Prevalence of diagnosed dementia in subjects with schizophrenia as compared to the general population.

Version 2

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Supervisors

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Abstract

Background: Cognitive impairment is a characteristic of dementia but it is also a well known feature in elderly patients with schizophrenia. Post mortem studies have failed to show an increase of neurodegenerative changes consistent with dementia diseases in subjects with schizophrenia. Both diagnoses are based on clinical evaluation of diagnostic criteria and as they in part share the same manifestations the conditions may be hard to distinguish. There is a risk that dementia in patients with schizophrenia remains undiagnosed. It is important to identify and diagnose dementia in elderly patients with schizophrenia to adjust the pharmacological and non pharmacological treatment. In the present study we compare the prevalence of diagnosed dementia among individuals with and without schizophrenia, in the population in Örebro county council.

Method: Data was collected from the diagnostic register at Örebro county council, about all individuals in Örebro county which had received a dementia diagnosis, a schizophrenia diagnosis or both. The prevalence of dementia was calculated for the year 2012. We defined schizophrenia as the ICD-10 diagnosis F20 and dementia was defined as F00, F01 and F03.

Results: The prevalence of dementia among subjects without schizophrenia was 2.05% and the corresponding number among subjects with schizophrenia was 1.99%. The difference was not statistically significant (p= 0.953)

Conclusion: There is no significant difference in prevalence of dementia diagnoses among patients with schizophrenia compared to the general population. There is a possibility that cognitive impairment is less likely to render a dementia diagnosis in patients with schizophrenia than in subjects without schizophrenia.
# Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abstract</td>
<td>1</td>
</tr>
<tr>
<td>Background</td>
<td>3</td>
</tr>
<tr>
<td>Cognitive impairment and dementia</td>
<td>3</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>4</td>
</tr>
<tr>
<td>Cognitive impairment in schizophrenia</td>
<td>5</td>
</tr>
<tr>
<td>Aim/objectives</td>
<td>7</td>
</tr>
<tr>
<td>Participants and Methods</td>
<td>7</td>
</tr>
<tr>
<td>Statistics</td>
<td>8</td>
</tr>
<tr>
<td>Ethics</td>
<td>8</td>
</tr>
<tr>
<td>Results</td>
<td>8</td>
</tr>
<tr>
<td>Discussion</td>
<td>10</td>
</tr>
<tr>
<td>References</td>
<td>15</td>
</tr>
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Background

Cognitive impairment and dementia

Cognition, literally meaning “the faculty of knowing”, is a loosely defined term referring to higher cortical functions of the brain, such as perception, consciousness, learning, memory, emotions, language, decision making and problem solving.[1] The Swedish Society for cognitive medicine (SFK) defines cognition as the human ability to learn, think and process information in the brain, which is required for a normal daily functioning.[2]

Dementia, from the Latin words de- (from, without) and mens (mind) is a neurodegenerative disorder characterized by progressive cognitive impairment.[3] The International Classification of Diseases (ICD) describes dementia (F00-F03) as organic syndromes with a detectable etiology that leads to cerebral dysfunction with cognitive impairment and psychiatric symptoms. Dementia diagnoses are clinical diagnoses based on diagnostic criteria. A dementia diagnosis requires at least 6 months duration of decline in memory together with decline in other cognitive abilities and emotional or social abilities, and absence of delirium.[4] The dementia diagnoses include dementia in Alzheimer's disease, dementia in vascular diseases and dementia in other specified diseases such as Creutzfeldt Jacob disease or Parkinson’s disease. There are also other diagnoses that comprise cognitive decline such as Organic amnesic syndrome (F04) and Delirium (F05). Mild cognitive disorder (F06.7) can be used in cognitive impairment which does not meet the criteria for any proper dementia diagnosis. There is also a group of substance related amnesic syndromes (F10-19) which manifests as cognitive impairment.[5] According to a review of 36 prevalence studies most researchers have found that the highest proportion of dementia is attributed to Alzheimer’s disease followed by vascular dementia.[6] There is no curative treatment for dementing disorders and hence the pharmacological treatment in dementia is symptomatically. There are two types of drugs that are approved for pharmacological treatment of cognitive impairment in Alzheimer’s disease: cholinesterase inhibitors and Memantine [7] that is a NMDA-receptor antagonist.[8] The Swedish National Board of Health and Welfare recommends treatment with cholinesterase inhibitors or Memantine in Alzheimer’s disease and in some cases in frontotemporal dementia but not in vascular dementia due to lack of evidence of significant improvement of cognitive functioning. The board also point out the non-pharmacological treatment as an important factor in treating and preventing behavioral problems in dementia.[7]
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Table 1 Prevalence of dementia in former studies. References: Matillas [10], Skoog [48], Fratiglioni [11], Prince [9].

