Metformin Use Is Associated With Slowed Cognitive Decline and Reduced Incident Dementia in Older Adults With Type 2 Diabetes: The Sydney Memory and Ageing Study

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OBJECTIVE

Type 2 diabetes (diabetes) is characterized by accelerated cognitive decline and higher dementia risk. Controversy exists regarding the impact of metformin, which is associated with both increased and decreased dementia rates. The objective of this study was to determine the association of metformin use with incident dementia and cognitive decline over 6 years in participants with diabetes compared with those not receiving metformin and those without diabetes.

RESEARCH DESIGN AND METHODS

A prospective observational study was conducted of $N = 1{,}037$ community-dwelling older participants without dementia aged 70–90 years at baseline (the Sydney Memory and Ageing Study). Exclusion criteria were dementia, major neurological or psychiatric disease, or progressive malignancy. Neuropsychological testing measured cognitive function every 2 years; a battery of tests measured executive function, memory, attention/speed, language, and visuospatial function individually. These were used to determine the measure of global cognition. Incident dementia was ascertained by a multidisciplinary panel. Total brain, hippocampal, and parahippocampal volumes were measured by MRI at baseline and 2 years ($n = 526$). Data were analyzed by linear mixed modeling, including the covariates of age, sex, education, BMI, heart disease, hypertension, stroke, smoking, and apolipoprotein Eε4 carriage.

RESULTS

Of $n = 1{,}037$, 123 had diabetes; 67 received metformin (DM+MF) and were demographically similar to those who did not (DM-noMF) and participants without diabetes (no-DM). DM+MF had significantly slower global cognition and executive function decline compared with DM-noMF. Incident dementia was significantly higher in DM-noMF compared with DM+MF (odds ratio 5.29 [95% CI 1.17–23.88]; $P = 0.05$).

CONCLUSIONS

Older people with diabetes receiving metformin have slower cognitive decline and lower dementia risk. Large randomized studies in people with and without diabetes will determine whether these associations can be attributed to metformin.

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Dementia is a devastating diagnosis for many of those affected, their families, and caregivers and substantially impacts society and medical and care services. Dementia statistics are sobering: most recent estimates show ~47 million people affected worldwide, with a doubling expected over the next 20 years (1). Type 2 diabetes (diabetes) is associated with increased risk of cognitive deficit and dementia (2–8). Midlife hypertension, obesity, and smoking increase risk of dementia by 30–65% (9–11); however, a staggering 60% of people with type 2 diabetes develop dementia (5,8). Cognitive dysfunction is considered an important comorbidity of diabetes, reflecting metabolic disease, cardiovascular disease, and frequently shared risk factors (2). Observational studies have shown that diabetes and its precedents of insulin resistance and obesity are strongly associated with Alzheimer disease (AD) (4). This has enormous implications in nations with both a rapidly ageing population and increasing rates of both obesity and diabetes. Cognitive decline affects the person with diabetes in multiple arenas of self-care, including discerning better foods, judging medication adjustments, operating equipment, and polypharmacy, in addition to the critical maintenance of financial and social independence.

Diabetes is postulated to promote dementia through accelerated cerebrovascular and neurodegenerative pathways via hyperglycemia, hyperinsulinemia, increased oxidative stress and inflammation (12), and cerebrovascular mechanisms. Further, insulin resistance and hyperinsulinemia may affect the pathogenesis of AD directly (13), with evidence of their influence on amyloid-β–related mechanisms and brain amyloid clearance (13).

Medications used to treat diabetes have been implicated in blunting the rate of cognitive decline, with some studies supporting beneficial associations with metformin (14–17), dipeptidyl peptidase 4 inhibitors (15), glucagon-like peptide 1 agonists (15), sodium–glucose cotransporter 2 inhibitors (15), and sulfonylureas (16,17), but not thiazolidinediones (17).

Epidemiological studies have mostly found that metformin was associated with lower dementia risk (14,16), better cognitive function (18), and lower incident dementia rates (14), with a recent meta-analysis reporting that metformin was associated with lower prevalence of cognitive impairment and dementia incidence (19). Two pilot randomized controlled trials have reported benefits of metformin on cognition (20,21). Few studies, however, have controlled for significant covariates that also contribute to dementia risk, including apolipoprotein E (APOE) genotype. Further, longer-term prospective studies examining associations among metformin use, diabetes, and brain volumes in the elderly incorporating control subjects and comprehensive covariate measures of dementia risk factors are lacking.

The main aim of this study was to test the hypotheses that, in older people with diabetes, metformin use is associated with lower levels of *1*) cognitive decline and *2*) incident dementia over 6 years. Secondary aims were to compare the above effects to those present in those without diabetes and also to examine the effects of diabetes and metformin use on changes in brain volume over 2 years. We interrogated the Sydney Memory and Ageing Study that has comprehensively measured cognitive function biennially over 6 years and brain volumes over 2 years.

RESEARCH DESIGN AND METHODS

Participants

The Sydney Memory and Ageing Study is a longitudinal population-derived cohort of 1,037 adults aged 70–90 years at baseline who were recruited through the compulsory electoral roll. Exclusion criteria were: insufficient English to complete assessments, a diagnosis of dementia, major neurological or psychiatric disease, progressive malignancy, and a baseline adjusted Mini-Mental State Examination score <24. The study was approved by the University of New South Wales and South Eastern Sydney Local Health District Human Research Ethics Committees (Sydney, New South Wales, Australia). Participants gave written informed consent. Patients or the public were not involved in the design, conduct, reporting, or dissemination plans of our research, as it was not possible or appropriate.

Data were collected every 2 years on 4 occasions over a 6-year period. Participants underwent a detailed standardized interview, recording all medical conditions, sociodemographic factors, years of education, and use of mobility aids. Non-English–speaking background (NESB) was defined as English literacy acquired after 9 years of age (22).

The presence of specific forms of atherothrombotic cardiac disease (acute myocardial infarction, angina, and cardiac failure), cerebrovascular disease (stroke and transient ischemic attack [TIA]), and hypertension were recorded in a detailed standardized medical history interview. Ascertainment required these diagnoses to have been made by a medical practitioner. The presence of type 2 diabetes (diabetes) was ascertained by self-reported diagnosis by a medical practitioner, report of glucose-lowering medications, or detection of a fasting glucose level >7.0 mmol/L. Weight and height were measured and BMI calculated (weight in kilograms/height in meters squared). Blood pressure was measured in the recumbent position after at least 5-min rest.

