Effects of intensive glucose lowering on brain structure and function in people with type 2 diabetes (ACCORD MIND): a randomised open-label substudy

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Summary

Background People with type 2 diabetes are at risk of cognitive impairment and brain atrophy. We aimed to compare the effects on cognitive function and brain volume of intensive versus standard glycaemic control.

Methods The Memory in Diabetes (MIND) study was done in 52 clinical sites in North America as part of Action to Control Cardiovascular Risk in Diabetes (ACCORD), a double two-by-two factorial parallel group randomised trial. Participants (aged 55–80 years) with type 2 diabetes, high glycated haemoglobin A_{1c} (HbA_{1c}) concentrations (>7·5%; >58 mmol/mol), and a high risk of cardiovascular events were randomly assigned to receive intensive glycaemic control targeting HbA_{1c} to less than 6·0% (42 mmol/mol) or a standard strategy targeting HbA_{1c} to 7·0–7·9% (53–63 mmol/mol). Randomisation was via a centralised web-based system and treatment allocation was not masked from clinic staff or participants. We assessed our cognitive primary outcome, the Digit Symbol Substitution Test (DSST) score, at baseline and at 20 and 40 months. We assessed total brain volume (TBV), our primary brain structure outcome, with MRI at baseline and 40 months in a subset of participants. We included all participants with follow-up data in our primary analyses. In February, 2008, raised mortality risk led to the end of the intensive treatment and transition of those participants to standard treatment. We tested our cognitive function hypotheses with a mixed-effects model that incorporated information from both the 20 and 40 month outcome measures. We tested our MRI hypotheses with an ANCOVA model that included intracranial volume and factors used to stratify randomisation. This study is registered with ClinicalTrials.gov, number NCT00182910.

Findings We consecutively enrolled 2977 patients (mean age 62·5 years; SD 5·8) who had been randomly assigned to treatment groups in the ACCORD study. Our primary cognitive analysis was of patients with a 20-month or 40-month DSST score: 1378 assigned to receive intensive treatment and 1416 assigned to receive standard treatment. Of the 614 patients with a baseline MRI, we included 230 assigned to receive intensive treatment and 273 assigned to receive standard treatment in our primary MRI analysis at 40 months. There was no significant treatment difference in mean 40-month DSST score (difference in mean 0·32, 95% CI –0·28 to 0·91; p=0·2997). The intensive-treatment group had a greater mean TBV than the standard-treatment group (4·62, 2·0 to 7·3; p=0·0007).

Interpretation Although significant differences in TBV favoured the intensive treatment, cognitive outcomes were not different. Combined with the non-significant effects on other ACCORD outcomes, and increased mortality in participants in the intensive treatment group, our findings do not support the use of intensive therapy to reduce the adverse effects of diabetes on the brain in patients with similar characteristics to those of our participants.

Funding US National Institute on Aging and US National Heart, Lung, and Blood Institute.

Introduction

People older than 70 years with type 2 diabetes have at least twice the likelihood of developing late-life cognitive impairment or dementia compared with those without type 2 diabetes.[1] The mechanisms underlying these cognitive disorders are increasingly thought to involve mixed pathology, with contributions from vascular, neurodegenerative, and neurovascular processes.[2] Pathophysiological mechanisms that have been implicated include inflammation, oxidative stress, energy imbalance, protein misfolding, glucocorticoid-mediated effects, and differences in genetic susceptibilities.[3,4] On the basis of extensive published work on the causes, management, and prevention of diabetes, we took as a premise that early intervention with treatment strategies that improve glycaemic control could mitigate the adverse effects of type 2 diabetes on the brain. There are no clinical trials testing the effects of early intervention on brain outcomes in older people with type 2 diabetes. Targeting this risk group, we designed the Memory in Diabetes (MIND) substudy, embedded in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial,[5,6] to test the primary hypothesis that at 40 months, people randomised to receive an intensive glycaemic treatment strategy targeting glycated haemoglobin A_{1c} (HbA_{1c}) to less than 6·0% (42 mmol/mol) would have better cognitive function and a

Lancet Neurol 2011; 10: 969–77
Published Online September 28, 2011 DOI:10.1016/S1474-4422(11)70188-0

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larger brain volume than people randomised to receive a standard strategy targeting HbA_{1c} to 7·0–7·9% (53–63 mmol/mol).

