IMPORTANCE Although schizophrenia is associated with several age-related disorders and considerable cognitive impairment, it remains unclear whether the risk of dementia is higher among persons with schizophrenia compared with those without schizophrenia.

OBJECTIVE To determine the risk of dementia among persons with schizophrenia compared with those without schizophrenia in a large nationwide cohort study with up to 18 years of follow-up, taking age and established risk factors for dementia into account.

DESIGN, SETTING, AND PARTICIPANTS This population-based cohort study of more than 2.8 million persons aged 50 years or older used individual data from 6 nationwide registers in Denmark. A total of 20,683 individuals had schizophrenia. Follow-up started on January 1, 1995, and ended on January 1, 2013. Analysis was conducted from January 1, 2015, to April 30, 2015.

MAIN OUTCOMES AND MEASURES Incidence rate ratios (IRRs) and cumulative incidence proportions (CIPs) of dementia for persons with schizophrenia compared with persons without schizophrenia.

RESULTS During 18 years of follow-up, 136,012 individuals, including 9,444 individuals with a history of schizophrenia, developed dementia. Schizophrenia was associated with a more than 2-fold higher risk of all-cause dementia (IRR, 2.13; 95% CI, 2.00-2.27) after adjusting for age, sex, and calendar period. The estimates (reported as IRR; 95% CI) did not change substantially when adjusting for medical comorbidities, such as cardiovascular diseases and diabetes mellitus (2.01; 1.89-2.15) but decreased slightly when adjusting for substance abuse (1.71; 1.60-1.82). The association between schizophrenia and dementia risk was stable when evaluated in subgroups characterized by demographics and comorbidities, although the IRR was higher among individuals younger than 65 years (3.77; 3.29-4.33), men (2.38; 2.13-2.66), individuals living with a partner (3.16; 2.71-3.69), those without cerebrovascular disease (2.23; 2.08-2.39), and those without substance abuse (1.96; 1.82-2.11). The CIPs (95% CIs) of developing dementia by the age of 65 years were 1.8% (1.5%-2.2%) for persons with schizophrenia and 0.6% (0.6%-0.7%) for persons without schizophrenia. The respective CIPs for persons with and without schizophrenia were 7.4% (6.8%-8.1%) and 5.8% (5.8%-5.9%) by the age of 80 years.

CONCLUSIONS AND RELEVANCE Individuals with schizophrenia, especially those younger than 65 years, had a markedly increased relative risk of dementia that could not be explained by established dementia risk factors.

Published online October 7, 2015.
Dementia is one of the major challenges for modern health care and places a substantial financial burden on society. The disorder is a clinical syndrome characterized by cognitive decline and impairment in activities of daily living. In the Western world, dementia affects 5% to 6% of persons older than 60 years. The prevalence of dementia is expected to double every 20 years through 2040 owing to changes in population demographics and increased life expectancy.

Schizophrenia affects approximately 1% of the population. The disorder is associated with disturbances in perception, communication, and thought process as well as abnormalities in behavior. These disturbances often lead to substantial functional impairment and social disability. Historically, schizophrenia was named dementia praecox by Kraepelin, as deficits in memory, attention, and visuospatial orientation are hallmarks of the disorder. Mounting evidence supports a neurodevelopmental origin for schizophrenia (ie, genetic vulnerabilities interact with prenatal or perinatal exposures) as well as a neurodegenerative origin for schizophrenia (ie, progressive deterioration of the central nervous system). Furthermore, it has been proposed that individuals with schizophrenia experience an “accelerated aging” that contributes to their reduced life expectancy. This theory is biologically plausible as schizophrenia is associated with premature death owing to age-related disorders, such as diabetes mellitus, cancer, and cardiovascular disease, but also because of shared risk factors between schizophrenia and age-related disorders (ie, advanced paternal age, low birth weight, and specific genes).

