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Association of antidiabetic medication use, cognitive decline, and risk of cognitive impairment in older people with type 2 diabetes: results from the population-based Mayo Clinic Study of Aging

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Abstract

Objective: To determine the cross-sectional and longitudinal associations between diabetes treatment type and cognitive outcomes among type II diabetics.

Methods: We examined the association between metformin use, as compared to other diabetic treatment (i.e., insulin, other oral medications, and diet/exercise) and cognitive test performance and mild cognitive impairment (MCI) diagnosis among 508 cognitively unimpaired at baseline type II diabetics enrolled in the Mayo Clinic Study of Aging. We created propensity scores to adjust for treatment effects. We used multivariate linear and logistic regression models to investigate the cross-sectional association between treatment type and cognitive test z-scores, respectively. Mixed effects models and competing risks regression models were used to determine the longitudinal association between treatment type and change in cognitive test z-scores and risk of developing incident MCI.

Results: In linear regression analyses adjusted for age, sex, education, body mass index, APOE ε4, insulin treatment, medical comorbidities, number of medications, duration of diabetes, and propensity score, we did not observe an association between metformin use and cognitive test performance. Additionally, we did not observe an association between metformin use and cognitive test performance over time (median=3.7 years follow-up). Metformin was associated with an increased risk of MCI (subhazard ratio (SHR) = 2.75; 95% CI = 1.64, 4.63, $p<0.001$). Similarly, other oral medication (SHR = 1.96; 95% CI = 1.19, 3.25; $p = 0.009$) and insulin (SHR = 3.17; 95% CI = 1.27, 7.92; $p = 0.014$) use were also associated with risk of MCI diagnosis.

Conclusions: These findings suggest that metformin use, as compared to management of diabetes with other treatments, is not associated with cognitive test performance. However, metformin was associated with incident MCI diagnosis.

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Keywords

cognition; type II diabetes; metformin

Introduction

Type II diabetes (T2D) is a recognized risk factor for poor cognitive outcomes, including cognitive decline, mild cognitive impairment (MCI), and dementia.[1, 2] It has been estimated that, 175,000 Alzheimer's disease (AD) cases in the United States could be attributable to T2D.[3] Approximately one-quarter of older adults are diabetic, and an additional 50% are pre-diabetic (i.e., the prodromal stage to T2D).[4] Both the American College of Physicians[5] and the American Diabetes Association[6] recommend metformin as the first line pharmaceutical treatment for T2D and pre-diabetes; thus, it is the most commonly prescribed medication for management of T2D. Given the high prevalence of T2D, it is becoming increasingly important to better understand the association between T2D and cognitive outcomes. Moreover, as T2D is diagnosed earlier in the lifecourse and its management becomes increasingly chronic, it is critical to determine whether T2D treatments impact cognitive outcomes.

It has been suggested that metformin, although associated with lowering of body weight and improvement of metabolic control, may also be associated with cognitive impairment.[7] Evidence from animal models suggests that metformin is associated with worse cognition and dementia-related pathology,[8, 9] though other studies have shown opposite associations.[10, 11] In humans, the available evidence for adverse effects of metformin in type II diabetics is limited. Among 126 diabetics, metformin users (n = 35) showed greater risk of cognitive impairment compared to non-users.[12] In contrast, one study in a small sample of metformin users (n = 23) found use was associated slower rates of decline on tests of verbal learning, working memory, and executive function over a period of four years.[13] Similarly, in a longitudinal study of 204 metformin users, long-term metformin use was associated with a reduced odds of cognitive impairment, as compared to non-users (n = 161).[14] However, these studies have suffered from small sample sizes and/or poor categorization of predictors, outcomes, mediators, and confounders.

In the present study, we investigated the cross-sectional and longitudinal associations between baseline diabetes treatment and cognitive outcomes among prevalent T2D cases enrolled in the population-based Mayo Clinic Study of Aging (MCSA). We compared diabetics using metformin to diabetics using other treatments (diet/exercise, other oral medications, and insulin). After taking into account glycemic control, we hypothesized that metformin use would be associated with poorer cognitive test performance.