Ascertainment of Metformin Exposure

All medications, durations of use, and dosage were recorded, which included the ascertainment of use of metformin at baseline. Participants were classified into the following groups: *1*) participants with diabetes receiving metformin (DM+MF), *2*) participants with diabetes not receiving metformin (DM-noMF), and *3*) participants without diabetes (no-DM).

Neuropsychological Measures

Standardized neuropsychological tests were administered by trained psychology graduates, examining five cognitive domains, described in detail elsewhere (22–24). Memory was evaluated by the Rey Auditory Verbal Learning Test (25), the Logical Memory Story A (26) (delayed recall), and the Benton Visual Retention Test recognition (27); processing speed by the Wechsler Adult Intelligence Scale-III Digit-Symbol-Coding (28) and the Trail Making Test Part A (29); language by the Category Fluency Test (Animals) (30) and the Boston Naming Test (30-item version) (31); visuospatial ability by Block Design from the Wechsler Adult Intelligence Scale-Revised (32); and executive function by the Letter Fluency Test (33) and the Trail Making Test Part B (29).

Raw scores on each test were converted to *z* scores, based on the means and SDs of a normal-cognition English-speaking background reference group derived from the baseline cohort (N = 504); this reference group specifically

excluded those with mild cognitive impairment. Domain scores were calculated by first averaging the *z* scores of component tests of a particular domain and then standardizing by converting these composite scores to *z* scores using their means and SDs within the baseline reference group, as described (24). Global cognition was obtained by averaging the domain scores and then transforming this composite into a *z* score using its mean and SD in the baseline reference group.

Dementia diagnosis was based on a multidisciplinary consensus panel consisting of psychiatrists of old age, neuropsychiatrists, and neuropsychologists using established DSM-IV (34)/DSM-5 (35) criteria for dementia conducted at each wave.

Laboratory Measures

Blood was collected after a 10-h overnight fast. Assay measurements were as follows: plasma glucose was measured by the glucose oxidase method (Beckman Coulter, Fullerton, CA). Total cholesterol, HDL cholesterol, triglycerides, and uric acid levels were measured by the timed end point method (Beckman Coulter); and LDL cholesterol by the Friedewald equation. hs-CRP was measured by near-infrared particle immunoassay rate (Synchron LXi; Beckman Coulter) (23,24). Tumor necrosis factor-α and interleukin-1β, -6, -8, and -10 were measured using cytometric bead array (BD Biosciences, San Diego, CA). Soluble vascular cell adhesion molecule-1 was measured using sandwich ELISA (Bender MedSystems GmbH, Vienna, Austria). APOE genotyping was determined by DNA analysis of peripheral blood or saliva (TaqMan; Applied Biosystems Inc., Foster City, CA). Nonnormally distributed variables were transformed (logarithmically: HDL cholesterol, triglycerides, CRP, vitamin B12, and insulin; or by normalized rank-order scores: glucose).

Structural Brain MRI and Volumetry

Brain MRI was offered to all participants; 529 accepted at baseline and, of those, 408 at 2 years. Data were acquired using a 3T Intera Quasar or a 3T Achieva Quasar Dual scanner (Philips Medical Systems) (23,24). Acquisition parameters for T1-weighted structural scans were: repetition time = 6.39 ms; time to echo = 2.9 ms; flip angle = 8°; matrix size = 256 × 256; field of view = 256 × 256 × 190; and slice thickness = 1 mm with no gap, yielding 1 mm^3 isotropic voxels. Gray matter (GM), white matter (WM), cerebrospinal fluid (CSF), and intracranial volume (ICV) were measured. Total brain volume was defined as the sum of GM and WM. Participants scanned by the different scanners were similar for demographic and imaging parameters, with no significant differences in age, sex, and years of education. GM, WM, CSF, and ICV were not significantly different, controlling for age and sex. To ensure scanning harmonization and that no error was introduced by scanner change, five participants were imaged on both scanners within 2 months; GM, WM, CSF, and ICV were similar between the two instruments, consistent with methods used by others (36).

Regional GM volumes were calculated using 90 parcellations, delineated by the Automated Anatomical Labeling atlas (37) using the voxel-based morphometry approach (38) (Statistical Parametric Mapping software; Wellcome Department of Imaging Neuroscience, London, U.K.). All T1-weighted scans were visually inspected. Using the Markov random-field option, T1 were delineated into regions using the ICBM 152 atlas as template. A series of customized templates and flow fields was generated by iterative registration with images registered to group templates to create the modulated warped tissue class images. Spatial normalization of GM to the Montreal Neurological Institute space was achieved using an affine transformation to the ICBM 152 template. The 12-mm full width at half-maximum Gaussian kernel smoothing was performed to generate the voxel-based GM volumes. A priori, three regions were selected (hippocampus, parahippocampus, and precuneus) based on evidence that atrophy is present in these regions in early presymptomatic AD (39).

Statistical Analyses

Variable distributions were examined and, where necessary, transformed to more closely approximate the normal distribution for use with parametric statistical procedures. Baseline demographic data were compared among the three groups (i.e., DM+MF, DM-noMF, and no-DM) using one-way ANOVA for continuous measures and logistical regression tests for binary-coded categorical variables. Baseline data on the key outcome variables of cognition and brain volumes were compared using linear mixed modeling, including the covariates of NESB, BMI, heart disease, diabetes, stroke, hypertension, systolic blood pressure, smoking, and APOEε4 genotype carriage.

We performed sample size calculations to determine if we had a sufficiently large sample to test one of the primary hypotheses, namely, to detect a difference in the rate of global cognitive decline between participants with diabetes using metformin (DM+MF) versus those not using metformin (DM-noMF) (using Stata 13). With a power level of $1 - \beta = 0.8$, a significance level of $\alpha = 0.05$, and using the repeated covariance matrix of global cognition scores across all four waves, the minimum sample size needed to detect a difference in the rate of global cognitive decline of 0.2 SD units/year (i.e., a small effect) in a repeated-measures ANOVA was $N = 44$ in total or $N = 22$/group. In the current study, the number of participants in the DM+MF and DM-noMF groups was 43 and 25, respectively, implying there were sufficient numbers in the study to detect a small difference in the rate of global cognitive decline among the groups.