Nevertheless, the association between schizophrenia and the risk of subsequent dementia remains unclear. Four prior studies have compared the risk of dementia among persons with vs those without schizophrenia using clinical dementia diagnoses, and their findings ranged from a 2.4-fold to a 16-fold higher risk of developing dementia. However, those studies were limited because they did not include individuals with onset of schizophrenia before the age of 30 years (potentially effecting generalizability, as the majority of persons with schizophrenia are diagnosed before the age of 30 years) or had an insufficient duration of follow-up for the cohort to display a clinically significant risk of developing dementia. Furthermore, a recent review of 20 longitudinal studies using cognitive screening tools or neuropsychological tests to examine the risk of cognitive decline (ie, beyond what can be attributed to the pathophysiologic factors of schizophrenia itself) in persons with schizophrenia found inconsistent results: 12 studies suggested significant cognitive decline, whereas 8 studies did not find a significant association.

Using administrative data, we aimed to estimate the risk of dementia in all persons with schizophrenia compared with persons without schizophrenia using a population-based cohort with sufficient sample size and follow-up time and a sufficient induction period for the cohort to display a clinically significant risk of dementia. This study also takes into account established risk factors of dementia, such as cardiovascular disease, diabetes, and substance abuse (SA).

**Methods**

A population-based cohort study was conducted from January 1, 1995, to January 1, 2013, using information on Danish citizens from nationwide registries. All data are recorded with reference to a civil registration number, which is a unique personal identification number assigned to all Danish residents. This number permits accurate linkage of recorded information at the personal level. Until December 31, 1993, the diagnostic system used in the Danish registers was the Danish version of the *International Classification of Diseases, Eighth Revision* (ICD-8). From January 1, 1994, the Danish version of the ICD-10 was used. Analysis was conducted from January 1, 2015, to April 30, 2015.

The study was approved by the Danish Data Protection Agency and the Danish Health and Medicine Authority. No informed consent from participants was needed as data were analyzed anonymously. Since the study was entirely based on register data, no ethical permission was required according to Danish law.

**Procedures**

**Study Population**

We used the Danish Civil Registration System to establish a population-based cohort consisting of all persons who were born in Denmark; alive on January 1, 1995; and aged 50 years or older at some point between 1995 and 2013. The Civil Registration System includes information on sex and date of birth as well as continuously updated information on vital status and migration since 1968.

**Schizophrenia**

Information on schizophrenia was obtained from the Danish Psychiatric Central Research Register (DPCR), which contains information on all admissions to psychiatric hospitals in Denmark since 1969 and outpatient mental health contacts (ie, psychiatric ambulatory care) since 1995. All inpatient admissions to and outpatient contacts (excluding emergency contacts) with a psychiatric hospital for schizophrenia between 1969 and 2013 were identified (eTable 1 in the Supplement).

**Dementia**

Information on dementia was obtained by combining data recorded in the Danish National Patient Register (DNPR), the DPCR, and the Danish National Prescription Registry. The DNPR contains information on all medical hospital admissions in Denmark since 1977 and outpatient medical contacts since 1995. The Danish National Prescription Registry contains information on all prescriptions dispensed at Danish pharmacies since 1995, including information on day of purchase and classification of drugs according to the Anatomical Therapeutic Chemical Classification System. The diagnostic workup of dementia is considered a specialist task in Denmark, which includes cognitive testing, assessment of activities of daily living, psychiatric evaluation, neuroimaging, physical examination, and laboratory testing. Approximately two-thirds of dementia cases are diagnosed within the sec-
ondary care setting and recorded in the registries. Hospital-based outpatient clinics from the disciplines of psychiatry, gastroenterology, and neurology assess patients with cognitive deficits as part of their general service, and 74% of dementia diagnoses in the registries are made by health care professionals from 1 of these 3 specialties. All inpatient or outpatient contacts with a medical or psychiatric hospital for dementia between 1969 and 2013 were identified according to a validated algorithm. In addition, we included information on prescriptions for anti-dementia drugs (ie, cholinesterase inhibitors, memantine) filled between 1995 and 2013 (eTable 2 in the Supplement). All persons with a dementia diagnosis before January 1, 1995, were excluded to ensure inclusion of only incident cases.