Methods

Participants

The MCSA is a prospective population-based study originally designed to characterize the incidence and prevalence of MCI in Olmsted County, Minnesota.[15] In 2004, Olmsted

County residents between the ages of 70 and 89 were identified for recruitment using an age- and sex-stratified random sampling design to ensure that men and women were equally represented in each 10-year age strata. The study was expanded to include those aged 50 years and older in 2012. The present study included 508 cognitively unimpaired at baseline participants with T2D, aged 50 years and older, who had complete cognitive assessments. The study protocols were approved by the Mayo Clinic and Olmsted Medical Center Institutional Review Boards. All participants provided written informed consent.

Participant Assessment

MCSA follow-up visits after the baseline visit were scheduled to occur approximately every 15 months. Each visit included a physician examination, an interview by a study coordinator, and neuropsychological testing by a psychometrist.[15] The physician examination included a medical history review, complete neurological examination, and administration of the Short Test of Mental Status.[16] The study coordinator interview included collecting demographic information, medical history, and questions about memory to both the participant and an informant using the Clinical Dementia Rating (CDR) scale.[17]

The neuropsychological battery included nine tests covering four domains: 1) memory (Auditory Verbal Learning Test Delayed Recall Trial[18]; Wechsler Memory Scale-Revised Logical Memory II & Visual Reproduction II)[19]; 2) language (Boston Naming Test[20] and Category Fluency[21]; 3) attention (Trail Making Test B[22] and WAIS-R Digit Symbol subtest[23]; and 4) visuospatial (WAIS-R Picture Completion and Block Design subtests).[23] We calculated sample-specific z-scores for all cognitive tests, and created domain scores by averaging the z-scores within each domain. We created a global cognitive score using the z-transformation of the average of the four domains.

Cognitive status determination

For each participant, cognitive performance in each domain was compared with the age-adjusted scores of individuals previously obtained using Mayo's Older American Normative Studies.[24–26] This approach relies on prior normative work and extensive experience with the measurement of cognitive abilities in an independent sample of subjects from the same population. Participants with scores approximately 1 standard deviation or more below the age-specific mean in the general population were considered for a diagnosis of possible MCI. At each visit, the final decision to diagnose MCI was based on a consensus agreement between the study coordinator, examining physician, and neuropsychologist who evaluated the participant, after taking into account education, prior occupation, visual or hearing deficits, and reviewing all other participant clinical information.[27] Individuals who performed in the normal cognitive range and did not meet criteria for MCI or dementia, which was diagnosed using DSM-IV criteria,[28] were deemed clinically unimpaired (CU).

Diabetes, diabetes treatment, and HbA1C determination

At enrollment a diagnosis and date of onset of T2D was determined for all MCSA participants via medical record abstraction by a nurse using the medical records-linkage system of the Rochester Epidemiology Project.[15, 29, 30] Medical record abstraction was also used to determine diabetes treatment and glycated hemoglobin (HbA1C) levels at baseline.

Baseline diabetes treatment was categorized into four categories for the purposes of this study: metformin only, insulin only, other oral agents (i.e., glipizide, glimepiride, glyburide, pioglitazone, rosiglitazone, repaglinide, glucagon, precise, sitagliptin, exenatide, liraglutide, canagliflozin, saxagliptin, rosiglitazone maleate, liraglutide) only, and diet and exercise only. We excluded participants who used combination therapy (e.g., insulin plus oral) to specifically investigate the association of each type of treatment with cognition.

Assessment of covariates

Demographic variables (e.g., age, sex, and education) were collected by self-report during the in-clinic exam. Participants' height (cm), weight (kg), waist (cm), and hip (cm) circumference were measured during the in-clinic exam, and used to calculate body mass index (BMI) (kg/m^2). Medical conditions, diabetes complications, diabetes duration, age of diagnosis, and the Charlson comorbidity index (CCI)[31] were determined for each participant by medical record abstraction. Depressive symptoms were assessed using the Beck Depression Inventory (BDI)[32]; participants with a score of ≥13 were considered to have clinical depression.[33] Participants' blood samples collected in-clinic were used to determine APOE genotype.

