Metformin vs sulfonylurea use and risk of dementia in US veterans aged ≥ 65 years with diabetes

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ABSTRACT

Objective: To determine whether metformin is associated with a lower incidence of dementia than sulfonylureas.

Methods: This was a retrospective cohort study of US veterans ≥ 65 years of age with type 2 diabetes who were new users of metformin or a sulfonylurea and had no dementia. Follow-up began after 2 years of therapy. To account for confounding by indication, we developed a propensity score (PS) and used inverse probability of treatment weighting (IPTW) methods. Cox proportional hazards models estimated the hazard ratio (HR) of incident dementia.

Results: We identified 17,200 new users of metformin and 11,440 new users of sulfonylureas. Mean age was 73.5 years and mean HbA1c was 6.8%. Over an average follow-up of 5 years, 4,906 cases of dementia were diagnosed. Due to effect modification by age, all analyses were conducted using a piecewise model for age. Crude hazard ratio [HR] for any dementia in metformin vs sulfonylurea users was 0.67 (95% confidence interval [CI] 0.61–0.73) and 0.78 (95% CI 0.72–0.83) for those <75 years of age and ≥ 75 years of age, respectively. After PS IPTW adjustment, results remained significant in veterans <75 years of age (HR 0.89; 95% CI 0.79–0.99), but not for those ≥ 75 years of age (HR 0.96; 95% CI 0.87–1.05). A lower risk of dementia was also seen in the subset of younger veterans who had HbA1C values $\geq 7\%$ (HR 0.76; 95% CI 0.63–0.91), had good renal function (HR 0.86; 95% CI 0.76–0.97), and were white (HR 0.87; 95% CI 0.77–0.99).

Conclusions: After accounting for confounding by indication, metformin was associated with a lower risk of subsequent dementia than sulfonylurea use in veterans <75 years of age. Further work is needed to identify which patients may benefit from metformin for the prevention of dementia. *Neurology*® 2017;89:1877–1885

GLOSSARY

ADA = American Diabetes Association; **CI** = confidence interval; **eGFR** = estimating glomerular filtration rate; **HbA1c** = hemoglobin A1c; **HR** = hazard ratio; **ICD-9** = *International Classification of Diseases-9*; **IPTW** = inverse probability of treatment weighting; **MCI** = mild cognitive impairment; **PS** = propensity score; **VA** = Veterans Administration; **VaD** = vascular dementia.

Dementia is estimated to develop in 60% of individuals with diabetes.^{1,2} Diabetes can promote both cerebrovascular disease and neurodegeneration through hyperglycemia, hyperinsulinemia, increased oxidative stress, and inflammation.^{3,4} Conversely, lifestyle interventions that foster metabolic health have been shown to improve cognition.⁵ There has therefore been growing interest in understanding the role of metabolic deregulation in the pathogenesis of dementia.^{6,7} In addition to promoting healthy living, identifying drugs that can help slow or prevent dementia is of major public health importance. Oral diabetes medications have been associated with a lower incidence of dementia in some studies.^{8,9}

Metformin, a biguanide, is currently first-line therapy for diabetes.¹⁰ It suppresses hepatic gluconeogenesis, decreases insulin resistance, and increases insulin sensitivity.¹¹ Preclinical evidence suggests metformin enhances neuronal survival through multiple mechanisms, including

Editorial, page 1848

Supplemental data
at Neurology.org

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activation of the mTOR pathway and suppression of tau hyperphosphorylation and inflammation.^{12–15} Some epidemiologic studies have found an association between metformin and dementia risk,^{9,16} while others have not.^{17,18} In contrast, sulfonylureas act primarily by increasing insulin secretion,¹⁹ and have an unclear association with dementia risk.¹⁷ Thus, metformin may have more neuroprotective properties than sulfonylureas, and this difference may be detectable in carefully conducted retrospective analysis.