Prospective data collected over the 6 years of observation were analyzed using linear mixed modeling to evaluate differences among groups in the rate of cognitive decline on each of the outcome measures. Study wave (baseline: wave 1; 2 years: wave 2; 4 years: wave 3; and 6 years: wave 4) was treated as a continuous variable representing time. Random effects for the intercept and time were included. Time and metformin group and their interaction were included as fixed effects in the analysis. Metformin users with diabetes were treated as the reference group and compared with the nonusers of metformin with diabetes and groups without diabetes. Coefficients for the fixed effect of group were interpreted as the estimated mean difference in baseline performance among groups. A negative coefficient for this term indicated that nonusers or those without diabetes displayed a lower level of baseline cognitive performance compared with metformin users. The coefficient for the group × time interaction was interpreted as the estimated mean difference between groups in the rate of change on the cognitive measure across the 6-year

study period. A negative coefficient for this term interaction indicated that nonusers or those without diabetes displayed a faster rate of cognitive decline compared with metformin users. Two linear mixed models were fit. In model 1, sex and mean-centered values of age and years of education were included as covariates alongside the specified fixed and random effects. In model 2 (the "fully adjusted model"), covariates were age, sex, BMI, heart disease, diabetes, stroke, hypertension, systolic blood pressure, smoking, NESB, and APOEε4 genotype carriage, each coded as binary variables with values of 1 and 0 representing the presence and absence of each risk factor, respectively. The analyses were repeated using brain volume data. In these analyses, model 1 covariates were age, sex, and intracranial volume; model 2 covariates were age, sex, BMI, heart disease, diabetes, stroke, hypertension, systolic blood pressure, smoking, intracranial volume, and APOEε4 genotype carriage.

To examine whether there were sex differences in the relationship between metformin use and cognitive performance and decline, we repeated the above analyses, but this time included all interactions among sex, group, and time. Estimates for the effects of metformin on baseline cognition and decline were obtained in men and women separately.

A Cox regression survival analysis was then performed to determine whether metformin use was related to dementia risk. Metformin group was treated as a categorical variable, and hazard ratios (HRs) for dementia were calculated for each pair of groups. To examine overall group differences in dementia risk controlling for sex, we included sex as a covariate. Then, to examine whether group differences were moderated by sex, analyses were repeated including a metformin group × sex interaction, and the estimated HRs were obtained for both men and women. As above, the analyses were first adjusted for age and education (model 1) and then for the remaining covariates (i.e., BMI, heart disease, diabetes, stroke, hypertension, systolic blood pressure, smoking, NESB, and APOεE4 genotype carriage). Analyses were performed using IBM SPSS Statistics 23.

RESULTS

Baseline Participant Characteristics

Table 1 shows baseline demographic, metabolic, and cognition data for 1,037 participants. Mean years of education was 12 (range 3–24), and most participants were Caucasian (98%). Of 123 participants with diabetes (12%), 67 were receiving metformin (DM+MF; 54%): 34 as a single medication, and 33 in combination with other medications, most frequently sulfonylureas (70%). Of participants with diabetes not receiving metformin (DM-noMF; $n = 56$), 34 were treated by diet alone. The frequency of use of other glucose-lowering medications were: sulfonylureas, $n = 52$; insulin, $n = 10$; glitazones, $n = 7$; and acarbose, $n = 2$. At baseline, most DM+MF participants had taken metformin for >5 years ($n = 39$; 60%); one-quarter had taken metformin for >10 years ($n = 16$; 24%). Only five participants (7.5%) had taken metformin for <12 months; duration data were missing in five participants.

At baseline, DM+MF had significantly lower systolic blood pressure and fewer TIAs compared with DM-noMF; otherwise, the two groups were similar. Compared with participants without diabetes (no-DM), DM+MF were more frequently male, had higher weight and BMI, and more frequently had heart disease and hypertension and lower HDL and LDL cholesterol but higher triglycerides. Inflammatory markers were similar among all groups.

A total of 568 (55.4%) participants had complete neuropsychological data for all four waves of data collection over the 6 years of observation. Participants with missing data ($n = 458$) were older (80.2 ± 4.9 vs. 77.7 ± 4.5 years; $P < 0.001$); had shorter education duration (11.2 ± 3.3 vs. 11.9 ± 3.6 years; $P = 0.001$); weighed less (71.5 ± 15.5 vs. 73.5 ± 15.0 kg; $P = 0.037$); had lower LDL (2.7 ± 0.8 vs. 2.9 ± 0.9 mmol/L; $P = 0.027$); had a history of heart disease (odds ratio [OR] 1.4; $P = 0.005$) or TIA (OR = 2.0; $P = 0.006$); were more likely of NESB (OR 1.7; $P = 0.001$); and had lower baseline scores on all cognitive measures (all $P < 0.001$).

Relationship Between Metformin Use and Baseline Cognitive Performance

There were no baseline cognitive performance differences between DM+MF compared with DM-noMF or no-DM in analyses using linear mixed modeling analysis and the fully adjusted model (model 2; covariates: BMI, heart disease, diabetes, stroke, hypertension, systolic blood pressure, smoking, APOEε4 genotype, and NESB) (Supplementary Table 1).

Relationship Between Metformin Use and Rate of Cognitive Decline Over 6 Years

Figure 1*A* shows the trajectories for global cognition by group over time. As expected in an older cohort, each group declined significantly during the 6-year observation period. The rates of change for global cognition and each domain were examined in mixed models (Table 2).

In the fully adjusted model 2, the rate of decline in global cognition was similar between DM+MF and no-DM; however, the rate of decline in DM+MF over 6 years was significantly less compared with DM-noMF ($P = 0.032$) (Fig. 1*A*). Hence, our hypothesis that metformin use is associated with less cognitive decline is supported. Likewise, the rate of decline in executive function was similar between DM+MF and no-DM, but significantly faster in DM-noMF (compared with DM+MF: $P = 0.006$) (Table 2 and Fig. 1*B*). The rate of decline was also faster in DM-noMF compared with DM+MF for memory, language, and attention/processing speed; however, these differences did not reach statistical significance.

