Original Article

Association of medication adherence quality measures for diabetes, hypertension, and hyperlipidemia with cognitive decline

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Abstract

Background: While diabetes, hypertension, and hyperlipidemia each are associated with increased risk of cognitive decline, little is known regarding how nonadherence to medications for these conditions is associated with cognitive decline risk. **Methods:** We identified patients enrolled in a Medicare Advantage Prescription Drug plan who were eligible for inclusion in the CMS Star Medication Adherence quality measures for diabetes, hypertension, and hyperlipidemia in 2018, 2019, and 2020. To achieve an adherence quality measure, patients had to meet 80% of the proportion of days for the medication. We used propensity score with inverse probability of treatment weighting to balance outcomes for baseline characteristics and logistic regression models to compare odds of cognitive decline outcomes across patient groups. **Results:** The study population of 99,774 individuals had a mean age of 71.0 years and was 49.1% female, 73.9% White, and 17.8% Black, with 62.0% living in an urban setting. Compared with patients who missed zero adherence measures, those who missed one measure had 23%–33% increased odds of cognitive decline (any decline OR = 1.23; dementia OR = 1.33; Alzheimer's disease OR = 1.27; all *P* values <0.01). Patients who missed 2–3 measures had 37%–96% increased odds of cognitive decline (any decline OR = 1.37; dementia OR = 1.58; Alzheimer's disease OR = 1.96; all *P* values <0.01). Patients who missed ≥4 adherence measures had the greatest odds of cognitive decline (any decline OR = 1.64; dementia OR = 2.05; Alzheimer's disease OR = 2.48; all *P* values <0.01). **Conclusion:** Not achieving CMS Star Medication Adherence quality measures for diabetes, hypertension, and hyperlipidemia therapies was associated with increased risk of cognitive decline outcomes.

Keywords: Alzheimer's disease, CMS star medication adherence quality measures, cognitive decline, dementia, medication adherence

Introduction

There are approximately 7 million Americans 65 years and older living with Alzheimer's disease (AD) and dementia.[1,2] Estimates for mild cognitive impairment suggest that nearly 12% of adults 65 and older report subjective cognitive decline.[3] The economic costs of dementia are estimated at $321 billion with an additional $271 billion contributed to unpaid caregiving; these costs will increase to nearly $1 trillion by 2050.[4]

Research suggests that other chronic diseases, including type 2 diabetes, hypertension, and hyperlipemia, may contribute to increased risk of cognitive decline, AD, and dementia.[5-7] Diabetes may add to global dementia risk through inflammation, hyperglycemia-associated vascular damage and brain atrophy,

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hypoglycemia-related declines in brain nutrient and oxygen availability, and decreases in brain-derived neurotrophic factor, which compound underlying pathologies.[8,9] There is an estimated 1.5- to 2.5-fold increased risk of dementia among older adults with diabetes compared with their peers without diabetes.[10-12] Hypertension is proposed as a causative factor for dementia due to its contributions to cerebral ischemia and hemorrhage, microvascular damage, disruption of the blood–brain barrier, decreased elasticity of vessels, and inflammation, all of which may affect AD amyloid pathology or contribute to vascular dementia risk directly.[6,13] In a national cohort population of 423,976 Korean adults, for each 10 mmHg increase in systolic blood pressure, the relative risk of incident dementia increased by 22% for adults aged 40–59 years of age, by 8% in subjects aged 60–69 years, and did not increase in the group 70 years of age and older.[14] This aligns with early research, suggesting that uncontrolled hypertension may be more strongly linked with dementia risk in adults 45–50 years of age than in adults over age 65.[15] Hyperlipidemia can contribute to cognitive deficits through intracranial atherosclerosis and carotid artery stenosis, which disrupt blood flow to and within the brain.[16] In a meta-analysis of 23,338 participants in 34 studies, individuals with elevated total cholesterol (>6.5 mmol/l) in midlife had more than twice the risk of developing AD compared with adults with normal cholesterol levels.[17]