Methods

Participants

ACCORD, described in detail elsewhere,[6] is a randomised, multicentre, double two-by-two factorial parallel treatment trial that tested the effect on cardiovascular disease events of treatment strategies to control blood glucose, blood pressure, and blood lipid concentrations. Participants targeted by ACCORD, which was done in 77 clinics in North America, were aged 45–79 years and had type 2 diabetes, high HbA_{1c} concentrations (>7·5%, >58 mmol/mol), and a high risk for cardiovascular disease events suggested by significant atherosclerosis, albuminuria, left ventricular hypertrophy, or at least two additional risk factors for cardiovascular disease. Key exclusion criteria were frequent or recent serious hypoglycaemic events, unwillingness to monitor glucose at home or inject insulin, body-mass index greater than 45 kg/m², serum creatinine level greater than 1·5 mg/dL (133 µmol/L), or other serious illness.[7]

The MIND study design has been described elsewhere.[5] All ACCORD participants who entered randomisation were eligible for MIND if they were recruited between Aug 21, 2003 (34 months after the start of ACCORD), and Dec 16, 2005, when the target sample size was reached. From this pool, we excluded participants younger than 55 years of age and those clinics (n=10) in the Veteran's Administration clinical centre network, because participants in this network were expected to be mainly men and we wanted to retain the overall sex balance. Additionally, 15 centres within the other six clinical centre networks declined to participate. The MIND participants were therefore drawn from 52 North American clinics in six of the seven clinical centre networks (webappendix pp 1–4).

Within MIND, a subset of the participants from four clinical centre networks (28 clinics) were recruited for the MRI substudy. Initially we targeted only participants randomised to the glycaemic and blood pressure trials within ACCORD, but halfway through our study we extended recruitment to participants in the lipid trial to meet our sample size goals. We excluded participants with standard MRI exclusions.[8] To enhance retention, recruitment focused on participants living within 2 h of an MRI scanner.

The National Heart Lung and Blood Institute (NHLBI) sponsored ACCORD and an NHLBI review panel and the institutional review board or ethics committee at each participating centre approved the protocol. The National Institute on Aging (NIA) in collaboration with NHLBI sponsored the MIND trial, which was approved by the institutional review board of all participating institutions (webappendix pp 1–4). Participants signed separate informed consent for MIND.

Randomisation and masking

Each clinic was part of one of seven clinical centre networks and reported to a central coordinating centre. A computer at the central coordinating centre generated unique randomisation sequences for every clinical site and electronically verified exclusion and inclusion criteria for every individual before assigning a treatment group. Clinic staff implemented the randomisation via secure access to the ACCORD trial website. Glycaemia trial treatment assignment was open label, and both clinic staff and patients were aware of the assigned glycaemic goal. The results of all ACCORD interim analyses were masked from study investigators.

Procedures

All ACCORD participants were randomly assigned to receive either intensive glycaemic treatment targeting HbA_{1c} to less than 6·0% (42 mmol/mol) or standard glycaemic treatment targeting HbA_{1c} to 7·0–7·9% (53–63 mmol/mol). Additionally, by use of the double two-by-two factorial design, participants in the blood-pressure trial were randomly assigned to receive either intensive blood pressure lowering treatment targeting systolic blood pressure to <120 mm Hg or standard treatment targeting systolic blood pressure to <140 mm Hg. Additionally, by use of the double two-by-two factorial design, participants in the lipid concentration trial were also randomly assigned to receive either fenofibrate or placebo, while good control of low-density lipoprotein cholesterol was maintained with simvastatin.[6]

The ACCORD therapeutic intervention achieved the target HbA_{1c} with a range of strategies decided by the attending physician and tailored to the individual participant. All participants received diabetes education, glucose-monitoring equipment, and antidiabetic drugs. Participants in the intensive glycaemic group were started on two or more classes of drugs. Doses were intensified or a new drug class was added monthly if HbA_{1c} concentrations were 6% (42 mmol/mol) or greater, or if more than 50% of premeal or postmeal capillary glucose readings were greater than 5·6 mmol/L (100 mg/dL). Standard glycaemic treatment was intensified whenever HbA_{1c} was 8% (64 mmol/mol) or greater, or more than 50% of capillary glucose readings were greater than 7·8 mmol/L (140 mg/dL). Anti-hyperglycaemic drugs that promoted hypoglycaemia (ie, insulin or insulin secretagogues) were reduced if HbA_{1c} was persistently below 7% (53 mmol/mol). All drug combinations from a standard formulary were permitted; specific drugs were reduced only for side-effects or contraindications.[9] The intensive intervention was stopped on Feb 6, 2008, when an increased risk (hazard ratio 1·22, 95% CI 1·01–1·46) for mortality was reported; participants in that group were moved to standard glycaemic treatment.[7] MIND assessments continued in accordance with the original protocol. Here we report the glycaemia results, since this was the main

intervention for which MIND was powered. Results for the other interventions will be reported elsewhere.