To explore this hypothesis, we sought to examine the association of metformin compared to sulfonylurea use with incident dementia in a large cohort of US veterans, using methods to carefully address bias and confounding. Analysis of drug effects outside randomized controlled trials must consider the influence of prevalent drug users and systematic differences in drug prescription (confounding by indication). This choice can be influenced by comorbidities, geographic region, and changing standards of care. It is especially likely in a comparison of diabetes

therapies. Renal insufficiency, which is common in patients with diabetes, is a relative contraindication for metformin.²⁰ To address the possibility of a prevalent user bias, we employed a new user study design, and to account for confounding by indication, we used propensity score methods.²¹

METHODS Study population. US veterans ≥ 65 years prescribed diabetes medications for the first time between 2001 and 2012 ($n = 432,922$) using national Veterans Administration (VA) clinical and administrative databases were included. Data were linked to Medicare to ensure full capture of comorbidities (parts A and B) and drug use (part D) outside the VA. We employed a new user design to ensure all cohort members had the same probability of receiving a single oral diabetes medication and reduce the risk of survivor and prevalent user biases.²¹ We required patients to (1) have at least 1 year of follow-up in the VA prior to first prescription (baseline) to exclude prevalent cases of diabetes and (2) be free of any diagnosis of dementia or mild cognitive impairment (MCI) prior to first prescription. Only those who remained on single diabetes therapy for 2 years following first prescription were included. During this time, patients could have been diagnosed with MCI, but were excluded if they received a diagnosis of dementia. Follow-up began after this 2-year period (index date).

Renal function is the main driver of oral diabetes therapy choice. Those missing information on renal function (either laboratory or ICD-9 code) and race (needed for estimating glomerular

Figure 1 Study scheme: Beginning with all US veterans who were ≥ 65 years of age and new users of single therapy of metformin or sulfonylureas in 2001–2012 ($n = 432,922$)

^aHad valid data for race, body mass index, renal function, and hemoglobin A1c. Those with diabetes complications were excluded. ^bDid not cross over to the other study drug and were not lost to follow-up. VA = Veterans Administration.

filtration rate [eGFR]) were excluded. In addition, those with advanced renal disease indicated by ICD-9 code or eGFR <30 mL/min/1.73 m² (calculated using the Chronic Kidney Disease Epidemiology Collaboration²² equation) were excluded, as this is a contraindication for metformin.¹⁰ A measure of diabetes severity by hemoglobin A1c (HbA1c) was also required for entry into the cohort. To focus on newly diagnosed patients with diabetes who were candidates for monotherapy, we excluded veterans with ICD-9 codes indicating diabetes with complications or HbA1c >9%. During follow-up, participants could take additional diabetes medications, but those who switched between metformin and a sulfonylurea were excluded. Entry into the cohort ended in 2012 to allow for sufficient follow-up to develop dementia.⁹ Outcomes were updated through January 2016. The final analysis cohort included 28,640 US veterans (figure 1).

Standard protocol approvals, registrations, and patient consents. We received approval and waiver of consent from the institutional review board at VA Boston for this retrospective study.

Diabetes drug use. To be included, participants had to have at least 2 outpatient prescriptions per year between baseline and

beginning of follow-up (index date). Medication lists were extracted from national VA data and manually reviewed by A.R.O. and J.A.D. Patients started on insulin were excluded as these patients were more likely to have a severe presentation of their disease and would be less comparable to users of a single oral agent. Other diabetes medications, such as thiazolidinediones, were excluded as they are unlikely to be used as initial oral monotherapy and were used at very low rates at baseline (<5%).

Dementia diagnosis. Primary outcome was diagnosis of any dementia. Secondary outcomes included AD and vascular dementia (VaD). Any dementia was defined using the following ICD-9 codes: 290.x, 291.2, 294.1, 294.11, 331.x (except 331.83 [MCI]), 333.0, 333.4, 797, 332.0, 294.8, 046.1, and 046.3. AD was defined using ICD-9 codes 331.0 and 290.0–290.3, while VaD was defined with ICD-9 codes 290.40, 290.41, 290.42, and 290.43.²³ VA records were supplemented by Medicare to capture dementia cases diagnosed outside the VA.

Covariates. Comorbidities were defined by ICD-9 code or defining medication. To identify high health care utilization, number of drug classes and visits to VA within the year prior to

Figure 2 Standardized difference percentage of covariates before and after inverse probability of treatment weighting

^aEstimated glomerular filtration rate (eGFR) by measured laboratory value or ICD-9 code. ^bTIA, stroke, cardiovascular disease. ^cMacular degeneration, glaucoma, impaired vision. BMI = body mass index; HbA1c = hemoglobin A1c; ICD-9 = *International Classification of Diseases-9*.

