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Effect of metformin on neurodegenerative disease among elderly adult US veterans with type 2 diabetes mellitus

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QS and SL contributed equally.

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ABSTRACT

Objective This study aimed to evaluate the association between metformin treatment and the risk of neurodegenerative disease (ND) among elderly adults with type 2 diabetes mellitus (T2DM).

Design/Setting/Participants This retrospective longitudinal cohort study examined the effects of the length of metformin exposure on ND among elderly US veterans with T2DM and insulin treatment using the Veterans Affairs electronic medical record database.

Primary and secondary outcome measures The primary clinical outcome was defined as diagnosis of ND including dementia, Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD) and mild cognitive impairment during the follow-up period. The secondary clinical outcomes were separately measured by AD, PD, HD, dementia and mild cognitive impairment.

Result Adjusted by propensity score weight, a total of 5528 patients (mean age, 63.2±10.9 years; male, 98%; white, 60%) with a median follow-up of 5.2 years were selected. Those with ND or other mental disorders at baseline or who were on insulin for less than two-thirds of the study period were excluded. The incidence rate of ND was 11.48 per 1000 person-years among patients with metformin treatment, compared with 25.45 per 1000 person-years for those without metformin. Compared with no metformin use, 2–4 years and >4 years of metformin exposure were significantly associated with lower risk of ND (adjusted HR (aHR)=0.62, 95% CI 0.45 to 0.85; aHR=0.19, 95% CI 0.12 to 0.31, respectively), while metformin exposure in the first 2 years showed no significant influence.

Conclusion We conclude that long-term metformin therapy (>2 years) was associated with lower incidence of ND among elderly veterans with T2DM. We need to conduct a study with more representative population and more robust method for causal inferences. Further investigation into the mechanism involved is needed along with randomised trials to confirm a potential neuroprotective effect of metformin.

Strengths and limitations of this study

- ► Large longitudinal cohort was used for evaluating the association between the length of metformin exposure and neurodegenerative disease (ND) among elderly adult veterans with type 2 diabetes mellitus.
- ► Propensity score weights were applied for balancing cohort demographics, clinical characteristics and antidiabetic medications at baseline.
- ► Serum vitamin B_{12} level, which potentially influences ND, was not available in the Veterans Affairs electronic medical record (EMR) database.
- ► The study is a retrospective study using EMRs with limited ability to ascertain the medication exposure and ND outcomes.

BACKGROUND

Neurodegenerative disease (ND) is an incurable and debilitating condition that results in progressive degeneration and/or death of neurons. ND, which primarily affects the neurons in the human brain and functioning, is an umbrella term for a range of conditions including dementia, Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD) and mild cognitive impairment.

ND is highly prevalent among the elderly population, and leads to great economic burden for patients, their families and society because these patients need both extensive care and support. AD is the sixth leading cause of death in the USA. Up to 5.3 million Americans currently have AD.[1] PD, the second most common ND after AD,[2] affects about one million Americans. In 2010, 35.6 million people lived with dementia, and the number is expected to double every 20 years, reaching 65.7 million by 2030 and 115.4 million by 2050.[3] A study on the US Medicare beneficiaries in 2008 found that the adjusted prevalence of dementia was 8.24%, varying from 5.96% to 9.55% across states.[4] Additionally, costs were estimated at $157–$215 billion in 2010.[5]

Type 2 diabetes mellitus (T2DM) is found to precipitate the burden of ND by increasing the risk of all types of dementia, AD and mild cognitive impairment by about 1.5-fold.[6–15]

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The risk of PD increased by 2.2 times among patients with T2DM compared with those without T2DM.[16] Glucose metabolism and brain insulin resistance due to diabetes may also play significant roles in AD and dementia.[17–20] Growing evidence suggests that insulin resistance causes cognitive decline and increases the risk of developing dementia, while stimulation of brain insulin signalling may have a protective role against cognitive deficits.[21] Patients with AD may be impaired by insulin resistance and insulin deficiency in the brain, through adverse energy metabolism in neurons and signalling pathways that are dependent on insulin and its receptors. Furthermore, downstream effects of hyperglycaemia such as increased oxidative stress and inflammation are also involved in AD.[22 23]

