11/634	12/617	15/596	18/573	21/541



No. on disability pension/total no.								
Patients	9/155	9/180	14/191	23/188	29/173	34/162	31/151	31/141
Comparison cohort	21/757	26/878	29/919	29/918	35/865	35/800	37/738	39/684

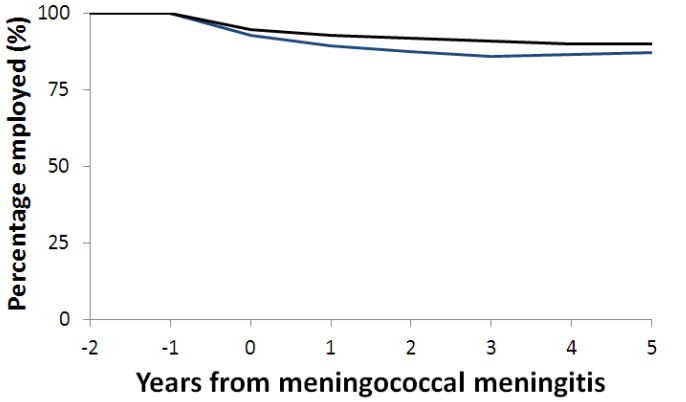


No. on disability pension/total no.								
Patients	5/996	8/1087	9/1160	11/1157	12/1060	13/975	15/900	17/855
Comparison cohort	58/4302	72/4668	81/4985	87/4982	94/4595	100/4216	100/3910	103/3682

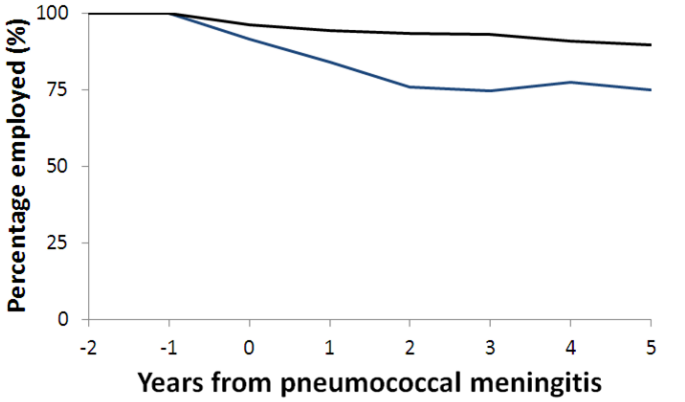


No. on disability pension/total no.								
Patients	4/66	4/78	5/87	10/86	12/80	18/74	15/68	15/62
Comparison cohort	6/299	6/346	8/391	9/389	10/348	11/323	14/303	15/282

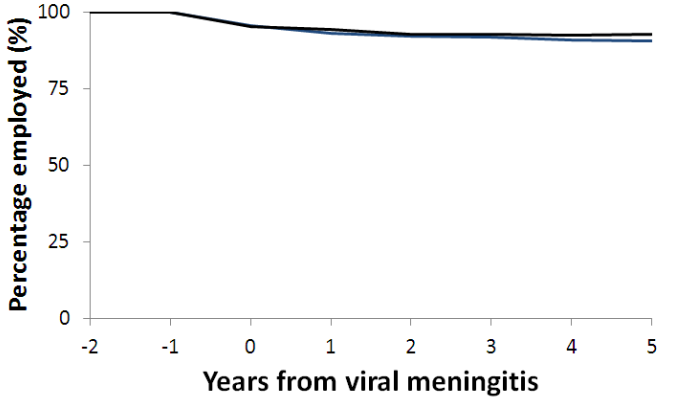
eFigure 4. Individuals employed 2 years before CNS infection and not having received disability pension. Proportions employed among meningococcal, pneumococcal, or viral meningitis and herpes simplex encephalitis patients (blue line) and members of the comparison cohorts (black line).



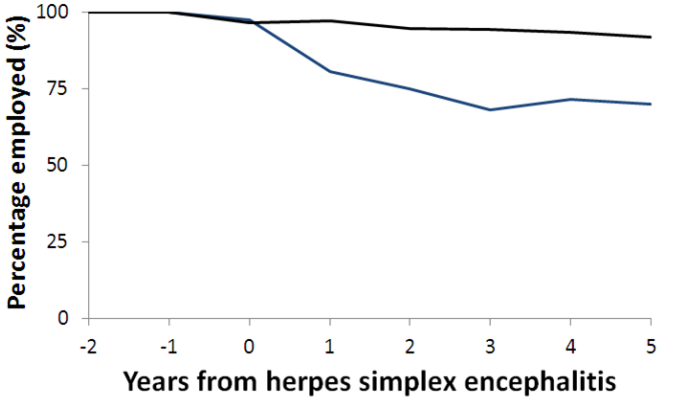
No. employed/total no.							
Patients	277/277	277/277	257/277	247/276	237/271	229/267	229/265	224/257
Comparison cohort	1324/1324	1324/1324	1252/1324	1228/1322	1202/1307	1168/1284	1134/1260	1111/1233



No. employed/total no.								
Patients	342/342	342/342	313/342	284/338	246/324	231/309	229/296	211/281
Comparison cohort	1625/1625	1625/1625	1562/1625	1533/1623	1465/1567	1398/1499	1304/1432	1227/1370

