Stroke

ORIGINAL CONTRIBUTION

Statin Use Is Not Associated With Reduced Cardio- and Cerebrovascular Hospitalizations in Older Adults With Dementia

Sonia Lech, PhD*; Raphael Kohl, MA*; Julie L. O'Sullivan, PhD; Tharusan Thevathasan, PhD, MD; Johanna Schuster, PhD; Adelheid Kuhlmey, PhD; Paul Gellert, PhD; Sevil Yasar, PhD, MD

BACKGROUND: Cardiovascular and cerebrovascular diseases are significant global health challenges and leading causes of death worldwide. Although there is substantial evidence supporting the positive effects of statins for both primary and secondary prevention of these diseases, evidence is lacking regarding the benefits in people with dementia. This study investigated the associations between statin use and cardiovascular and cerebrovascular hospitalizations in nursing home residents with and without dementia.

METHODS: This retrospective cohort study of nursing home residents with and without dementia using insurance claims data was conducted in Germany between January 2015 and December 2019. Propensity score-based models were used to evaluate the association of statin use with hospitalizations due to cerebrovascular and cardiovascular events among nursing home residents with and without dementia. Subgroup analyses were performed based on the presence or absence of atherosclerotic cardiovascular disease, dementia type, presence of hyperlipidemia, and newly prescribed statin use, as well as age groups, care dependency level, and sex.

RESULTS: The final sample included data from 96 162 individuals, 37 262 without dementia, and 58 900 with dementia. Statin use was associated with an increased risk of hospitalization due to cardiovascular or cerebrovascular events among people with dementia (hazard ratio [HR], 1.06 [95% CI, 1.01–1.12]; P=0.023). Moderate and high statin intensity was associated with an increased risk of hospitalization (moderate: HR, 1.15 [95% CI, 1.07–1.23]; P<0.001; high: HR, 1.55 [95% CI, 1.15–2.10]; P=0.005) In subgroup analyses, we found an association between statin use and increased risk of hospitalization among individuals without atherosclerotic cardiovascular disease (HR, 1.30 [95% CI, 1.12–1.52]; P<0.001), with vascular dementia and Alzheimer disease (HR, 1.18 [95% CI, 1.06–1.32]; P=0.003; HR, 1.14 [95% CI, 1.00–1.31]; P=0.047, respectively) as well as among newly prescribed statin users (HR, 2.71 [95% CI, 2.33–3.15]; P<0.001). Among individuals without dementia, we found no differences (HR, 1.03 [95% CI, 0.96–1.11]; P=0.397) in the primary analysis and subanalyses except for the high statin intensity group (HR, 1.51 [95% CI, 1.04–2.19]; P=0.029) and among participants with newly prescribed statins (HR, 1.99 [95% CI, 1.56–2.52]).

CONCLUSIONS: In our study, statin use was associated with an increased risk of hospitalization due to cardiovascular or cerebrovascular events among people with dementia. These findings highlight the need for further research and cautious consideration of statin use in people with dementia.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: cardiovascular disease ■ cause of death ■ hyperlipidemia ■ nursing home ■ propensity score

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Nonstandard Abbreviations and Acronyms

AD	Alzheimer disease
ASCVD	atherosclerotic cardiovascular disease
HR	hazard ratio
PwD	people living with dementia
PwoD	people without dementia
VaD	vascular dementia

Cardiovascular disease and cerebrovascular disease represent a significant global health burden and a leading cause of death.[1] Globally, in 2019, 18.6 million deaths were attributed to cardiovascular disease, representing a significant increase compared with 12.1 million in 1990.[2] In the United States, coronary heart disease was the leading cause of death attributable to cardiovascular disease (41.3%), followed by other (17.3%) and stroke (17.2%).[3] With an aging population, cardiovascular and cerebrovascular disease prevalence is rising.[4,5] With increasing age, not only comes an increase in the prevalence of cardiovascular and cerebrovascular disease, but also an increase in the prevalence of dementia.[6,7] A recent estimation indicated global escalations in the number of people living with dementia (PwD) from 57.4 million cases in 2019 to 152.8 million cases in 2050.[8]

Statins are used for primary[9] and secondary[10] prevention of cardiovascular and cerebrovascular disease. Studies examining the preventive effect of statins on these diseases often exclude PwD.[11] A recent systematic review and meta-analysis on the benefits and harms of statins in PwD found insufficient evidence to thoroughly evaluate the efficacy of statins among this population.[11] Additionally, studies report that statin use is more likely to be discontinued[12–14] among PwD. A recent meta-analysis showed that the mean survival from dementia diagnosis to death for all-cause dementia was 4.8 years, for Alzheimer disease (AD) was 5.8 years, and for vascular dementia (VaD) was 3.2 years.[15] Therefore, cardiovascular and cerebrovascular disease and dementia pose a competing risk for mortality.

Studies have shown that cognitive impairment is frequently listed as an exclusion criterion due to concerns about lack of capacity or ability to comply with procedures[16] resulting in the exclusion of PwD from clinical trials. There is currently no research published evaluating the effect of statin use in PwD on cardiovascular and cerebrovascular outcomes; thus, there is a lack of evidence to support guidelines for the care of PwD.[17] The present study aims to fill this knowledge gap by investigating associations between statin use and hospitalization due to cardiovascular and cerebrovascular events in a cohort of nursing home residents living with and without dementia. By studying nursing home residents, we have assessed the most vulnerable population with a high prevalence of cardiovascular and cerebrovascular diseases and dementia. In addition to comparing statin use in those with and without dementia, we also investigated the same outcomes in numerous subgroups stratified by age, sex, level of care dependency, dementia type, statin dose, and history of cardiovascular or cerebrovascular disease. We have recently studied the same population and found that statin use in this population was associated with significantly reduced mortality[18]; therefore, we hypothesized that statin use in PwD and people without dementia (PwoD) reduces hospitalizations due to cardiovascular and or cerebrovascular events.

