Introduction

The worldwide dementia prevalence has been estimated to increase to 42 million in 2020 and 81.1 million in 2040. There is an international consensus in favour of early diagnosis and treatment of dementia that facilitates full involvement of patients and caregivers in the treatment and care. However, under-diagnosis of dementia is a general problem in Europe and even though the
incidence of dementia diagnoses in Denmark has increased in the period from 1970 to 2004, the number of diagnoses in 2003 is estimated to be lower than in other European countries.4

Alzheimer’s disease is the most frequent cause of dementia in the western part of the world.3 In Denmark, assessment of Alzheimer’s disease primarily takes place in specialized areas of geriatrics, neurology and psychiatry, and usually occurs in the secondary health-care sector.6 The geographical distance to a secondary health-care provider for diagnosis and treatment could be a barrier that contributes to under-diagnosis of Alzheimer’s disease. Although most health-care services are free of charge in Denmark,7 patients need a referral from a general practitioner to gain access to a secondary health-care provider.8 A previous study in Denmark has found a positive correlation between the frequency of referrals from general practitioners and the number of specialists and hospitals in the Danish municipalities.9 Geographical distance to a secondary health-care provider is also found to be a barrier for diagnosis and treatment of patients in other areas of research.10-12 and especially reduces access to diagnosis, treatment and care of dementia as a consequence of difficulties with transportation for the patient and caregivers.13,14 However, an on-going centralization of specialized health care and hospitals in Denmark, especially pronounced since 2007, has decreased the numbers of hospitals nationwide and increased the travel distance to a health-care provider.7 The centralization may be an obstacle for contact with the secondary health-care provider for less mobile patients and may contribute to under-diagnosis of Alzheimer disease in Denmark. Investigating whether the incidences of Alzheimer diagnoses have changed during a period of health-care centralization as well as the association between distance to diagnostic service and Alzheimer diagnoses may clarify whether geographical distance to diagnostic service contributes to under-diagnosis of Alzheimer disease in Denmark.

The aims of this study were to examine the incidence of Alzheimer diagnoses in the period 2000–2009 and to investigate the association between distance to Alzheimer Clinics and Alzheimer diagnoses.

Methods

Databases

It is Denmark possible to retrieve and link information from multiple national registers on individual level. The Danish Civil Registration System provided information on dates of births, household size and place of residence and has existed since 1968.13 The Danish National Patient Registry provided information on all hospital diagnoses and was established in 1977.16 The Danish National Prescription Registry provided information on all prescription drugs sold in Denmark since 1994.17 Finally, the Income Statistics Registry provided information on income for every individual in Denmark since 1970.18

Study population

To report the incidence of Alzheimer diagnosis from 2000 to 2009, we included all individuals aged 65+ years living in Denmark from 1 January 2000 or at the date of their 65th birthday if younger than 65 years. For the second aim, individuals, without an Alzheimer diagnosis, were followed from 1 January 2008 or at the date of their 65th birthday if younger than 65 years at 1 January 2008 and until an Alzheimer diagnosis, death, emigration or 31 December 2009.

Distance to an Alzheimer clinic and covariates

Information on hospitals with outpatient clinics with diagnosis and treatment services for Alzheimer disease, Alzheimer clinics, was used to calculate the distances in kilometres from the centre of the municipality to the closest Alzheimer clinic. Covariates included age, gender, household size and income.

Outcome

The outcome, Alzheimer diagnosis, was measured by first prescription of medication for Alzheimer’s disease (The Anatomical Therapeutic Chemical Classification System (ACT) code: N06DA02, N06DA03, N06DA04, N06DX01) or first Alzheimer diagnosis (The International Classification of Diseases and Related Health Problems 10th Revision (ICD-10) code: DG.30, DF.00). The internal validity of Alzheimer diagnoses in the Danish National Patient Registry is high19 and Alzheimer medication is mostly used for Alzheimer disease and only prescribed to some patients with Lewy body and Parkinson disease.

Statistics

Joinpoint regression model

The annual incidence of Alzheimer diagnoses was calculated as the number of diagnoses per 100 000 individuals aged 65–74 and 75+ years. Time trends were analysed using joinpoint regression, which detects whether there is a change in the trend during the study period, a joinpoint, and if the change is significant.20 The maximum number of joinpoints was set to 2. The analyses were performed with joinpoint regression program version 4.0.4 (National Cancer Institute, National Institute of Health).