Former estimates of the prevalence of dementia is presented in table 1. Prince et al. state that Sweden among the other Scandinavian countries exhibits a greater prevalence of dementia than the mean western European country.[9] In line with this statement, a screening study in a population in Umeå have found a higher prevalence of dementia than the western European estimates made by Prince et al. [10] In contrast, screening data from the Swedish Kungsholmen project resembles the European prevalence numbers.[11] The National Board of Health and Welfare estimated the total number of individuals with dementia in Sweden in 2005 to 142 200 and the corresponding number in Örebro county council to 1982 individuals.[12] It is unclear how the prevalence of dementia in Sweden changes over time. Some studies have reported a steady prevalence of dementia [13] while others have found that the prevalence is increasing both in Sweden and worldwide.[9,10] Dementia is a major cause of death among elderly people. A Swedish study calculated the mortality rate for dementia to 2.4 per 100 person-years.[14] The seven year survival rate in dementia has been calculated to 5.1% in men and 11.1% in women.[15]

**Schizophrenia**

When Emil Kraepelin first introduced the disorder in his textbook from 1893, he named it dementia praecox, a term borrowed from Arnold Pick. The disorder was later renamed schizophrenia by Eugen Bleuler. Schizophrenia is derived from the Greek words schizein (to split) and phren (mind).[3] Schizophrenia is a psychotic disorder characterized by delusions,
hallucinations, disorganized thinking and behavior, abnormal motor behavior and negative symptoms. [16]

Schizophrenia is considered a chronic psychotic disease. The pharmacological treatment comprises a group of drugs generally referred to as antipsychotic drugs. They primarily work as dopamine receptor antagonists but many of them also express effects on other receptors such as Histamine-H1 and 5-HT receptors. Antipsychotics can be classified as “typical” referring to the first generation of antipsychotics that produces pronounced extrapyramidal side effects, and “atypical” referring to more recently developed substances with reduces extrapyramidal side effects.[8] In a study from USA the 12 month prevalence of diagnosed schizophrenia was estimated to between 0.51-0.53% in 2002. [17] The Swedish National Board of Health and Welfare estimated the prevalence of schizophrenia in Sweden in 2010 to 0.45%.[18] Individuals with schizophrenia are prone to both higher morbidity and mortality than the general population and the reduction in life expectancy in schizophrenia has been calculated to 19.9 years in Sweden, mainly due to increased morbidity. [19] Common comorbid conditions in schizophrenia include congestive heart failure and chronic obstructive pulmonary disease among others.[20] Geriatric schizophrenia is one of the most expensive medical conditions in society.[21]

**Cognitive impairment in schizophrenia**

Cognitive decline is a well recognized characteristic of schizophrenia [22] but the genesis of this effect is still unknown. Different theories have been brought out; including that cognitive impairment may be the long term outcome of schizophrenia, the effect of neuroleptic medication or a complicating dementia disease. Many post mortem studies have been carried out to show neuropathological signs of Alzheimer’s disease in deceased schizophrenic patients with major cognitive impairment but, although a few studies have shown increased Alzheimer-related neuropathological changes [23], most studies find no evidence of increased incidence of Alzheimer’s disease in patients with schizophrenia.[24-26] Few studies have been done on the incidence of other dementia markers in elderly with schizophrenia but some studies have found a negative correlation between the activity of the chemical dementia marker, cholineacetyltransferase and cognitive function. [26] Other studies have found a correlation between sub diagnostic Alzheimer related changes and cognitive decline.[27]
Ever since Kraepelin’s days there has been an ongoing discussion about whether schizophrenia is a neurodevelopmental or a neurodegenerative disorder. There is great consensus of early structural brain changes which is detectable at the onset of schizophrenia. Among the most demonstrated changes are increased ventricular volume[28] and decreased volume of gray matter[29,30] but most earlier studies have failed to show any progressive structural changes related to the disease[28-30] leading to the assumption of a neurodevelopmental pathogenesis. However, with improving MRI-techniques, recent prospective MRI-studies have been able to show significantly larger progressive loss of both gray and white matter in individuals with schizophrenia than in healthy twins and in controls,[31,32] suggesting a neurodegenerative course of the disease that might explain the cognitive deterioration. Clinical observations and cognitive testing confirms the assumption of cognitive deficits at the onset of schizophrenia. [33] and there is evidence for partial cognitive improvement after the acute onset of schizophrenia. [34] It is not entirely clear how cognitive abilities in schizophrenia changes over time. A 20 year follow up showed no general progressive cognitive decline after the onset of schizophrenia. [34] This opinion is opposed by studies in older schizophrenic patients, showing more pronounced progression in cognitive decline in schizophrenic patients than in the general population.[35,36]