Metformin is a widely used first-line drug for type 2 diabetes therapy and is generally well tolerated.[24 25] It is used in many stages of T2DM progression and in combination with sulfonylureas and other secretagogues, thiazolidinediones and insulin.[16 17] The pharmacological effect of metformin on ND is still unclear and controversial. It affects the central nervous system by crossing the blood–brain barrier,[26] yet the exact mechanism and sites of its actions remain uncertain. Several studies have reported the effect of metformin on brain functioning; however, most of the results were from in vitro and animal studies.[27–32] Population-based studies have reported the effect of metformin on brain functioning with conflicting results. One longitudinal study using a Singapore ageing population found that long-term treatment (>6 years) with metformin may reduce the risk of cognitive decline (OR=0.27, 95% CI 0.12 to 0.60).[33] The other population-based study in Taiwan showed that patients with T2DM taking metformin had lower risk of dementia than without (HR=0.76, 95% CI 0.58 to 0.98).[34] However, worse cognitive performance among patients who were on metformin than those who were not may be due to vitamin B_{12} deficiency,[35] and long-term use of metformin may be associated with a slightly increased risk of AD in those aged 65 or older.[36] These studies linking metformin and ND had several limitations, such as insufficient information on the duration of T2DM and metformin use, strength of metformin, and the inability to control the potential use of other medications and comorbidities that could be major confounding factors. The Singapore study had a relatively small sample size, and both Singapore and Taiwan studies are not representative of the US population. The conflicting results suggest that the findings of cerebral effect associated with metformin use may either be beneficial or adverse depending on

1. the study design,
2. different study populations with comorbidities,
3. subtypes or severity of ND, or
4. the duration and dosage of metformin therapy.

To our knowledge, there is no large cohort study that has examined the association between metformin use and ND longitudinally in patients with T2DM, especially among veterans in the USA. This study aimed to examine the association between the length of metformin therapy and ND, including AD, PD, HD, dementia and mild cognitive impairment, among elderly veteran adults.

METHODS

This study is a retrospective longitudinal cohort study which examines the association between the length of metformin exposure and ND among elderly veterans with T2DM (≥50 years old) using the Veterans Affairs (VA) database (2004–2010).

The index date was defined as the first date of diabetes diagnosis (International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM): 250.xx). The follow-up period started from the index date until the occurrence of ND outcomes, death or the end of available data; the baseline period looked back 12 months prior to the index date.

Data source

VA electronic medical records (EMRs) were extracted from the Veterans Integrated Services Network 16 (VISN 16) data warehouse. The data warehouse covers 445 000 veterans from VISN 16's 10 medical centres and 40 community-based outpatient clinics in the South Central region (Arkansas, Louisiana, Mississippi, Oklahoma, and parts of Alabama, Florida, Missouri and Texas), which represents about 7.8% of US veterans.

Sample selection

The study identified 150 435 patients with ≥2 diagnoses of T2DM (ICD-9: 250.x1, 250.x2) and ≥50 years old as of their first diagnosis of T2DM. There were 41 696 patients that remained after excluding those with either

1. an ND before index date,
2. a mental disorder (ICD-9-CM: 290–319),
3. drug abuse (ICD-9-CM: 304–305),
4. alcohol abuse (ICD-9-CM: 303.0–303.9),
5. a cognitive impairment due to intracranial or head injury (ICD-9-CM: 850–854, 959.01, 907.0),
6. subsequent effects of cerebrovascular disease (ICD-9-CM: 438.xx), or
7. a severe disease such as cancer (ICD-9-CM: 140–184, 186–239), AIDS (ICD-9-CM: 042), renal failure (chronic kidney disease (CKD) stage V or dialysis or end-stage renal disease (ESRD)) (ICD-9-CM: 585.5, 585.6, 285.21, 403.01, 404.02, 404.03, 584.5–584.9, 753.13) or cirrhosis (ICD-9-CM: 570, 571.0–571.3, 571.5, 572.2, 572.3, 572.4, 572.8) any time during the study period. In addition, patients who were pregnant at or after the index date (ICD-9-CM: 630–677, V22.2) were excluded from the sample. For selecting the patients with similar progression of diabetes, 6046 patients exposed to insulin for at least two-thirds of the study period were identified as the final sample.

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Outcomes and major covariates

The primary clinical outcome was defined as the first diagnosis of the overall ND, including AD (ICD-9-CM: 331.0), PD (ICD-9-CM: 332.x), HD (ICD-9-CM: 333.4), dementia (ICD-9-CM: 290.0–290.43, 294.8, 294.1) and mild cognitive impairment (ICD-9-CM: 331.83). The secondary clinical outcomes were separately measured by AD, PD, HD, dementia and cognitive impairment.