Optimally treating diabetes, hypertension, and hyperlipidemia may decrease the risk of cognitive decline and dementia,[18-20] though results from individual randomized, placebo-controlled trials are conflicting. The Systolic Hypertension in Europe (Syst-Eur) and Perindopril Protection Against Recurrent Stroke Study (PROGRESS) trials demonstrated up to a 50% reduced rate of dementia in patients using specific antihypertensive agents, but the Study on Cognition and Prognosis in the Elderly (SCOPE) and the Systolic Hypertension in the Elderly Program (SHEP) trial found no significant difference in the incidence of dementia between the intervention and placebo groups.[21] A meta-analysis of 20 RCTs reported a pro-cognitive class effect of using antidiabetic agents to improve mild cognitive impairment and AD outcomes,[22] but a Cochrane Database review found no evidence that type 2 diabetes treatments prevent or delay cognitive impairment.[23] Another meta-analysis noted that insulin increased dementia risk and thiazolidinediones decreased risk.[24] Geifman *et al.*[25] reanalyzed patient-level data from failed clinical trials and observed slower progression of cognitive decline in patients who used simvastatin, but an RCT of pravastatin to prevent dementia found no difference in cognitive decline between the intervention and placebo groups during a three-year follow-up period.[26] Many of these trials were not designed to evaluate cognitive outcomes, and study design may have contributed to the inconsistent findings for cognitive benefits related to the use of these medication classes.[27]

Older adults with declining cognitive function or dementia have low medication adherence,[28] and medication adherence appears to worsen as cognitive function declines.[29] Although there is extensive research on interventions to increase adherence of one or possibly two medication classes,[30] less is known about the association of better medication adherence for multiple chronic conditions with Alzheimer's disease/dementia status.[31] Further, to our knowledge there is no real-world evidence on the association between Centers for Medicare and Medicaid Services (CMS) Star Medication Adherence quality measures achievement to prescribed therapies for type 2, noninsulin dependent diabetes, hypertension (e.g., renin-angiotensin system antagonists), and hyperlipidemia (statins) simultaneously and cognitive decline risk. In patients with all three conditions, adherence measures are not occurring in a silo, and it is unknown how achieving multiple adherence measures over several years may impact cognitive health outcomes. An understanding of the relationship between multiple medication adherence and cognitive outcomes provides value to primary care providers who may work with patients to mitigate adherence barriers. The objective of this study was to examine the association between achieving CMS Star Medication Adherence quality measures for type 2, noninsulin-dependent diabetes, hypertension (e.g., renin angiotensin system antagonists), and hyperlipidemia (e.g., statins) medications over three years (nine total measures) and incidence of cognitive decline, dementia, and Alzheimer's disease.

Methods

Data source

We utilized Humana's Research Database, which contains protected health information (PHI)-compliant patient enrollment, medical claims, and pharmacy claims for Medicare beneficiaries. We used a PHI-compliant unique identifier to reliably link data from each data source. We did not utilize patient PHI data for this research.

Study design and patient selection

We used a retrospective cohort study design to identify patients who qualified for CMS Star Medication Adherence quality measures for diabetes, statin, and renin-angiotensin system antagonist (RASA) for calendar years 2018, 2019, and 2020. Eligible patients were 19–89 years of age, enrolled in a Medicare Advantage Prescription Drug (MAPD) plan with continuous enrollment for 2017 through 2021. To qualify for each CMS Star Medication Adherence quality measure, we required the patient to have ≥2 filled prescriptions per year, on different dates of service for each condition. The quality measure specification requires that the first fill of the medication class must be at least 91 days prior to the end of the measurement period. We required that the three index prescriptions, for each of diabetes, statin, and RASA therapies, were filled between 1/1/2018 and 3/31/2018, and we excluded patients who started treatment after March 31, 2018. We excluded patients if they had any claim related to cognitive decline as indicated by the use of cognition-enhancing therapies, diagnosis for dementia, or diagnosis for Alzheimer's disease between 1/1/2017 and 12/31/2017. To achieve a medication adherence measure, patients must have a proportion of days