Analyses examined whether APOEε4 carriage and hyperlipidemia moderated the associations between the groups. No moderating effects were found (Table 2).

Sex-specific analyses showed that for females, but not for males, there was a greater decline in both global cognition and executive function in DM-noMF compared with DM+MF ($P = 0.044$ and 0.038, respectively) (Supplementary Table 2 and Supplementary Fig. 1). However, the difference in the sizes of these sex-specific effects did not meet statistical significance (Supplementary Table 2).

Relationship of Metformin Use and the Rate of Decline in Brain Volumes Over 2 Years

Participants were invited to undertake MR in a substudy to measure brain volumes at baseline and at 2 years; ~50% accepted. Supplementary Table 3 shows

Table 1—Baseline characteristics: the Sydney Memory and Ageing Study, categorized by diabetes status and metformin use

	Type 2 diabetes					
	DM+MF (N = 67)	DM-noMF (N = 56)	No-DM (N = 903)	DM+MF vs. DM-noMF, P*	DM+MF vs. no-DM, P*	DM-noMF vs. no-DM, P*
Descriptives						
Sex (female), *N* (%)	22 (32.8)	25 (44.6)	520 (57.6)	0.18	<0.001	0.06
Age (years)	78.25 (4.6)	80.0 (4.7)	78.8 (4.8)	0.14	0.68	0.20
Education (years)	12.2 (3.9)	11.1 (3.0)	11.6 (3.5)	0.24	0.42	0.81
Physical measures						
Weight (kg)	83.0 (18.2)	76.5 (15.7)	71.6 (14.6)	0.07	<0.001	0.72
BMI (kg/m^2)	30.1 (5.6)	28.28 (4.7)	26.8 (4.3)	0.09	<0.001	0.057
Systolic BP (mmHg)	142 (20)	152 (22)	145 (21)	0.02	0.55	0.031
Diastolic BP (mmHg)	80 (10)	82 (11)	84 (11)	0.52	0.07	0.87
Prevalence of vascular diseases and dementia risk factors						
Heart disease, *N* (%)	34 (51.5)	21 (37.5)	291 (32.4)	0.12	0.002	0.43
Stroke, *N* (%)	2 (3.0)	5 (9.3)	34 (3.8)	0.17	0.75	0.06
TIA, *N* (%)	5 (7.6)	11 (20.4)	53 (6.0)	0.048	0.60	<0.001
Hypertension, *N* (%)	51 (77.3)	40 (72.7)	529 (58.7)	0.57	0.004	0.043
Ever smoked, *N* (%)	43 (64.2)	37 (66.1)	475 (52.7)	0.83	0.07	0.06
APOEε4, *N* (%)	10 (20.0)	9 (24.3)	169 (23.8)	0.63	0.54	0.94
Laboratory measures						
Total cholesterol (mmol/L)	4.0 (0.9)	4.3 (0.8)	4.8 (1.0)	0.28	<0.001	0.006
HDL cholesterol (mmol/L)	1.2 (0.3)	1.2 (0.5)	1.5 (0.4)	0.98	<0.001	0.002
LDL cholesterol (mmol/L)	2.1 (0.8)	2.5 (0.7)	2.9 (0.9)	0.07	<0.001	0.08
Triglycerides (mmol/L)	1.4 (0.8)	1.3 (0.7)	1.0 (0.5)	0.78	<0.001	0.014
Insulin (μU/mL)	21.2 (16.6)	19.5 (9.9)	14.9 (6.2)	0.58	<0.001	0.003
Vitamin B12 (pmol/L)	155 (72)	187 (96)	212 (298)	0.88	0.39	0.88
Uric acid (mmol/L)	0.32 (0.09)	0.31 (0.10)	0.3 (0.10)	0.93	0.55	0.88
CRP (mg/L)	1.9 (1.9)	3.1 (2.7)	2.9 (5.1)	0.53	0.35	0.99
TNF-α (pg/mL)	2.4 (2.5)	2.3 (1.9)	2.9 (13.3)	0.99	0.97	0.96
sVCAM-1 (pg/mL)	1.1 (0.4)	1.2 (0.8)	1.1 (0.8)	0.87	0.83	0.49
Interleukin-1β (pg/mL)	3.5 (3.3)	3.0 (1.8)	3.3 (7.2)	0.95	0.98	0.97
Interleukin-6 (pg/mL)	7.2 (4.9)	7.9 (5.9)	6.2 (7.9)	0.92	0.72	0.49
Interleukin-8 (pg/mL)	20.5 (8.5)	20.3 (8.2)	19.9 (13.4)	0.99	0.96	0.99
Interleukin-10 (pg/mL)	2.8 (1.8)	2.7 (1.2)	2.6 (2.1)	0.97	0.77	0.96
Cognitive domain measures (z scores ± SD)						
Global cognition	−0.84 (1.32)	−1.78 (1.47)	−0.8 (1.53)	0.023	0.98	0.003
Memory	−0.61 (1.26)	−1.3 (1.23)	−0.55 (1.27)	0.13	0.99	0.024
Attention/speed	−0.46 (1.18)	−1.29 (1.8)	−0.45 (1.42)	0.033	0.94	0.008
Language	−0.73 (1.39)	−1.56 (1.79)	−0.84 (1.52)	0.10	0.99	0.014
Executive function	−0.76 (1.49)	−1.37 (1.52)	−0.6 (1.55)	0.15	0.99	0.05
Visuospatial function	−0.32 (1.01)	−0.84 (1.13)	−0.31 (1.17)	0.43	0.97	0.332
Brain volume	N = 33	N = 22	N = 467			
Total GM and WM	957.2 (109.1)	887.8 (119.3)	957.4 (105.6)	0.061	0.99	0.012
GM	544.1 (6.1)	517.5 (70.8)	544.9 (68.9)	0.37	0.99	0.19
WM	413.1 (66.1)	370.4 (59.6)	412.5 (54.9)	0.022	0.99	0.003
CSF	663.6 (100.3)	678.4 (132.2)	682.8 (126.0)	0.91	0.69	0.99
Hippocampus	6.7 (0.8)	6.6 (0.8)	6.8 (0.8)	0.81	0.98	0.61
Parahippocampus	7.7 (1.1)	7.5 (1.1)	7.7 (1.0)	0.88	0.99	0.83
Precuneus	18.0 (2.4)	16.8 (3.3)	17.9 (2.7)	0.30	0.99	0.18
ICV	1,620.8 (151.7)	1,566.2 (22.4)	1,640.2 (176.6)	0.54	0.83	0.16