Cox regression model

Cox regression models were applied to investigate the association between distance to an Alzheimer clinic and Alzheimer diagnosis. The Cox regression was left truncated at 1 January 2008, 65th birthday or immigration, and individuals were followed until an Alzheimer diagnosis, death, emigration or until 31 December 2009. Investigating log-minus-log plot and interaction with risk time assessed the assumption of proportional hazard. We did not detect evidence of violation. Directed acyclic graphs were used to clarify the underlying causal network and thereby identify potential confounders.21 These confounders consisted of gender, age, household size and income. To ensure timely correct categorization of Alzheimer diagnoses, the observational time was divided into two periods at the time of a diagnosis or medication. Furthermore, observational time was prior to the analyses divided into bands of 1-year intervals. Age was updated at the start of each band.

The association between distance to an Alzheimer clinic and Alzheimer diagnosis was not linear. Therefore, to ensure best ‘local fit’ for the association, we performed a piecewise regression by including the variable distance to an Alzheimer clinic as cubic splines in the regression model. Splines allow estimates of the association as a piecewise function, which is composed of lines. The lines are connected at different values of the distance variable, so-called knots. The values of the knots were defined according to the 5th, 50th and 95th percentiles of the distance variable. Additionally, we performed the analysis with the distance variable as a categorical variable.

All analyses were tested at a level of 5% significance and all analyses were performed with SAS version 9.2.

Results

Incidence of Alzheimer diagnoses

The results from the joinpoint analyses of the incidence of Alzheimer diagnosis per 100 000 individuals aged 65–74 and 75+ years during the period 2000–2009 are shown in figure 1. From 2000 to 2009, the incidence increased from 79.83–152.01 diagnoses per 100 000 individuals aged 65–74 years. From 2000 to 2002, the annual incidence increased significantly by 32.5% [95% confidence interval (CI): 7.1–63.8]. In 2002, there was a joinpoint (P < 0.001), a significant change in the incidence, and thereafter the incidence stagnated (0.4%, 95%
The annual incidence increased significantly by 29.1% (95% CI: 11.0–50.2) from 2000 to 2003. In 2003, there was an increased from 343.1 to 982.3 diagnoses per 100 000 individuals aged 65–74 years (black dots) and 75+ years (black triangles) in Denmark 2000–2009 and best joinpoint model estimates (white dots and triangles).

Hazard ratio for diagnoses of Alzheimer’s disease
A total of 830 869 individuals were aged 65+ years in 2008 and additionally 131 306 turned 65 years through follow-up. Baseline characteristics are shown in table 1. The average distance to an Alzheimer clinic was 19.1 km and the distance ranged from 0 to 107 km, the population had a mean age of 75.3 years and 56.7% were women.

In groups of individuals with longer distance to an Alzheimer clinic, fewer were diagnosed with Alzheimer’s disease; 60.5% had <20 km to an Alzheimer clinic and 1.0% of them were diagnosed with Alzheimer’s disease, 24.6% had 20–39 km and 0.8% of them were diagnosed with Alzheimer’s disease, 9.1% had 40–59 km and 0.6% of them were diagnosed with Alzheimer’s disease and 5.8% had 60+ km and 0.8% of them were diagnosed with Alzheimer’s disease.

Compared with individuals without an Alzheimer diagnosis, the 8605 individuals diagnosed with Alzheimer’s disease in the 2-year study period had a significantly shorter mean distance to an Alzheimer clinics (16.6 vs. 19.1 km, P<0.001).

The results from the Cox regression analysis with cubic splines of the distance to an Alzheimer clinic are illustrated in figure 2. The results showed significantly adverse associations between distance to Alzheimer clinics and Alzheimer diagnoses at the distances 1–95 km.

The results from the Cox regression analysis with categories of the distance to Alzheimer clinics are illustrated in figure 3 and showed similar results. Compared with individuals with 0–19 km to an Alzheimer clinic, the hazard ratio for an Alzheimer diagnosis was 0.80 (95% CI: 0.70–0.92) at 20–39 km and 0.65 (95% CI: 0.52–0.81) at 40–59 km.

Discussion
This study is the first to report the incidence of Alzheimer diagnoses in Denmark in the period 2000–2009 and to investigate the association between geographical distance to an Alzheimer clinic and likelihood of getting an Alzheimer diagnosis.