**Comorbid Illnesses**

Information on comorbid chronic conditions known to be risk factors for dementia but also known to occur with higher incidence in persons with schizophrenia included diabetes mellitus, ischemic heart disease (IHD), congestive heart failure (CHF), atrial fibrillation or flutter, peripheral vascular disease (PVD), cerebrovascular disease, and SA. Information on medical comorbidities other than diabetes was obtained from the DNPR for the period between 1990 and 2013 using a validated algorithm (eTable 3 in the Supplement). Information on diabetes was obtained from the Danish National Diabetes Register for the period between 1990 and 2013 using a validated algorithm (eTable 4 in the Supplement). Information on SA (excluding tobacco abuse) was obtained from the DPCR or the DNPR for the period between 1969 and 2013 (eTable 5 in the Supplement).

**Civil Status**

Information on civil status between 1995 and 2013, dichotomized into living with a partner (ie, marriage, registered partnership, or cohabitation) or living alone (ie, living without a partner, including widows and widowers), was obtained from Statistics Denmark, which provides a data bank with societal information on all residents in Denmark from 1980 onward.

**Statistical Analysis**

Follow-up started on January 1, 1995, or the person’s 50th birthday, whichever came last, and ended on January 1, 2013, on the date of a diagnosis of dementia, on the person’s 100th birthday, on the day of emigration, or on the day of death, whichever came first.

Incidence rate ratios (IRR) for dementia, comparing persons with and without schizophrenia, were calculated using log-linear Poisson regression analysis with the logarithm of the person-years as an offset variable. We fitted 4 survival analysis models to the dementia outcome and adjusted stepwise for demographics (ie, age, sex, and calendar period), civil status, medical comorbidity (ie, a diagnosis of diabetes, IHD, CHF, atrial fibrillation or flutter, PVD, and cerebrovascular disease), and SA. We conducted 3 subanalyses. First, we evaluated the association between schizophrenia and dementia in subgroups characterized by demographics, civil status, medical comorbidity, and SA. Second, we evaluated the association between schizophrenia and dementia after restricting our dementia definition to diagnoses from the registers and diagnoses from the DPCR. Finally, we compared the effect of early- and late-onset schizophrenia (before or after the age of 40 years, respectively) in the subgroup of persons diagnosed with schizophrenia after 1975 or at an age younger than 40 years. We stratified the follow-up on persons younger than 65 years vs older than 65 years to account for the correlation between age at onset of schizophrenia and age under risk in the study. All IRRs were adjusted for age, sex, and calendar period. All variables, with the exception of sex, were treated as time-dependent variables. Adjustments for age and calendar period were performed using 2-year age bands and 1-year time bands, respectively. We used 2-sided significance tests for all analyses, with P < .05 considered significant.

Cumulative incidence proportions (CIPs) for the outcome of all-cause dementia were estimated between the ages of 50 and 90 years for persons with and without schizophrenia. Aalen-Johansen curves were used with age as the time scale and competing risk of death was taken into account. Point estimates with corresponding 95% CIs were calculated for the risk of dementia at the ages of 65 and 80 years. Analyses were performed with appropriate components of the STATA, version 13, statistical software program (StataCorp).

**Results**

We observed 2,845,440 individuals for up to 18 years (mean, 11.0 years) (Table 1), of whom 20,683 had or developed schizophrenia. Overall, 136,012 individuals developed dementia, including 944 individuals with a history of schizophrenia (Table 2).