Table 1 Baseline characteristics of 28,640 veterans with type 2 diabetes who are new users of single diabetes therapy^a

	Metformin (n = 17,200)	Sulfonylureas (n = 11,440)	p Value
Age, y			
≥65–69	7,424 (43.2)	2,384 (20.8)	<0.001
≥70–74	4,735 (27.5)	2,998 (26.2)	
≥75–79	3,259 (19.0)	3,261 (28.5)	
≥80	1,782 (10.4)	2,797 (24.5)	
Race			
Black	1,724 (10.0)	1,111 (9.7)	0.293
White	14,929 (86.8)	9,995 (87.4)	
Other	547 (3.2)	334 (2.9)	
Male	16,986 (98.8)	11,328 (99.0)	0.038
Body mass index category, kg/m²			
Underweight: <20	65 (0.4)	63 (0.6)	<0.001
Normal: 20–25	1,519 (8.8)	1,453 (12.7)	
Overweight: 25–30	6,306 (36.7)	4,860 (42.5)	
Obese: >30	9,310 (54.1)	5,064 (44.3)	
HbA1c %			
<7	10,650 (61.9)	6,080 (53.2)	<0.001
7–8	5,545 (32.2)	4,280 (37.4)	
>8	1,005 (5.8)	1,080 (9.4)	
eGFR ^b			
≥30–45 mL/min/1.73 m²	127 (0.7)	2,444 (21.4)	<0.001
≥45–60 mL/min/1.73 m²	2,689 (15.6)	4,236 (37.0)	
≥60 mL/min/1.73 m²	14,384 (83.6)	4,760 (41.6)	
Coronary artery disease	7,801 (45.4)	6,652 (58.2)	<0.001
Heart failure	522 (3.0)	623 (5.5)	<0.001
Atrial fibrillation	2,026 (11.8)	2,054 (18.0)	<0.001
Hypertension	15,515 (90.2)	10,510 (91.9)	<0.001
Hyperlipidemia	15,487 (90.0)	9,720 (85.0)	<0.001
Peripheral artery disease	2,283 (13.3)	2,057 (18.0)	<0.001
TIA/stroke	3,047 (17.7)	2,663 (23.3)	<0.001
Eye disease ^c	4,469 (26.0)	3,135 (27.4)	0.008
Cancer	5,318 (30.9)	3,926 (34.3)	<0.001
Arthritis	5,676 (33.0)	3,577 (31.3)	0.002
Substance abuse	3,388 (19.7)	1,585 (13.9)	<0.001
Major psychiatric disease	988 (5.7)	468 (4.1)	<0.001
Number of drug classes, mean (SD)	6.76 (3.5)	7.28 (3.65)	<0.001
Number of visits prior to baseline, mean (SD)	7.9 (9.6)	7.6 (8.38)	0.023
Average year at first prescription	2008	2005	<0.001
Insurance type ^d			
VA only	4,074 (23.7)	1,707 (14.9)	<0.001
VA and Medicare	12,650 (73.6)	9,245 (80.8)	

Continued

baseline were counted. Because height and weight may not be routinely updated in this clinical database, measurements for height were within 5 years and for weight within 1.5 years. Creatinine and HbA1c values closest to baseline were chosen, with a window of 2 years before and up to 1 week after baseline. For all other variables, the value closest to baseline was taken. See appendix e-1 at *Neurology.org* for a full list of included covariates and definitions.

Statistical analysis. Baseline demographics were assessed using *t* tests for continuous variables and χ^2 tests for categorical variables. We developed a propensity score (PS) and used the inverse probability of treatment weighting (IPTW) estimation method in order to utilize the entire cohort.²⁴ The PS model included 23 variables: race, sex, body mass index, HbA1c, renal function, and comorbidities associated with both the exposure and outcome such as coronary artery disease, stroke, atrial fibrillation, heart failure, hypertension, and cancer (figure 2). To capture functional status, we included arthritis and visual comorbidity. We included geographic region of care, number of VA outpatient visits the year prior to baseline, and number of medication classes at baseline as markers of both of medical complexity and utilization of VA. Interaction terms for year of first prescription by kidney function, region, and HbA1c were included in the IPTW model to allow for changing American Diabetes Association (ADA) guidelines for prescription of metformin over time.²⁵ Year was not included as it would be directly related to cumulative dose received. The IPTW model was examined for overlap and trimmed at 20%.²⁶ See appendix e-2 for further details. Cox proportional hazards models estimated the risk of subsequent dementia. Age was used as the time to event variable.