A cognitive test battery was administered at baseline and 20 months and 40 months after randomisation. The cognitive battery tested for verbal memory, processing speed, and executive function, which are typically impaired in people with type 2 diabetes.[10] Specific test selection, described in more detail elsewhere,[5] took into account the context of standardised testing in several clinics by trained lay staff, clinic time, and patient burden, as well as whether the tests had been previously used in studies of cognition and diabetes.[11] Our primary cognitive outcome was the number of correctly completed cells on the 40-month Digit Symbol Substitution Test (DSST), an omnibus test of psychomotor speed that also requires reasoning and working memory.[12] The results of this test have a normal distribution in the age-group of MIND participants, have been shown to change over time, are associated with diabetes and other cardiovascular outcomes, and might be less sensitive to educational level than those of other tests.[13] Secondary cognitive outcomes were memory, measured with the Rey Auditory Verbal Learning Test (RAVLT), and executive function, measured with the Stroop test.[5] The widely used Mini-Mental State Examination (MMSE) of general cognitive function was administered to allow comparisons with other studies. Quality control by the MIND coordinating centre (described elsewhere[5,14]) included tester certification and recertification, review of recorded test sessions, a tester helpdesk, and continual review of data entry and test-score distributions for unusual trends.

We chose total brain volume (TBV) as our primary MRI endpoint on the basis of evidence that diabetes can lead to mixed vascular and neurodegenerative changes,[15,16] evidence of change in TBV over time,[17] and the relation of TBV to cognitive function and decline. Rates of whole brain atrophy are sensitive and powerful markers of disease progression in patients with Alzheimer's disease[18,19] and differ between people with and without diabetes;[20,21] smaller values predict future cognitive disorders.[22] Our secondary MRI outcome was abnormal white matter (AWM) tissue volume, which is indicative of diffuse and focal ischaemic, demyelinating, and inflammatory processes leading to small vessel disease, and is associated with diabetes and impaired cognition.[21,23]

Brain MRI was done at baseline and at 40 months. The standardised MRI scan protocol,[5] used for all participants, was run on 1·5 T scanners and included a three-dimensional fast spoiled gradient-echo T1-weighted (TR=21 ms, FA=30°, TE 8 ms), two-dimensional axial fast spin-echo fluid attenuated inversion recovery (TR=8000 ms, TI=2000 ms, TE=100 ms), and proton-density/T2-weighted (TR=3200 ms, $TE_{1,2}$=27 ms and 120 ms) sequences. Voxel size was 1·5 by 0·9 by 0·9 mm for the three-dimensional T1-weighted sequence and 3·0 by 0·9 by 0·9 mm for the two-dimensional sequences. The three-dimensional T1-weighted scans were used to study brain morphology, including volume, and the fast spin-echo scans were used to study pathological effects.

An operator at each centre ran the standardised magnetic resonance sequences that were programmed into the scanner and did not change during the study. MRI quality control accorded with the American College of Radiology's (ACR) MRI quality control programme. Digital images acquired at each centre were sent to the MRI quality control centre for in-house review on an as-received basis. According to ACR phantom analyses, MRI scanner performance was stable across MRI sites and over the duration of our study.

For more on **ACR's MRI quality control programme** see http://www.acr.org/accreditation/mri.aspx

Our image analysis was done with previously described methods,[24,25] based on an automated multispectral computer algorithm that classifies all supratentorial brain tissue into 92 volumetric anatomical regions of interest characterised as CSF, grey matter, or white matter. Grey and white matter were further characterised as normal and abnormal. AWM represented both diffuse small-vessel disease and the hyperintensities that surround focal lesions. Grey matter and white matter regions of interest were summed to estimate TBV; TBV and CSF were summed