The length of metformin exposure was categorised into five levels by exposure years over the study period from the index date to the time the first clinical outcome happened, death or the end of data availability. These levels include

1. never had metformin treatment,
2. metformin treatment ≤1 year,
3. 1–2 years (including 2 years),
4. 2–4 years (including 4 years) and
5. >4 years.

The length cut-off was determined by quartiles of the length of metformin exposure distribution. Further, a binary variable for metformin treatment represented patients who had any length of metformin treatment or never had metformin treatment. The metformin average daily dosage during the entire follow-up period was calculated by metformin dosage and total prescription/refill date.

The agents in use for treatment of T2DM were identified at baseline and classified as insulin secretagogues (sulfonylurea, meglitinide and nateglinide), agents that may increase insulin sensitivity (metformin, glucagon-like peptide-1 (GLP-1) agonists, dipeptidyl peptidase 4 (DPP-4) inhibitors, amylin analogue and thiazolidinediones) and others (alpha-glucosidase inhibitors and other agents used for T2DM). Antihypertension medications include beta-blockers, ACE inhibitors, angiotensin II receptor blockers, calcium channel blockers and diuretics. Medications to treat hyperlipidaemia include statins, niacin, bile acid resins, fibric acid derivatives and cholesterol absorption inhibitors.

Microvascular complications, macrovascular complications, renal disease, tobacco use (305.1) and obesity (278.00, 278.01, V85.30–85.54) at baseline were identified by ICD-9-CM codes and controlled for in the analysis. Microvascular complications were defined as any diagnosis of neuropathy (249.5, 250.5, 362.0, 362.1, 379.23), nephropathy (249.4, 250.4, 791.0) or retinopathy (249.6, 250.6, 353.5, 356.9, 536.3, 713.5, 337.1, 357.2, 354, 355). Macrovascular complications included atherosclerosis (440), peripheral vascular disease (249.7, 250.7, 443, 447, 785.4), stroke (430–438), coronary artery disease (410–414) and congestive heart failure (398.91, 428). Renal disease was defined as diabetes with renal manifestations (250.4), other disorders of kidney and ureter (593), proteinuria (791.0), or chronic kidney disease (stage I–III) (585.1–585.4).

Statistical analysis

Demographic characteristics were described for the entire sample and comparison cohorts by mean with SD and number (n) with percentage (%). We compared the statistical differences between subcohorts of metformin use and never used metformin as well as the length of metformin exposure by one-way analysis of variance for continuous variables and χ^2 test for categorical variables.

To mitigate differences in patients' baseline characteristics across the metformin cohorts, inverse probability weight was used to estimate propensity score weights (PSW) by controlling age, gender, race, medical history (including microvascular complications, macrovascular complications, hypertension, hyperglycaemia, hyperlipidaemia, renal disease, mental disease, obesity and tobacco use) and other oral antidiabetic medications (all oral antidiabetic medications other than metformin, including insulin secretagogues, insulin sensitisers and others) at baseline period.

The incidence rates of ND were presented for the entire sample and metformin exposure subcohorts with and without PSW. Further, propensity score-weighted multivariate Cox proportional hazard model was used to estimate the HRs between metformin treatment cohorts, adjusting the average dosage of metformin and other medication use (antidiabetic medication, antihypertension medication and antidyslipidaemia medication) during follow-up and oral antidiabetic medication use at baseline. PSW-adjusted HRs (aHRs) and 95% CI were presented, as well as a two-tailed α level of 0.05 to determine statistical significance. The cohort of patients without metformin exposure was assigned as the reference group for all comparative analyses. SAS V.9.4 software was used to conduct statistical analysis.

Patients and public involvement statement

Patients or the public were not involved in this study.

RESULTS

We identified a total of 6046 patients with T2DM, with a median follow-up of 5.2 years. The mean age was 63.20±10.90 years old, 97.62% of the sample were male, and 59.97% were white (online supplementary appendix table 1). There were 2993 (49.50%) patients who never received metformin therapy during the entire follow-up period, while 932 (15.42%), 566 (9.36%), 789 (13.05%) and 766 (12.67%) patients had less than 1 year, 1–2 years, 2–4 years and more than 4 years of metformin treatment, respectively.