To examine the effect of age and possible nonproportional hazards, piecewise analysis by age categories was performed. This allowed hazard ratios (HRs) to change by age group. We dichotomized age at 75 years by convention. In subgroup analyses, we explored the outcome of interest in those with normal or impaired renal function, dichotomized at eGFR <60 mL/min/1.73 m², reflecting the clinical definition of moderate chronic kidney disease; severity of HbA1c at baseline, dichotomized at 7%, reflecting current diabetes treatment guidelines; and by race.

A 2-sided *p* value <0.05 was considered statistically significant. All analyses were performed in SAS 9.2 and 9.4 (SAS Institute, Cary, NC).

RESULTS Study characteristics. Between 2001 and 2012, we identified 17,200 new users of metformin and 11,440 new users of sulfonylureas. Mean age was 73.5 ± 5.9 years and mean HbA1c was 6.8% ± 0.78. Metformin users were more likely to be younger, have better renal function, and have fewer comorbidities compared to sulfonylurea users (table 1). As expected, renal function was significantly different between the 2 groups. After using the IPTW method, all variables were balanced between the 2 groups with an absolute standard difference <10% confirming the IPTW method was appropriate for this analysis^{27,28} (figure 2).

There were significant changes in prescribing pattern over time. In 2001, sulfonylureas were used most frequently (75.2%); however, by 2012, metformin

Table 1 Continued

	Metformin (n = 17,200)	Sulfonylureas (n = 11,440)	p Value
VA and Medicaid	63 (0.4)	27 (0.2)	
VA, Medicare, and Medicaid	413 (2.4)	461 (4.0)	

Abbreviations: HbA1c = hemoglobin A1c; ICD-9 = *International Classification of Diseases-9*; VA = Veterans Administration.

^aUnless otherwise indicated, all data are n (%).

^bEstimated glomerular filtration rate (eGFR) by measured laboratory value using the Chronic Kidney Disease Epidemiology Collaboration equation²² or ICD-9 code.

^cMacular degeneration, glaucoma, impaired vision.

^dMay not add to 100% due to rounding.

was the primary oral diabetes medication (86.6%). The median year for highest sulfonylurea prescriptions was 2004 and for metformin was 2008. Further, there was a difference in prescribing patterns across the United States as the 2006 ADA guidelines,²⁵ recommending metformin as first-line oral therapy, were adopted. By 2012, in the northeast, southeast, and western United States, nearly 90% of first diabetes prescriptions were metformin, while in the central United States, metformin was the first choice 78% of the time.

Main analysis. Over 5.0 (± 3.1) years of follow-up after the index date, 4,906 cases of dementia were diagnosed; 2,177 (12.7%) in metformin users and 2,729 (23.9%) in sulfonylurea users. In addition, at index date, rates of MCI were lower in metformin users (6.8%) compared to sulfonylurea users (8.9%). Specific codes for AD were indicated in 35.2% of metformin users with dementia and 39.7% of sulfonylurea users with dementia, while VaD was specified in 11.9% metformin users with dementia and 14.6% of sulfonylurea users with dementia. This reflects the general underuse of specific dementia codes.²³

Proportional hazards assumption was tested and demonstrated significant effect modification by age ($p < 0.05$). All results are therefore presented as

a piecewise analysis by age. For those <75 years and ≥ 75 years at index date, crude HRs for dementia in metformin users compared to sulfonylurea users was 0.67 (95% confidence interval [CI] 0.61–0.73) and 0.78 (95% CI 0.72–0.83), respectively (table 2).

After accounting for confounding by indication using the IPTW method, the protective association between metformin and dementia risk was attenuated but remained significant in those <75 years (HR 0.89; 95% CI 0.79–0.99) but not in those ≥ 75 years (HR 0.96; 95% CI 0.87–1.05). The results were similar, although not significant, when we restricted the outcome to those with a diagnosis of AD or VaD (table 2). In sensitivity analysis, to ensure prevalent dementia was excluded, time to index date was extended to 4 years and results did not change.

