USE OF STATINS AND RISK OF HOSPITALIZATION WITH DEMENTIA: A DANISH POPULATION-BASED CASE-CONTROL STUDY.

Short title: Statins and risk of dementia

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Abstract

Several epidemiological studies have indicated reduced risk of dementia among users of statins. We assessed the risk of hospitalization with dementia associated with use of statins in a population-based case-control study in four Northern Danish counties in the period 1991-2005. We identified 11,039 cases with dementia and 110,340 age- and gender-matched population controls using data from the National Patient Registry, the Danish Psychiatric Central Register and the Civil Registration System. Prescriptions for statins filled before the admission for dementia were identified using population-based prescription databases. We used conditional logistic regression analysis to compute relative risk of hospitalization with dementia associated with use of statins using non-users as reference group. We found an overall reduced risk of hospitalization with dementia among statin users (adjusted odds ratio (OR) 0.67, 95% confidence intervals (CI): 0.60-0.75). The reduced risk associated with statin use remained robust in various subanalyses, however, we found no clear dose-response pattern between the number of filled prescriptions for statin and the risk of hospitalization with dementia.

In conclusion, we found a reduced risk of hospitalization with dementia among users of statins, however, whether this association is causal remains to be clarified.

Key words: statins, dementia, risk, epidemiology, case-control study.

Introduction

Vascular and lipid-related mechanisms are thought to have a role in the pathogenesis of both Alzheimer's disease and vascular dementia.[1,2] It is therefore possible that treatment with lipid-lowering drugs, including statins, could lessen the risk of dementia and slow the progression of the disease. In addition to their beneficial effects on cholesterol levels, statins have other pharmacological effects that may influence the pathogenesis of Alzheimer's disease and dementia, including anti-inflammatory, antioxidant and neuroprotective effects.[3] However, the epidemiological evidence is contradictory. Several observational studies, primarily case-control and cross-sectional studies, have shown a protective role of statins,[4-16] but a number of cohort studies have not found a clear association between statins and reduced risk of dementia.[6,10,14] Most randomized controlled trials have not demonstrated any protective effect of statins, but it should be noted that many of those published so far were primarily designed to evaluate the vascular effects, using cognitive function as a surrogate measure for dementia only as a secondary endpoint.[17,18] Results from a recent randomized controlled trial with a 1-year exposure to either atorvastatin or placebo found that statins may have a positive effect on the progressive deterioration of cognitive function and behaviors anticipated in mild to moderate Alzheimer's disease.[19]

The lack of consistency in the existing observational studies may reflect differences in the study design and analytic methods. Also the potential effects of indication bias may influence the results as patients prescribed statins may have a lower baseline risk of dementia compared with other patients. This hypothesis is supported by the fact that some physicians might be less motivated to prescribe long-term preventive agents

to patients who shows signs of cognitively impairment.[20,21] Further, unaccounted confounding such as socioeconomic factors could also affect the results of the observational studies. Physicians may be more likely to prescribe statins to patients who are highly educated, who have knowledge about the drugs, who are concerned about their future health, and who actually ask for the prescriptions/treatment.[22]

Here we conducted a large population-based case-control study based on prospectively collected data to further explore the association between use of statins and the risk of hospitalization with dementia.

Methods

Study Population

We conducted the study within the population of North Jutland, Aarhus, Viborg and Ringkøbing Counties, Denmark from January 1st 1991 to December 31st 2005.

The National Health Service provides tax-supported health care for all inhabitants in Denmark, *i.e*., guaranteeing free access to general practitioners and hospitals, and refunds a variable proportion of costs of medication prescribed by physicians. Since 1968, the Danish Civil Registration System has maintained electronic records of the entire Danish population and assigned a unique identification number (i.e the civil registry number) to all Danish residents at birth. All services are registered by use of the civil registry number, and it is used in all public Danish registers. Use of the civil registry number secures valid linkage between various population-based registers.

Cases of Dementia

We used computerized data from the National Patient Registry[23] and the Danish Psychiatric Central Register[24] to identify cases hospitalized with dementia in North Jutland (January 1992 to December 2005), Aarhus (January 1997 to December 2005), Viborg and Ringkøbing (January 1999 to December 2005) corresponding to the availability of computerized prescription data with a minimum length of prescription history for all cases and controls of one year.