covered (PDC) of ≥80% for the medication(s) in each measure during the calendar year. The PDC score is the percentage of days in the measurement period covered by prescription claims. CMS uses the Pharmacy Quality Alliance (PQA) technical specifications to define the achievement of adherence measures.[32] We divided patients into four groups based on the number of adherence measures missed over three years: 1. Missed zero of nine adherence measures (3 measures over 3 years), 2. Missed one adherence measure, 3. Missed 2–3 adherence measures, and 4. Missed ≥4 adherence measures.

Ethical approval

This study followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. The Humana Healthcare Research Human Subject Protection Office (HHR HSPO) used the US Department of Health and Human Services regulations 45 CFR 46 and the Office of Human Research Protections Guidance on Coded Private Information or Specimens Use in Research, Guidance (2008) to determine this study did not constitute human subjects research and did not require institutional review board oversight. The decision was based on the determination that the research involved only analysis of coded information, and the researchers could not readily identify the individuals from which the information was derived.

Outcomes

We measured cognitive decline by the presence of at least one diagnosis code on medical claims for dementia, Alzheimer's disease, cognitive disturbance not demented, mild cognitive impairment, or by the presence of at least one prescription claim for cognition-enhancing therapy (rivastigmine, galantamine, donepezil, or memantine). Appendix A presents the relevant ICD-10 codes for dementia, Alzheimer's disease, cognitive disturbance, and mild cognitive impairment.

Statistical analysis

We reported baseline population demographic and clinical characteristics using summary statistics. We reported means [standard deviation (SD)] for continuous variables and counts and frequencies (%) for categorical variables. We utilized three separate binary logistic regression models to estimate a propensity score for each patient (i.e., a conditional probability of being treated given the observed baseline characteristics). We calculated weights for each patient as the inverse of the probability of receiving the treatment that they received, and we stabilized the weights to reduce the variance of the effect estimate, therefore accounting for extreme observations.[33] Then, we used the inverse probability of treatment weighting (IPTW) with the propensity score to balance differences in baseline characteristics (age, gender, race, health plan type, low-income subsidy/dual Medicaid eligibility (LIS/dual eligible), region, and Elixhauser comorbidity and Diabetes Complications Severity Index (DCSI) scores and minimize potential selection bias when evaluating study outcomes.[34,35] We included the stabilized weights in the outcome models; i.e., we fit weighted logistic regression models to evaluate the association between the adherence measure groups and cognitive outcomes. We performed analyses using SAS version 8.3 (SAS Institute Inc., Cary, NC, USA).

Results

Population characteristics

We identified 99,774 patients who met all eligibility criteria [Figure 1]. The cohort had a mean age of 71.1 years and was 49.1% female, 73.9% White, and 17.8% Black, with 62.0% living in an urban setting. Demographics for unmatched/unweighted cohorts are presented in Table 1. After applying IPTW, there were no significant differences between the groups in age, gender, race, health plan type, low-income subsidy/dual Medicaid eligibility (LIS/dual eligible), region, and baseline Elixhauser comorbidity and Diabetes Complications Severity Index (DCSI) scores.