Statistical analyses

We used Kruskal–Wallis equality-of-populations rank test to examine participant characteristics by baseline treatment group. To make pairwise comparisons between treatment groups, we used Dunn's test for continuous variables and Fisher's exact test for dichotomous variables. We then developed propensity scores to account for differences in diabetes treatment use. Propensity scores were created using logistic models. Specifically, we estimated treatment effects from the available data by computing the average of the difference between the observed and potential effects for each subject in both groups. Propensity score estimations included age, sex, BMI, APOE ε4, CCI score, number of medications, duration of diabetes, diabetes complications, and HbA1C.

We utilized multivariate linear and logistic regression models to determine the cross-sectional association between diabetes treatment and cognitive test performance or MCI diagnosis. Models were adjusted for age, sex, education, BMI, APOE ε4, CCI score, number of medications, duration of diabetes, age of T2D diagnosis, diabetes complications, and the propensity score.

To determine the association between metformin use and change in cognitive test performance, we utilized mixed effects models only including participants who had one or more follow-up visits. Models were adjusted for age, sex, education, BMI, APOE ε4, CCI score, number of medications, duration of diabetes, and the propensity score. Each model additionally included time (indicating change in cognitive test performance over follow-up) and an interaction term of treatment type and time (indicating change in cognitive test performance over follow-up as a function of baseline treatment type) as covariates. We specified a random intercept and slope, and used an unstructured covariance matrix. We additionally used competing risks regression models with age as the time scale and adjusted for sex, education, BMI, APOE ε4, CCI score, number of medications, duration of diabetes,

diabetes complications, and the propensity score, to determine the association between treatment type and risk of MCI. Patients that progressed directly to dementia were excluded from analyses. Using graphical methods, we determined that proportional hazard assumptions were not violated. All statistical analyses were completed with Stata version 13.0 (StataCorp, College Station, TX).

Results

Type II diabetic participants varied based on treatment by age, CCI score, number of medications, cognitive impairment status, duration of T2D, age of T2D diagnosis, T2D complications, death and loss to follow-up, and memory, visuospatial and global z-scores (Table 1). Pairwise comparisons between treatment groups are detailed in Table 1. Cross-sectionally, there was no association between metformin use or any other diabetes treatment and global or domain-specific cognitive performance in multivariate models (Table 2).

In mixed effects models, we did not observe any cross-sectional association between diabetes treatment type and cognitive test performance, echoing findings from our linear regression models (Table 3). However, longitudinally, insulin use was associated with declining memory (B=−0.16, 95% CI −0.25, −0.07), attention (B=−0.11, 95% CI −0.20, −0.02), and global (B=−0.13, 95% CI −0.21, −0.05) z-scores over time. There were no statistically significant associations between metformin use and change in cognitive test performance.

In competing risk regression models, we found diabetes treatment was associated with incident MCI diagnosis. Of the 503 participants included in the analysis, 120 developed MCI and 51 died during follow-up over a maximum of 12.34 years of follow-up (median=3.6, interquartile range 1.5, 5.3). Metformin was associated with an increased risk of MCI (subhazard ratio (SHR) = 2.75; 95% CI = 1.64, 4.63, $p<0.001$). Similarly, other oral medication (SHR = 1.96; 95% CI = 1.19, 3.25; $p = 0.009$) and insulin (SHR = 3.17; 95% CI = 1.27, 7.92; $p = 0.014$) use were also associated with risk of MCI diagnosis.