Schizophrenia was associated with a more than 2-fold higher risk of dementia (IRR, 2.13; 95% CI, 2.00-2.27) when compared with persons without schizophrenia (Figure 1). Adjusting this estimate for civil status and medical comorbidities did not change the estimate substantially (civil status: IRR, 1.98; 95% CI, 1.86-2.12; comorbidities: IRR, 2.01; 95% CI, 1.89-2.15), whereas the adjustment for SA attenuated the association (IRR, 1.71; 95% CI, 1.60-1.82).

The association between schizophrenia and dementia risk was stable when evaluated in subgroups characterized by demographics and comorbidities, although the IRR was higher.
among individuals younger than 65 years (IRR, 3.77; 95% CI, 3.29-4.33), men (IRR, 2.38; 95% CI, 2.13-2.66), those living with a partner (IRR, 3.16; 95% CI, 2.71-3.69), those without cerebrovascular disease (IRR, 2.23; 95% CI, 2.08-2.39), and those without SA (IRR, 1.96; 95% CI, 1.82-2.11) (Figure 1).

The IRR estimate was unaffected by restricting the dementia definition to the 129,546 diagnoses recorded in the register (IRR, 2.19; 95% CI, 2.05-2.34), but the estimate was slightly higher after restricting the dementia definition to the 63,323 diagnoses from the DPCR (IRR, 2.57; 95% CI, 2.37-2.80). The risk of dementia was lower for persons with early- vs late-onset schizophrenia among persons younger than 65 years (early-onset: IRR, 2.83; 95% CI, 2.31-3.48; late-onset: IRR, 4.19; 95% CI, 3.49-5.02; \(P = .005\)) and among persons older than 65 years (early-onset: IRR, 1.40; 95% CI, 1.14-1.74; late-onset: IRR, 1.86; 95% CI, 1.70-2.04; \(P = .02\)).

Among persons with dementia, the diagnosis was made before the age of 65 years for 22.4% (211 of 944) of persons with schizophrenia and for 6.3% (8539 of 135,068) of persons without schizophrenia (Figure 1). The absolute risk of developing dementia (ie, CIP) by the age of 65 years was 1.8% (95% CI, 1.5%-2.2%) for persons with schizophrenia compared with 0.6% (95% CI, 0.6%-0.7%) for persons without schizophrenia, whereas the corresponding CIPs by the age of 80 years were 7.4% (95% CI, 6.8%-8.1%) and 5.8% (95% CI, 5.8%-5.9%), respectively (Figure 2).

Discussion

This large, population-based cohort study showed that the risk of dementia was more than 2-fold higher in persons with schizophrenia compared with those without schizophrenia. The relative risk of dementia was almost 4-fold higher among individuals younger than 65 years. In absolute numbers, 7.4 of 100 persons with schizophrenia developed dementia before the age of 80 years compared with 5.8 of 100 persons without schizophrenia.

Persons with schizophrenia may be at higher risk of developing dementia for several reasons. First, persons with schizophrenia are at increased risk of developing several chronic conditions, which are also well-established risk factors for dementia, including diabetes mellitus,30,31 IHD,32-34 CHF,33,35 atrial fibrillation or flutter,35,36 PVD,33,34 cerebrovascular disease,30,31 and SA.30,37 The risk of dementia in persons with schizophrenia decreased when adjusted for SA, which suggested that comorbid SA is an important confounder or an intermediate variable for the association. In contrast, the association was unaffected when adjusting for other comorbidities or for civil status. However, the excess risk accounted for by comorbidity could be underestimated, as physical conditions may be underdiagnosed among persons with schizophrenia.32,40 Because the IRR estimate varied when evaluated for age, civil status, SA, and cerebrovascular disease, these factors seem to modify the association between schizophrenia and dementia risk. We were unable to include information on educational level or adverse health risk factors (ie, smoking, sedentary lifestyle, and high body mass index) that might be associated with risk of dementia, which introduced the possibility of residual confounding. In summary, potentially modifiable factors such as comorbidity or adverse health risk factors cannot be excluded as important opportunities to prevent dementia in persons with schizophrenia.