Cognitive impairment in schizophrenia is still a matter of debate. Dementia is a clinical diagnosis based on diagnostic criteria’s and may be difficult to distinguish from cognitive impairment in schizophrenia and other conditions. This may result in misdiagnosing of the patient. Kørner et al. have shown in a Danish population that people with late onset schizophrenia are at higher risk of getting a dementia diagnosis.[37] At the same time there are studies indicating that people with dementia with behavioral changes are at risk of being misdiagnosed with late onset schizophrenia.[38] Misdiagnosing may be harmful for the patient as the pharmacological and non pharmacological treatment as well as the social interventions to a large extent depend on what diagnosis the patient recieve. Several studies conclude that antipsychotic medication is associated with increased mortality in individuals with dementia. Some studies have found this association only for typical antipsychotics [39,40], particularly haloperidol [41] but others have shown increased mortality related to both typical and atypical antipsychotic drugs in subjects with dementia. [41,42] Antipsychotic medication in dementia is also associated with accelerated cognitive deterioration, [43,44] increased frequency of cardiovascular events, [45] stroke [46] and femur fractures.[40] Therefore it is important to find and diagnose dementia in patients with schizophrenia to
evaluate and adjust the pharmacological treatment. The prevalence of dementia diagnosis in schizophrenia can give an indication of how cognitive impairment in schizophrenia is evaluated in clinical practice. Few have studied the prevalence of dementia among schizophrenic patients as compared to the general population. A study in an elderly population in USA found that the rates of diagnosed dementia among subjects with schizophrenia was significantly higher (64.46%) as compared to patients without schizophrenia (32.31%). [20] To our knowledge no studies of the prevalence of dementia among patients with schizophrenia have been carried out in Sweden.

Aim/objectives

The aim of the present study is to determine if the prevalence of diagnosed dementia in subjects with schizophrenia differs from the prevalence of diagnosed dementia in the general population in Örebro county council.

Participants and Methods

Information about all diagnoses made in Swedish health care is registered in a diagnostic register based on the personal identity number. The data are registered in association with the patient’s visits to the physician. We received our data from the diagnostic register of Örebro county council, after permission from the senior hospital administrator. We collected information about all individuals in Örebro county council who had received either a dementia diagnosis, a schizophrenia diagnosis or both, at least once between Jan. 1 2005 and Dec. 31 2013. For these individuals we also received data about sex, age, date of diagnosis, and in which department the patient received the diagnosis. We collected information from both in and out patient care. All ages and both men and women were included. The age data given in the sample as well as in this report is the current age of the subjects in 2013. We
defined dementia as the ICD-diagnoses F00 – dementia in Alzheimer’s disease, F01 – Vascular dementia, and F03 – Dementia unspecified. We chose not to include the F02 diagnoses because of their complicating etiology related to other specified diseases, but individuals with F02-diagnoses were not excluded from the study if they had also received one of the diagnoses in our inclusion criteria. Schizophrenia was defined as the ICD-diagnoses F20. In our data, no information about date of death was available and therefore we were not able to calculate the prevalence of dementia for the whole span of years but had to select a specific year. We chose to look at the last possible year and as we had incomplete data for 2013 from primary care, we selected the year 2012. We were primarily interested in the gradual cognitive decline occurring with increasing age. Thus, we were interested in subjects diagnosed with dementia in old age and we excluded the rather few persons with early age dementia, possibly secondary to injuries or abuse. The prevalence and incidence of dementia among patients diagnosed with schizophrenia where compared to the corresponding values in the general population. For the general population in Örebro county council in 2012, we used data from “Statistics Sweden” (SCB).