Sensitivity analyses

We additionally investigated whether adjusting for chronic kidney disease altered the association between treatment type and cognitive outcomes, but found it did not. We further used interaction terms to investigate whether sex, CCI score, APOE ε4 genotype, diabetes duration (<8 vs. ≥8 years), or HbA1c (<6.4 or ≥6.4), were effect modifiers, but found no evidence that they were. Finally, we conducted analyses excluding those who switched from metformin use at baseline to another type of treatment during follow-up, but found this did not substantially alter the results.

Finally, we compared type II diabetics using combination therapy to the participants included in the study, who used only one type of treatment. At baseline, participants using combination therapy differed from the participants in the study on the following variables: BMI, Charlson comorbidity index, number of medications, myocardial infarction, HbA1c, duration of diabetes, diabetes complications, and memory z-score.

Discussion

In the present study of 508 older type II diabetics, we did not observe a cross-sectional or longitudinal association between metformin use and cognitive test performance. However, metformin, but not other oral medications or insulin, was associated with greater risk of MCI diagnosis over follow-up. We did not find any evidence of effect modification by sex, CCI score, APOE ε4 genotype, duration of diabetes, or HbA1c.

Metformin acts by activating 5' adenosine monophosphate-activated protein kinase (AMPK), which in turn impacts vitamin B12 levels. Overactivation of AMPK is associated with increased Alzheimer's-related pathology (phosphorylated tau, dendritic spine loss), but inhibiting AMPK protects against Alzheimer's pathology (amyloid-beta).[34] AMPK is regulated by tumor necrosis factor-α and adiponectin. Past findings suggest that there is an association between higher adiponectin and worse neurocognitive outcomes.[35] Therefore, future research needs to better understand the relationship between metformin use in T2D and neuroimaging and cognitive outcomes considering these mediating pathways. Findings will have clinical implications for treatment and management of T2D. Indeed, it has been suggested that clinicians regularly test B12 levels of type II diabetic patients in order to manage this potential risk [36]. This is particularly pertinent as T2D is developed earlier in the lifecourse and management becomes increasingly chronic.

Evidence from animal models suggests that metformin use is associated with cognition and dementia-related neuropathology, but the direction of the findings has been inconclusive. In a mouse model of neurodegeneration, treatment with metformin, as compared to treatment with donepezil, was associated with hippocampal neuron generation and better spatial memory performance.[10] Additionally, in adult male Wistar rats, metformin treatment was associated with better cognitive test performance and reduced inflammation and oxidative stress, which may have implications for reductions in tau phosphorylation.[11] Contrastingly, in a model of older mice those treated with metformin, as compared to controls, showed reduced neurotrophic factors and impaired visuospatial ability.[8] In a model of older mice, metformin treatment did not improve blood glucose or body weight and was associated with poorer visuospatial outcomes.[9] There is some suggestion that the differences observed in animal models may be due to age differences.

Past studies examining the association between metformin use and cognitive outcomes have shown mixed effects. In a sample of 211 diabetics aged 65 to 69 at baseline, the association of treatment (diet, oral hypoglycemic agents, insulin) with cognitive function was investigated over a period of four years. Participants who used only metformin ($n = 23$) showed significant protective effect on tests of verbal learning, working memory, and executive function.[13] Similarly, in a longitudinal study of 204 metformin users, long-term metformin use (>6 years) was associated with a reduced odds of cognitive impairment, measured with the Mini Mental Status Examination (MMSE) as compared to non-users ($n = 161$).[14] In contrast, among 126 diabetics, metformin users ($n = 35$) showed greater risk of cognitive impairment, assessed with the MMSE, compared to non-users.[12] However, among those who used calcium supplements, this association was no longer significant, which suggests that the association was mediated by vitamin B12 levels. With perhaps the

exception of the study by Ng and colleagues, past studies have used smaller sample sizes than the present study. Additionally, studies such as those by Moore et al. and Ng et al. used less sensitive measures (i.e., MMSE) of cognitive impairment than were used in the present study. Moreover, although Moore and colleagues considered whether B12 and calcium levels impacted the association, the present study investigated several potential effect modifiers compared to past studies. Our findings suggest that metformin use, or indeed use of other diabetic treatments, is not strongly associated with cognitive test performance but is associated with incident cognitive impairment.