METHODS

Study Population

Our retrospective study is based on the German statutory health and long-term care insurance fund Allgemeine Ortskrankenkasse data. We used data from 282 963 nursing home residents in Germany who lived in a nursing home for at least 1 day in January 2016. The total observation period covers the period between January 2015 and December 2019, with a baseline period of 12 months (January 2015–December 2015). The data includes basic demographic information (age and sex), information on care dependency according to the German Social Code, Book XI (≤2: lowest care dependency; 5: highest care dependency), all inpatient and outpatient diagnostic codes (German Modification of the *International Classification of Diseases, Tenth Revision*), and prescribed medication (Anatomical Therapeutic Chemical Codes). The authors are unable to make the data from this study available. For research purposes, access to health and long-term care insurance fund data in Germany is possible under the conditions of the German Social Code (SGB V § 287).

Exposure

We classified all individuals who had received a statin prescription in at least 2 quarters during the 12-month baseline period (January 1, 2015–December 31, 2015) as statin users. Statin prescriptions include all statins approved in Germany, including atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, and simvastatin. Unfortunately, we have no information on which specific indication may have led to the statin prescription. All other individuals who did not match this criterion were classified as statin nonusers. Further, we considered individuals with at least 1 inpatient or 2 outpatient diagnoses in 2 quarters within the baseline period as PwD. Dementia diagnoses included F00-F03, G30, G31.0-G31.-G31.8 (German Modification of the *International Classification of Diseases, Tenth Revision* GM). All individuals who did not match this criterion were classified as PwoD.

Outcome

Our study's primary outcome of interest is hospitalization due to cardiovascular or cerebrovascular disease events. As such, we considered all hospitalizations with a discharge diagnosis of G45-46, I20-I25, and I61-I64 (German Modification of the *International Classification of Diseases, Tenth Revision*). We also evaluated the effect of the competing risk of all-cause mortality.

Whenever we found both events in the same timeframe (month of record), we classified them as cardiovascular or cerebrovascular events, as they must have occurred first.

Variables of Interest

Sociodemographic data (age and sex), morbidity (*International Classification of Diseases, Tenth Revision* diagnosis of atrial fibrillation, arthritis, cancer, cardiovascular disease, cerebrovascular disease, chronic kidney disease, depression, diabetes, heart failure, hypertension, hepatitis, hyperlipidemia, liver disease, obesity, and schizophrenia (Table S1), as well as the number of comorbidities based on the mentioned diagnoses), medication (Anatomical Therapeutic Chemical codes of antiplatelet medication, antithrombotic medication, cardiovascular medication, diabetic medication and nonstatin lipid-lowering medication; Table S2), care level (according to German Social Code, Book XI, care levels ranging from ≤2=lowest care dependency to 5=highest care dependency) as well as the number of hospital admissions within the baseline period were obtained for each individual and included in the analysis as covariates.

Statistical Analysis

To address our research question, individuals were divided into 2 sets with 2 treatment groups each. The sets are PwD and PwoD, respectively, and the groups are statin nonusers (untreated reference groups) and statin users (treated group). To be able to estimate the average treatment effect among the treated we used a nearest neighbor propensity score matching to balance the statin user groups with the statin nonuser groups in each set regarding age, sex, atrial fibrillation, arthritis, cancer, cardiovascular disease, cerebrovascular disease, chronic kidney disease, depression, diabetes, hyperlipidemia, hypertension, liver disease, obesity, schizophrenia, antiplatelet medication, and cardiovascular medication. Individual characteristics of matched groups were compared at baseline using standardized mean differences.

For our primary analysis, we applied a competing risk analysis to examine the association between statin use (statin user versus statin nonuser) and hospitalizations due to cardiovascular or cerebrovascular events. The competing event towards the cardiovascular or cerebrovascular event was all-cause mortality. The outcome of the model was whichever of the competing events occurred first. Kaplan-Meier curves were used to graphically present the assumption of proportional hazards across all groups. To avoid misclassification bias, individuals who fulfilled the criterion for statin use or for dementia after the baseline period were right-censored. For the PwD set, 2043 individuals were right-censored due to a change in statin use. For the PwoD, 1652 were censored due to a change in statin use, 11 395 were censored due to a change in the dementia diagnosis, and 89 were censored due to a change in statin use and dementia diagnosis. Furthermore, we right-censored individuals who were lost to follow-up during the observation period (PwD, n=256; PwoD, n=127). Reasons for loss to follow-up are leaving the nursing home (without entering another; eg, for home-care) or a change of insurance provider (Figure 1). We did not adjust for polypharmacy since it was present in the majority of participants, with an average number of medications of n=9.38 (SD=4.82). Furthermore, we conducted subgroup analyses based on distinct categories of statin dosage intensity (low, moderate, and high), allowing us to examine potential differences in outcomes across varying levels of exposure. This analysis was restricted to individuals whose statin dose remained consistent throughout the whole observation period. In separate subanalyses, we first included and later excluded participants with a history of atherosclerotic cardiovascular disease (ASCVD), specific medical procedures associated with ASCVD (Table S3), and use of antithrombotic medication as a surrogate measure for ASCVD. We also performed subanalyses by dementia type (VaD and AD) and inclusively in participants with a history of hyperlipidemia. Further subanalyses included stratifications by sex (male, female), age (60–79, 80–84, 85–89, 90+ years), and care dependency level (≤2, 3, 4, 5). Potential bias stemming from uncertain exposure durations was addressed by including only statin users who were newly classified as statin users after January 1, 2016, which meant that participants had no statin prescriptions during the first 6 months of 2015 but had 6 months of prescriptions in the last 6 months of. All subgroup analyses were conducted using inverse probability weighting to minimize potential biases, applying the same covariates used in the original propensity score model. This approach allowed us to estimate the average treatment effect among the treated within each subgroup, ensuring methodological consistency with the primary analysis. Additionally, we performed a sensitivity analysis using lagged exposure models at 6, 12, and 18 months within the analyses of newly prescribed statin users to address potential reverse causation. To further assess the robustness of our findings, we conducted a sensitivity analysis that differentiated outcomes into ischemic events (I63), hemorrhagic events (I61), other cardiovascular events (I20-24; I64, G45-46), and death. All tests of significance were based on a $P<0.05$ level and a CI of 95%. All statistical analyses were performed using R (version 4.2.2).