Statistics

The statistical significance was calculated by means of a Chi square test with an alpha set at 0.05.

Ethics

The study can be considered part of the internal work for quality improvement in the psychiatric care and hence no ethical approval is needed. The patients have not been asked to provide consent to participate in this study. All our data where de-identified and no individual data is presented in the report. The risk that any patient will come to harm by this study is therefore very small.

Results

In the complete material we found that 8 299 unique individuals in Örebro county council had received a dementia diagnosis at least once in 2005-2013. 1 112 individuals had received a schizophrenia diagnosis during the same time. 44 individuals had received both schizophrenia- and dementia diagnoses in the time span.
In 2012 the population in Örebro county council was 285,506 individuals. We found that the prevalence of dementia in all age groups was 0.74%. The prevalence of schizophrenia was 0.19% the same year.

The group from 2012 that we decided to further investigate comprised 95,712 individuals between 55-94 years of age. Of them, 50,580 (53%) were women and 45,132 were men.

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<td>44184</td>
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Table 2: Diagnoses in 2012

The total number of dementia diagnoses in the general population and in the subjects with schizophrenia respectively, in the 55-94 year olds in 2012 is presented in table 2.

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<tr>
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Table 3: Diagnoses received 2012 in individuals age 55-94.

The prevalence of schizophrenia was 0.26%. Slightly higher among men (0.27%) than women (0.26%). The prevalence of dementia in the group without schizophrenia, aged 55-94 was 2.05% . 1.85% among men and 2.23% among women. In different age groups the prevalence was 0.1% in age 55-64, 0.7 % in age 65-74, 3.9 % in age 75-84 and 11.2 % in age 85-94. The prevalence of dementia among subjects with schizophrenia was 1.99% in age 55-94. There was no significant difference between the groups (p= 0.953) In 2012 there was only one new case of dementia among subjects with schizophrenia, corresponding to an incidence of 0.4 % in that year. Among subjects without schizophrenia there were 780 new cases of dementia and the incidence was 0.8% in 2012.

In the complete material from 2005-2013 the majority of the dementia diagnoses were made for the first time in primary care in both the subjects with schizophrenia and in the general
population. Among the 44 subjects with both schizophrenia and dementia, the dementia diagnosis was also commonly made by the psychiatric care. (fig.1)

In the complete material we found that subjects with schizophrenia received dementia diagnosis earlier (with a peak between 71-80 years) than subjects without schizophrenia (with a peak between 81-90 years). None of the 44 subjects that had received both schizophrenia and dementia diagnoses in 2005-2013 were older than 91 years in 2013.

**Fig. 2** Place of diagnosis for cases of diagnosed dementia in subjects with schizophrenia in the complete material (2005-2013).

**Fig. 3** Cases of diagnosed dementia in the complete material from 2005-2013

**Discussion**

The primary finding of the present study was that there is no significant difference in the prevalence of diagnosed dementia among subjects with schizophrenia compared to the general population in Örebro county council. No former Swedish study has investigated this relationship and it is therefore hard to be confident if this finding is true for Sweden as a whole. Our finding of 1.99% prevalence of dementia in subjects with schizophrenia is in great contrast to Hendrie et al.’s finding of a 64.46% prevalence.[20] There are several possible
explanations for this discrepancy. Their study was carried out on a population receiving care at a specific hospital providing care for uninsured individuals. This may in contrast to the sample selection in this study constitute a selection bias that also may be an explanation for the different results. Also it is likely that the difference is at least partly attributed to their broader definition of dementia that included all types of dementia disorders in contrast to our definition which was restricted to the ICD-diagnoses F00, F01 and F03. In the present study the prevalence of dementia among subjects with schizophrenia (1.99%) was slightly lower than the prevalence in the general population (2.05%), although the difference was not statistically significant. Alzheimer’s disease is the most common type of dementia disease. [6] Prohownik et al. have managed to show an increase of Alzheimer related neuropathological changes in diseased subjects with schizophrenia. [23] The validity and reliability of his finding is however questioned by the fact that it was based upon informal neuropathological diagnostic criteria for Alzheimer’s disease, used before the establishment of formal criteria. As several other studies have shown no increase in neuropathologic features of Alzheimer’s disease among patients with schizophrenia [24-26] one could argue that Alzheimer’s disease would be diagnosed to the same extent among patients suffering from schizophrenia as in the general population. Very little was found in the literature about the rate of neuropathological changes of vascular origin in elderly with schizophrenia. This makes it difficult to estimate the impact of vascular dementia on the overall prevalence of dementia among subjects with schizophrenia. However, as the most common treatment of schizophrenia, i.e. antipsychotic medication is associated with increased frequency of cardiovascular events, [45] and stroke [46], the prevalence of vascular dementia might be increased in subjects with schizophrenia. It is possible to hypothesize that the rate of proper dementia diseases in schizophrenic subjects, in line with the observation of this study, might at least equal that of the general population. However we have not studied the prevalence of dementia disorders or even dementia symptoms but the prevalence of dementia diagnoses.