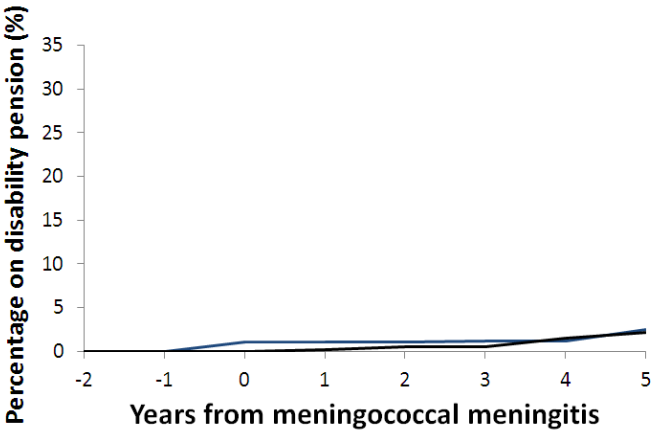


No. employed/total no.								
Patients	1088/1088	1088/1088	1040/1088	1011/1084	917/995	846/921	765/842	724/798
Comparison cohort	4270/4270	4270/4270	4070/4270	4021/4267	3642/3924	3319/3579	3051/3295	2897/3121

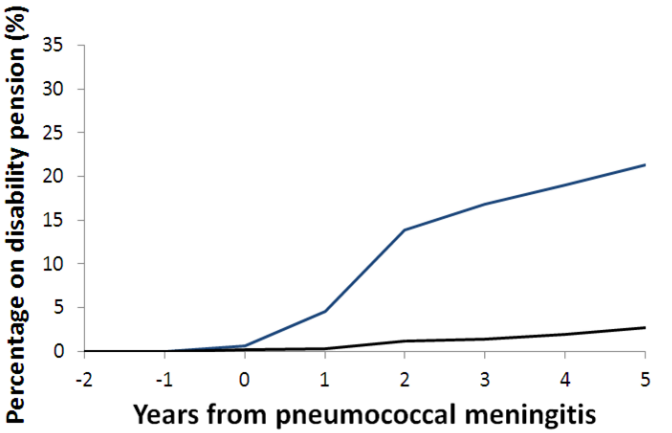


No. employed/total no.								
Patients	83/83	83/83	81/83	66/82	54/72	45/66	45/63	42/60
Comparison cohort	369/369	69/369	356/369	358/368	312/329	282/299	258/276	236/257

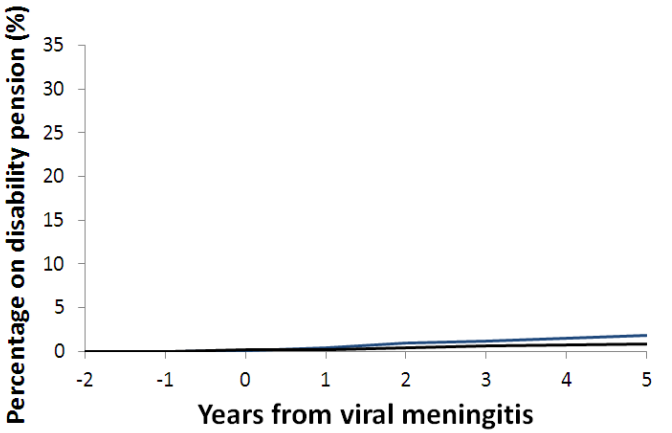
eFigure 5. Individuals employed 2 years before CNS infection and not having received disability pension. Proportions receiving disability pension among meningococcal, pneumococcal, or viral meningitis and herpes simplex encephalitis patients (blue line) diagnosed after 1994 and members of the comparison cohort (black line).



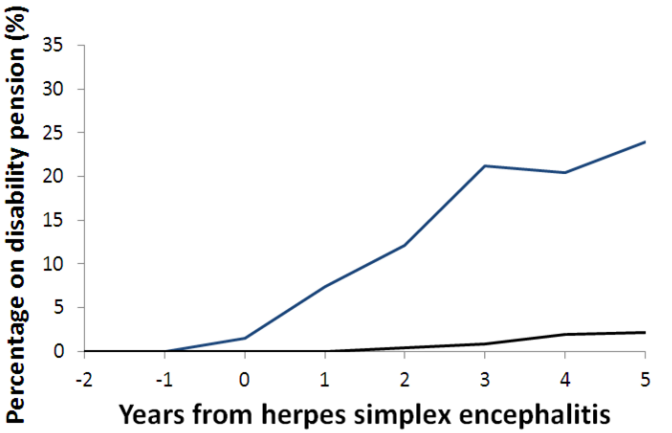
No. on disability pension/total no.								
Patients	0/96	0/96	1/96	1/96	1/91	1/87	1/85	2/80
Comparison cohort	0/443	0/443	0/443	1/442	2/430	2/410	6/389	8/366



No. on disability pension/total no.								
Patients	0/157	0/157	1/157	7/154	20/144	22/131	23/121	23/108
Comparison cohort	0/756	0/756	1/756	2/756	8/703	9/636	11/576	14/518



No. on disability pension/total no.								
Patients	0/959	0/959	1/959	4/955	8/866	9/792	11/714	12/672
Comparison cohort	0/3746	0/3746	5/3746	7/3744	14/3401	19/3058	19/2774	21/2600



No. on disability pension/total no.								
Patients	0/68	0/68	1/68	5/68	7/58	11/52	10/49	11/46
Comparison cohort	0/295	0/295	0/295	0/294	1/255	2/225	4/202	4/183