Approvals and Registration

The ethical board of the Charité approved the study—Universitätsmedizin Berlin (EA1/162/22). The requirement for obtaining informed consent from participants was waived by §75 Abs.1 SGB X (German Social Code).

Data Availability

The authors are unable to make the data from this study available. For research purposes, access to health and long-term care insurance fund data in Germany is possible under the conditions of the German Social Code (SGB V § 287). Requests for data access can be made by submitting a formal proposal specifying the recipient and purpose of the data transfer to the responsible supervisory authority. For assistance in obtaining access, please contact the first or corresponding author or wido@wido.bv.aok.de.

RESULTS

Participants

We analyzed data from 96 162 individuals, 37 262 within the set of PwoD and 58 900 individuals within the set of people with dementia. Sociodemographic results are presented in Table. A complete comparison of characteristics before and after propensity

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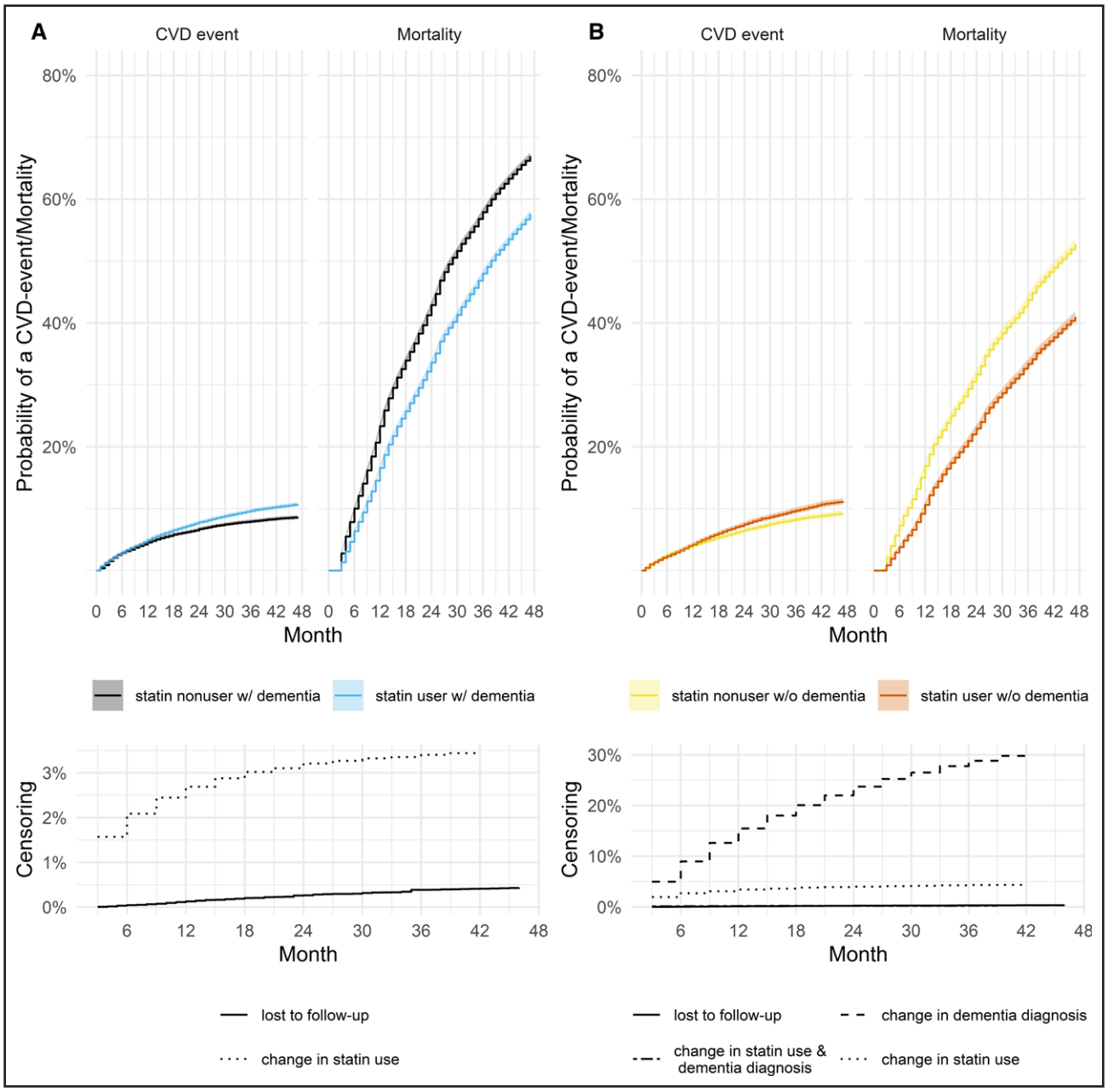

Figure 1. Kaplan-Meier curve of the risk of a cardiovascular disease (CVD) event and death associated with statin use and the presence of dementia in nursing home residents.
A, People with dementia (PwD). **B**, People without dementia (PwoD).

score matching is presented in Tables S4 and S5. For PwoD, the mean age was 82.2 years (SD±8.75), with 66.9% of the participants being female. The most frequent care level was 2, with 39.3%. A total of 66.2% had a diagnosis of hyperlipidemia, 41.7% had a history of diabetes, and 87.2% had a history of hypertension. 45.8% had a history of cardiovascular disease, and 54.1% had a history of cerebrovascular disease (Table).