The prevalence of hypertension, hyperlipidaemia and renal disease in these patients at baseline was 65.88%, 44.86% and 7.43%, respectively. Of the patients, 25.44% and 32.14% had history of microvascular and macrovascular complications at baseline, respectively. Only 30.45% of patients had good glycaemic control (haemoglobin A1c ≤7%) at baseline. Between the five metformin exposure cohorts, the microvascular and macrovascular complications rates were significantly different, as well as glycaemic control (table 1). Patients who were exposed to metformin were more likely to have worse glycaemic control, less microvascular complications and more

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Table 1 PSW-adjusted patient characteristics at baseline period

	All patients		Length of metformin exposure										
			Non-metformin**		≤1 year		1–2 years		2–4 years		>4 years		
Characteristics	n	SD/%	n	SD/%	n	SD/%	n	SD/%	n	SD/%	n	SD/%	P value
Number of patients	5530		2756	49.85	849	15.35	513	9.28	710	12.84	700	12.68	
Demographic characteristics													
Age (years), mean±SD	63.24	±10.85	63.4	±11.33	62.78	±11.27	63.04	±10.03	62.8	±9.84	63.79	±9.18	0.250
Male, n (%)	5408	97.81	2693	97.70	830	97.77	502	97.77	695	97.86	688	98.23	0.944
Race, n (%)													
White	3303	59.75	1645	59.67	505	59.52	310	60.40	431	60.77	412	58.83	0.984
Black	1297	23.45	647	23.46	203	23.93	115	22.32	158	22.26	174	24.87	
Others	929	16.80	465	16.86	140	16.54	89	17.28	121	16.97	114	16.31	
History of medications													
Oral antidiabetic medication													
Insulin secretagogues	1874	33.89	780	28.31	319	37.60	186	36.19	276	38.87	313	44.60	<0.001
Others	50	0.90	30	1.08	12	1.41	2	0.31	5	0.74	1	0.19	
Antihypertension medication	5018	90.76	2508	91.00	772	90.89	470	91.54	642	90.45	626	89.39	0.694
Antilipid medication	3863	69.87	1923	69.77	591	69.67	367	71.56	498	70.14	484	69.01	0.911
Medical characteristics													
Microvascular complications	1434	25.94	715	25.95	211	24.90	139	27.16	185	26.09	183	26.10	0.926
Macrovascular complications	1737	31.42	866	31.43	267	31.49	154	29.99	229	32.26	221	31.47	0.949
Hypertension	3689	66.71	1834	66.53	561	66.11	344	66.92	471	66.32	479	68.41	0.886
Hyperglycaemia	3874	70.06	1931	70.06	595	70.07	362	70.42	500	70.45	486	69.38	0.994
Hyperlipidaemia	2460	44.49	1238	44.91	377	44.36	225	43.91	317	44.69	303	43.19	0.943
Renal disease	404	7.31	210	7.63	62	7.32	40	7.76	50	7.08	42	5.94	0.636
Mental disease	901	16.29	452	16.40	141	16.63	78	15.26	113	15.96	116	16.59	0.964
Obesity	923	16.70	465	16.85	138	16.21	84	16.40	127	17.92	110	15.66	0.821
Tobacco	562	10.17	283	10.26	91	10.77	54	10.49	74	10.44	60	8.54	0.643

*Reference group.
PSW, propensity score weight.

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Table 2 Unadjusted and PSW-adjusted number of cases by metformin exposure cohorts

	Unadjusted		Adjusted by PSW										
	Whole population		Whole population		Length of metformin exposure								
					Non-metformin*		≤1 year		1–2 years		2–4 years		>4 years		P value
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	
ND	433	7.16	396	7.15	219	7.95	78	9.14	37	7.25	45	6.28	17	2.45	<0.001
Dementia	334	5.52	312	5.63	174	6.32	49	5.77	39	7.58	34	4.70	16	2.30	0.002
PD	100	1.65	95	1.71	54	1.93	24	2.92	6	1.19	10	1.34	1	0.10	0.003
AD	71	1.17	63	1.15	31	1.13	19	2.27	5	1.01	6	0.89	2	0.28	0.006
Mild cognitive impairment	19	0.31	19	0.34	8	0.28	2	0.28	3	0.51	4	0.53	3	0.36	0.824

*Reference group.
AD, Alzheimer's disease; ND, neurodegenerative disease; PD, Parkinson's disease; PSW, propensity score weight.