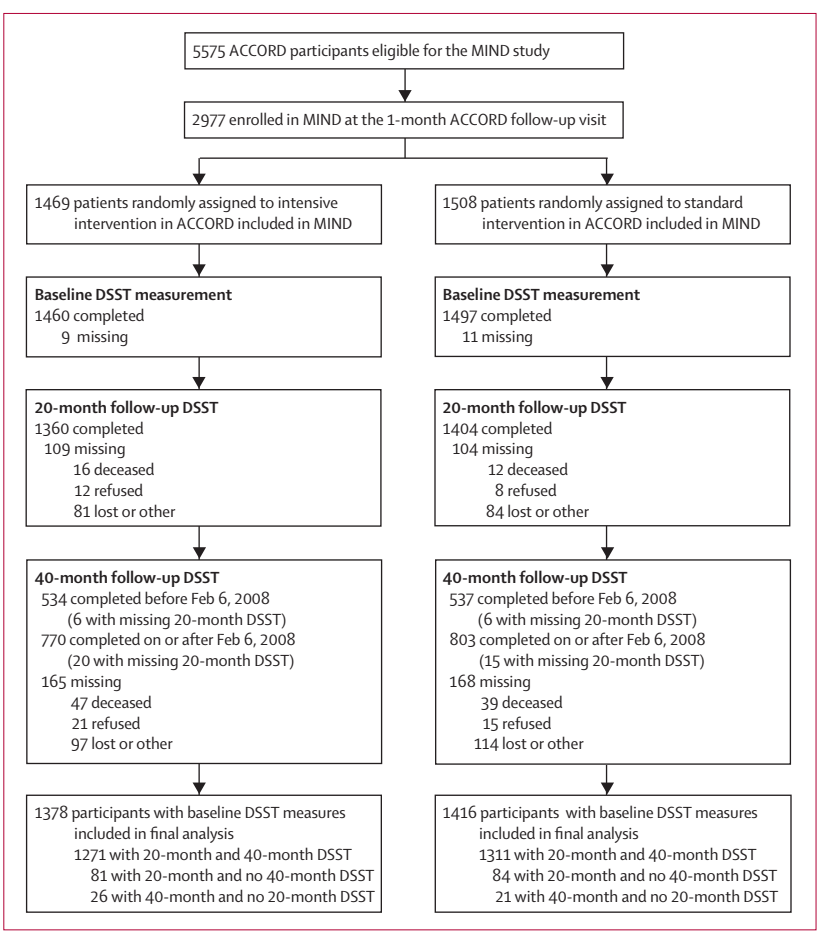

***Figure 1*: Trial profile for the primary cognitive outcome**
DSST=Digit Symbol Substitution Test.

to estimate intracranial volume (ICV), a measure of head size. Each participant's processed scan was reviewed by a trained individual who removed any scans verified to have failed to reach a stable solution. ICV, an integrated measure of the stability of the MRI operator, scanning, and image analysis, did not significantly change between baseline and follow-up examinations (baseline mean ICV 1132·34 cm³, follow-up mean ICV 1132·32 cm³; p=0·4651 by paired *t* test).

	Intensive-treatment group	Standard-treatment group
Participants	1469 (49%)	1508 (51%)
Age (years)	62·3 (5·7)	62·7 (5·9)
Women	697 (48%)	691 (49%)
Education		
Less than high school graduate	208 (14%)	184 (12%)
High school graduate or GED	374 (26%)	395 (26%)
Some college/technical school	512 (35%)	515 (34%)
College graduate or more	375 (26%)	414 (28%)
Clinical centre network		
Canada	153 (10%)	147 (10%)
Western	300 (20%)	310 (21%)
Minnesota and Iowa	329 (22%)	345 (23%)
Ohio and Michigan	172 (12%)	187 (12%)
Northeast	194 (13%)	180 (12%)
Southeast	321 (22%)	339 (23%)
Ethnic origin		
White	1020 (69%)	1054 (70%)
Black	242 (17%)	242 (16%)
Hispanic	105 (7%)	107 (7%)
Other	102 (7%)	105 (7%)
Smoking status		
Current	172 (12%)	180 (12%)
Former	641 (44%)	654 (43%)
Never	654 (45%)	673 (45%)
Systolic blood pressure (mm Hg)	135·3 (17·3)	135·7 (18·2)
Diastolic blood pressure (mm Hg)	75·1 (10·5)	74·5 (10·8)
Duration of diabetes (years)	9 (5–14)	9 (5–15)
HbA_{1c} (mmol/mol)	8·3% (1·0); 67 (10·9)	8·3% (1·1); 67 (12·0)
Total cholesterol (mmol/L)	4·73 (1·05)	4·75 (1·12)
Low-density lipoprotein (mmol/L)	2·68 (0·86)	2·67 (0·88)
High-density lipoprotein (mmol/L)		
Women	1·22 (0·31)	1·22 (0·31)
Men	0·99 (0·25)	1·00 (0·23)
Body-mass index (kg/m²)	33·0 (5·4)	32·9 (5·3)
History of cardiovascular disease	427 (29%)	442 (29%)
Depression (patient health questionnaire >10*)	215 (15%)	226 (15%)
DSST score†	52·5 (15·7)	52·6 (16·1)
RAVLT score‡	7·6 (2·6)	7·5 (2·5)
Stroop score§	32·4 (17·4)	31·6 (15·9)
MMSE score¶	28 (26–29)	28 (26–29)