Data are mean (SD) or as indicated. Continuous variables were compared by ANOVA and categorical variables by χ^2 tests. Comparisons between groups were not adjusted for covariates. Nonnormally distributed data were logarithmically transformed for comparisons. BP, blood pressure; sVCAM-1, soluble vascular cell adhesion molecule-1; TNF-α, tumor necrosis factor-α. *P values from post hoc Scheffé comparisons for continuous variables and logistic regression for categorical variables.

baseline descriptive data for participants who did and did not participate in the MR substudy. Global cognition was similar between those who participated compared with those that declined in both the no-DM and DM+MF groups. In contrast, in the DM-noMF group, global cognition and the domain scores for executive function and attention and processing speed were lower at baseline in those who declined MR. No-DM participants undertaking MR were healthier,

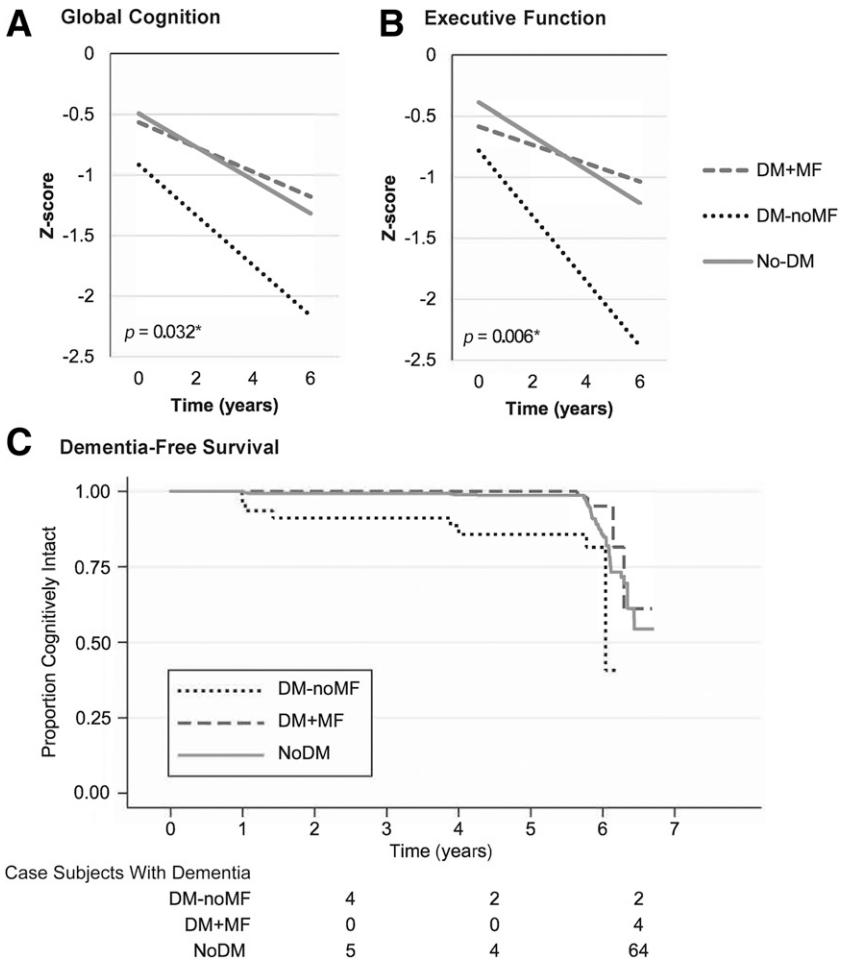

Figure 1—Diabetes with metformin use is associated with lesser decline in global cognition (*A*) and executive function (*B*) and greater dementia-free survival (*C*) compared with diabetes without metformin. Fitted trajectories in analyses with the covariates of age, sex, BMI, heart disease, diabetes, stroke, hypertension, systolic blood pressure, smoking, NESB, and APOEε4 genotype carriage.

with significantly lower rates of heart disease, stroke, and hypertension compared with the groups with diabetes. Disease burden in DM+MF and DM-noMF was similar, however.

Table 3 shows the baseline and 2-year data for brain volumes. No differences were found in the brain volume outcome measures at baseline, nor at 2 years. Supplementary Table 4 shows the results of brain volume mixed-model analyses. The fully adjusted model 2 found no difference in the rate of change in any brain volume measure between DM+MF and DM-noMF and control subjects without diabetes.

Relationship of Metformin Use and the Risk of Incident Dementia Over 6 Years

Ninety-one case subjects with dementia were reported throughout the 6-year observation, with 73 in no-DM (affecting 8.2% of that group), 8 in DM-noMF (i.e., 14.5% of that group), and 4 in DM+MF (6% of the group with diabetes receiving metformin). Of the 936 remaining censored case subjects, 320 were lost to follow-up, and the remaining 616 were dementia free at the final assessment wave at 6 years.

The HRs for comparisons between metformin groups for the Cox regression models showed that metformin use was associated with an 81% reduction in incident dementia risk (HR 0.19 [95% CI 0.04–0.85]; $P = 0.030$) compared with participants with diabetes not receiving metformin in a model containing the covariates of age, sex, BMI, heart disease, diabetes, stroke, hypertension, systolic blood pressure, smoking, NESB, and APOEε4 genotype carriage. Hence, our second hypothesis that metformin use is associated with lower risk of dementia is supported. DM-noMF had a threefold higher risk of incident dementia compared with no-DM (HR 3.03 [95% CI 1.17–7.88]; $P = 0.023$). Incident dementia rates were similar between DM+MF and no-DM (HR 1.74 [95% CI 0.52–5.90]; *P* was not significant). The estimated dementia-free survival curves are shown in Fig. 1*C*.