For people with dementia, the mean age was 83.4 years (SD±7.4), with 69.8% of the participants being female. The most frequent care level was 4, with a total of 38.3%. 71.1% reported a history of hyperlipidemia, 42.5% had a history of diabetes, 87.0% reported a history of hypertension, 46.2% had a history of cardiovascular disease, and 58.5% had a history of cerebrovascular disease (Table).

Hospitalization Due to Cardiovascular and Cerebrovascular Events in Nursing Home Residents With Dementia

The average observation period among PwD was 2.3 years (SD±1.4). During the study period, 4528

Table. Propensity Score Matched Baseline Characteristics of Included Nursing Home Residents From Health Insurance Data Between With and Without Dementia

	Without dementia			With dementia		
	Statin users (n=18 631)	Statin nonusers (n=18 631)		Statin users (n=29 450)	Statin nonusers (n=29 450)	
Characteristic	N (%)		SMD	N (%)		SMD
Age, y	81.63±8.62*	82.67±8.85*	0.119	83.12±7.49*	83.75±7.39*	0.085
Age category, y			0.112			0.062
60–79	6796 (36.5)	6011 (32.3)		8317 (28.2)	7550 (25.6)	
80–84	3996 (21.4)	3795 (20.4)		7147 (24.3)	7230 (24.6)	
85–89	4323 (23.2)	4727 (25.4)		8128 (27.6)	8664 (29.2)	
≥90	3516 (18.9)	4098 (22.0)		5858 (19.9)	6006 (20.4)	
Male sex	6390 (34.3)	5582 (30.0)	0.093	9191 (31.2)	8558 (29.1)	0.047
Care dependency level†			0.116			0.222
≤2	7601 (40.8)	7050 (37.8)		4066 (13.8)	3296 (11.2)	
3	6549 (35.2)	6320 (33.9)		9394 (31.9)	7746 (26.3)	
4	3478 (18.7)	3794 (20.4)		11 237 (38.2)	11 275 (38.3)	
5	1003 (5.4)	1467 (7.9)		4753 (16.1)	7133 (24.4)	
Comorbidities						
Arthritis	4860 (26.1)	5184 (27.8)	0.039	7366 (25.0)	7494 (25.4)	0.010
Atrial fibrillation	5727 (30.7)	6008 (32.2)	0.032	8825 (30.0)	9095 (31.9)	0.020
Cancer	3619 (19.4)	3734 (20.0)	0.016	5511 (18.7)	5449 (18.5)	<0.005
Cardiovascular disease	8574 (46.0)	8489 (45.6)	0.009	13 593 (46.2)	13 629 (46.3)	0.002
Cerebrovascular disease	10 242 (55.0)	9899 (53.1)	0.037	17 155 (58.3)	17 297 (58.7)	0.010
Chronic kidney disease	6730 (36.1)	6913 (37.1)	0.020	10 924 (37.1)	10 956 (37.2)	0.002
Depression	4804 (25.8)	4785 (25.7)	0.002	8223 (27.9)	8061 (27.4)	0.012
Diabetes	7865 (42.2)	7663 (41.1)	0.022	12 557 (42.6)	12 481 (42.4)	0.005
Heart failure	7755 (41.6)	8768 (47.1)	0.110	12 132 (41.2)	13 241 (45.0)	0.076
Hepatitis	52 (0.3)	68 (0.4)	0.015	65 (0.2)	63 (0.2)	0.001
Hyperlipidemia	12 448 (66.8)	12 215 (65.6)	0.026	20 933 (71.1)	20 966 (71.2)	0.002
Hypertension	16 214 (87.0)	16 282 (87.3)	0.011	25 587 (86.9)	25 664 (87.1)	0.008
Liver disease	293 (1.6)	297 (1.6)	0.002	444 (1.5)	358 (1.2)	0.025
Obesity	1745 (9.4)	1684 (9.0)	0.011	1898 (6.4)	1791 (6.1)	0.015
Schizophrenia	724 (3.9)	706 (3.8)	0.005	1062 (3.6)	957 (3.2)	0.020
Number of comorbidities	4.92±2.05*	4.98±2.10*	0.027	4.97±2.08*	5.01±2.09*	0.020
Number of hospital admissions	0.12±0.73*	0.17±0.94*	0.058	0.14±0.75*	0.18±0.87*	0.054
Medications						
Antiplatelet	1569 (8.4)	1119 (6.0)	0.093	2030 (6.9)	1491 (5.1)	0.077
Antipsychotic	3404 (18.3)	3427 (18.4)	0.003	11 324 (38.5)	11 438 (38.8)	0.008
Antithrombotic	9875 (53.0)	7020 (37.7)	0.312	14 477 (49.2)	10 364 (34.8)	0.286
Cardiovascular	17 285 (92.8)	17 476 (93.8)	0.041	26 380 (89.6)	26 483 (89.9)	0.012
Diabetic	6091 (32.7)	5208 (28.0)	0.103	9375 (31.8)	7867 (26.7)	0.113
Nonstatin lipid-lowering	39 (0.2)	98 (0.5)	0.052	33 (0.1)	113 (0.4)	0.055
Statin intensity						
Low	1584 (8.5)	NA		2444 (8.3)	NA	
Moderate	16 532 (88.9)	NA		26 289 (89.4)	NA	
High	486 (2.6)	NA		668 (2.3)	NA	

NA indicates not available; and SMD, standard mean differences.

*Expressed as mean±SD.

†Care level was defined according to the German Social Code, Book XI– care levels range from ≤2=lowest care dependency to 5=highest care dependency.

hospitalizations due to cardiovascular and cerebrovascular events and 35 320 deaths occurred. Of these, 2621 hospitalizations and 16 920 deaths occurred among statin users with dementia (Figures 1 and 2).