Data are n (%), mean (SD), or median (IQR). GED=General Educational Development Test. DSST=Digit Symbol Substitution Test. RAVLT=Rey Auditory Verbal Learning Test. MMSE=Mini-Mental State Examination. *Possible range 0–27. †Number of correct cells (possible range 0–133). ‡Total number of words recalled (possible range 0–15). §Possible range –160 to 220. ¶Possible range 0–30.

Table 1: **Baseline characteristics of the ACCORD-MIND cohort**

Statistical analyses

We estimated a sample size of 1400 participants per treatment group would, at 40 months, detect an 18% difference between groups (1 point on the DSST) with about 90% power, assuming a two-sided 0·05 type 1 error level, 15% dropout, and a 40-month DSST SD of 7·5, adjusted for baseline DSST.

We estimated an MRI sample size of 320 participants per group would detect a 20% difference in TBV (3·3 cm³) between groups at 40 months, with about 90% power, assuming a two-sided 0·05 type 1 error level, 15% dropout, and a TBV SD of 12·1, adjusted for baseline TVB.[17]

We tested our cognitive function hypotheses with a mixed-effects model that incorporated information from both our 20-month and 40-month outcome measures.[26] In this model we assumed the probability of missing outcomes depended only on previous recorded outcomes or on factors in the model. Our basic model included terms for the glycaemia intervention and a visit effect, and an interaction term between the two. In a randomised trial the baseline covariates are independent of the random assignment,[27] so we could improve the efficiency of our analysis by including in the model the baseline cognitive score and the factors used to stratify randomisation: second trial assignment (blood pressure or lipid), randomised group allocation within the blood-pressure and lipid trials respectively, clinical centre network, and history of cardiovascular disease.

Our MRI hypotheses were tested with an ANCOVA model that included ICV and factors used to stratify randomisation. We log transformed the highly skewed baseline and 40-month AWM data; we present the back-transformed estimates of treatment differences, which is the ratio of the treatment-specific geometric means.[28] We assessed robustness of the MRI results to missing 40-month data (including those due to death) in three multiple-imputation regression models that used baseline MRI information for imputation. In one model imputation was based on data pooled across treatment groups, a second based imputation on data from each treatment group separately, and a third assessed how much change in TBV would have been needed in the participants receiving intensive glycaemic treatment for whom 40-month data were missing for the treatment comparison to no longer be significant. Following the finding that participants in the intensive-treatment group gained more weight than those in the standard-treatment group,[7] we did post-hoc exploratory analyses for treatment differences in oedematous disorders (pretibial oedema, worsened ankle swelling, coronary heart failure, pulmonary oedema, new or worsened shortness of breath, or nocturia), or whether weight