Sensitivity Analysis

Analyses were repeated to exclude participants on insulin ($n = 11$). The faster decline observed in DM-noMF compared with DM+MF persisted in global cognition ($\beta = -0.214$ [95% CI -0.41 to -0.02]; $P = 0.034$) and executive function ($\beta = -0.427$; SE 0.143 [95% CI -0.71 to -0.15]; $P = 0.003$). Global cognitive and executive function decline remained comparable between DM+MF and no-DM. In the Cox regression analysis, DM+MF continued to display significantly lowered incident dementia risk compared with DM-noMF (HR 0.186 [95% CI 0.041–0.84]), whereas the incident dementia risk did not differ between the DM+MF and no-DM groups.

Power Analysis

A post hoc power analysis was conducted to determine if the study had sufficient statistical power to detect a significant difference in the rate of global cognitive change between groups, specifically DM+MF versus DM-noMF. Based on a significance level of 0.05, the sample sizes of the DM+MF ($N = 43$) and DM-noMF ($N = 25$) groups at the final wave of data collection at 6 years, the observed covariance matrix of global cognition scores across the four waves, and the adjusted means for global cognition at each wave, the observed power to detect a significant group-by-time interaction using a repeated-measures ANOVA (i.e., a significant difference in the rate of global cognitive change between groups) was $1 - \beta = 0.94$. This result indicates that we had a 94% probability of detecting the difference in the rate of global cognitive change as large as we did. These power analyses confirm the sample size was sufficient to observe a significant difference in global cognitive change between the DM-noMF and DM+MF groups and thus evaluate for potential neuroprotective effects of metformin.

CONCLUSIONS

This study found that metformin use over 6 years in older people with

Table 2—Metformin use in the elderly with diabetes and change in cognition over 6 years (linear mixed models including covariates): the Sydney Memory and Ageing Study

			Model 1[a]			Model 2[b]		
Measure	Group difference	Subanalysis	β[d]	CI	*P*	β[d]	CI	*P*
Global cognition	Rate of change in DM+MF over 6 years		−0.24	(−0.35, −0.13)	<0.001	−0.20	(−0.32, −0.09)	0.001
	Rate of change in DM-noMF vs. DM+MF	Overall[c]	−0.16	(−0.34, 0.02)	0.07	−0.21	(−0.40, −0.02)	0.032
		APOEε4 × group	−0.18	(−0.63, 0.28)	0.45	−0.13	(−0.57, 0.32)	0.57
		High cholesterol × group	−0.26	(−0.72, 0.21)	0.28	−0.15	(−0.54, 0.24)	0.46
	Rate of change in no-DM vs. DM+MF	Overall[c]	−0.04	(−0.16, 0.07)	0.44	−0.07	(−0.19, 0.05)	0.26
		APOEε4 × group	0.17	(−0.13, 0.47)	0.27	0.19	(−0.11, 0.49)	0.21
		High cholesterol × group	0.18	(−0.17, 0.40)	0.42	0.06	(−0.20, 0.32)	0.64
Memory	Rate of change in DM+MF over 6 years		−0.13	(−0.22, −0.04)	0.006	−0.10	(−0.20, 0.01)	0.06
	Rate of change in DM-noMF vs. DM+MF	Overall[c]	−0.07	(−0.21, 0.08)	0.38	−0.08	(−0.25, 0.09)	0.34
		APOEε4 × group	−0.12	(−0.52, 0.28)	0.55	−0.12	(−0.50, 0.27)	0.55
		High cholesterol × group	−0.11	(−0.51, 0.29)	0.59	−0.08	(−0.41, 0.26)	0.65
	Rate of change in no-DM vs. DM+MF	Overall[d]	0.001	(−0.10, 0.10)	0.99	−0.04	(−0.15, 0.06)	0.45
		APOEε4 × group	0.14	(−0.13, 0.40)	0.31	0.14	(−0.12, 0.40)	0.29
		High cholesterol × group	0.08	(−0.16, 0.33)	0.51	0.07	(−0.15, 0.28)	0.56
Attention/ speed	Rate of change in DM+MF over 6 years		−0.27	(−0.39, −0.16)	<0.0001	−0.26	(−0.39, −0.14)	<0.001
	Rate of change in DM-noMF vs. DM+MF	Overall[c]	−0.07	(−0.26, 0.12)	0.49	−0.07	(−0.27, 0.13)	0.49
		APOEε4 × group	−0.25	(−0.73, 0.23)	0.30	−0.23	(−0.69, 0.23)	0.33
		High cholesterol × group	−0.16	(−0.64, 0.33)	0.52	−0.07	(−0.49, 0.35)	0.73
	Rate of change in no-DM vs. DM+MF	Overall[c]	0.02	(−0.11, 0.14)	0.79	0.01	(−0.12, 0.14)	0.89
		APOEε4 × group	0.15	(−0.16, 0.47)	0.34	0.18	(−0.13, 0.49)	0.26
		High cholesterol × group	−0.02	(−0.32, 0.29)	0.91	−0.04	(−0.32, 0.24)	0.79
Executive function	Rate of change in DM+MF over 6 years		−0.19	(−0.34, −0.04)	0.01	−0.15	(−0.32, 0.02)	0.08
	Rate of change in DM-noMF vs. DM+MF	Overall[c]	−0.24	(−0.48, −0.01)	0.05	−0.38	(−0.66, −0.11)	0.006
		APOEε4 × group	−0.15	(−0.79, 0.50)	0.66	−0.11	(−0.74, 0.51)	0.72
		High cholesterol × group	−0.39	(−1.02, 0.24)	0.22	−0.40	(−0.92, 0.11)	0.13
	Rate of change in no-DM vs. DM+MF	Overall[c]	−0.09	(−0.25, 0.06)	0.23	−0.12	(−0.30, 0.05)	0.16
		APOEε4 × group	0.14	(−0.31, 0.58)	0.55	0.15	(−0.29, 0.58)	0.52
		High cholesterol × group	0.17	(−0.23, 0.56)	0.41	0.09	(−0.25, 0.44)	0.59
Language	Rate of change in DM+MF over 6 years		−0.19	(−0.29, −0.09)	<0.001	−0.20	(−0.30, −0.09)	<0.001
	Rate of change in DM-noMF vs. DM+MF	Overall[c]	−0.07	(−0.23, 0.09)	0.39	−0.06	(−0.21, 0.12)	0.51
		APOEε4 × group	0.10	(−0.32, 0.52)	0.65	0.10	(−0.30, 0.51)	0.62
		High cholesterol × group	−0.31	(−0.72, 0.10)	0.14	−0.22	(−0.56, 0.13)	0.22
	Rate of change in no-DM vs. DM+MF	Overall[c]	0.02	(−0.08, 0.12)	0.69	0.03	(−0.08, 0.14)	0.57
		APOEε4 × group	0.18	(−0.11, 0.46)	0.22	0.17	(−0.11, 0.45)	0.23
		High cholesterol × group	−0.05	(−0.30, 0.21)	0.71	−0.07	(−0.29, 0.16)	0.57