Medication adherence measures and cognitive decline

As patients increasingly missed CMS Star Medication Adherence quality measures, there was a stair-step increase in the odds of incident cognitive decline, dementia, Alzheimer's disease,

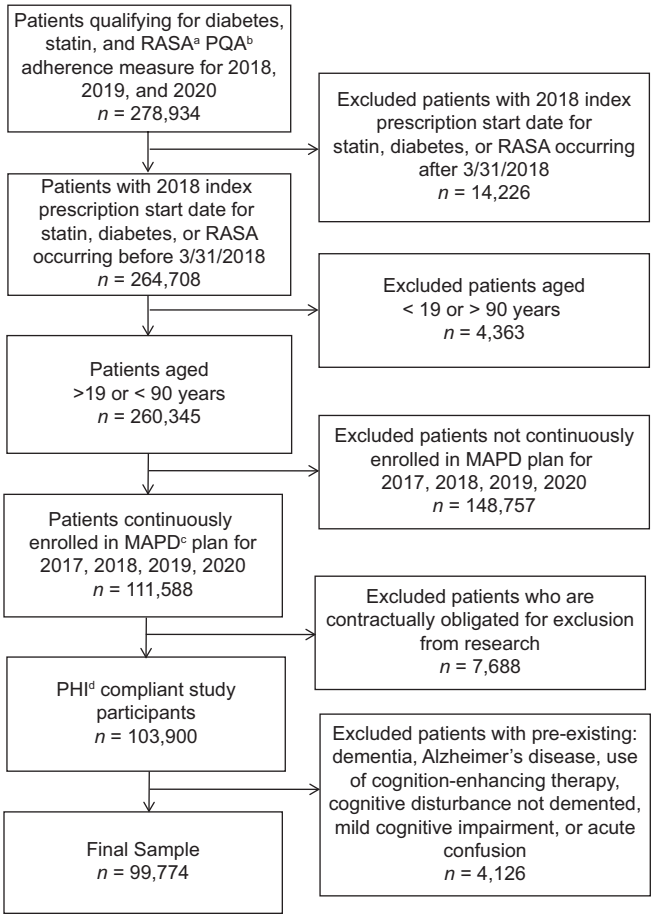

Figure 1: Attrition Diagram. [a]RASA = Renin angiotensin system antagonist. [b]PQA = Pharmacy Quality Alliance. [c]MAPD = Medicare Advantage Prescription Drug. [d]PHI = Protected health information

mild cognitive impairment, or use of a cognition-enhancing therapy [Table 2]. Compared with patients who missed zero of nine CMS Star Medication Adherence quality measures, those who missed one quality measure had a 23% increased odds of any cognitive decline (OR = 1.23; CI = 1.16–1.31), a 33% increased odds of dementia (OR = 1.33; CI = 1.22–1.50), a 27% increased odds of Alzheimer's disease (OR = 1.27; CI = 1.06–1.53), a 29% increased odds of mild cognitive impairment (OR = 1.29; CI = 1.17–1.42), and a 39% increased odds of using a cognition-enhancing therapy (OR = 1.39; CI = 1.24–1.55). For patients who missed the CMS Star Medication Adherence quality measures 2–3 times, there was a 37% increased odds of any cognitive decline (OR = 1.37; CI = 1.28–1.6), a 58% increased odds of dementia (OR = 1.58; CI = 1.43–1.73), a 96% increased odds of Alzheimer's disease (OR = 1.96; CI = 1.64–2.35), a 35% increased odds of mild cognitive impairment (OR = 1.35; CI = 1.21–1.50), and a 57% increased odds of using a cognition-enhancing therapy (OR = 1.57; CI = 1.39–1.77) compared with those who missed zero of nine medication adherence quality measures. For patients who missed ≥4 CMS Star Medication Adherence quality measures, there was a 64% increased odds of any cognitive decline (OR = 1.64; CI = 1.46–1.83), a 105% increased odds of dementia (OR = 2.05; CI = 1.75–2.39), a 148% increased odds of Alzheimer's disease (OR = 2.48 CI = 1.85–3.29), a 54% increased odds of mild cognitive impairment (OR = 1.54; CI = 1.28–1.85), and a 125% increased odds of using a cognition-enhancing therapy (OR = 2.25; CI = 1.87–2.71)