The National Patient Registry, established in 1977, store data on all discharges from non-psychiatric hospitals in the county, including the civil registry number, dates of admission and discharge, surgical procedure(s) performed, and up to 20 discharge diagnoses assigned by the treating physician, whereas the Danish Psychiatric Central

Register, established in 1969, store data on all discharges from all psychiatric hospitals and psychiatric departments in general hospitals, including the civil registry number, dates of admission and discharge, and all diagnoses assigned by the treating physician.

The diagnoses were classified according to the Danish version of the International Classification of Diseases (ICD), 8th until the end of 1993 and the 10th revision thereafter. Based on the data going back to 1977 or 1969, we constructed the hospital history for all persons, who were residents in the counties, and hereafter identified all patients, who were registered with a diagnosis of dementia (ICD-8: 29009, 29010, 29018, 29019, 29309, 29319; ICD-10: F00, F01, F03, G30) during the study period. After excluding cases that were not residents in the counties at study start, and cases with unconfirmed diagnoses of dementia during the hospital stay (modification code 1 or 2 in the ICD-8 period), a total of 11,039 cases were available for analysis.

Population controls

For each dementia case, we aimed to identify 10 age- and gender-matched controls from the general population of the county through the Civil Registration System using risk set sampling,[25] *i.e.*, the controls had to be alive and at risk of hospitalization with dementia at the time the corresponding case was diagnosed (index date). The Civil Registration System is updated daily, keeps electronic records on vital status (dead or alive), date of death, and residence of all Danish inhabitants. We identified a total of 110,340 population controls.

Data on statin use

We used the population-based prescription databases[26] of North Jutland, Aarhus, Viborg and Ringkøbing to obtain data on prescriptions for statins, as statins are only available by prescription in Denmark. The databases were initiated on 1 January 1991 in North Jutland, 1996 in Aarhus, and 1998 in Viborg and Ringkøbing.

The counties are served by pharmacies equipped with electronic accounting systems that are primarily used to secure reimbursement from the Danish National Health Service. The registered data include type of drug and the date the prescription is filled. We identified all prescriptions for statins (fluvastatin, simvastatin, atorvastatin, pravastatin, lovastatin, cerivastatin, and rosuvastatin (ATC codes: C10AA01-07, B04AB01-04) filled by cases and controls before the index date. The cases and controls were then classified according to their use of statins: either having filled no prescriptions of statins in the last five years or having filled one or more prescriptions of statins within the last five years. Users of statins within the last five years were further classified according to their total number of filled prescriptions within the five years, *i.e.*, 1-4 prescriptions, 5-10 prescriptions, 11-19 prescriptions, and >19 prescriptions.

Data on possible confounding factors

Data on possible confounding factors were obtained from the National Patient Registry, the prescription databases, and the Prevention Registry at Statistics Denmark. We obtained information on prior discharge diagnoses of hypertension, stroke, ischemic heart disease, invasive coronary revascularizations, alcohol-related diseases, diabetes mellitus, and chronic bronchitis and emphysema (as a proxy for severe smoking) from the National Patient Registry. Data from the prescription databases included all prescriptions for other lipid-lowering drugs than statins,

antiplatelets, antihypertensives, high-dose aspirin, non-aspirin nonsteroidal anti-inflammatory drugs (NSAIDs), peroral anticoagulants, hormone replacement therapy, insulin and other antidiabetic drugs filled within 5 years before hospitalization with dementia or the corresponding date for controls.

Data on socioeconomic status of both cases and controls were obtained from the Prevention Registry at Statistics Denmark.[27] This registry collects data from several other registers, i.e. health-related registers, registers on living conditions, and registers of population statistics. The cases and controls were classified according to marital status (single, married or co-habiting), employment status (old-age pensioner, self-employed or salaried employed), gross income (below 20^{th} percentile, 20th-40^{th}, 40^{th}-60^{th}, 60^{th}-80^{th}, above 80^{th} percentile), and educational level (university degree, short/medium-term formal education, basic vocational education, unspecified).