Figure 1 Incidence rates of clinical outcomes by metformin exposure status. Black bar: number of cases per 1000 person-years among patients who never received metformin treatment for indicated disease. Grey bar: number of cases per 1000 person-years among patients who received any length of metformin treatment for indicated disease. ND, neurodegenerative disease.

macrovascular complications as compared with those who never used metformin.

To increase comparability across metformin exposure cohorts, PSW was applied and the PSW-adjusted patient characteristics are shown in table 1. Total weighted sample included 5530 patients, and this included 2756 (49.85%) patients in the group who had never received metformin treatment, 849 (15.35%) patients who received less than 1 year of metformin treatment, 513 (9.28%) patients who had 1–2 years of metformin, 710 (12.84%) patients who had 2–4 years of metformin, and 700 (12.68%) patients who were treated by metformin longer than 4 years. Using the PSW method, all demographic characteristics, comorbidities, chronic conditions and medications at baseline were comparable between metformin exposure cohorts, except for oral antidiabetic medication.

In table 2, we detected 433 cases of ND (7.16%): 334 cases of dementia (5.52%), 100 patients with PD (1.65%), 71 patients with AD (1.17%) and 19 cases of mild cognitive impairment (0.31%). After PSW adjustment, slight changes on the number of cases were shown (ND=396, dementia=312, PD=95, AD=63 and mild cognitive impairment=19). No HD cases were identified in this study.

The incidence rates adjusted by PSW between patients who received metformin treatment and those who did not are displayed in figure 1. In the cohort with metformin exposure, 11.48 ND cases per 1000 patients per year were found, compared with 25.45 ND cases per 1000 patients per year in the group without metformin exposure. The incidence rate of dementia was 8.46 cases and 19.82 cases per 1000 person-years in the group with and without metformin treatment, respectively. The incidence rates of PD and AD were all lower in the metformin treatment group than in the non-metformin treatment group.

In the PSW-adjusted multivariate Cox proportional hazard model (table 3), ≤1 year of metformin had insignificantly higher risk of ND (aHR=1.16, 95% CI 0.89 to 1.51), compared with the non-metformin treatment group. Also, using the non-metformin treatment group as reference, 1–2 years of metformin exposure decreased the risk but with no statistical significance (aHR=0.80,

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Table 3 PSW-adjusted HR by Cox proportional HR regression

	Length of metformin exposure							
	≤1 year vs no		1–2 years vs no		2–4 years vs no		>4 years vs no	
	aHR*	95% CI	aHR*	95% CI	aHR*	95% CI	aHR*	95% CI
ND	1.16	0.89 to 1.51	0.80	0.56 to 1.13	0.62	0.45 to 0.85	0.19	0.12 to 0.31
Dementia	0.88	0.64 to 1.21	1.02	0.72 to1.44	0.55	0.38 to 0.79	0.22	0.13 to 0.37
PD	1.51	0.93 to 2.46	0.56	0.24 to 1.31	0.59	0.29 to 1.17	0.04	0.00 to 0.37
AD	2.19	1.21 to 3.94	0.86	0.33 to 2.21	0.63	0.26 to 1.50	0.17	0.04 to 0.70
Mild cognitive impairment†	0.86	0.19 to 3.81	1.50	0.36 to 6.19	1.43	0.41 to 4.95	0.78	0.19 to 3.19

*Non-metformin treatment cohort was the reference group for adjusted HR (aHR) estimation.
†Bad estimation due to small number of events.
AD, Alzheimer's disease; ND, neurodegenerative disease; PD, Parkinson's disease; PSW, propensity score weight.

95% CI 0.56 to 1.13), while the cohorts of 2–4 years and ≥4 years of metformin exposure were both significantly associated with lower risk of ND, with aHR=0.62 (95% CI 0.45 to 0.85) and aHR=0.19 (95% CI 0.12 to 0.31), respectively.

The results of each subtype of ND in general were similar with ND. The cohorts with metformin exposure greater than 2 years had significantly lower risk of dementia. Compared with the non-metformin treatment group, the aHR was 0.55 (95% CI 0.38 to 0.79) in the cohort receiving 2–4 years of metformin treatment. In the cohort with ≥4 years of metformin exposure, the aHR decreased to 0.22 (95% CI 0.13 to 0.37). The significantly lower risk of PD was only associated with ≥4 years of metformin exposure, compared with the non-metformin treatment group (aHR=0.04, 95% CI 0.00 to 0.37). For AD, ≤1 year of metformin had significantly higher risk (aHR=2.19, 95% CI 1.21 to 3.94), while the cohort with ≥4 years of metformin exposure had significantly lower risk (aHR=0.17, 95% CI 0.04 to 0.70) (non-metformin treatment as the reference group). Due to the limited number of mild cognitive impairment cases, no statistical significance was found between metformin-exposed cohorts.