More recently, some researchers have proposed accelerated aging as one of the explanations for the reduced longevity in persons with schizophrenia.11 In line with this hypothesis, a recent British study identified patterns of macrostructural abnormalities in magnetic resonance images of the brain that are seen in both schizophrenia and Alzheimer disease, revealing a connection between the 2 disorders.41 These findings indicate that both neurobiological and environmental factors could contribute to the excess risk of dementia in persons with schizophrenia.

Four previous longitudinal studies identified a total of 196 persons with schizophrenia who developed a clinical dementia diagnosis15-18; the studies found relative risks for the development of dementia ranging from 2.4 to 16. As the median age at onset is 28 years for schizophrenia19 and 81 years for schizophrenia.

### Table 2. Number of Incident Cases of Dementia and Person-years at Risk

<table>
<thead>
<tr>
<th>Variable</th>
<th>Incident Dementia, No. (%)</th>
<th>Person-years at Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total dementia cases</td>
<td>136,012 (100)</td>
<td>31,347,186</td>
</tr>
<tr>
<td>Age for dementia onset, y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65</td>
<td>8750 (6.4)</td>
<td>18,341,908</td>
</tr>
<tr>
<td>≥65</td>
<td>127,262 (93.6)</td>
<td>13,005,278</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>52,901 (38.9)</td>
<td>14,763,666</td>
</tr>
<tr>
<td>Women</td>
<td>83,111 (61.1)</td>
<td>16,583,520</td>
</tr>
<tr>
<td>Calendar period</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1995-1998</td>
<td>20,828 (15.3)</td>
<td>6,521,515</td>
</tr>
<tr>
<td>1999-2002</td>
<td>29,109 (21.4)</td>
<td>6,812,298</td>
</tr>
<tr>
<td>2003-2006</td>
<td>34,422 (25.3)</td>
<td>7,026,506</td>
</tr>
<tr>
<td>2007-2010</td>
<td>34,261 (25.2)</td>
<td>7,261,185</td>
</tr>
<tr>
<td>2011-2012</td>
<td>17,392 (12.8)</td>
<td>3,725,682</td>
</tr>
<tr>
<td>Civil status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Living with a partnera</td>
<td>50,581 (37.2)</td>
<td>20,657,637</td>
</tr>
<tr>
<td>Living aloneb</td>
<td>85,109 (62.7)</td>
<td>10,562,712</td>
</tr>
<tr>
<td>Missing</td>
<td>122 (0.1)</td>
<td>126,837</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>135,068 (99.3)</td>
<td>31,170,435</td>
</tr>
<tr>
<td>Yes</td>
<td>944 (0.7)</td>
<td>176,751</td>
</tr>
<tr>
<td>Comorbidity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>19,935 (14.7)</td>
<td>2,492,805</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>25,709 (18.9)</td>
<td>2,931,237</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>12,731 (9.4)</td>
<td>866,699</td>
</tr>
<tr>
<td>Atrial fibrillation or flutter</td>
<td>16,273 (12.0)</td>
<td>1,148,610</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>8834 (6.5)</td>
<td>908,392</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>30,496 (22.4)</td>
<td>1,916,734</td>
</tr>
<tr>
<td>Substance abuse</td>
<td>8,193 (6.0)</td>
<td>1,131,903</td>
</tr>
</tbody>
</table>

a Living with a partner included persons living in marriage, registered partnership, or cohabitation.
b Living alone included widows and widowers.
dementia, it is difficult to establish studies with sufficient size and follow-up time to include all persons with schizophrenia and allow for a sufficient induction period between a diagnosis of schizophrenia and a diagnosis of dementia. Three of the previous studies included only persons with onset of schizophrenia after the age of 30 years, which may impede generalizability of the results for most persons with schizophrenia who are diagnosed before the age of 30 years, and the fourth study was limited by a small sample size. Our study used a large population-based cohort with complete follow-up and sufficient observation time for most of the cohort to display a clinically significant risk of dementia. Therefore, selection bias and loss to follow-up cannot explain our findings. Information on schizophrenia and dementia has high validity, which minimized the risk of information bias. The positive predictive value (PPV) has been shown to be 87% for schizophrenia in the DPCR and 86% for all-cause dementia in the DPCR and the DNPR, although the PPV for dementia diagnoses has been shown to be as low as 59% among individuals younger than 65 years.