There is evidence of both early [33] and progressive [35,36] cognitive impairment in schizophrenia and as the dementia diagnosis is based upon diagnostic criteria mainly comprising cognitive dysfunction, it is possible that diagnosed dementia should be expected to be more prevalent among subjects with schizophrenia than in the general population. A 20 year follow up failed to show any difference in progressive cognitive impairment in subjects with schizophrenia as compared to subjects without schizophrenia but the mean age of the participants in the study was 22.8 years at onset and the author points out that cognitive
decline in schizophrenia may occur mainly in patients older than 65 years.[34] Since the subjects in the present study were 55-94 years of age it is likely that the subjects with schizophrenia express a higher rate of cognitive impairment than the average group. Hence there is a possibility that the actual rate of dementia in the schizophrenia group might be higher than the calculated prevalence in this study and that our result is the consequence of undiagnosed cases of dementia among subjects with schizophrenia. A Canadian study found that patients with schizophrenia were less likely to receive a dementia diagnosis than non schizophrenic individuals with the same cognitive and functional assessment score[47] and there is evidence that behavioral disorders in elderly are at risk of being misclassified as symptoms of schizophrenia[38] This supports the thesis that there might be additional cases of dementia in the schizophrenia group ant it may be another possible explanation of the relatively low prevalence of dementia among subjects with schizophrenia in this study compared to the study by Hendrie et al. In contrast Kørner et al. states that patients with late onset schizophrenia express a higher risk of receiving a dementia diagnosis than individuals in the general population. The authors however point out that it is possible that the psychotic symptoms assessed as schizophrenia might be early signs of a beginning dementia.[37] In our material the majority of the patients with both schizophrenia and dementia diagnoses had received their dementia diagnosis in primary care. The psychiatric care is the second most common department in which patients with schizophrenia receive a dementia diagnosis. In Örebro county council, there is a special unit for evaluation of subjects with early signs of dementia, placed at the Department of Geriatrics. However, they have limited resources and they are not responsible for the evaluation of patients known at the Department of Psychiatry. As most patients with schizophrenia have regular contact with the psychiatric care it could be expected that this department would recognize and diagnose most of the dementia diagnoses in patients with schizophrenia. The wide variety of different diagnosing departments might possibly be an indication that the psychiatric care does not succeed in recognizing all cases of dementia in patients with schizophrenia.

The prevalence of schizophrenia in 2012 in this study was calculated to 0.26% in the 55-94 year olds and 0.19 in all age groups. Our results are lower than both the former estimate of between 0.51-0.53% in USA [17] and the estimate of the Swedish National Board of Health and Welfare of 0.45%. [18] Although schizophrenia might possibly be mistaken for dementia in older patients, schizophrenia is generally appearing in early adulthood and would be expected to be diagnosed before the age of probable dementia diseases. The great impact of
schizophrenia on both the life of the individual and on society makes it unlikely that the low prevalence in this study is attributed to undiagnosed cases of schizophrenia.