In the fully adjusted model (Figure 2A), statin use was associated with an increased risk of hospitalization due to cardiovascular or cerebrovascular events among people with dementia compared with the nonusers (hazard ratio [HR], 1.06 [95% CI, 1.01–1.12]; *P*=0.023). In the subanalysis focusing on the statin dose intensity, we found that moderate and high intensity statin usage was associated with an increased risk of hospitalization compared with statin nonusers (HR, 1.15 [95% CI, 1.07–1.23]; *P*<0.001; HR, 1.55 [95% CI, 1.15–2.10]; *P*=0.005, respectively) while low intensity statin usage did not differ significantly (HR, 0.94 [95% CI, 0.75–1.19]; *P*=0.625). In additional subanalyses for individuals with history of ASCVD we did not find a significant association between statin user and hospitalization when compared with nonusers with a history of ASCVD (HR, 1.04 [95% CI, 0.98–1.10]; *P*=0.192); however, there was significantly increased association among statin users and hospitalizations in individuals without history of ASCVD (HR, 1.30 [95% CI, 1.12–1.52]; *P*<0.001). There was a significant association of increased risk of hospitalization among statin users compared with nonusers with a history of VaD (HR, 1.18 [95% CI, 1.06–1.32]; *P*=0.003) and with AD (HR, 1.14 [95% CI, 1.00–1.31]; *P*=0.047). Within the group of individuals with a history of hyperlipidemia, we did not find a significant difference between statin users and nonusers (HR, 1.03 [95% CI, 0.96–1.09]; *P*=0.406). Among individuals with newly prescribed statins, we found an association of an increased risk of hospitalization due to cardiovascular and cerebrovascular events among statin users compared with nonusers (HR, 2.71 [95% CI, 2.33–3.15]; *P*<0.001). However, sensitivity analyses controlling for lagged exposure show higher risks for hospitalizations, while the lagged exposure reduces the risk (Figure S1). We also performed additional analyses stratifying individuals by sex, age, and care dependency level (Figure S2) and found that female nursing home residents with dementia who used statins had a higher risk for events compared with nonusers (HR, 1.09 [95% CI, 1.02–1.16]; *P*=0.010).

In a sensitivity analysis that differentiates the CVD event outcome (ischemic event, hemorrhagic event or other CVD event),we found that statin use was not associated with increased risk of hospitalization due to ischemic or hemorrhagic events (HR, 0.99 [95% CI, 0.92–1.07]; *P*=0.785; HR, 0.95 [95% CI, 0.79–1.20]; *P*=0.642, respectively) while statin use and other CVD events were associated with increased hospitalization risk (HR, 1.17 [95% CI, 1.08–127]; *P*<0.00; Figure 3).

Hospitalization Due to Cardiovascular and Cerebrovascular Events in Nursing Home Residents Without Dementia

The average observation period among PwoD was 2.0 years (SD±1.4). During the study period, 2450 hospitalizations due to cardiovascular and cerebrovascular events and 12 551 deaths occurred. Of these, 1431 events and 5727 deaths occurred among statin users without dementia.

We performed the same analyses for this cohort, and in the fully adjusted model (Figure 2B), we found only significant associations between statin use and hospitalizations when focusing on the dose intensity. We e found that high dose intensity was significantly associated with an increased risk of hospitalization compared with statin nonusers (low: HR, 1.08 [95% CI, 0.81–1.14]; *P*=0.607; moderate: HR, 1.07 [95% CI, 0.97–1.18]; *P*=0.174; and high: HR, 1.51 [95% CI, 1.04–2.19]; *P*=0.029). Additionally, we found a significant association between statin use and hospitalizations among the newly prescribed statin user group compared with statin nonusers (HR, 1.99 [95% CI, 1.56–2.52]; *P*<0.001). However, as with the PwD sample, a sensitivity analysis controlling for lagged exposure showed higher risks for hospitalizations, while the lagged exposure reduced risk (Figure S3).

In further subanalyses, we stratified the data by sex, age, and care dependency level (Figure S1). In PwoD aged 90 years+, statin use was associated with significantly higher event risk compared with nonusers (HR, 1.25 [95% CI, 1.05–1.50]; *P*=0.014).

The subanalysis which differentiates the CVD event outcome (ischemic event/hemorrhagic event/other CVD event) found that statin use was associated with reduced hospitalizations due to hemorrhagic events (HR, 0.68 [95% CI, 0.47–0.97]; *P*=0.032) while ischemic and other CVD events were not significantly associated (HR, 1.02 [95% CI, 0.91–1.14]; *P*=0.770; HR, 1.08 [95% CI, 0.97–1.20]; *P*=0.146, respectively; Figure 3).

DISCUSSION

In this study, we examined the association between statin use and hospitalization due to cardiovascular and cerebrovascular events in nursing home residents in Germany. The novel finding of our study was that statin use was associated with an increased risk of hospitalization due to cardiovascular or cerebrovascular events among people with dementia. We found a trend of increased risk of hospitalization among PwD without a history of ASCVD. Further, among PwD, events were significantly higher among statin users with AD and VaD, and among newly prescribed statin users, statin use was associated with an increased risk of hospitalization in both people with and without dementia. Finally, moderate and high