Supplementary analyses. After IPTW adjustment, younger metformin users who at baseline had an HbA1c $\geq 7\%$ (HR 0.76; 95% CI 0.63–0.91), had good renal function (HR 0.86; 95% CI 0.76–0.97), and were white (HR 0.87; 95% CI 0.77–0.99) had a lower risk of any dementia compared to sulfonylurea users. Among those who were ≥ 75 years, there was a suggestion of metformin benefit in those with HbA1c $\geq 7\%$ (HR 0.90; 95% CI 0.79–1.04) (table 3). Examining specific diagnoses of AD or VaD within each age category revealed no significant association between metformin or sulfonylurea use after adjusting for IPTW estimation.

We examined the use of additional outpatient antidiabetic prescriptions from index date to end of follow-up: rates of insulin and thiazolidinediones were higher in sulfonylurea users (12.5%) vs metformin users (3.5%). Other antidiabetic drug prescriptions were $<2\%$ (appendix e-3). In sensitivity analysis, we excluded insulin and thiazolidinedione users ($n = 2,033$) from the main analysis and results did not change: for those <75 years, HR 0.84, 95%

Table 2 Risk of incident dementia in 28,640 veterans with type 2 diabetes who are new users of metformin compared to sulfonylureas, stratified by age

Outcome	Age category, y	Metformin (n = 17,200), events/total	Sulfonylurea (n = 11,440), events/total	Crude model		Propensity score, IPTW-adjusted	
				HR (95% CI)	p Value	HR (95% CI)	p Value
Primary outcome: any dementia	<75	889/10,437	697/4,125	0.67 (0.61–0.73)	<0.001	0.89 (0.79–0.99)	0.033
	≥ 75	1,288/6,763	2,032/7,315	0.78 (0.72–0.83)	<0.001	0.96 (0.87–1.05)	0.332
Secondary outcome: Alzheimer dementia	<75	262/10,437	225/4,125	0.73 (0.62–0.86)	<0.001	0.93 (0.76–1.14)	0.469
	≥ 75	504/6,763	858/7,315	0.74 (0.67–0.82)	<0.001	0.95 (0.82–1.10)	0.486
Secondary outcome: vascular dementia	<75	90/10,437	96/4,125	0.70 (0.53–0.92)	0.010	1.11 (0.78–1.59)	0.551
	≥ 75	169/6,763	303/7,315	0.67 (0.56–0.80)	<0.001	0.91 (0.71–1.17)	0.479

Abbreviations: CI = confidence interval; HR = hazard ratio; IPTW = inverse probability of treatment weighting.

Table 3 Subgroup analysis of the risk of any incident dementia among US veterans with type 2 diabetes who are new users of metformin compared to sulfonylureas, stratified by age

Group	Age category, y	Metformin (n = 17,200), events ^a /total		Sulfonylurea (n = 11,440), events ^a /total		Crude model		Propensity score, IPTW-adjusted	
						HR (95% CI)	p Value	HR (95% CI)	p Value
Impaired renal function (eGFR <60 mL/min/1.73 m ²)	<75	123	1,013	336	1,947	0.90 (0.74–1.10)	0.313	1.16 (0.91–1.47)	0.223
	≥75	363	1,803	1,291	4,733	0.81 (0.72–0.90)	<0.001	0.95 (0.83–1.08)	0.409
Normal renal function (eGFR ≥60 mL/min/1.73 m ²)	<75	766	9,424	361	2,178	0.66 (0.59–0.74)	<0.001	0.86 (0.76–0.97)	0.019
	≥75	925	4,960	741	2,582	0.76 (0.70–0.84)	<0.001	0.98 (0.89–1.09)	0.737
HbA1c <7%	<75	582	6,570	383	2,178	0.68 (0.61–0.77)	<0.001	0.92 (0.80–1.06)	0.264
	≥75	773	4,080	1,117	3,902	0.74 (0.68–0.81)	<0.001	0.95 (0.84–1.07)	0.419
HbA1c ≥ 7%	<75	307	3,867	314	1,947	0.65 (0.56–0.75)	<0.001	0.76 (0.63–0.91)	0.003
	≥75	515	2,683	915	3,413	0.83 (0.75–0.92)	<0.001	0.90 (0.79–1.04)	0.148
Black	<75	83	1,207	75	546	0.71 (0.53–0.95)	0.022	0.95 (0.66–1.38)	0.789
	≥75	94	517	149	565	0.77 (0.61–0.99)	0.042	0.87 (0.63–1.21)	0.417
White	<75	771	8,891	595	3,445	0.67 (0.60–0.73)	<0.001	0.87 (0.77–0.99)	0.028
	≥75	1,152	6,038	1,843	6,550	0.77 (0.71–0.82)	<0.001	0.96 (0.88–1.06)	0.454
Other	<75	35	339	27	134	0.63 (0.39–1.02)	0.062	0.77 (0.44–1.33)	0.346
	≥75	42	208	40	200	1.09 (0.73–1.63)	0.682	0.97 (0.58–1.60)	0.898