Statistical Analysis

We formed contingency tables and used conditional logistic regression analysis to compute crude and adjusted odds ratios (ORs) of hospitalization with dementia according to use of statins. Since we used risk set sampling of controls, these ORs are unbiased estimates of the corresponding incidence rate ratio.[25] Non-users were used as the reference group in all analyses. We adjusted for a previous history of hypertension, stroke, ischemic heart disease, invasive coronary revascularizations, alcohol-related diseases, diabetes mellitus, chronic bronchitis, and emphysema, and for current use of other lipid-lowering drugs than statins, antiplatelets, antihypertensives, high-dose aspirin, non-aspirin NSAIDs, peroral anticoagulants, hormone replacement therapy, and socioeconomic status in the logistic regression analyses. Information on socioeconomic status was missing for a part of the study

population, and these subjects were given a separate "missing" classification for those variables for inclusion in the adjusted models. We also did the analyses excluding these subjects. Stratified analyses were performed by age, gender, calendar time period (1992-2000, 2001-2005), and prior cardiovascular disease (stroke, ischemic heart disease, invasive coronary revascularizations). The analyses were done using SAS version 8.02 (SAS Institute Inc., Cary, NC, USA).

Results

Table 1 shows the descriptive data for the 11,039 dementia cases and 110,340 controls.

Among cases and controls, 389 (3.5%) and 4,855 (4.4%), respectively, filled at least one prescription for statins in the last five years before a hospital diagnosis of dementia or index date among controls. Hypertension, stroke, ischemic heart disease, alcohol-related disease, diabetes mellitus, chronic bronchitis and emphysema were more prevalent among cases than controls, and more cases than controls had filled prescriptions for antiplatelets, antihypertensives, high-dose aspirin, insulin and oral antidiabetic drugs. Cases were also more likely to be single and old-age pensioner.

After adjusting for possible confounding factors, and further adjustment for socioeconomic status, use of statins was associated with a reduced risk of hospitalization with dementia (adjusted OR 0.63 (95% CI: 0.56-0.70), and 0.67 (95% CI: 0.60-0.75), respectively) (Table 2). The result was similar when excluding cases and controls with missing information on socioeconomic status (adjusted OR 0.68 (95% CI: 0.60-0.78)).

We found no clear association between the number of filled prescriptions for statins and risk of hospitalization with dementia; the adjusted ORs were 0.53 (95% CI: 0.43-0.67), 0.78 (95% CI: 0.63-0.96), 0.57 (95% CI: 0.45-0.71), and 0.86 (95% CI: 0.69-1.06) for 1-4 prescriptions, 5-10 prescriptions, 11-19 prescriptions, and >19 prescriptions, respectively.

The association between statin use and risk of hospitalization with dementia remained robust in all subanalyses when stratifying by age, gender, calendar period and prior cardiovascular disease. The lowest risk estimates associated with statin use were

found among patients younger than 60 years (adjusted OR 0.48 (95% CI: 0.19-1.21)) or 80 years or older (adjusted OR 0.55 (95% CI: 0.44-0.68)) and among patients with prior cardiovascular disease (adjusted OR 0.46 (95% CI: 0.38-0.56)).

In contrast, use of hormone replacement therapy among women was not associated with risk of hospitalization with dementia (adjusted OR 0.96, 95% CI: 0.89-1.02).

Finally, we also looked at the risk estimates obtained for some of the known risk factors for dementia in our analyses in order to qualify the validity of our dataset. The adjusted ORs for a history of hypertension, stroke or diabetes mellitus were 1.22 (95% CI: 1.15-1.30), 1.84 (95% CI: 1.72-1.96), and 1.58 (95% CI: 1.46-1.71), respectively.

Discussion

In this population-based case-control study, users of statins had a clearly decreased risk of hospitalization with dementia. The association appeared not to be explained by a wide range of possible confounding factors, including socioeconomic factors, and the association remained robust in subanalyses stratified by age, gender, calendar time period, and prior cardiovascular disease. However, we found no clear association between numbers of filled prescriptions for statin and the risk of hospitalization with dementia.

The main strengths of our study included the population-based design, and the ability to link different data sources with prospectively collected data. By use of these databases the potential difficulties with recall bias are avoided.