	Intensive-treatment group	Standard-treatment group	Difference in means*
DSST			
Baseline†	52·55	52·55	..
20 months	51·51 (51·09 to 51·93)	50·98 (50·57 to 51·39)	0·53 (–0·06 to 1·12); p=0·0756
40 months‡	50·93 (50·50 to 51·35)	50·61 (50·19 to 51·03)	0·32 (–0·28 to 0·91); p=0·2997
40-month change	–1·62 (–2·05 to –1·20)	–1·94 (–2·36 to –1·52)	..
RAVLT			
Baseline†	7·51	7·51	..
20 months	7·87 (7·77 to 7·96)	7·85 (7·76 to 7·94)	0·02 (–0·11 to 0·15); p=0·7897
40 months	7·98 (7·88 to 8·08)	7·99 (7·90 to 8·08)	–0·01 (–0·14 to 0·12); p=0·8929
40-month change	0·47 (0·37 to 0·57)	0·48 (0·39 to 0·57)	..
Stroop test			
Baseline†	32·0	32·0	..
20 months	30·87 (30·16 to 31·57)	31·46 (30·77 to 32·16)	–0·60 (–1·59 to 0·40); p=0·2375
40 months	31·45 (30·73 to 32·17)	32·06 (31·34 to 32·77)	–0·61 (–1·62 to 0·40); p=0·2383
40-month change	–0·55 (–1·27 to 0·17)	0·06 (–0·66 to 0·77)	..
MMSE			
Baseline†	27·39	27·39	..
20 months	27·26 (27·14 to 27·38)	27·27 (27·15 to 27·39)	–0·01 (–0·18 to 0·16); p=0·9268
40 months	27·05 (26·93 to 27·17)	27·06 (26·93 to 27·18)	–0·01 (–0·18 to 0·16); p=0·9328
40-month change	–0·34 (–0·46 to –0·22)	–0·33 (–0·46 to –0·21)	..
TBV (cm³)			
Baseline†	927·5	927·5	..
40 months‡	914·4 (912·5 to 916·4)	909·8 (908·0 to 911·6)	4·6 (2·0 to 7·3); p=0·0007
40-month change	–13·0 (–15·0 to –11·1)	–17·7 (–19·5 to –15·9)	..

Data are least squares mean (95% CI). For DSST, RAVLT, and MMSE a negative change value represents a worsening score. For the Stroop test, a positive change value represents a worsening score. For TBV, a negative change value represents a decline in volume. Because of data skewness, data for abnormal white matter were analysed on a multiplicative rather than an additive scale. To avoid confusion, these results have been presented in the text. DSST=Digit Symbol Substitution Test. RAVLT=Rey Auditory Verbal Learning Test. MMSE=Mini-Mental State Examination. TBV=total brain volume. *Difference calculated as intensive-treatment group minus standard-treatment group means. †Baseline mean is the overall mean for both groups combined as measured before randomisation. This value is used to obtain the least squares means estimates at follow-up. Models are adjusted for baseline cognitive score and the factors used to stratify randomisation: second trial assignment (blood pressure or lipid concentration), randomly assigned group allocation within the blood pressure and lipid concentration trials, clinical centre network, and history of cardiovascular disease. ‡Pre-specified co-primary outcomes.

Table 2: **Outcomes by endpoint**

gain was associated with TBV and AWM within treatment groups.

We did prespecified subgroup analyses for sex, history of cardiovascular disease, treatment group in the lipid or blood pressure trials, and clinical centre network. Post-hoc exploratory subgroup analyses included baseline age (<60, 60–69, ≥70 years),[29] duration of diabetes (<5, 6–10, 11–15, ≥16 years),[14,30] and DSST (<47, 47–59, ≥60).[31]

We tested all hypotheses at the two-sided 0·05 level. We did all statistical analyses with S-Plus 8.0 or SAS 9.2. This study is registered with ClinicalTrials.gov, number NCT00182910.

Role of the funding source

Staff from the NHLBI (ACCORD sponsor) served on the executive and steering committees that made decisions on study design, methods, and data collection. The NIA (MIND sponsor) had no role in the study design, in the collection, analysis, and interpretation of the data, in writing the report, or in the decision to submit the paper for publication. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Of the 2957 (99%) of 2977 MIND participants with a baseline DSST assessment (figure 1), 2794 (94%) had at least 20-month or 40-month follow-up and were included in our final analysis. Completion rates for the other tests were similar to those for the DSST. Participants with missing follow-up data were older, had a higher systolic blood pressure, and a lower baseline DSST but were otherwise similar to those with complete data.

Our trial participants had a mean age of 62·5 years (5·8) and were similar to the overall eligible ACCORD sample (webappendix p 6) and the treatment groups were similar to each other (table 1). The substantial separation achieved in median HbA_{1c} between the intensive-treatment (6·6%; 49 mmol/mol) and standard-treatment (7·5%; 58 mmol/mol) groups was similar to that in the main ACCORD trial. When the intensive glycaemic intervention was stopped and participants in that group

