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Oral diabetes medication and risk of dementia in elderly patients with type 2 diabetes

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ABSTRACT

Aim: To examine the effect of oral diabetes medication on the risk of dementia in an elderly cohort with type 2 diabetes.

Methods: This was a population-based cohort study using the Korean National Health Insurance claims data from 2002 to 2013. Elderly subjects (60 years of age or older) with and without type 2 diabetes were included; patients with new-onset type 2 diabetes were further divided into the oral diabetes medication group and no-medication group.

Results: Among 278,290 patients with type 2 diabetes, 56,587 developed dementia (20.3%) over 11 years of follow-up. Type 2 diabetes was associated with a 1.69-fold increased risk of dementia (95% CI 1.66–1.72). Among patients with newly diagnosed type 2 diabetes, the risk of dementia was lower in the oral diabetes medication group than in the no-medication group (adjusted hazard ratio [aHR], 0.79; 95% CI 0.77–0.81). Lower risk of dementia was particularly noticeable in all of the combination therapy groups and especially lower in the combination therapy group treated with dipeptidyl peptidase 4 inhibitor (aHR 0.48, 95% CI 0.45–0.51).

Conclusion: Overall, the use of oral diabetes medication in type 2 diabetes patients significantly decreased the risk of dementia.

1. Introduction

A remarkable increase in life expectancy and population aging is continuing globally. Diabetes is among the leading chronic disease worldwide that causes disabilities and death. The global prevalence of diabetes among adults over 18 years of age has risen from 4.7% in 1980 to 8.5% in 2014 [1]. According to the Centers for Disease Control and Prevention, type 2 diabetes makes up more than 90% of all diagnosed cases of diabetes in adults [2]. Diabetes prevalence is projected to increase by 4.5-fold in elderly population, over the age of 65 years, compared to 3-fold increase in the total population, between 2005 and 2050 [3].

Diabetes is a strong risk factor for dementia [4–8]. Yet, only a few studies have been performed to elucidate the impact of oral diabetes agents (ODAs) on dementia, with inconsistent

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findings [9–12]. Studies dealing with elderly subjects are particularly scarce. Several mechanisms have been proposed for the association between diabetes and dementia, such as insulin resistance, inflammation, oxidative stress, and formation of advanced glycation end products [13–16]. The pathology of glucose metabolism suggest that disruption of an insulin-related mechanism can lead to brain insulin resistance. This is called "brain diabetes" which, theoretically, can be alleviated by ODAs because they efficiently regulate blood glucose, modulate glucose sensitivity, and improve insulin resistance [6]. Given that aging is a common risk factor for both type 2 diabetes and dementia, it is crucial to clarify the effect of different ODAs on the development of dementia in elderly population.

In this study, we conducted a population-based analysis of an elderly cohort to investigate whether the use of ODAs can decrease the risk of dementia in type 2 diabetes patients. We also examined the incidence of dementia in relation to the duration of diabetes.

2. Methods

2.1. Data sources

Data were obtained from the Korean National Health Insurance Service Database (NHIS) from January 1, 2002, to December 31, 2013. NHIS contains medical claims data for more than 90% of the total population in Korea. This database contains individual beneficiary information, as well as healthcare service information including diagnosis, procedures, and prescriptions. These reports contain information on the diagnosis that has been coded in accordance with the International Classification of Diseases, Tenth Revision [ICD-10]. Data on elderly subjects used for this study contains stratified random samples of claims data; the size of the samples was calculated and extracted to improve representativeness of the socio-demographic characteristics, diagnosis, and healthcare services including prescription drugs. The elderly cohort of 558,147 participants was randomly selected from the general population of 5.5 million people and followed for 11 years until 2013 unless a participant died or emigrated.

2.2. Ethical approval

Medical claims data from NHIS are available for public access. Data are encrypted to protect personal information and are provided with anonymous identification numbers. This study was approved by the Institutional Review Board of Chungbuk National University (CBNU-201703-ETC-425-01).