The association between metformin and cognition may be mediated by B12 levels or inflammatory response. Higher metformin dosages are associated with decreases in serum vitamin B12 levels.[37] Reduced B12 levels have been associated with risk of cognitive impairment[38], and evidence suggests that B12 supplementation may be associated with improved cognitive outcomes.[39] Indeed, it has been suggested that clinicians regularly test B12 levels of type II diabetics in order to manage this potential risk.[38] This is particularly pertinent as T2D is developed earlier in the lifecourse and management becomes increasingly chronic. Additionally, evidence from animal models suggests that metformin can decrease inflammatory responses in relation to cognition.[40, 41] To address this, future studies could consider whether pro-inflammatory markers may confound, mediate, or modify the association between diabetes treatment type and cognitive outcomes.

This study has multiple strengths, including an extensively phenotyped, large, population-based sample of diabetics, multiple measures of cognitive outcomes, a thorough investigation of potential confounders and effect modifiers, and a longitudinal design. Still, limitations must also be considered. First, although we attempted to address differences in treatment groups through use of propensity scores and adjustment of covariates, there still may be fundamental differences in treatment groups that cannot be corrected with statistical methods. Additionally, we were not able to consider the mediating effects of vitamin B12 and pro-inflammatory markers. Vitamin B12 has not been measured in the MCSA, and pro-inflammatory levels are available in only a small subset of type II diabetic participants. Examining the potential biological mechanisms linking metformin and neuroimaging and cognitive outcomes in large cohort studies will be critical to understanding the link between treatment and outcomes. Finally, individuals who consent to participation in the MCSA tend to be healthier than individuals who are not, thus potentially introducing bias. However, because the MCSA uses a population-based sampling frame, this is less of a concern.

Finally, in this study we examined only prevalent cases of T2D and were not able to account for duration or dose of metformin. Although we were able to adjust for duration of T2D, future research should further examine whether there is a difference between treatment and cognitive outcomes based on prevalent versus incident diabetes cases. Additionally, past evidence has suggested that decreases in serum B12 levels are dependent on dose of metformin.[37] Similarly, duration of metformin use may be associated cognitive outcomes.[14] Therefore, studies should consider these components of metformin use when investigating the association between metformin treatment and cognitive outcomes in type II diabetics.

The already high and increasing prevalence of T2D means understanding the link between T2D and cognitive outcomes is critical. If this association is affected by diabetes treatment, this could have implications for clinical guidelines. Additional larger scale longitudinal studies are needed. Future research should work to understand if and how this association may be moderated by vitamin B12, and whether dose or duration of metformin use impacts the associations.

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Key points:

1. Metformin use in type II diabetics was not associated with cognitive test performance.
2. No other treatments were associated with cognitive test performance in type II diabetics.
3. Metformin is associated with incident MCI.

Table 1.

Baseline characteristics of type II diabetics, median (IQR) or *n* (%)