Table 1: Baseline Characteristics by Cohort

Variable[a]	Missed 0 times (*n*=59,958) (Weighted *n*=59,959)[b]	Missed 1 time (*n*=21,368) (Weighted *n*=21,366)[b]	Missed 2–3 times (*n*=14,850) (Weighted *n*=14,851)[b]	Missed ≥4 times (*n*=3,598) (Weighted *n*=3,659)[b]	Missed 1 vs. Missed 0 Weighted *P*[c]	Missed 2–3 vs. Missed 0 Weighted *P*[c]	Missed ≥4 vs. Missed 0 Weighted *P*[c]
Age, mean (SD)	71.1 (± 7)	71.1 (± 7)	71.0 (± 7)	71.2 (± 7)	0.912	0.710	0.217
Female, *n* (%)	29,555 (49.3)	10,537 (49.3)	7,333 (49.4)	1,826 (49.9)	0.951	0.975	0.332
Geographic region, *n* (%)							
Northeast	1,430 (2.4)	537 (2.5)	364 (2.4)	79 (2.2)	0.552	0.112	0.743
Midwest	11,384 (19)	3,996 (18.7)	2,743 (18.5)	694 (19)			
South	41,282 (68.9)	14,712 (68.9)	10,210 (68.7)	2,515 (68.7)			
West	5,863 (9.8)	2,121 (9.9)	1,535 (10.3)	370 (10.1)			
Population density—Urban, *n* (%)	37,329 (62.3)	13,301 (62.3)	9,243 (62.2)	2,301 (62.9)	0.992	0.976	0.299
Race, *n* (%)							
White	44,323 (73.9)	15,785 (73.9)	10,912 (73.5)	2,700 (73.8)	0.991	0.991	0.904
Black	10,650 (17.8)	3,799 (17.8)	2,688 (18.1)	648 (17.7)			
Other	4,986 (8.3)	1,782 (8.3)	1,252 (8.4)	311 (8.5)			
Plan type, *n* (%)							
HMO	32,981 (55)	11,753 (55.0)	8,154 (54.9)	1,994 (54.5)	1.000	0.998	0.879
PPO	21,357 (35.6)	7,609 (35.6)	5,320 (35.8)	1,325 (36.2)			
Other	5,622 (9.4)	2,004 (9.4)	1,378 (9.3)	340 (9.3)			
LIS and/or dual eligibility, *n* (%)	12,843 (21.4)	4,590 (21.5)	3,198 (21.5)	772 (21.1)	0.849	0.943	0.532
Elixhauser comorbidity index[d], mean (SD)	3.49 (± 2.1)	3.49 (± 2.1)	3.45 (± 2.1)	3.43 (± 2.1)	0.945	0.240	0.519
RxRisk score[e], mean (SD)	6.68 (± 2.4)	6.68 (± 2.4)	6.66 (± 2.4)	6.63 (± 2.4)	0.927	0.908	0.881
DCSI score[f], mean (SD)	1.16 (± 1.4)	1.16 (± 1.4)	1.14 (± 1.4)	1.16 (± 1.4)	0.923	0.964	0.267
≥1 Inpatient admission, *n* (%)	4,942 (8.2)	1,762 (8.2)	1,220 (8.2)	292 (8)	0.989	0.847	0.994
≥1 Emergency department visit, *n* (%)	14,167 (23.6)	5,049 (23.6)	3,503 (23.6)	840 (23)	0.990	0.941	0.980

[a]Measurements were made on the date of index or over a 1-year time period relative to that index date for inpatient admissions and emergency department visits. [b]The total weighted sample size will appear only approximately equal for categorical counts due to rounding. [c]Differences were evaluated by weighted χ^2 tests for categorical variables and weighted *t* tests for continuous variables. [d]The Elixhauser comorbidity index uses 31 categories of ICD-9 and ICD-10 diagnosis codes to calculate a score that is associated with hospital charges, length of stay, and mortality. [e]The RxRisk-V score is a pharmacy-specific comorbidity index based on the identification of 45 distinct medical condition categories via their associated medication treatment. [f]The Diabetes Complications Severity Index (DCSI) uses seven categories of complications, which are cardiovascular disease, nephropathy, retinopathy, peripheral vascular disease, stroke, neuropathy, and metabolic disease, to calculate a score to predict adverse outcomes including hospitalization and mortality based on the number and severity of complications associated with diabetes