Continued on p. 2698

Table 2—Continued

Measure	Group difference	Subanalysis	Model 1[a] β[d]	Model 1[a] CI	Model 1[a] *P*	Model 2[b] β[d]	Model 2[b] CI	Model 2[b] *P*
Visuospatial	Rate of change in DM+MF over 6 years		−0.09	(−0.17, −0.01)	0.04	−0.05	(−0.14, 0.04)	0.26
	Rate of change in DM-noMF vs. DM+MF	Overall[c]	0.01	(−0.12, 0.14)	0.92	−0.04	(−0.19, 0.11)	0.59
		APOEε4 × group	−0.20	(−0.55, 0.14)	0.25	−0.18	(−0.52, 0.15)	0.29
		High cholesterol × group	−0.02	(−0.38, 0.33)	0.89	−0.05	(−0.35, 0.25)	0.74
	Rate of change in no-DM vs. DM+MF	Overall[c]	−0.03	(−0.12, 0.05)	0.46	−0.07	(−0.16, 0.02)	0.15
		APOEε4 × group	0.01	(−0.22, 0.24)	0.92	0.05	(−0.18, 0.28)	0.69
		High cholesterol × group	0.14	(−0.09, 0.37)	0.22	0.04	(−0.15, 0.24)	0.67

Data are β coefficients (β), CIs, and *P* values. [a]Adjusted for sex and mean-centered values of age and years of education. [b]Adjusted for sex and mean-centered values of age and years of education, NESB, BMI, heart disease, stroke, hypertension, systolic blood pressure, smoking, and APOEε4 genotype carriage. [c]Overall results come from separate analysis in which sex is included as a covariate without interactions with group. [d]For rows labeled "Rate of change in DM+MF over 6 years," β reflects the average annual rate of change in cognitive test performance for participants with diabetes using metformin. For rows labeled "Overall," β reflects the difference between groups in their average change in cognitive test performance per year, in standardized units, adjusting for model covariates. Specifically, it is the annual rate of change in cognitive test performance for the first group minus the annual rate of change in cognitive test performance for the second group (e.g., DM+MF). Negative values indicate that the first group had a slower rate of decline in cognitive test performance per year (in standardized units) compared with the second group. For the "APOEε4 × group" rows, β reflects the difference between groups (e.g., DM-noMF vs. DM+MF) in the effect of APOE carriage (vs. noncarriage) on the annual rate of change in cognitive test performance. For the "High cholesterol × group" rows, β reflects the difference between groups (e.g., DM-noMF vs. DM+MF) in the effect of having hyperlipidemia (vs. not) on the annual rate of change in cognitive test performance.

diabetes was associated with lesser decline in global cognition and executive function and reduced the risk of dementia compared with older people with diabetes not receiving metformin. Importantly, participants with diabetes receiving metformin had declines in cognition and incident dementia rates that were not different from those without diabetes, despite the higher burden of cardiovascular and dementia risk factors in those with diabetes. Detangling the potential impact of longer-duration diabetes, more profound insulin deficiency, or more difficult to control type 2 diabetes with insulin deficiency (as captured by the surrogate index of insulin therapy examined in sensitivity analysis excluding participants on insulin) did not alter our results. No association was found between metformin use and the change in brain volumes, albeit over a shorter period of 2 years.

The current study adds to the existing literature supporting that metformin may have neuroprotective effects. The majority of epidemiological studies of people with diabetes have found that metformin use was associated with lower dementia risk (14,16) and better cognitive function (18). Incident dementia rates at 5 years were reduced by 35% in people aged >65 years with newly diagnosed diabetes prescribed metformin compared with sulfonylureas (14). One study that reported higher AD rates with metformin appears flawed in that it used cross-sectional analyses and did not account for the survival bias evident, since metformin users lived longer and were older (40).

Further, a number of major metformin randomized controlled trials have examined cognition post hoc and postcompletion. These are useful, but limited by a lack of baseline assessments, use of basic cognitive testing (such as the Mini-Mental State Examination), or the relative youth of participants. First, the Action to Control Cardiovascular Risk in Diabetes-Memory in Diabetes (ACCORD-MIND) study, a randomized study of tightened glucose control using all available medications versus standard control, found no between-arm difference on cross-sectional measures of cognition at study end over 3 years, though brain volume decline was attenuated (41), consistent with an effect of glucose lowering on slowing neurodegeneration and warranting further detailed studies of biomarkers and more detailed imaging.

Table 3—Brain volumes, diabetes, and metformin use at baseline and at 2 years in the Sydney Memory and Ageing Study

	Type 2 diabetes DM+MF (*n* = 22)		Type 2 diabetes DM-noMF (*n* = 13)		No diabetes (*n* = 288)		*P*	
	Baseline	2 years	Baseline	2 years	Baseline	2 years	Baseline	2 years
Total GM and WM (cm^3)	972.4 (97.3)	925.5 (85.8)	930.1 (139.8)	899.6 (148.9)	961.7 (102.7)	935.3 (105.4)	0.49	0.47
GM (cm^3)	555.5 (55.8)	535.4 (60.6)	539.4 (82.8)	528.9 (91.9)	546.8 (64.3)	536 (72)	0.76	0.94
WM (cm^3)	417 (62)	390.1 (69.4)	390.7 (69.7)	370.7 (67.7)	414.9 (55.5)	399.3 (61.8)	0.31	0.26
CSF (cm^3)	651.6 (85.1)	663.3 (103.2)	710.3 (140.7)	711 (136.4)	684.5 (128.3)	657.1 (126.7)	0.37	0.32
Hippocampus (cm^3)	6.9 (0.9)	6.8 (1.1)	6.9 (0.9)	6.5 (1.1)	6.8 (0.7)	6.7 (1.1)	0.61	0.69
Parahippocampus (cm^3)	7.9 (1.1)	7.8 (1.2)	7.9 (1.3)	7.7 (1.2)	7.7 (1)	7.7 (1.1)	0.32	0.91
Precuneus (cm^3)	18.6 (2)	16.9 (1.9)	17.4 (4)	16.4 (4.4)	17.9 (2.7)	16.6 (2.8)	0.42	0.83

Data are mean (SD). Comparisons were conducted using one-way ANOVA.