2.3. Study population

We identified elderly subjects aged 60 or older with one or more outpatient claims from 2002 to 2013. Then we considered patients who had one or more outpatient claims for type 2 diabetes as a case group using the ICD-10 code E11. The entry date was set as the date of the first outpatient visit regardless of diabetes, and the index date was defined by the first visit with type 2 diabetes. We excluded patients with a diagnosis of type 1 diabetes (E10), malnutrition-related diabetes mellitus (E12), and other specified diabetes mellitus (E13) from the control group to avoid potential confounding from other types of diabetes. To investigate the association of diabetes medication and dementia, newly diagnosed type 2 diabetes patients were identified by excluding patients with claims data during 1 year prior to the index date. ODA group was defined by the presence of oral diabetes agent within one year of onset of diabetes whereas non-ODA group included patients without the history of ODA. Those who had ever received treatment with diabetes medication including sulfonylureas, meglitinides, alpha-glucosidase inhibitors, thiazolidinediones, biguanide, and dipeptidyl peptidase 4 (DPP4) inhibitors and who had at least two outpatient visits were defined as the ODA group. The control (no-medication) group was comprised of type 2 diabetes patients without ODA prescription. We collected records for these six different classes of ODAs; the monotherapy group included patients who were treated with one drug and the combination therapy group those who were prescribed more than one ODA. Combination therapy included both simultaneous and serial treatment with ODAs.

2.4. Measures and variables

The main outcome measure was the incidence of dementia. Subjects were observed until the diagnosis of dementia, National Health Insurance program withdrawal, death, or the end of the study period (December 31, 2013). Follow-up time was the period from index date (first diagnosis of type 2 diabetes) to the end date. Diabetes duration was defined as the period from the first diagnosis of type 2 diabetes to the last type 2 diabetes–related visit. The development of dementia was defined as the appearance of the respective ICD-10 code (Alzheimer's dementia: F00; vascular dementia: F01; dementia in other diseases classified elsewhere: F02; unspecified dementia: F03; Alzheimer's disease: G30) between the index date and the last date of observation. Subjects with a history of dementia prior to the index date were excluded.

Patient demographics including age, sex, comorbidities, and ODAs were collected. Comorbidities included hypertension (ICD-10 code: I10-I13), stroke (I60-I69), dyslipidemia (E78), and ischemic heart disease (I20-I25). Charlson comorbidities index (CCI) [17], duration of type 2 diabetes, and follow-up time were also considered as covariates. The CCI was calculated using claims prior to the date of dementia onset.

2.5. Statistical analysis

The chi-square test was performed for categorical variables and a two-sample t-test was performed for continuous variables to evaluate the difference in dementia development between the ODA and control groups. The follow-up time was calculated from the date of first diagnosis of type 2 diabetes to the date of the end of the study. We used the chi-square test to compare the rate of dementia in the ODA and control groups in relation to the duration of diabetes (i.e., less than 2 years, 3–4 years, 5–6 years, 7–8 years, more than 8 years). The Cox proportional hazards regression model

was used to measure the effect of ODAs on dementia, adjusted for covariates. All data analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) and statistical significance was inferred at a two-sided p-value of <0.05.

3. Results

We identified 92,723 patients (16.6%) with dementia between 2002 and 2013 among 558,147 elderly subjects. There were 278,290 type 2 diabetes patients without dementia before the index date. The incidence of dementia was higher in type 2 diabetes patients than in those without diabetes ($p < 0.0001$, n = 56,587 and 36,136, respectively). Odds ratio for dementia was 1.69 (95% CI, 1.66–1.72) after adjusting for age, sex, CCI, and comorbidities.

To clarify the relationship between dementia and ODAs, we considered only newly diagnosed type 2 diabetes patients to disregard the influence of diabetes as such on the incidence of dementia. Of the 278,290 patients with type 2 diabetes, 118,976 were newly diagnosed patients and 44,148 patients had at least two outpatient claims of ODAs (Fig. 1). The mean age of newly diagnosed subjects at diagnosis was 71.7 ± 6.2 years, and 59.7% of the study population were women. The majority had hypertension (68.1%) and dyslipidemia (76.8%), 15.7% had history of stroke and 20.2% had ischemic heart disease. Patients diagnosed with dementia were older (73.4 ± 6.5 vs. 71.3 ± 6.1, $p < 0.0001$), showed higher CCI scores (4.7 ± 2.9 vs. 4.5 ± 2.9, $p < 0.0001$), and had more frequent comorbidities than subjects without dementia except dyslipidemia (Table 1).