In the sensitivity analyses, metformin users who had any length of exposure were found to have significantly lower risk of ND, dementia and PD compared with the non-metformin treatment group. However, the length of metformin exposure did not show protective effects on AD and mild cognitive impairment. When length of metformin was dichotomised into two groups (greater than 2 years of metformin exposure and less than 2 years of metformin exposure), greater than 2 years of metformin exposure was associated with a significantly lower risk of developing ND, dementia, PD or AD, when compared with the patients who never used metformin. However, less than 2 years of metformin exposure did not demonstrate that potential benefit for any kind of ND (table 4).

DISCUSSION

The findings from this study contribute to the literature and provide a better understanding of the effects of long-term metformin use on ND. There have been very few large longitudinal cohort studies that have evaluated the relationship between metformin use and ND in patients with T2DM, especially among veterans in the USA.

We found that metformin treatments at both 2–4 years and more than 4 years were shown to have significant risk reduction of incidence of ND in patients with T2DM than in patients in non-metformin treatment group during the study period. Similar results were shown in the analysis on subtypes of outcome, dementia. Only more than 4 years of metformin exposure was shown to be associated with lower incidences of PD and AD. Our findings were consistent with previous studies. Wahlqvist *et al*[16] reported that metformin alone reduced the risk of PD by 60%, while the protective effect diminished if metformin was combined

Table 4 Sensitivity analysis: PSW-adjusted HR by Cox proportional HR regression

	Any length of metformin vs none		Metformin ≤2 years vs none		Metformin >2 years vs none	
	aHR*	95% CI	aHR*	95% CI	aHR*	95% CI
ND	0.69	0.57 to 0.85	1.00	0.80 to 1.26	0.39	0.29 to 0.52
Dementia	0.63	0.50 to 0.79	0.90	0.69 to 1.18	0.36	0.26 to 0.50
PD	0.63	0.41 to 0.96	1.04	0.65 to 1.65	0.30	0.15 to 0.58
AD§	1.03	0.63 to 1.69	1.71	0.99 to 2.93	0.39	0.18 to 0.85
Mild cognitive impairment	1.13	0.45 to 2.82	1.12	0.36 to 3.49	1.00	0.34 to 2.94

*Non-metformin treatment cohort was the reference group for adjusted HR (aHR) estimation.
AD, Alzheimer's disease; ND, neurodegenerative disease; PD, Parkinson's disease; PSW, propensity score weight.

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with insulin.[16] It is important to note that it is still not clear if insulin use is beneficial or harmful to ND.[22 27 37 38] One study demonstrated that intranasal insulin may be associated with reduced and improved cognitive function among patients with Apolipoprotein (APOE)-ε4 positive and APOE-ε4 negative genotype, respectively, as compared with a placebo group.[39] Some clinical studies have failed to show the improvement in cognition among patients with T2DM even after good glycaemic control,[37] while others reported insulin increased the risk of dementia up to 4.3 times when compared with those without T2DM.[40] However, the combination treatment of insulin and metformin was associated with lower risk of ND in our study. Not only when combined with insulin, metformin with sulfonylureas was found to diminish the increased risk of PD by using sulfonylureas alone.[41] Combination therapy of metformin plus rosiglitazone or glyburide significantly improved working memory in a randomised, double-blind trial consisting of 145 elderly adults with T2DM.[42]

Metformin is now established as first-line therapy for T2DM. However, it has been underprescribed in previous years with the possible reason of fear for potential risks and adverse effects, such as lactic acidosis.[41] For example, in one study, approximately 65% of newly diagnosed patients with T2DM were prescribed with metformin and the number dropped to 25% in the population with ongoing T2DM,[43] possibly due to concerns of side effects due to comorbidities.[28] In our study sample, about 50% of elderly veterans with T2DM did not have metformin treatment during the entire follow-up period. Only about 26% patients received more than 2 years of metformin medication within the mean follow-up of 4.2 years. Because our selected population with insulin treatment was not newly diagnosed with T2DM, the metformin prescription rates were consistent with the literature.