Although the overall positive predictive value of a dementia diagnosis recorded in the National Patient Registry and the Danish Psychiatric Central Register is high (i.e. approximately 85%),[28] an important limitation was the lack of details about the dementia diagnosis among the cases, including type of dementia and onset of symptoms. This information is relevant as the effects of statins on vascular dementia and Alzheimer's disease may differ and as dementia is commonly first recognized or diagnosed several years after symptom onset. If an individual has early signs or symptoms of dementia, physicians might be less inclined to maintain preventive treatment, when the overall health deteriorates,[29] introducing indication bias in which an individual with prevalent or early dementia has less chance of receiving treatment than the control. The latter appeared not to be a major problem in our study as more cases than controls filled prescriptions for other drugs used for long-term primary- and secondary prevention of cardiovascular disease, *e.g.* antihypertensives and

antiplatelets. Another limitation of our study includes lack of information on non-hospitalized dementia cases. However, this most likely leads to non-differential misclassification and will thus bias the estimates towards unity. Similar, any Berksons bias or surveillance bias arising due to a potential increased probability of users of statins to be registered with a dementia diagnosis would also result in conservative risk estimates.

It has previously been discussed that statin users may be "healthy users" - younger, healthier, better educated and socioecomomically privileged persons, who may be more likely to receive preventive treatments than the less privileged and frail.[30] In general, severe confounding by socioeconomic differences is unlikely given Denmark's universal health care. However, we have recently reported a weak socioeconomic gradient in statin use among Danish men in the mid-90s,[31] indicating that socioeconomic factors could also be a confounding factor in the association between use of statins and risk of dementia. However, such an explanation in unlike since the gradient was not found among women and that it decreased in magnitude over time among men. Some of the existing observational studies that found a reduced risk of dementia, did adjust for educational level as a crude measure of socioeconomic status.[5-9,15] We added marital status, employment status and gross income in order to get a better measure of socioeconomic status.[32,33] After adjustment for these factors, we still found a decreased risk of dementia among statin users. Notably, use of hormone replacement therapy in women, which may also be subject to the "healthy user effect", had no effect on the risk of hospitalization with dementia in our study.

Although we adjusted for a number of confounding factors, we can, however, still not entirely exclude the possibility that our results remain influenced by residual, unmeasured or unknown confounding.

Finally, it should be noted that in spite of the relatively large sample size, the low frequency of statin use among cases and controls in our study resulted in limited statistical precision for several of the presented risk estimates as indicated by the relatively wide confidence intervals. This low use of statins reflects a general low use of statins in Denmark.[34,35]

Our finding that users of statins have an overall reduced risk of dementia, is in agreement with other observational studies.[4,5,7-9,11-13,19]

We found no association between the number of filled prescriptions for statins and the risk of hospitalization with dementia, which is consistent with the lack of a dose-response relationship between use of statins and dementia in other observational studies,[10,12-14] and suggests that statins may not directly cause the reduced risk of dementia. However, an increased number of statin prescriptions could possibly also reflect more severe cardiovascular disease, which overwhelms the potential beneficial effects of the increased statin dosage.

Besides the beneficial effect on cholesterol levels, statins have other pharmacological effects that may influence the pathogenesis of Alzheimer's disease and dementia. The possible biological mechanisms include 1) stimulation of α-secretase activity,[36] 2) modulation of APP metabolism and Aβ production,[37] 3) immunomodulation leading to attenuation of inflammatory markers (*e.g.* C-reactive protein and cytokines),[38,39] 4) reduction of lipoprotein oxidation and free radical injury,[40] 5) increase in cerebral

endothelial nitric oxide synthase and cerebral circulation,[41] and 6) activation of signal transcription (Rho-GTPases) through depletion of downstream isopreniods.[42]

In conclusion, we found a reduced risk of hospitalization with dementia among users of statins, and our findings therefore provide some support to the hypothesis that statins may protect against the development of dementia.

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Table 1. Descriptive characteristics of cases hospitalized with dementia and age- and gender-matched population controls.