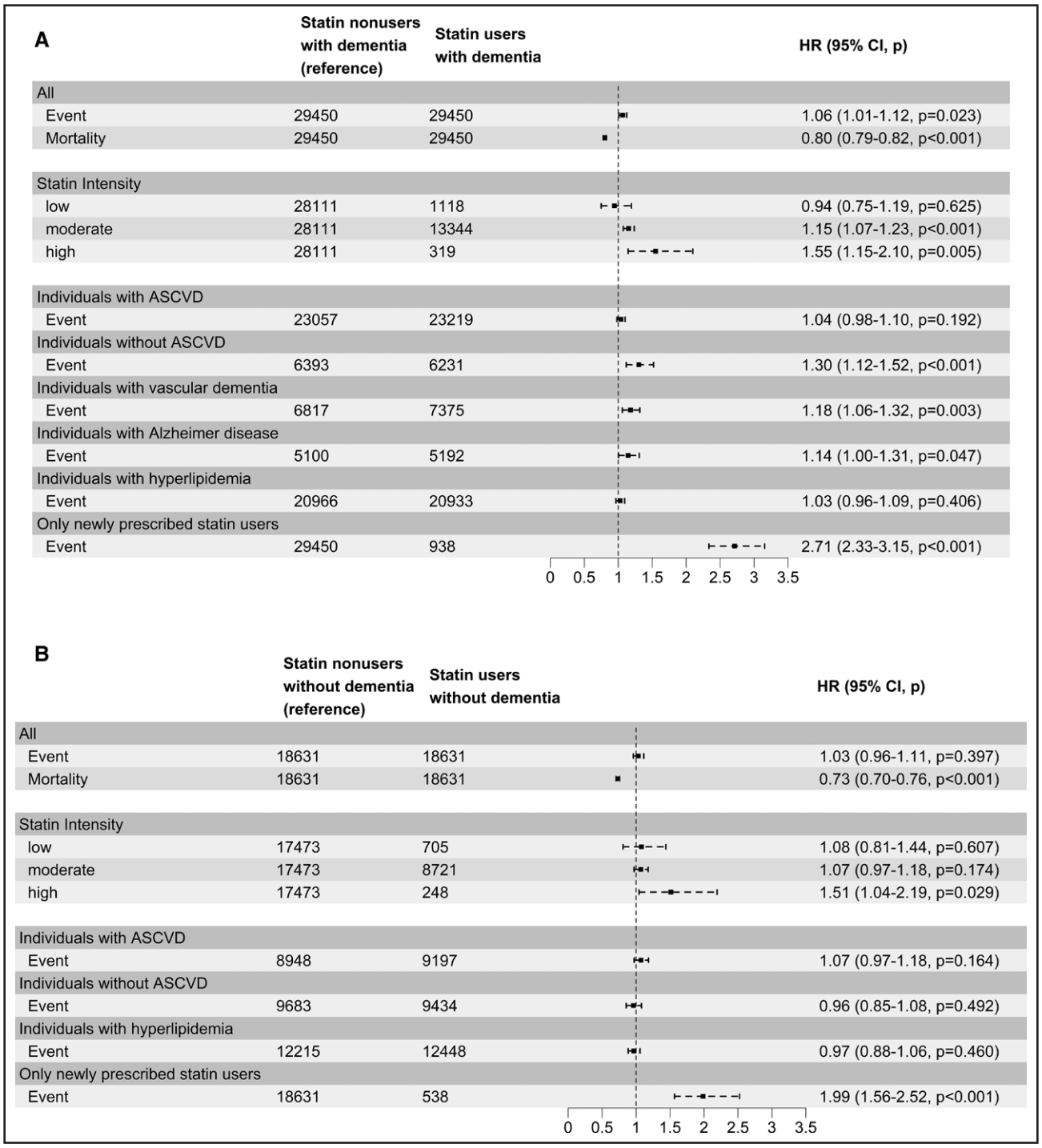

Figure 2. Associations between statin use and hospitalizations due to cerebrovascular and cardiovascular events using propensity score-matched data of nursing home residents.
A, People with dementia (PwD). **B**, People without dementia (PwoD). Models were fully adjusted for age, sex, care level, cardiovascular disease, cerebrovascular disease, depression, diabetes, heart failure, hyperlipidemia, hypertension, obesity, hepatitis, liver disease, number of comorbidities, antipsychotic medications, antithrombotic medications, cardiovascular medications, and nonstatin lipid-lowering medications, and number of hospital admissions. Numbers in each group represent the number at risk. ASCVD indicates atherosclerotic cardiovascular disease; and HR, hazard ratio.

statin dose intensity was associated with an increased risk of hospitalization.

The US Preventive Services Task Force Recommendation Statement has updated the recommendation regarding statin use in people aged 40 to 75 years who have no history of ASCVD and who have 1 or more cardiovascular risk factors (such as hyperlipidemia, diabetes, hypertension, or smoking). However,