	T2DM (N=508)	Diet/Exercise (N=130)	Metformin (N=200)	Other Oral (N=162)	Insulin Only (N=16)	p
Age [a, d, e]	74.6 (70.7, 80.5)	76.9 (71.9, 81.3)	72.1 (67.2, 75.7)	76.9 (72.6, 82.7)	75.6 (72.3, 81.5)	<0.001
Male	302 (59.5)	73 (56.2)	129 (64.5)	91 (56.2)	9 (56.3)	0.472
Education	14 (12, 16)	13 (12, 16)	14 (12, 16)	13.5 (12, 16)	14 (12.5, 15)	0.441
APOE ε4	130 (25.6)	39 (30.0)	54 (27.0)	34 (21.0)	3 (18.8)	0.546
BMI	30.2 (27.0, 34.2)	29.9 (26.8, 33.1)	30.4 (27.5, 34.3)	30.1 (26.8, 34.6)	30.0 (27.5, 34.5)	0.513
Depression (BDI>13) [a, b, e, f]	43 (8.6)	17 (13.4)	12 (6.1)	11 (6.9)	3 (20.0)	0.013
CCI [b-f]	4 (2, 6)	3 (2, 5)	4 (2, 5)	5 (3, 7)	6 (4, 9)	<0.001
Number of medications [a, b]	8 (6, 11)	7.5 (5, 10)	9 (7, 12)	8 (6, 10)	9 (6.5, 11)	0.012
Hypertension	459 (90.4)	117 (90.0)	178 (89.0)	150 (92.6)	14 (87.5)	0.941
Stroke	25 (4.9)	7 (5.4)	7 (3.5)	10 (6.2)	1 (6.3)	0.975
CABG	49 (9.7)	12 (9.2)	19 (9.5)	16 (6.9)	2 (12.5)	0.997
MI	108 (21.3)	21 (16.2)	41 (20.5)	41 (25.3)	5 (31.3)	0.508
HbA1C [a-e]	6.3 (5.8, 6.8)	5.9 (5.6, 6.1)	6.5 (6.1, 7.2)	6.4 (5.9, 6.9)	6.2 (5.9, 6.9)	<0.001
Duration of T2D (years) [a-d]	6.6 (3.5, 10.7)	3.4 (1.6, 7.7)	7.8 (5.2, 12.2)	6.4 (3.6, 10.9)	10.6 (2.4, 29.2)	<0.001
Age of T2D diagnosis [a-d, f]	66.6 (60.3, 72.9)	71.0 (65.3, 77.0)	62.8 (55.9, 66.7)	69.7 (63.2, 74.6)	62.6 (51.2, 71.7)	<0.001
T2D complications [a-c]	185 (36.4)	25 (19.2)	80 (40)	71 (43.8)	9 (56.3)	<0.001
Died [b-f]	85 (16.7)	18 (13.8)	22 (11.0)	38 (23.5)	7 (43.8)	<0.001
Withdrew [d]	197 (38.8)	54 (41.5)	70 (35.0)	67 (41.3)	6 (37.5)	0.044
Z-scored memory [a, d]	−0.08 (−0.77, 0.68)	−0.25 (−0.92, 0.52)	0.12 (−0.61, 0.81)	−0.17 (−0.88, 0.52)	−0.01 (−0.83, 0.72)	0.005
Z-scored attention	0.10 (−0.52, 0.71)	0.05 (−0.60, 0.68)	0.20 (−0.46, 0.78)	0.02 (−0.61, 0.72)	0.06 (−0.90, 0.30)	0.324
Z-scored language	0.05 (−0.58, 0.67)	0.04 (−0.54, 0.60)	0.17 (−0.47, 0.68)	−0.15 (−0.80, 0.67)	−0.008 (−0.83, 0.52)	0.163
Z-scored visuospatial [d]	0.04 (−0.69, 0.72)	0.07 (−0.71, 0.68)	0.18 (−0.58, 0.86)	−0.16 (−0.81, 0.47)	0.38 (−0.67, 0.72)	0.036
Z-scored global [a, d]	0.004 (−0.62, 0.64)	−0.02 (−0.62, 0.57)	0.19 (−0.47, 0.86)	−0.16 (−0.83, 0.43)	0.14 (−0.61, 0.66)	0.009
Follow-up time	3.7 (1.8, 5.4)	3.7 (1.7, 5.3)	3.6 (1.7, 5.3)	3.8 (1.8, 5.4)	4.0 (2.6, 6.6)	0.251

BMI, body mass index; WHR, waist-to-hip ratio; BDI, Beck Depression Inventory; CABG, coronary artery bypass grafting; CCI, Charlson comorbidity index; MCI, mild cognitive impairment; MI, myocardial infarction.