The prevalence of dementia in the general population in this study is lower than the estimates of all earlier studies presented in table 1. These differences is most likely attributable to the fact that former Swedish studies are screening studies in contrast to this study which investigates the prevalence of diagnosed dementia. One of the studies represented in the table 1, Fratiglioni et al. has calculated the lowest prevalence numbers in all age groups. [11] Their study in contrast to the other studies was restricted to dementia in Alzheimer’s disease. The study was carried out on a population living on Kungsholmen in Stockholm. One could argue that the study population are less exposed to risk factors and are subject to more protective factors and hence the prevalence numbers received in the study are not representative for the whole Swedish population. The calculated prevalence in the present study compared to the former prevalence estimates of the screening studies indicates that there might be undiagnosed cases of dementia not only among schizophrenic subjects but even in the general population. The Swedish National Board of Health and Welfare estimated the total number of individuals with dementia in Örebro county council in 2005 to 1982 individuals.[12] This corresponds to a prevalence number of 0.72% that equals the prevalence of 0.74% in all age groups in 2012, calculated in this study. One interesting finding when studying the dementia diagnoses in the complete material was that the subjects with schizophrenia seemed to receive their dementia diagnoses at a younger age than the average group. No individual with both schizophrenia and dementia diagnoses was older than 91 years in 2013. This means that no subject with schizophrenia in Örebro county council, who were older than 85 years in 2005 have received a dementia diagnosis since that year. Dementia diseases is associated with a higher mortality [14,15] but this fact however cannot completely explain our finding as our material contains even the subjects who have deceased since 2005. The mortality rate in schizophrenia is increased. [19] and one explanation of our finding may be that there are few subject with schizophrenia who reach advanced age.

In general the prevalence numbers in this study were low as compared to data from earlier studies. There are several weaknesses in the setting of this study that might explain these differences. When restricted to the year of 2012 the subjects who had received both a dementia diagnosis and a schizophrenia diagnosis were only five individuals and that was not enough to demonstrate any significant difference between the groups. We used data from the
diagnostic register at the county council. For the register to be updated, it requires that the patients visit a physician at least once a year to get the diagnoses registered. When calculating the prevalence numbers for the different diagnoses in the group from 2012 we have only included those individuals who have received the current diagnosis in 2012. There may be individuals who has received diagnosis previous years and thus can be expected to have the disease, but that are not included in our calculation because they have not visited any physician in 2012. Subjects with previous diagnoses who have visited a physician in 2012 but where the current diagnosis of our investigation has not been registered are also not included in our calculation. It is likely that patients with schizophrenia or dementia have regular visits to a physician and it can therefore be expected that most of the subjects that have received a diagnosis of schizophrenia or dementia would have had the current diagnosis registered in 2012. However there might be patients who refuse to visit the physician or who are in a steady state in their disease and do not get their diagnoses registered each year. In patients with both schizophrenia and dementia diagnosis, who visit a physician for follow up on one diagnosis there is a possibility that the other diagnosis may not be registered. We calculate the prevalence of dementia among subjects with schizophrenia from data about how many individuals who had received both dementia and a schizophrenia diagnosis in 2012. We did not take into account which one of the two diagnoses that were the first. Hence the prevalence of dementia in schizophrenic subjects in our results, also comprises the prevalence of late onset schizophrenia in subjects with dementia. We have chosen not to regard this fact as it seems unlikely that a proper schizophrenia diagnosis would appear after the onset of a dementia disease. These possible cases may be considered initially misclassified cases of dementia.

The incidence of dementia among subjects with schizophrenia was only 1 individual in 2012 and there is no available data to compare this result to. There are however sources of error in this finding. The individuals counted as new cases of dementia among subjects with schizophrenia were only those who had received the combination of dementia and schizophrenia diagnoses in the same year for the first time. There may be individuals that have received one of the diagnoses any previous year and the other diagnosis in 2012. These subjects can be expected to have both diseases in 2012 and should be considered new cases of dementia and schizophrenia in combination but are excluded because of the lacking diagnosis registration. On the other hand there might be subjects who have received both schizophrenia and dementia diagnoses previous years but not both diagnoses on the same year before 2012.
These individuals should not be considered new cases but are included in the incidence calculation in this study. There is one major strength in this analysis. We have received data on diagnoses for the entire population and all diagnosing Departments in Örebro county council. This area comprising both city and country side communities, can be considered representative for the general population in Sweden. This study contributes to the understanding of how cognitive impairment in patients suffering from schizophrenia is evaluated by physicians. The analysis concludes that dementia diagnoses are made to the same extent among patients with schizophrenia as in the general population and there is a possibility that some cases of severe cognitive impairment in geriatric patients with schizophrenia remain undetected or at least undiagnosed. Further studies are needed to investigate if the findings of this analysis are true for the whole Swedish population. Future studies may consider taking into account the death dates of the subjects.

References