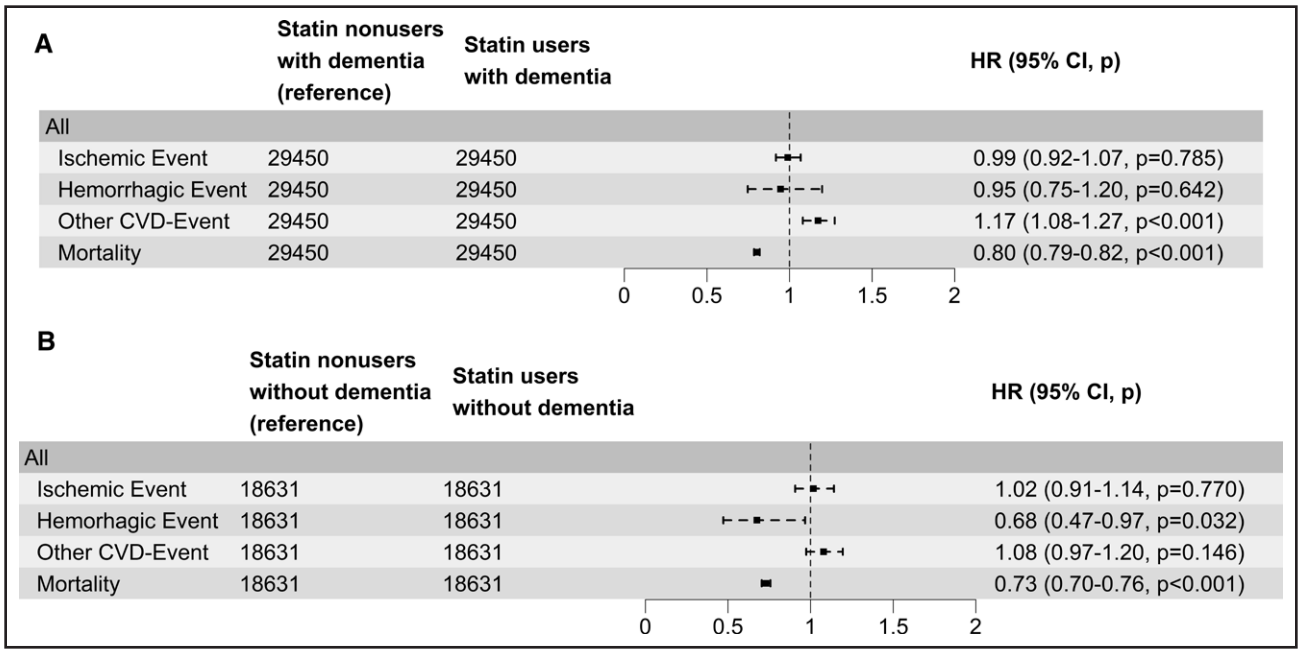

Figure 3. Associations between statin use and hospitalizations due to ischemic, hemorrhagic, and other cardiovascular disease (CVD) events using propensity score-matched data of nursing home residents.
A, People with dementia (PwD). **B**, People without dementia (PwoD). Models were fully adjusted for age, sex, care level, cardiovascular disease, cerebrovascular disease, depression, diabetes, heart failure, hyperlipidemia, hypertension, obesity, hepatitis, liver disease, number of comorbidities, antipsychotic medications, antithrombotic medications, cardiovascular medications, and nonstatin lipid-lowering medications, and number of hospital admissions. Numbers in each group represent the number at risk. HR indicates hazard ratio.

the guidelines do not include PwD. Few studies have evaluated the effects of statins on PwD regarding cerebrovascular and cardiovascular event risk. A recent systematic review and meta-analysis by Davis et al[11] on the benefits and harms of statins in PwD found insufficient evidence to evaluate the efficacy of statins in this population because none of the 5 randomized controlled trials included reported outcomes related to cerebrovascular and cardiovascular events. In the present study, we aimed to fill this gap.

We found that statin use was not associated with reduced risk for hospitalizations due to cardiovascular and cerebrovascular events among nursing home residents with dementia. In contrast, we found statin use was associated with an increased risk of hospitalization due to cardiovascular or cerebrovascular events only among people with dementia, which suggests a higher underlying atherosclerotic burden and potentially less resilience in this group. The findings of an increased risk of hospitalization among both people with and without dementia among newly prescribed statin users could be however partially explained by biases. In the nursing home population, statins are most likely initiated for secondary prevention after a recent event. Thus, our findings may be due to increased events that these patients are at risk for, resulting in reverse causation bias. This is supported by our sensitivity analysis, which showed that when using an 18-month lag, the association has been significantly reduced. The surveillance bias should also be considered in our study. Statin initiation is usually due to a recent myocardial infarction or stroke, which results in increased medical surveillance and possibly increased hospitalizations. This could possibly also explain the findings of increased hospitalizations among statin users without ASCVD history in this population.

Polypharmacy and specific medications have also been associated with an increased risk of hospitalization.[19] Cardiovascular medications, including diuretics, nitrates, and alpha receptor blockers, are well known to cause orthostatic hypotension[20] and have been adjusted for in our study; however, they have not altered our results. Antipsychotic use has also been associated with increased cardiovascular and cerebrovascular events,[21] however, in our sample, antipsychotic use was similar between PwD and PwoD; therefore, antipsychotics cannot explain the difference between results. We also need to consider interactions between statins and anticoagulants, including warfarin, apixaban, and rivaroxaban, which have been associated with altered metabolism, potentially leading to adverse hemorrhagic cerebrovascular events[22]; therefore, they could also contribute to increased hospitalizations.

Among PwD, events were significantly higher among statin users with AD and VaD. This may be related to vascular risk factors since AD and VaD incidence is associated with vascular risk factors.[23,24] Another plausible explanation for this observation could be the presence of survival bias within our sample. In our study,

PwD in our sample may represent an inherently frail survivor population, which could explain the increased hospitalization rates observed. This would suggest that these patients might be more susceptible to complications or comorbidities that necessitate hospitalization, regardless of statin use. This assumption may be supported by results from the same sample on mortality: in their previous research, the authors of this article, using the same data set and population, showed that statin use was associated with 20% lower all-cause mortality among PwD and found similar associations between statin use and risk reduction in all-cause mortality among statin users when the analysis was stratified by dementia type (VaD, AD) and by ASCVD status.[19] These results were similar to the findings by Orkaby et al[25] This suggests that while statins may contribute to a reduction in mortality risk, they do not necessarily translate into a reduced rate of hospitalizations due to cardiovascular and cerebrovascular events among PwD. Statins have been suggested to exert their beneficial effects in AD and VaD independently of their lipid-lowering effects, through other mechanisms. These potential mechanisms include anti-inflammatory properties, reduced oxidative stress,[10] neurotrophic properties, activation of neurogenesis,[10] and neuroprotective mechanisms by numerous potential pathways.[26] Imaging data further support these plausible mechanisms through which statins may exacerbate neurovascular dysfunction.[27,28] The beneficial effects of statin use in older participants in all-cause mortality with and without dementia, independent of ASCVD history, suggest a possible systematic effect of statin, such as an anti-inflammatory effect. While the increased risk for cardio- and cerebrovascular events seen only in people with dementia suggests a localized impact of statin on a vulnerable dementia brain. One such potential explanation could be that statins, by decreasing cholesterol levels in the brain, may cause damage to the neurovascular unit, resulting in reduced excitability and synaptic plasticity, impaired metabolism, and increased blood-brain barrier permeability and dysregulation of cerebral blood flow.[29] Therefore, statins may increase the cerebrovascular and neurodegenerative pathological processes in the already vulnerable brain of PwD. Further, the present findings report higher hospitalization rates among moderate and high statin users could also be explained by the exact biological mechanism, regardless of dose. However, when interpreting current results, it is essential to note that our study's overall number of events was relatively low. This low event rate could limit the statistical power of our analyses, increasing the likelihood of random variation influencing our findings. The limited number of events means that our results could be influenced by factors other than statin use, such as differences in health care access or preferences regarding hospitalizations in this study. However, when interpreting current results, it is important to note that our study's overall number of events was relatively low. This low event rate could limit the statistical power of our analyses, increasing the likelihood of random variation influencing our findings. The limited number of events means that our results could be influenced by factors other than statin use, such as differences in health care access or preferences regarding hospitalizations in this study population. Another potential explanation for our results could be that statins, by decreasing cholesterol levels in the brain, may cause damage to the neurovascular unit, resulting in reduced excitability and synaptic plasticity, impaired metabolism, and increased blood-brain barrier permeability and dysregulation of cerebral blood flow.[29] Therefore, statins may increase the cerebrovascular and neurodegenerative pathological processes in the already vulnerable brain of PwD.