Prior studies examining the relationship between metformin treatment and ND have shown conflicting results. Nonetheless, several in vitro studies have demonstrated that metformin may help to reduce neuronal injury associated with T2DM by its ability to sensitise neuronal insulin resistance.[27–32] Gupta *et al*[38] demonstrated that treatment with metformin enhanced insulin action and prevented amyloid β generation and tau protein hyperphosphorylation.[38] Metformin normalises the reduction of cell proliferation and neuroblast differentiation in the subgranular zone of the hippocampal dentate gyrus in Zucker diabetic fatty rats.[29] It has also promoted neurogenesis and enhanced spatial memory in C57/129J mice,[30] prevented etoposide-promoted neuronal death in association with the emergence of oxidative stress,[31] reduced oxidative stress in the brain of Goto-Kakizaki rats, a model of non-obese T2DM,[32] and improved oxygen-glucose deprivation-induced neuronal injury.[44] The protective effects were supported by several population-based studies such as the Singapore ageing study[33] and a population-based study in Taiwan.[34] These concur with our results, but beyond the findings on dementia and cognitive impairment in the Singapore and Taiwan studies, our study also found that metformin associated with low risk of ND, AD and PD.

Whether the findings of cerebral effects associated with metformin use are beneficial or adverse depends on study design, lack of sufficient information on comorbidities, treatment information, relatively small sample size and short follow-up time. Our longitudinal cohort study carefully selected samples and generated the comparison cohorts. The time-varying treatment was converted to the length of treatment on metformin to avoid biased results.[45] For instance, CKD is considered a major contraindication of metformin prescription, as there were no significant differences of history of CKD across metformin exposure subgroups at baseline after PSW. The VA EMR database in the USA is unique in its large longitudinal sample size and availability of extensive outpatient, inpatient and pharmacy data as well as mortality information. Integrated health systems have their advantages in regard to the measurement of length of metformin exposure and long-term outcomes and mortality. We examined the length of metformin exposure and its influence on the occurrence of ND. To the best of our knowledge, no study has examined the length of metformin exposure and used it as a major influential factor for ND in a cohort such as ours. Additionally, when controlling confounders in the regression model, we also applied PSW to ensure the cohorts were comparable at baseline. The other medications for T2DM and dosage of metformin at follow-up period were also taken into account in the regression model.

CONCLUSIONS

We conclude that long-term metformin therapy, longer than 2 years of metformin exposure, was associated with lower incidence of ND and the subtype outcome of dementia among elderly veterans with T2DM. Similar risk reduction occurred in PD and AD but associated with longer (>4 years) metformin treatment. Such protective benefit cannot be duplicated to other subtype diseases, like mild cognitive impairment, most likely due to the limited number of events. We need to conduct a study with more representative population using more robust method for causal inferences. Further investigation into the mechanism involved is needed along with randomised trials to confirm a potential neuroprotective effect of metformin.

Limitations

Our study has multiple limitations. As a retrospective study, unobserved heterogeneity may exist. The numbers of events for some subtype diseases may be too small to detect statistical significance. Additionally, more than 90% of patients in our sample are male. Thus, the results may be hard to generalise to both genders. To avoid potential bias due to lacking T2DM duration in our data, we selected long-term insulin users as our target population (who were on insulin for more than two-thirds over the entire study period), and balanced the medical history and medication use at baseline.

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Furthermore, pharmacy data were only available within the VA health system. Prescriptions outside the VA and over-the-counter (OTC) drugs were unable to be captured. Vitamin B supplements are administered OTC and it was difficult for us to assess the intake of vitamin B_{12}. Because vitamin B_{12} levels are not a regularly ordered lab test for the diabetes population and serum vitamin B_{12} levels were not available in our analysis, vitamin B_{12} level changes were not estimated. However, patients receiving long-term metformin treatment were more likely to take vitamin B_{12} supplement as the deficiency is easily corrected. Loss of follow-up may lead to selection bias, although the selected sample was continuously followed for more than 5 years in median. Last, our study design aimed to test the association between length of metformin treatment and risk of ND by converting the time-varying variable to the length of treatment over the follow-up period, while inverse probability of treatment weighting in marginal structural model may be an alternative modelling to address time-varying treatment and confounders.[45] Therefore, a large-scale, prospective cohort study may be needed to confirm the relationship and establish a more definitive conclusion about the causality between metformin exposure and incidence of ND.

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