Table 2: Association Between Cognitive-related Outcomes and Adherence Quality Measures, Adjusted Analysis

Outcomes	Missed 0 adherence measures	Missed 1 adherence measure	Missed 2–3 adherence measures	Missed ≥4 adherence measures
Any cognitive decline	ref	1.23 [1.16, 1.31][a]	1.37 [1.28, 1.46]	1.64 [1.46, 1.83]
Dementia	ref	1.33 [1.22, 1.45]	1.58 [1.43, 1.73]	2.05 [1.75, 2.39]
Alzheimer's disease	ref	1.27 [1.06, 1.53]	1.96 [1.64, 2.35]	2.48 [1.86, 3.29]
Cognitive disturbance not demented	ref	1.19 [1.07, 1.32]	1.19 [1.05, 1.35]	1.43 [1.16, 1.76]
Mild cognitive impairment	ref	1.29 [1.17, 1.42]	1.35 [1.21, 1.50]	1.54 [1.28, 1.85]
Use of cognition-enhancing therapy	ref	1.39 [1.24, 1.55]	1.57 [1.39, 1.77]	2.25 [1.87, 2.71]

[a]Odds Ratios with 95% confidence intervals

versus those who missed zero of nine medication adherence quality measures.

As the number of CMS Star Medication Adherence quality measures missed increased, there was a stair-step increase in the percentage of patients who experienced each cognitive-related outcome [Figure 2]. For any measure of cognitive decline, 7.8% of patients who missed zero of nine medication adherence quality measures, 9.8% of patients who missed one medication adherence quality measure, 10.8% who missed 2–3 medication adherence quality measures, and 12.1% who missed ≥4 medication adherence quality measures experienced the outcome. For dementia, 2.6% of patients who missed zero of nine medication adherence quality measures, 3.6% of patients who missed one measure, 4.2% who missed 2–3 medication adherence quality measures, and 5% who missed ≥4 medication adherence quality measures experienced the outcome. For Alzheimer's disease, 0.6% of patients who missed zero of nine medication adherence quality measures, 0.8% of patients who missed one medication adherence quality measure, 1.2% who missed 2–3 measures, and 1.5% who missed ≥4 medication adherence quality measures experienced the outcome. For mild cognitive impairment, 2.3% of patients who missed zero of nine medication adherence quality measures, 3.1% of patients who missed one medication adherence quality measure, 3.1% who missed 2–3 medication adherence quality measures, and 3.5% who missed ≥4 medication adherence quality measures experienced the outcome. For the use of cognition-enhancing therapy, 1.6% of patients who missed zero of nine medication adherence quality measures, 2.3% of patients who missed one measure, 2.5% who missed 2–3 medication adherence quality measures, and 3.3% who missed ≥4 medication adherence quality measures experienced the outcome.