Further, the present findings report that higher hospitalization rates among moderate and high statin users could also be explained by the exact biological mechanism, regardless of dose. Finally, in the present study, we observed no significant difference in ASCVD-related outcomes between statin users and nonusers. This finding contrasts with earlier research. However, several factors may explain this discrepancy. First, PwD often exhibit advanced vascular pathology, including small vessel disease and dysfunction of the neurovascular unit, which may reduce the physiological effectiveness of statins.[30] Second, the timing and clinical context of statin initiation are crucial. In our cohort of frail, institutionalized older adults, statins may have been prescribed late in the disease course when irreversible vascular damage and coexisting neurodegeneration reduce the likelihood of therapeutic benefit. This aligns with growing evidence that the efficacy of statins diminishes in advanced age and late-stage disease.[31–33] Third, PwD frequently face competing risks of mortality, which may obscure cardiovascular-specific outcomes. Although our previous work using this cohort found that statins were associated with reduced all-cause mortality in PwD, the current analysis suggests that these survival benefits may not extend to reductions in cardiovascular or cerebrovascular hospitalizations. This may indicate that statins contribute to attenuating disease severity rather than preventing acute events or that mechanisms beyond lipid-lowering account for the observed mortality reduction.[34,35]

Strengths and Limitations

The strengths of this study include its large sample size of multimorbid older adults with dementia residing in nursing homes. Our analyses used claims data from a large, nationwide sample of nursing home residents, providing valuable insights into the effect of real-world statin treatment and hospitalizations due to cerebrovascular

and cardiovascular events. The strength of our study is the large sample size and our ability to perform numerous subanalyses. However, limitations must be considered. First, the dementia diagnosis was not based on adjudication but on diagnostic codes, leading to potential under- or misdiagnosis of dementias. Second, we lacked information on the severity of dementia, a critical factor influencing hospitalization rates. Third, we cannot entirely rule out the possibility that frailty, rather than statin use alone, may explain the increased risk of hospitalization as a major risk factor for hospitalization. Frailty is also commonly associated with statin discontinuation in PwD. However, our analyses accounted for the number of comorbidities, level of care dependency, and hospitalizations during the baseline period as proxies for frailty or overall poor health status—an approach consistent with that used in comparable studies.[25] Fourth, we did not investigate the potential adverse effects of statins, including myalgias, impacts on functional status, or quality of life. These issues are major concerns for nursing home residents and their families.[36] Future research should include those aspects when examining the effects of statin use among older adults. Lastly, the low number of events observed is a major limitation that reduces the statistical power of our analyses, thereby increasing the possibility that random variation could influence our findings. As a result, while the higher hospitalization rates among PwD taking statins are noteworthy, they should be interpreted cautiously. Further, our study's exploratory nature involved testing numerous hypotheses without formal correction for multiplicity, which may elevate the risk of false positive findings. Consequently, some statistically significant results could reflect chance rather than genuine effects due to the inflated type I error from multiple testing.[37]

Conclusions

In conclusion, our study suggests no benefit of statins in PwD, and in fact, the present findings indicate an association between statin use and an increased risk of hospitalization due to cardiovascular or cerebrovascular events among PwD. This finding must be contextualized within the limitations of our study, including the potential for survival bias and the low overall incidence of events. Based on that, clinicians should consider individualized risk-benefit assessment when considering statin use in older people with dementia, especially in newly prescribed patients. Larger and more heterogeneous samples and prospective studies are needed to confirm these findings and clarify the underlying mechanisms.

ARTICLE INFORMATION

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Data and materials are available from the corresponding author on reasonable request. The data used in this study cannot be made available in the article, the supplementary files, or in a public repository due to German data protection laws (Bundesdatenschutzgesetz). Therefore, data are stored on a secure drive in the Wissenschaftliches Institut der AOK to facilitate replication of the results. Generally, access to data of statutory health insurance funds for research purposes is possible only under the conditions defined in the German Social Law (SGB V § 287). Requests for data access can be sent as a formal proposal, specifying the recipient and purpose of the data transfer, to the appropriate data protection agency. Access to the data used in this study can only be provided to external parties under the conditions of the cooperation contract of this research project and after written approval by the AOK. For assistance in obtaining access to the data, please contact wido@wido.bv.aok.de. We are indebted to Dr Kathrin Jürchott for their support and guidance throughout the process.

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Disclosures

None.

Supplemental Material

Tables S1–S5
Figures S1–S3

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