The overall incidence of dementia in the ODA group during 5.3 years of follow-up was 8603, whereas 16,317 subjects developed dementia during 3.8 years of follow-up in the control group. Considering the difference in the follow-up periods, the overall risk of developing dementia was lower in the ODA group than in the control group (crude HR: 0.66; 95% CI: 0.64–0.68). The lower risk of dementia in the ODA group than in the control group was consistent among different types of dementia (Alzheimer's dementia, vascular dementia, and other dementias). After adjusting for sex, age, CCI score, and comorbidities, we observed a slight increase in aHR than in crude HR, and found a consistently reduced risk of dementia (overall and each type) in ODA users (Table 2).

To examine the differences between different types of ODAs in relation to the risk of dementia, we examined the medication history in the ODA group. In the monotherapy groups, sulfonylurea was prescribed the most, followed by metformin. In general, the risk of dementia tended to be lower in combination therapy groups than in monotherapy groups. In an unadjusted model, we found that all combination therapy groups had lower risk of dementia compared with the control group. The DPP4 inhibitor combination group had 52% lower risk of dementia when compared with the control group ($p < 0.0001$) (Table 3).

To further examine the association of dementia with ODA combination therapy, we performed subgroup analyses in

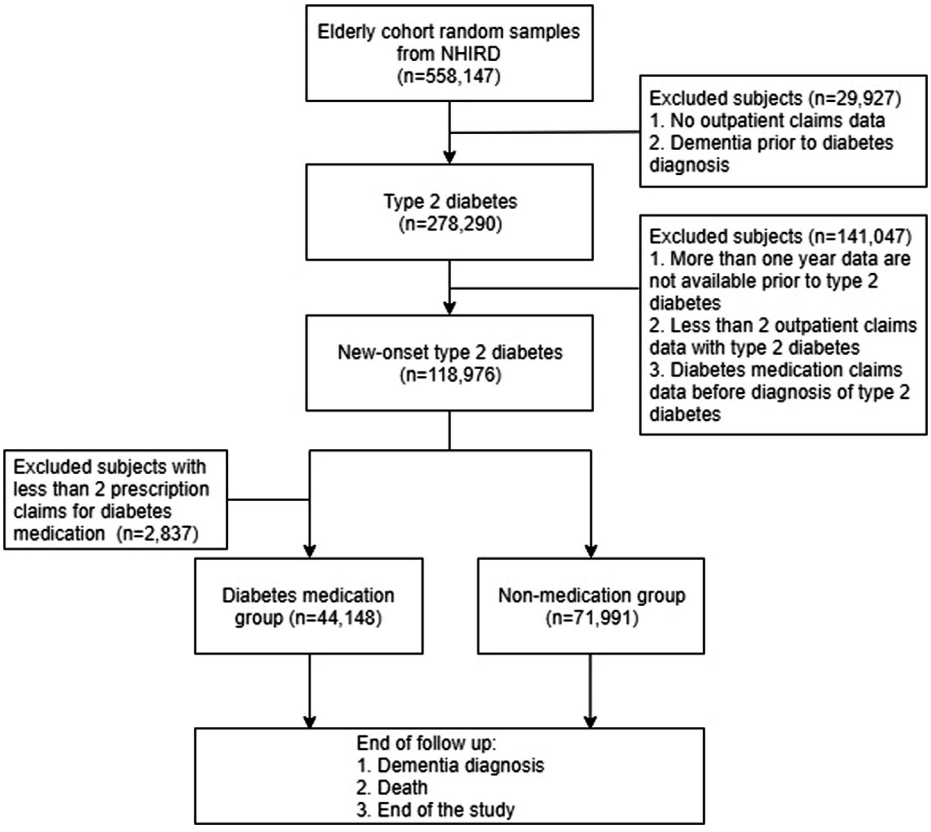

Fig. 1 – Flow chart of patient selection.

Table 1 – Correlation of baseline characteristics with incidence of dementia in subjects with newly diagnosed type 2 diabetes mellitus.