Discussion

We used real-world data and followed a large cohort of patients for three years to assess the achievement of nine CMS Star Medication Adherence quality measures for diabetes, hypertension (RASA), and hyperlipidemia (statins). As patients increasingly missed adherence quality measures, they experienced increased risk of incident cognitive decline, dementia, Alzheimer's disease, mild cognitive impairment, and use of cognition-enhancing therapies. These findings align with data suggesting that diabetes, hypertension, and hyperlipidemia may contribute to increased risk of cognitive decline, AD, and dementia.[6,7,36] Further, the connection between missed medications to manage these conditions and increased cognitive decline is biologically plausible. Unmanaged hypertension can have effects on the structure and function of cerebral blood vessels, which may impair brain function and promote ischemic tissue injury.[37] Hypertension disrupts the blood–brain barrier and promotes inflammation, both of which may contribute to vascular dementia and Alzheimer's disease.[6,14,38] Unmanaged diabetes may contribute to dementia through a number of pathways. The inflammation and hyperglycemia associated with the disease may lead to vascular damage and brain atrophy,[8,9] while insulin resistance may prevent the hormone from performing critical actions in brain tissue.[39] Hyperlipidemia is believed to have a direct effect on brain health through its negative impacts on the vasculature that supports the brain.[40] The compromised vasculature may in turn contribute to brain changes including microinfarcts, microhemorrhages, loss of tissue integrity, and loss of structural and functional connectivity.[41]

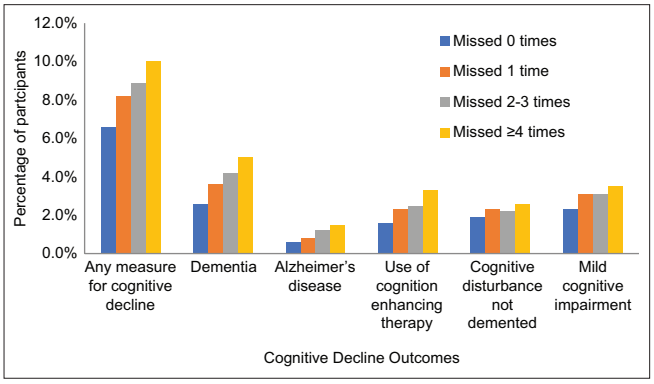

Figure 2: Cognitive Decline Outcomes across Diabetes, Statin, and RASA Medication Adherence Quality Measure categories

Causality and the directionality of the association cannot be assumed, however. Evidence suggests cognitive decline also may cause medication nonadherence.[28] Further, it is possible a patient could have early cognitive decline that is too subtle to be captured diagnostically. This preexisting, early-stage cognitive decline could be the cause of lower medication adherence, and in this scenario, medication nonadherence could be a marker of cognitive decline rather than the cause of decline. Among older individuals with atrial fibrillation, cognitive impairment was found to be a significant risk factor for poor medication adherence.[42] A systematic review noted Alzheimer's disease/dementia was associated with nonadherence among patients taking medication for dyslipidemia.[43]

Our study contributes to a better understanding of how achieving multiple quality measures over time may positively affect the odds of being diagnosed with incident cognitive decline, dementia, Alzheimer's disease, and mild cognitive impairment, and the use of cognitive-enhancing therapy. Previous work in this space has focused on one medication adherence quality measure at a time, while the current study considered all three CMS Star Medication Adherence quality measures over three years.

The study brings additional value to addressing a health issue that is of concern to many adults. An American Association of Retired Persons survey of 3,022 adults 40 and older found that 48% believe they will have dementia at some point in the future.[44] The proportion of adults aged 65 and older with dementia is 10%,[45] suggesting that concern about dementia is very high relative to the actual risk of developing the condition. Highlighting medication adherence may prove useful to the achievement of overall health goals, including healthy cognitive

aging, for patients with multiple chronic conditions. Additionally, our work may offer insights into the importance of medication adherence as a marker of cognitive decline among individuals with diabetes, hypertension, and hyperlipidemia. If nonadherence is an early indicator of cognitive decline, it offers the opportunity for deploying care management resources for affected individuals. Greater support and assistance with medication adherence may improve outcomes for affected individuals and bring needed attention to cognitively vulnerable patients.

Future research could explore the relationship between outreach efforts to groups who miss medication adherence quality measures and cognitive changes over time. Additional work considering intermediate outcomes that increase the risk of dementia also could be valuable. For example, hypertension is a known risk factor for stroke, and stroke, in turn, may contribute to cognitive decline over time.[46] Studying the relationship between medication adherence and stroke in the short-to-medium term and cognitive outcomes in the longer term could yield additional insights into the relationship between medication adherence and cognition.