Incidence of Alzheimer diagnoses
We observed that the early increases in Alzheimer diagnoses from 2000 to 2002/03 were followed by stagnation until 2009. Studies have reported contrasting results of the last decades’ incidence and prevalence of dementia and Alzheimer’s disease. An American study found that the incidence of Alzheimer’s disease was significantly higher in the period 1991–2001 compared with 1984–1990. Another American study that investigated trends of dementia and Alzheimer’s disease over time in three geographical cohorts found a significant decrease of 30% in both dementia and Alzheimer’s disease incidence from 1985 to 1994, no significant change in dementia incidence from 1997 to 2008 and no difference in prevalence of either dementia or Alzheimer’s disease between the years 1991 and 2001. However, a study reported an insignificant decrease of 25% in age-specific incidence of dementia in a cohort from the year 2000 compared with a cohort from the year 1990 from the Rotterdam study. These findings are supported by a study in England and Wales, which reported a 24% lower prevalence in 2011 than expected given the aging population.

A number of explanations clarify the reasons for the stagnation of the incidence of Alzheimer diagnoses after 2002/03 in our study. The stagnation could be caused by a restrictive approach towards Alzheimer medication in Denmark causing some physicians to be less likely to diagnose and prescribe Alzheimer medication. This might result in continuous under-diagnosis of Alzheimer’s disease in 2003 in Denmark as Phung et al. have reported. Another possible explanation is a catch-up effect increasing the incidence of diagnoses and causing a reduction in the number of under-diagnosed individuals until 2002/03 resulting in stagnation afterwards. The catch-up effect may have been caused by an elevated awareness due to improvements in clinical dementia practice, e.g. founding of dementia clinics and introduction of drugs against Alzheimer’s disease, which has improved diagnosis since mid-1990s. Finally, previous extrapolation of incidence of Alzheimer disease in the study period may have failed by not taken improved health conditions of elderly into account. The stagnation could be caused by a healthier elderly population with lower level of Alzheimer’s disease compared with earlier generations, as it was indicated by Matthews et al. The incidence of major risk factors for Alzheimer disease like diabetes and cardiovascular diseases have decreased in the period 2000–2009 among elderly above 65 years in Denmark and may explain the stagnation in Alzheimer diagnoses.

Distance to Alzheimer clinic
We found that increased distance to Alzheimer clinic was associated with decreased diagnosis of Alzheimer’s disease in Denmark, which is a country with generally short distances and where the roads and infrastructure have high quality. A literature review regarding barriers for diagnoses and treatment of dementia in Europe outlined the following as barriers for diagnoses and treatment; cost of care, restrict diagnoses and treatment to specialists, fear of stigma among family and care givers, general practitioners'
perception of inadequate knowledge and skills to diagnose and treat dementia, lack of time and resources, under-recognition of dementia symptoms among other health-care providers, e.g. at nursing homes, and finally inefficient communication between primary and secondary health sector. By highlighting the impact of geographical distribution of diagnostic service, our results add new knowledge on barrier for Alzheimer diagnoses and treatment.

Our findings could be explained by the frequency of referrals from the general practitioners to Alzheimer clinics. Within the area of dementia, studies have found that shortage of geriatric training, unavailable and inaccessible treatment, social stigma, and poor co-ordination and communication with specialists caused a decrease in referrals from general practitioners to specialists for both diagnosis and care of dementia patients. These barriers could be expected to be more frequent in rural areas with longer distance to a secondary health-care provider compared with urban areas. This is supported by several studies. The year before diagnosis, patients in rural areas are found to visit the general practitioner more often and the secondary health-care system less often compared to patients in urban areas. In rural areas, lack of general practitioners trained in geriatrics and access to diagnostic service are found to be barriers for dementia diagnosis. Lack of specialists and not knowing how to get in contact with health-care providers are reasons for unmet health care needs among dementia patients from rural areas.

Finally, care givers play an important role for diagnoses of Alzheimer disease and whether they seek health care may also be affected by geographical distance. A multinational study by Wilkinson et al. found that 74% of care givers were the first to notice Alzheimer symptoms, but seeking health care was often delayed due to stigma, which may be more pronounced in rural areas. Patients and care givers’ willingness to travel longer distances to reach a health-care provider could also explain the findings. Previous studies have found that distance to a secondary health-care provider especially reduces access to diagnosis, treatment and care of dementia as a consequence of difficulties with transportation for the patient and caregivers. This finding is supported by a study from the USA showing that dementia patients fail to utilize referrals because of stigma, frailty and logistic problems with transportation to non-local specialists. Additionally, studies found that individuals from rural areas compared with urban areas less frequently use primary as well as secondary health care. As individuals from rural areas probably have long geographical distance to both primary and secondary health care, this could indicate that individuals with longer geographical distance are less likely to seek health care. However, a small American study found that there was no difference in the number of Alzheimer diagnoses between individuals living in nursing homes in rural areas compared with urban areas. The results could, however, be explained by the strict inclusion of only individuals living at nursing homes, where the staff help the elderly to easier access to health care and diagnoses. Finally, difference in performing skills to detect and diagnose Alzheimer’s disease between Alzheimer clinics in Denmark could be confounding the association if individuals with longer geographical distances also were referred to Alzheimer clinics with less qualified diagnostic service. In other areas of study, an adverse associations between the size of the hospital and treatment results have been found, and a study in Denmark have reported a problem with misdiagnosis of Alzheimer’s disease as dementia without specification, which may be more pronounced at some hospitals.