	Dementia (n = 24,920)	No dementia (n = 91,219)
Sex, n (%)		
Male	8406 (33.73)	38,361 (42.05)
Female	16,514 (66.27)	52,858 (57.95)
Age, years, mean ± SD	73.4 ± 6.5	73.37 ± 6.54
Age, n (%)		
60–69	7728 (31.01)	39,210 (42.98)
70–79	12,718 (51.04)	42,691 (46.80)
80–89	4166 (16.72)	8751 (9.59)
90 or older	308 (16.72)	567 (0.62)
Charlson Comorbidity Index, mean ± SD	3.4 ± 2.6	4.71 ± 2.87
Hypertension, n (%)		
Yes	17,525 (70.33)	61,612 (67.54)
No	7395 (29.67)	29,607 (32.46)
Stroke, n (%)		
Yes	5974 (23.97)	12,274 (13.46)
No	18,946 (76.03)	78,945 (86.54)
Ischemic heart disease, n (%)		
Yes	5255 (21.09)	18,171 (19.92)
No	19,665 (78.91)	73,048 (80.08)
Dyslipidemia, n (%)		
Yes	17,998 (72.22)	71,253 (78.11)
No	6922 (27.78)	19,966 (21.89)

combination groups that consisted of more than a thousand patients. The risk of dementia was significantly lower in combination of sulfonylurea plus metformin when compared to sulfonylurea alone (aHR: 0.73; 95% CI, 0.67–0.79), but the risk was higher in metformin plus sulfonylurea group when metformin monotherapy was a reference group (aHR 1.18, 95% CI, 1.09–1.28). In metformin sub-analysis, most of the statistically significance were shown as increased risk of dementia except for three-drug combination of metformin, sulfonylurea, and DPP4 inhibitor (Table S1). Sulfonylurea and DPP4 inhibitor combination showed lowest risk of dementia when sulfonylurea alone was a reference group (aHR 0.36, 95% CI, 0.20, 0.65). Three-drug combination therapy in the group treated with metformin, sulfonylurea, and DPP 4 inhibitor was associated with decreased risk of dementia in both metformin and sulfonylurea subgroup analyses (aHR 0.61 and 0.37, 95% CI, 0.53–0.68 and 0.33–0.42, respectively) (Table S1 and S2). Combination therapy with sulfonylurea, glucosidase inhibitor, and metformin was associated with a decreased risk of dementia in comparison with sulfonylurea monotherapy (aHR 0.80, 95% CI, 0.74–0.87) (Table S2).

We analyzed the effect of the duration of type 2 diabetes on the risk of dementia in newly diagnosed type 2 diabetes patients. In both the ODA and control groups, the prevalence of dementia increased significantly in proportion to the duration of diabetes for up to 8 years, but the difference was not statistically significant after 9 years of diabetes. The ODA group had a lower rate of developing dementia than the control group when diabetes lasted less than 8 years (Fig. 2).

4. Discussion

This population-based elderly-cohort study found that patients with type 2 diabetes have a 1.7-fold increased overall risk of dementia. Treatment with ODAs decreased the risk of dementia and this association remained strong and consistent after adjusting for potential confounding factors. In subgroup analysis, the risk of dementia was significantly lower in a group with three-drug combination therapy with metformin, sulfonylurea, and DPP4 inhibitor. However, combination therapies with metformin showed increased the risk of dementia in comparison with metformin monotherapy. Furthermore, the use of ODAs delayed the onset of dementia in comparison with no treatment.

A meta-analysis found the global prevalence of dementia from all causes to be between 5% and 7% in adults aged 60 or older [18]. According to the Korean Dementia Observatory 2017, the prevalence of dementia in the elderly (65 years and older) was 9.8% [19]. We found a somewhat higher rate of dementia (12%). Previous studies reported 1.5–2.5 fold higher risk of dementia in the elderly with type 2 diabetes when compared with patients without type 2 diabetes [20,21]. Our data confirmed the association between type 2 diabetes and increased risk of dementia.

Whether diabetes treatment might increase the risk of dementia is controversial. This possibility has been raised for metformin, which has been shown to increase the β-amyloid peptide level by up-regulating β-secretase transcription in neurons [10]. Another study, which used a large-scale case-control design, demonstrated an increased risk of

Table 2 – Dementia risk according to oral diabetes medication use.