Abbreviations: CI = confidence interval; eGFR = estimated glomerular filtration rate; HbA1c = hemoglobin A1c; HR = hazard ratio; IPTW = inverse probability of treatment weighting.

^a Any dementia.

CI 0.75–0.94 ($p = 0.003$), and ≥75 years HR 0.93, 95% CI 0.85–1.02 ($p = 0.117$).

In addition, we examined the group of 8,255 individuals excluded because of missing HbA1c values. These individuals were excluded from the main analysis as reasons for missing data were unclear, likely not random, and there was evidence that they were systematically different. As a group, they were older, had their first diabetes medication prescription earlier, were more likely to be from the central United States, and had more vascular comorbidities and fewer psychiatric comorbidities. In this group, after using the IPTW method, patients <75 years who received metformin also had a lower risk of dementia compared to those who received sulfonylureas (HR 0.81; 95% CI 0.67–0.97).

DISCUSSION In this retrospective new-user study of 28,640 older veterans, we found that age substantially modified the relationship between antidiabetic drug use and dementia risk. Metformin was associated with an 11% lower risk of dementia than sulfonylureas in patients <75 years, but no difference was seen in those ≥75 years. A protective association of metformin, compared to sulfonylureas, was also seen in subsets of patients of white race, preserved renal function, and poorer diabetes control. Our findings support the hypothesis that metformin may provide more neuroprotection than sulfonylureas.

That the protective association of metformin and dementia, compared to sulfonylureas, was only present in younger patients can have a number of interpretations. Patients over age 75 years are more likely to be frail and have multiple comorbidities including cognitive impairment and microvascular disease that contribute to the risk of dementia, attenuating the drug effect. Further, treating diabetes earlier in life may allow for lifestyle modification, such as increased physical activity, which is one of the few possible preventive strategies for dementia.²⁹ The underlying mechanisms of dementia in younger and older patients differ,³⁰ and it is possible that potential benefits of metformin in reducing the risk of dementia are more effective in a younger population.

Of interest in our data was the suggestion that metformin may provide more protection of cognition in individuals with elevated baseline HbA1c. Elevated HbA1c is a marker of poor glycemic control and is correlated with an increased risk of diabetes complications, including dementia.³¹ Treatment with metformin may modify this risk. Conversely, the risk of overtreatment and hypoglycemia are also associated with dementia,³² and may contribute to the lack of benefit seen in those with a lower HbA1c.

When examining those excluded due to missing HbA1c measurement at baseline, we found that this cohort was significantly different; however, the overall

finding of a protective association between metformin and dementia remained consistent. It is possible that these individuals were not followed as closely and received different care.

Our study design and analysis are different from prior work in important ways. We focused exclusively on new users of oral diabetes medications who were without diabetes complications or advanced renal disease in order to reduce confounding and survival bias. Thus, our population can be assumed to have diabetes of shorter duration and less severity than other cohorts, making it more difficult to detect a difference between groups. The rationale for using a new-user design is illustrated by a matched study of 570 cases and 747 controls nested in the General Practice Research Database in the United Kingdom that examined the association of long-term use of diabetes medications and dementia.¹⁷ Long-term metformin use was associated with a 71% increased risk of dementia. By not using a new user design, the study did not account for prevalent user or survivor bias. Survival is a key consideration, as metformin users tended to have fewer comorbidities and live longer than sulfonylurea users, putting them at increased risk of developing dementia.