Limitations

This study uses claims data that may be subject to coding errors, which may lead to underestimates of incident cognitive decline, Alzheimer's disease, and dementia. This study uses only a 1-year wash-out period in the measurement of incident cognition-related outcomes, and early stages of cognitive decline are not easily identified by ICD-10 codes. This could lead to an underestimate in the incidence of the outcome measures. The retrospective nature of the study precludes any determination of cause and effect between medication adherence and subsequent diagnosis of cognitive decline, Alzheimer's disease, and dementia. This study utilized data for Humana MAPD beneficiaries only, so the results may not be generalizable to the overall US population.

The use of claims data as the primary data source inhibits the ability to directly control for certain confounders. Cognitive decline may also be influenced by genetics, other comorbid conditions, diet, exercise, socioeconomic factors beyond dual eligibility/low-income subsidy and urbanicity, and education levels, which are unable to be captured in administrative claims or patient enrollment data. Future research should seek to integrate additional data sources to capture the full range of factors influencing cognitive decline.

Conclusions

This study used real-world data to examine the relationship between the achievement of CMS Star Medication Adherence quality measures and cognitive outcomes. As patients continued to miss medication adherence quality measures, they experienced increased risk of incident cognitive decline, dementia, Alzheimer's disease, mild cognitive impairment, and use of cognition-enhancing therapies. Retrospective data cannot prove cause and effect. However, our findings suggest that a focus on achieving medication adherence quality measures may offer an avenue for supporting better cognition-related outcomes, which may have value to patients and primary care providers. Healthcare providers may help patients improve adherence behaviors and assist with barrier mitigation strategies.

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Author contributions

Concept and design: TAB, LNC, IBP. Definition of intellectual content: TAB, SWD. Literature search: SWD, IBP. Data acquisition and statistical analysis: PNR. Analysis and interpretation of data: PNR, SWD, IBP. Manuscript preparation: SWD. Manuscript editing and manuscript review: PNR, TAB, LNC, SWD, IBP. We certify that all authors have met the ICMJE criteria for authorship as follows: 1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published.

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Conflicts of interest

PNR and IBP are salaried employees of Humana Healthcare Research and hold Humana stock earned as part of employment. SWD is a salaried employee of Humana Healthcare Research. TAB and LNC are salaried employees of Humana and hold Humana stock earned as part of employment. Humana Inc. offers Medicare Advantage health plans and participates in the CMS Star rating medication adherence quality measure program, which may be viewed as a financial conflict of interest.

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Appendix A: ICD-10 Diagnosis Codes to Identify Study Outcomes

Outcome	IDC-10 CM Diagnosis Code	Description
Alzheimer's disease	G30.x	Alzheimer's disease
Dementia	F05	Delirium due to known physiological condition
Dementia	F03.90	Unspecified dementia without behavioral disturbance
Dementia	F03.91	Unspecified dementia with behavioral disturbance
Dementia	G31.0*	Frontotemporal dementia
Dementia	G31.01	Pick's disease
Dementia	G31.09	Other frontotemporal dementia
Dementia	G31.83	Dementia with Lewy bodies
Dementia	R41.81	Age-related cognitive decline
Dementia	F02.81	Dementia in other diseases classified elsewhere with behavioral disturbance
Dementia	F02.80	Dementia in other diseases classified elsewhere without behavioral disturbance
Cognitive disturbance not demented	F06.8	Other specified mental disorders due to known physiological condition
Cognitive disturbance not demented	G31.1	Senile degeneration of the brain, not elsewhere classified
Cognitive disturbance not demented	G31.9	Degenerative disease of the nervous system, unspecified
Mild cognitive impairment	G31.84	Mild cognitive impairment, so stated