	Oral diabetes medication use	Follow-up period, years, mean ± SD	Incidence of dementia, n	Crude HR (95% CI)	Adjusted HR (95% CI)[a]
Dementia, overall	Yes	5.3 ± 2.8	8603	0.66 (0.64, 0.68)	0.79 (0.77, 0.81)
	No	3.8 ± 2.8	16,317	1	1
Alzheimer's dementia	Yes	5.4 ± 2.8	5687	0.67 (0.64, 0.69)	0.80 (0.77, 0.83)
	No	3.9 ± 2.8	10,677	1	1
Vascular dementia	Yes	4.8 ± 2.7	2506	0.68 (0.64, 0.71)	0.78 (0.75, 0.82)
	No	3.5 ± 2.6	4755	1	1
Other types of dementia	Yes	4.9 ± 2.7	4205	0.65 (0.62, 0.67)	0.78 (0.75, 0.81)
	No	3.5 ± 2.7	8317	1	1

HR: hazard ratio.

[a] Adjusted for age, sex, comorbidities, and Charlson comorbidities index.

Table 3 – Risk of dementia by oral diabetes medication.

Medication	Incidence of dementia, n	Crude HR (95% CI)	Adjusted HR (95% CI) [a]
Sulfonylurea			
Monotherapy	1,96	1.11 (1.05, 1.18)**	1.08 (1.02, 1.15)*
Combination therapy	5809	0.77 (0.71, 0.82)***	0.77 (0.75, 0.80)***
Meglitinide			
Monotherapy	46	0.98 (0.73, 1.30)	0.93 (0.70, 1.25)
Combination therapy	826	0.69 (0.64, 0.74)***	0.87 (0.81, 0.93)***
Glucosidase inhibitor			
Monotherapy	131	1.05 (0.88, 1.24)	1.02 (0.86, 1.21)
Combination therapy	2517	0.65 (0.63, 0.68)***	0.83 (0.79, 0.86)***
Biguanide			
Monotherapy	849	0.58 (0.54, 0.62)***	0.67 (0.63, 0.72)***
Combination therapy	5849	0.60 (0.58, 0.62)***	0.75 (0.73, 0.77)***
Thiazolidinedione			
Monotherapy	38	0.76 (0.55, 1.05)	0.76 (0.55, 1.04)
Combination therapy	1225	0.61 (0.57, 0.64)***	0.82 (0.77, 0.87)***
Dipeptidyl peptidase 4 inhibitor			
Monotherapy	4	0.29 (0.11, 0.77)*	0.31 (0.12, 0.82)*
Combination therapy	1183	0.35 (0.33, 0.37)***	0.48 (0.45, 0.51)***

HR: hazard ratio.
[a] Adjusted for age, sex, comorbidities, and Charlson comorbidities index.
* $P < 0.05$.
** $P < 0.001$.
*** $P < 0.0001$.

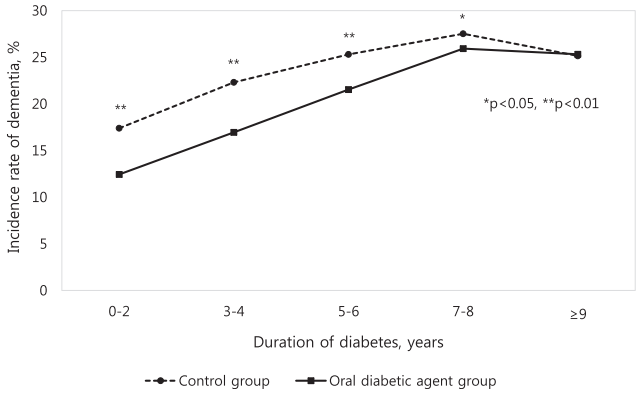

Fig. 2 – Incidence of dementia by diabetes duration (*p < 0.05, **p < 0.01).

dementia with metformin use [22]. However, several other human studies have shown that metformin and sulfonylurea use can decrease the risk of dementia in comparison with the absence of treatment [11,23]. In a study by Hsu et al., the risk of dementia was reduced from 1.77 to 1.49 in the combined-medication group taking both metformin and sulfonylurea compared to monotherapy with metformin or sulfonylurea [11]. In our study, sub-analyses were conducted using monotherapy groups as a reference to focus on various combinations of ODAs in order to evaluate association with add-on ODAs. Our finding that sulfonylurea and metformin combination reduced the risk of dementia in comparison with sulfonylurea treatment alone is consistent with the study by Hsu et al. [11]. Three-drug combinations also lowered the risk of dementia when sulfonylurea and metformin were used together with thiazolidinedione or DPP4 inhibitor. However, sulfonylurea and thiazolidinedione combination therapy increased the risk of dementia in comparison with sulfonylurea monotherapy. These results cannot be explained in mechanism. While studies dealing with three-drug combination therapy are rare, a higher relative rate of dementia has been reported in thiazolidinedione users than in those taking metformin [21]. The inconsistencies between previous studies and our results may partially be attributed to different numbers of patients and criteria for inclusion or exclusion of subjects, which include race, age, comorbidities, concurrent use of medication, severity of diabetes etc. In the initial design of our study, patients with newly diagnosed type 2 diabetes were selected so that the effect of insulin resistance would not be significant.