**Strengths and limitations**

There are several strengths of this study. The study was nationwide and the inclusion of the entire Danish population aged 65+ years during the study period eliminated potential of selection bias.
Furthermore, the data were on individual level and recorded prospectively. The analyses were adjusted for important confounders and a validated endpoint was used. Finally, as Alzheimer disease is underdiagnosed in Denmark, the decrease in diagnoses in geographical areas close to an Alzheimer clinic does not imply over-diagnosis of Alzheimer’s disease in these areas. There are some important limitations as well. The study was an observational study and can thereby not reject the risk of unknown confounders, e.g. quality of diagnostic service at the Alzheimer clinics. A second limitation is that Alzheimer medication may not be a reliable indicator for Alzheimer diagnoses. The effect of Alzheimer medication has been questioned during the study period, which may have decreased the prescription pattern. However, this limitation should be reduced by measuring Alzheimer diagnoses by both Alzheimer medication and diagnoses of Alzheimer’s disease. A last limitation is a potential of the result being biased by calculating the distance to an Alzheimer clinic as the shortest distance to a hospital with diagnostic service in the region. The bias results from patients’ option to choose treatment at the same specialization level at any hospital or specialist outside the hospitals in Denmark since 1993. There may therefore be a bias if some individuals use specialists or a hospital outside their region. However, out-patients’ use of free choice of health care is low in Denmark and patients who choose, most often select clinics closest to their home and clinics recommended by their general practitioner.

Implications for policy

The stagnated Alzheimer diagnosis incidence from 2002 (65–74 years) to 2003 (75+ years) may indicate that the reported under-diagnosis of dementia in Denmark has not improved. This could imply a need for increased awareness and improved diagnostic services in Denmark. Improved information for general practitioners on the early signs and symptoms of Alzheimer’s disease may increase referrals and the possibility of receiving an appropriate diagnostic workup. Furthermore, health-care policy makers should compare benefits of centralization of health-care systems with the adverse effects of increasing the geographical distance. The adverse effects could be most pronounced among patient groups similar to Alzheimer patients.

Conclusions

The finding of a stagnated incidence and adverse association between distance to an Alzheimer clinic and likelihood of getting a diagnosis of Alzheimer’s disease suggests that centralization of the health-care system has serious adverse effects for some elderly patients.

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Key points


References

The risk of fall injury in relation to commonly prescribed medications among older people—a Swedish case-control study

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Background: Older people not only consume more medication but they also represent a group at high risk for adverse effects such as injurious falls. This study examines the association between the medications most commonly prescribed to older people in Sweden and fall injuries. **Methods:** This is a population-based, matched, case-control study of 64 399 persons aged ≥ 65 years in Sweden admitted to hospital because of a fall injury between March 2006 and December 2009, and four controls per case matched by gender, date of birth and place of residence. The prevalence of the 20 most commonly prescribed medications was compiled for the 30-day period before the index date. The association between those medications and injurious falls was estimated with odds ratios and corresponding 95% confidence intervals using conditional logistic regression. **Results:** Ten of the top 20 most commonly prescribed medications, and in particular the three medications affecting the central nervous system (CNS), significantly increased the risk of fall injuries (highest for opioids and antidepressants) but not the seven cardiovascular ones, who had a protective effect (lowest for angiotensin converting enzyme inhibitors and selective calcium channel blockers). **Conclusions:** The adverse effect of several commonly prescribed medications may seriously threaten their positive effects on the well-being and quality of life of older people. Their association with injurious falls is of particular concern as falls are prevalent and often leading to severe consequences. This needs to be acknowledged so physicians and patients can make informed decisions when prescribing and using them.

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**Introduction**

The world population is aging both in absolute and relative terms. This demographic transition is paralleled by a change in the burden of disease, whereby non-communicable diseases are becoming more prevalent than communicable ones, and premature death is progressively giving way to a higher life expectancy and increased morbidity. Among the main causes of disability, fall injuries rank high. In older people, they often lead to hospitalization and a long period of medical treatment, and they can cause considerable morbidity with significant physical, psychological and social consequences. In many instances, fall-related injuries can be fatal. Individual factors that have a well-documented association with falls are age, sex and health status, though these factors can be...