Our study was also limited by a lack of important clinical information. Most important, the validity of a dementia diagnosis among persons with schizophrenia is unknown. It can be a challenge to diagnose dementia in persons with schizophrenia owing to preexisting cognitive dysfunction, negative symptoms, and behavioral problems. However, the diagnosis of dementia has high validity for other disorders with preexisting cognitive impairments, such as Down syndrome. In Denmark, neurologists, psychiatrists, and geriatricians make most dementia diagnoses, and their diagnoses of dementia have a PPV of 95%. The vertical dotted line represents the overall estimate without stratification (IRR, 2.13). AF indicates atrial fibrillation or flutter; CHF, congestive heart failure; IHD, ischemic heart disease; IRR, incidence rate ratio; and PVD, peripheral vascular disease.
of cognitive function compared with baseline is required. Therefore, we expect that physicians, and in particular psychiatrists, diagnose only severe cognitive impairment, beyond that which can be attributed to schizophrenia in and of itself, as dementia. Moreover, there is the risk that even subtle cognitive deficits or behavioral problems in persons with schizophrenia could be interpreted as signs of dementia by physicians with less knowledge of the psychopathological features of schizophrenia, which would overestimate the association. On the other hand, dementia may also be underdiagnosed in persons with schizophrenia owing to misattribution of dementia symptoms to the schizophrenia in and of itself (ie, diagnostic overshadowing) and owing to underdiagnosing of comorbidity in general in persons with schizophrenia, which would underestimate the association. Finally, the data here are strongly suggestive but require longitudinal verification of decline in function well beyond age expectation to confirm that these are true dementias and not the cross-sectional diagnosis of a physician seeing the patient for a diagnostic workup.

Because approximately two-thirds of all cases of dementia in Denmark are diagnosed within the secondary health care system, some cases of dementia diagnosed in primary care or private psychiatric and neurologic practices are not referred to the secondary health care system. Consequently, some of these cases are not included in our study, unless these cases are registered with dementia at a subsequent hospitalization or if they fill prescriptions for anti-dementia drugs. In addition, this study was conducted in a country with free and equal access to health care, and the association may not apply to other types of health care systems. However, this scenario limits potential bias induced by incentives for diagnosing dementia in persons with schizophrenia to improve their access to health care.

Persons with schizophrenia die, on average, 15 to 20 years prematurely compared with the general population. Consequently, those who live long enough to develop dementia would represent a selected group of more healthy persons, and our results could thereby underestimate the true risk of dementia in persons with schizophrenia. This theory was also supported by our finding of a lower CIP of dementia for persons with schizophrenia after adjusting for SA. Thus, additional studies are warranted to elucidate the pathophysiologic factors of the link between schizophrenia and dementia, and more knowledge is needed to develop targeted interventions to prevent dementia in this high-risk population.

Conclusions

Persons with schizophrenia may be at high risk of developing dementia. The relative risk appears to be particularly high in persons younger than 65 years with schizophrenia. The results did not change substantially after adjusting for established risk factors of dementia, such as cardiovascular disease and diabetes, although the association attenuated slightly after adjusting for SA. Thus, additional studies are warranted to elucidate the pathophysiologic factors of the link between schizophrenia and dementia, and more knowledge is needed to develop targeted interventions to prevent dementia in this high-risk population.

REFERENCES

Long-term Risk of Dementia in Persons With Schizophrenia

Original Investigation Research