Sub-analyses of two-drug or three-drug combinations with metformin have not shown statistical significance except in the metformin, sulfonylurea, and DPP4 inhibitor combination. This could be due to the fact that we used metformin monotherapy as a reference and metformin monotherapy itself showed a statistically significant link with dementia (Table 3). This is in contrast to the previous concerns that metformin use increases the risk of dementia; we found no significant difference in the risk of dementia between combination therapy with metformin and metformin monotherapy. Sub-analyses with thiazolidinedione or DPP4 inhibitor showed no statistical significance in the incidence of dementia, which could be due to the limited number of users in each group. While the number of reported combined medication studies is limited, our study analyzed a combination of three

drugs in a large number of patients. In the real clinical environment, the number of patients undergoing multidrug therapy is higher than that of patients taking only one ODA. Therefore, the strength of our research is that it reflects reality better than the previous studies.

The risk of dementia appeared to be proportionate to the duration of diabetes in the present study. The rate of dementia in patients with less than 8 years of diabetes was significantly lower in the ODA group than in the control group, suggesting a protective effect of ODA against dementia. Also, earlier use of ODAs was shown to delay the onset of dementia, but not after 8 years of diabetes. Not receiving an appropriate treatment despite a long period of type 2 diabetes can be risky by itself, resulting in various complications. A study done in Mexican Americans reported that antidiabetic medications prevented the decline in physical and cognitive functions better in patients who had diabetes for more than 5 years than in those who had it for 2–5 years [24]. This discrepancy does not solely rely on the mechanism of ODA action, but rather reflects the diversity of patient populations and complexity of diabetes.

Positive effects of ODAs on cognitive function have been hypothesized, with possible mechanisms including glucose control, insulin sensitizing, anti-inflammatory effects, lowering beta-amyloid deposition, and beneficial effects on cerebrovascular dysfunction, mitochondrial biogenesis, and anti-oxidative enzymes [25–30]. It is not known whether the beneficial effect of ODAs on dementia involves diabetes control or other mechanisms. Various ODAs work via different mechanisms and even when stated the mechanisms are not completely understood. It is therefore challenging to correlate the underlying mechanisms of ODA action with dementia, but apparent epidemiologic findings of our study could be an important guide in understanding the possible benefit or risk of ODAs in terms of dementia.

Several limitations need to be addressed. First, this study relied on a diagnostic code and prescription records to define the patients' disease and medication taken. Therefore, assumptions were made regardless of patients' actual condition. To reduce this heterogeneity, patients with two or more ODA prescription records were defined as those taking medication, and patients who had never been prescribed an ODA medication were defined as the non-medication group. Moreover, patients with type 2 diabetes who had two or more outpatient claims were included, and only those who had no history of diabetes for more than 365 days before the first diagnosis of type 2 diabetes were selected as new-onset type 2 diabetes patients. In this way, the reliability of the results on association between type 2 diabetes duration and dementia could be improved. But, the prevalence of T2DM could be overestimated as we defined diabetes by one or more outpatient claims. Another limitation was that data such as concurrent medications, blood pressure, blood sugar, and smoking and drinking habits could not be considered. Nonetheless, the strengths of our study include a large-scale population with representative sample cohort. A relatively long follow-up period (11 years) is another strong point.

We have confirmed that dementia incidence in type 2 diabetes patients was significantly higher than those without diabetes. Our results revealed the likelihood of lowering the risk of dementia in patients taking more than one diabetes medication, especially in three-drug combination. Although the exact mechanism remains unclear and is probably multifactorial, our findings raise interesting possibilities about the role of ODAs used in combination in mitigating the risk of dementia. Further research is warranted to clarify such association between specific ODA combinations and risk of dementia in patients with type 2 diabetes.

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Declaration of Competing Interest

No potential conflicts of interest relevant to this article were reported.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2019.07.004.

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