The Diabetes Prevention Program Outcomes Study (DPPOS), an observational extension of the longer-term impact of metformin versus intensive lifestyle versus control subjects (mean 3 years of intervention), found no associations between arms on cognition, measured 14 years post-randomization (42). Importantly, however, higher HbA_{1c} levels at follow-up were associated with lower cognitive function, regardless of whether diabetes developed. Similar results were found cross-sectionally postcompletion in the Finnish Diabetes Prevention Study: higher glycemia was associated with worse cognition (43). These three large-scale trials support neuroprotective effects of glucose lowering; however, cautious interpretation is required, since some studies had no baseline or prospective measures. A recent meta-analysis examined the best available evidence on metformin use and dementia, reporting that few studies met criteria for methodological rigor (19). Metformin use was associated with less prevalent cognitive impairment (OR 0.55 [95% CI 0.38–0.78]), and dementia incidence was also reduced (HR 0.76 [95% CI 0.39–0.88]) (19).

Two recent pilot randomized controlled trials have examined the effects of metformin on cognition a priori. In a pilot study of $n = 80$ subjects with amnestic mild cognitive impairment, metformin was associated with improved recall at 12 months (20). Greater improvements were evident in those with higher baseline insulin and HbA_{1c} levels and without the APOEε4 genotype (20). Diabetes prevalence was 7%, but diabetes presence did not statistically drive the findings (20). A second randomized controlled trial of 100 participants with diabetes or prediabetes and cognitive impairment assigned participants to donepezil plus metformin or acarbose (a glucose-lowering medication that sequesters glucose in the gut). Improved cognitive function was found with a combination of metformin and donepezil only (21). These encouraging preliminary findings require examination in larger samples over the longer term, with detailed neurodegenerative and metabolic biomarkers to confirm and understand important intermediaries.

Metformin, recommended globally as first line in the treatment of type 2 diabetes, is an AMPK activator that suppresses hepatic glucose production, increases insulin-mediated glucose uptake, and decreases fatty acid oxidation (44). Metformin reduces advanced glycation end products (45), which promote tissue degeneration and the microvascular complications of hyperglycemia in neural, renal, and vascular tissues. Preclinical and clinical studies have shown metformin has neuroprotective effects on brain structure and function. Metformin improved neuronal survival via activation of the mammalian target of rapamycin pathway in the brain with suppressed tau phosphorylation and cerebral inflammation (46); tau phosphorylation is associated with insulin resistance and type 2 diabetes in preclinical models and is associated with resistance to clearance and cognitive decline (47). Metformin prevented neuronal insulin resistance, which has AD characteristics in cellular models (48). In rodents, metformin decreased histopathological changes of AD (49), improved memory function and neuronal survival, and decreased neuroinflammation (50).

This study is one of few observational studies examining diabetes that includes APOE genotype as a covariate. The APOEε4 genotype is strongly associated with increased risk of AD; thus, we included it as a covariate in our analyses. There is emerging evidence, however, that the APOEε4 genotype may impair neuronal insulin signaling in mice (51). Human postmortem studies have shown that the neuronal insulin resistance in AD was not related to insulin signaling pathway defects (52); further mouse studies suggest endosomal entrapment of the insulin receptor (53). Thus, by controlling for the APOEε4 genotype in our study, we may have underestimated the associations of cognitive decline and metformin. Further studies in this important area of genetic predisposition and metformin effects are awaited.

Strengths of the current study include detailed assessment of cognition using a battery of neuropsychological tests repeated on four occasions during the 6-year observation period, the large cohort size, performance of brain MRI with specific volumetric assessment of brain regions in a large subgroup, and examination of community-dwelling subjects and panel-adjudicated determination of incident dementia based on accepted international criteria. Strengths in the analytical design include use of linear mixed modeling to address, as best can be done statistically, the bias introduced by nonrandom attrition and the inclusion of important covariates influencing brain ageing. Study limitations include the observational study design, the potential for selection bias and survivor bias to influence results, despite the modeling approaches undertaken, and the relatively short duration of MR brain volume measures. Further, dropouts had lower cognition performance at baseline compared with those who remained in the study for the entire observation period. These participants also had higher rates of the dementia risk factors of heart disease and stroke; thus, the cohort may have included survivor bias, in which case our estimates of the association between diabetes and cognitive decline and incident dementia may have been underestimated. Further, it is possible that the natural history of type 2 diabetes phenotypes with more rapid cellular ageing associated with β-cell dysfunction and insulin deficiency may also be associated with other cellular ageing, such as central neuropathy manifesting as cognitive decline and dementia (2). As such, there may be treatment biases in such individuals to more insulin- or sulfonylurea-based therapies and dropping of metformin. Sensitivity analyses attempted to account for such an effect but may not have fully accounted for this treatment selection bias. Midlife medication use was not collected; its nonavailability may have contributed to underestimation of associations found. Another limitation is the possibility that people with declining cognition may have medication rationalization with dropping of metformin to simplify therapy. If this was a substantial effect, we may have expected baseline differences in cognition; while global cognition and executive function were slightly lower in DM-noMF compared with DM+MF, these differences were not significant. Nevertheless, metformin treatment selection biases may still have influenced the trajectory of future decline, which cannot be conclusively determined in an observational study. Finally, the study phenotype did not include measures of HbA_{1c} nor hypoglycemic events; thus, associations between hypoglycemia severity or glucose control and the rate of cognitive decline could not be examined. However, HbA_{1c} measures during the observation period might not capture the legacy effects of glycemic control prior to study entry.

In conclusion, metformin use in older people with type 2 diabetes was associated with slowing of the decline in global cognition and decreased risk of incident dementia. Randomized controlled studies are required to determine whether metformin may have a protective effect against dementia or cognitive decline, both in people with diabetes and, given metformin's long safety record, older people without diabetes.

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