	Cases (%)	Controls (%)
Total	11,039 (100.0)	110,340 (100.0)
Age (years)		
0-59	239 (2.2)	2,412 (2.2)
60-79	4,194 (38.0)	41,983 (38.0)
≥80	6,606 (59.8)	65,945 (59.8)
Gender		
Male	4,217 (38.2)	42,149 (38.2)
Female	6,822 (61.8)	68,191 (61.8)
Discharge diagnosis of		
Hypertension	1,624 (14.7)	10,789 (9.8)
Stroke	1,520 (13.8)	6,907 (6.3)
Ischemic heart disease	1,769 (16.0)	13,705 (12.4)
Invasive coronary revascularizations	191 (1.7)	2,403 (2.2)
Alcohol-related diseases	266 (2.4)	462 (0.4)
Diabetes mellitus	947 (8.6)	4,946 (4.5)
Chronic bronchitis and emphysema	721 (6.5)	6,072 (5.5)
Liver cirrhosis	2 (<0.1)	53 (0.1)
Prescription for		
Statins	389 (3.5)	4,855 (4.4)
Other lipid-lowering drugs than statins	25 (0.2)	358 (0.3)
Antiplatelets	3,137 (28.4)	23,847 (21.6)
Antihypertensives	7,017 (63.6)	67,037 (60.8)
High-dose aspirin	2,885 (26.1)	21,875 (19.8)
Non-aspirin NSAIDs	5,069 (45.9)	50,234 (45.5)
Peroral anticoagulants	649 (5.9)	5,837 (5.3)
Hormone replacement therapy	1,157 (10.5)	12,013 (10.9)
Insulin or oral antidiabetic drugs	1,053 (9.5)	6,945 (6.3)
Marital status		
Single	6,850 (62.1)	65,573 (59.4)
Married or co-habiting	2,433 (22.0)	39,734 (36.0)
Missing	1,756 (15.9)	5,033 (4.6)
Employment status		
Old-age pensioner	9,162 (83.0)	101,103 (91.6)
Self-employed or salaried employed	121 (1.1)	4,204 (3.8)
Missing	1,756 (15.9)	5,033 (4.6)

Gross income		
Below 20th perc	1,625 (14.7)	20,532 (18.6)
20th-40th perc	2,253 (20.4)	23,071 (20.9)
40th-60th perc	2,131 (29.3)	22,949 (20.8)
60th-80th perc	1,837 (16.7)	20,185 (18.3)
Above 80th perc	1,437 (13.0)	18,570 (16.8)
Missing	1,756 (15.9)	5,033 (4.6)
Educational level		
University degree	79 (0.7)	1,050 (0.9)
Short/medium-term formal education	925 (8.4)	10,730 (9.7)
Basic vocational education	293 (2.7)	3,755 (3.4)
Unspecified	7,986 (72.3)	89,772 (81.4)
Missing	1,756 (15.9)	5,033 (4.6)

Table 2. Crude and adjusted odds ratios (ORs) with 95% confidence intervals (CI) for hospitalization with dementia according to use of statins and the total number of filled prescriptions for statins.

	Cases (%) (N=11,039)	Controls (%) (N=110,340)	ORs (95%CI)	Adjusted ORs* (95%CI)	Adjusted ORs† (95%CI)
Non-users in the last 5 years	10,650 (96.48)	105,485 (95.60)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Use of statins within the last 5 years	389 (3.52)	4,855 (4.40)	0.78 (0.70-0.87)	0.63 (0.56-0.70)	0.67 (0.60-0.75)
Number of prescriptions					
1-4 prescriptions	86 (0.78)	1,301 (1.18)	0.49 (0.39-0.62)	0.49 (0.39-0.62)	0.53 (0.43-0.67)
5-10 prescriptions	111 (1.01)	1,168 (1.06)	0.73 (0.59-0.89)	0.73 (0.59-0.89)	0.78 (0.63-0.96)
11-19 prescriptions	88 (0.80)	1,366 (1.24)	0.53 (0.42-0.67)	0.53 (0.42-0.67)	0.57 (0.45-0.71)
>19 prescriptions	104 (0.94)	1,020 (0.92)	0.81 (0.66-1.00)	0.81 (0.66-1.00)	0.86 (0.69-1.06)

* Adjusted for use of antiplatelets, antihypertensives, high-dose aspirin, non-aspirin NSAIDs, peroral anticoagulants, lipid-lowering drugs, and hormone replacement therapy, and previous diagnoses of hypertension, stroke, ischemic heart disease, invasive coronary revascularization, alcohol-related diseases, diabetes mellitus and chronic bronchitis or emphysema (as a proxy for smoking).

† Adjusted for marital status, employment stratus, gross income, educational level, use of antiplatelets, antihypertensives, high-dose aspirin, non-aspirin NSAIDs, peroral anticoagulants, lipid-lowering drugs, and hormone replacement therapy, and previous diagnoses of hypertension, stroke, ischemic heart disease, invasive coronary revascularization, alcohol-related diseases, diabetes mellitus and chronic bronchitis or emphysema (as a proxy for smoking).