[a]Diet/exercise different from metformin

[b]Diet/exercise different from other oral different

[c]Diet exercise different from insulin

[d]Other oral different from metformin

[e] Insulin different from metformin

[f] Insulin different from other oral

Table 2.

Cross-sectional association between treatment and neurocognitive outcomes among T2DM at baseline by treatment

Cognitive	N	B (95% CI)	p
Memory	501		
Diet/exercise		Reference	
Metformin		0.14 (−0.08, 0.35)	0.207
Other oral		0.18 (−0.03, 0.40)	0.094
Insulin		0.19 (−0.27, 0.66)	0.417
Attention	488		
Diet/exercise		Reference	
Metformin		−0.08 (−0.28, 0.13)	0.461
Other oral		0.04 (−0.16, 0.25)	0.682
Insulin		−0.03 (−0.51, 0.45)	0.901
Language	489		
Diet/exercise		Reference	
Metformin		−0.06 (−0.29, 0.16)	0.587
Other oral		−0.02 (−0.25, 0.21)	0.859
Insulin		−0.02 (−0.52, 0.47)	0.921
Visuospatial	487		
Diet/exercise		Reference	
Metformin		−0.09 (−0.32, 0.14)	0.424
Other oral		−0.12 (−0.35, 0.10)	0.287
Insulin		0.26 (−0.24, 0.77)	0.306
Global	477		
Diet/exercise		Reference	
Metformin		−0.01 (−0.21, 0.19)	0.922
Other oral		0.03 (−0.17, 0.23)	0.786
Insulin		0.24 (−0.22, 0.70)	0.305

Model adjusted for age, sex, education, BMI, APOE ε4, CCI, number of medications, T2D duration, age of T2D diagnosis, T2D complications, and propensity score

Table 3.

Longitudinal association between diabetes treatment and cognitive test performance by treatment group

	Memory (N=444)		Attention (N=434)		Language (N=437)		Visuospatial (N=436)		Global (N=430)	
	B (95% CI)	**p**	**B (95% CI)**	**p**	**B (95% CI)**	**p**	**B (95% CI)**	**p**	**B (95% CI)**	**p**
Diet/exercise	Reference		Reference		Reference		Reference		Reference	
Metformin										
Metformin	0.16 (−0.05, 0.37)	0.130	−0.04 (−0.24, 0.16)	0.676	−0.06 (−0.27, 0.15)	0.586	−0.11 (−0.32, 0.10)	0.319	0.009 (−0.19, 0.20)	0.926
Metformin*Time	0.01 (−0.03, 0.05)	0.525	0.01 (−0.02, 0.05)	0.523	0.01 (−0.02, 0.05)	0.488	0.02 (−0.007, 0.05)	0.144	0.02 (−0.02, 0.05)	0.315
Other oral										
Other oral	0.13 (−0.08, 0.34)	0.219	0.01 (−0.19, 0.21)	0.920	−0.06 (−0.27, 0.15)	0.586	−0.05 (−0.26, 0.17)	0.666	0.01 (−0.18, 0.21)	0.893
Other oral*Time	−0.008 (−0.05, 0.03)	0.683	−0.002 (−0.04, 0.03)	0.915	0.01 (−0.02, 0.05)	0.489	0.01 (−0.02, 0.04)	0.436	0.01 (−0.02, 0.04)	0.544
Insulin										
Insulin	0.10 (−0.05, 0.009)	0.673	0.07 (−0.42, 0.57)	0.770	−0.10 (−0.60, 0.39)	0.690	0.03 (−0.48, 0.55)	0.897	0.17 (−0.32, 0.66)	0.502
Insulin*Time	−0.16 (−0.25, −0.07)	<0.001	−0.11 (−0.20, −0.02)	0.016	−0.06 (−0.14, 0.02)	0.141	−0.07 (−0.13, 0.0002)	0.051	−0.13 (−0.21, −0.05)	0.002

Model adjusted for age, sex, education, BMI, APOE ε4, CCI, number of medications, T2D duration, age of T2D diagnosis, T2D complications, and propensity score.

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