A study nested in a large population-based Taiwanese cohort used a new-user design¹⁶ to assess the risk of incident dementia in patients with new-onset diabetes taking a single oral medication. Of these, 1,033 were prescribed metformin and 796 received a sulfonylurea. The authors found no difference in dementia risk between groups. In addition to the study's small sample size, it did not address confounding by indication. We used the IPTW propensity approach to account for systematic differences in renal function between groups. Renal function is a critical clinical consideration in drug choice, as metformin is contraindicated in individuals with substantial renal impairment.^{20,33} Prior studies have included renal function in an aggregate score of comorbidities,⁹ not addressed it,¹⁷ or did not adjust for it.¹⁶

Strengths of our study include the large sample size and robust statistical methodology to account for survivor bias, prevalent user bias, and confounding by indication. There are also several limitations that must be acknowledged in the interpretation of our results. First, we relied on administrative codes from a clinical database to identify our exposure and outcomes. While we are able to validate certain outcomes, such as cancer against the VA Central Cancer Registry, it is not possible to adequately validate the definition of dementia. This may have resulted in some misclassification bias. In addition, using claims data in the VA may lead to an underrepresentation of dementia cases while Medicare codes may lead to an overrepresentation of cases.^{23,34} This is

a retrospective study, although we used statistical methods to ensure robust results. Using a population of veterans resulted in very few women in our study and may limit generalizability to the general US population. Requiring complete laboratory data may have introduced bias to our results. To address this, we separately examined those who were excluded due to missing laboratory data and found similar results. Although we used multiple statistical approaches to address confounding, residual confounding is possible due to other medications such as anticholinergics (associated with increased dementia risk) and antihypertensives (e.g., angiotensin receptor blockers associated with reduced dementia risk). In addition, it is possible that despite our including indicators of resource utilization in the propensity score, sulfonylurea users may have been followed more closely by their physicians due to their higher burden of multimorbidity, leading to ascertainment bias. We did not have information on educational level or lifestyle factors that could influence the outcome. Patients were allowed to take other diabetic and nondiabetic medications after the index date and it is unclear how these may have influenced dementia risk. However, dementia is a neurodegenerative process occurring over many years, which is why we required at least 2 years on single drug treatment before follow-up began.

Treatment with metformin has been shown to improve memory function, decrease neuroinflammation, and enhance neuronal survival in diabetic mice.³⁵ Metformin is especially attractive as possible chemoprevention and treatment for cerebrovascular disease and dementia as it is widely used, well-tolerated, and inexpensive. Perhaps the most promising evidence comes from a recent pilot study of 80 older adults (mean age 65 years) with amnesic MCI who were randomized to metformin or placebo for 12 months and demonstrated improvement in total recall.³⁶ In contrast, we did not include individuals with MCI at baseline, although there were likely many individuals with undiagnosed MCI in our cohort.

There are several ongoing trials exploring the effect of metformin on MCI (Insulin Resistance and Mild Cognitive Impairment [IRMCi] study),³⁷ biomarkers of MCI and Dementia,³⁸ and healthy aging and cognition (Metformin in Longevity [MILES] trial),³⁹ that will help shed light on the true effects of metformin on cognition. Our study suggests that stratifying by age may be important in identifying which older adults are more likely to derive benefit from metformin to lower the risk of dementia.

AUTHOR CONTRIBUTIONS

Dr. Orkaby: study concept and design, interpretation of data, drafted manuscript. Dr. Cho: study concept and design, interpretation of data, revision of manuscript for important intellectual content. Dr. Cormack:

analysis and interpretation of data, revision of manuscript for important intellectual content. Dr. Gagnon: analysis and interpretation of data, statistical supervision, revision of manuscript for important intellectual content. Dr. Driver: study concept and design, acquisition of data, interpretation of data, critical revision of manuscript for intellectual content, study supervision.

ACKNOWLEDGMENT

The authors thank the US veterans who participated in this research and Lisa Nussbaum, MA, MBA, for help with revisions.

STUDY FUNDING

This research is funded by Veterans Affairs Merit Review Award Clinical Science R&D I01CX000934-01A1 (Dr. Driver).

DISCLOSURE

The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

Received December 20, 2016. Accepted in final form August 1, 2017.

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