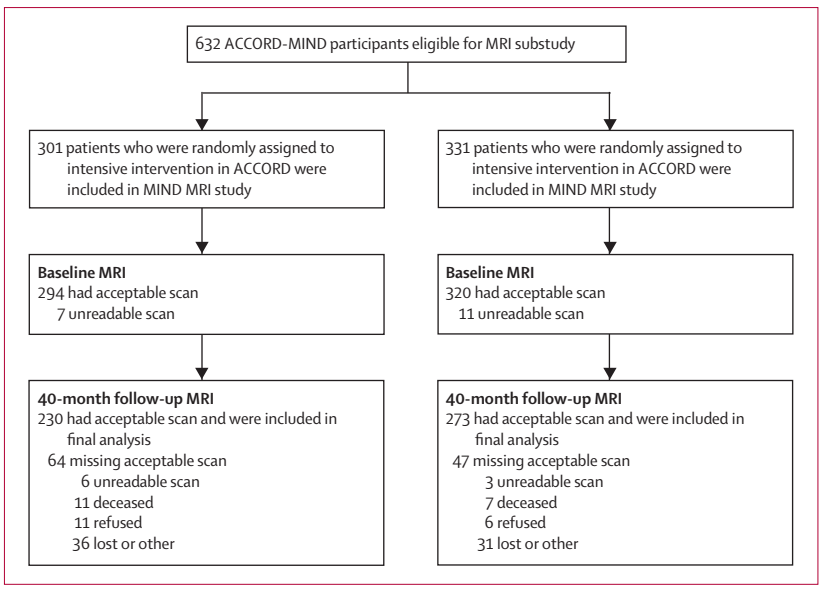

Figure 2: **Trial profile for the primary MRI outcome**

were moved to the standard glycaemic treatment,[7] participants in the intensive-treatment group of the cognitive substudy had received treatment for a median of 39 months (IQR 34–40) and those in the MRI substudy had received treatment for 35 months (31–40). Mortality in the MIND participants in the intensive-treatment group (n=47) versus the standard-treatment group (n=39; hazard ratio 1·27, 95% CI 0·83–1·93) was consistent with that recorded overall in ACCORD.

DSST scores significantly declined in both treatment groups (table 2). At 20 months, the between-group difference in DSST scores approached statistical significance, but at 40 months the difference was attenuated and not significant (table 2). There were no consistent subgroup differences by intervention (webappendix p 9).

During follow-up, there was a small increase in mean RAVLT scores within both groups, but no significant difference between groups (table 2). Performance on the Stroop test improved slightly in the intensive-treatment group and declined slightly in the standard-treatment group, but there was no difference between treatments (table 2). There were no consistent subgroup differences by intervention for either cognitive test (webappendix pp 10–11).

Of the 632 participants recruited into our MRI substudy, 614 (97%) participants (figure 2) had a successful baseline MRI and were similar for baseline characteristics to all other MIND participants (webappendix p 7) and between treatment groups (table 3). A higher proportion (p=0·0273) had a successfully processed repeat scan in the standard treatment group (273; 85 %) compared with the intensive treatment group (230; 78%). Reasons for missing scans (webappendix p 8) were similarly distributed across treatment groups. More follow-up scans were missing for participants aged 60 years or older (76 [20%] of 382) compared with those younger than 60 years (35 [15%] of 232).

At 40 months, the intensive-treatment group had significantly greater TBV compared with the standard-treatment group (table 2). Although TBV declined in both groups, the TBV of the intensive-treatment group declined less: 13·0 cm³ (0·41% per year) compared with 17·7 cm³ (0·57% per year) in the standard-treatment group. Our imputation-based sensitivity analyses showed similar results. The participants in the intensive group who missed a 40-month MRI would have to experience, on average, a greater than 22·0 cm³ decline (73% increase over the change in those with recorded data) for the results to become non-significant. The effect on TBV of the interventions did not differ by subgroup (previous cardiovascular disease p=0·1508, sex p=0·6336, clinical centre network p=0·6509, diabetes duration p=0·7167, age p=0·4824, and DSST p=0·4650).

At 40 months, there was significantly more AWM in the intensive-treatment group (geometric mean 1·89 cm³; 95% CI 1·78–2·00) compared with the standard-treatment group (1·71 cm³, 1·62–1·80; ratio of geometric means 1·10 cm³, 1·02–1·19; p=0·0156). However, this effect seemed to be restricted to participants younger than 60 years (interaction between the glycaemia intervention and baseline age p=0·0045; ratio of intensive to standard geometric means for patients younger than 60 years [n=197] 1·30 [95% CI 1·15–1·48], ratio for patients 60–69 years [n=245] 0·98 [0·87–1·09], and ratio for patients 70 years and older [n=61] 1·07 [0·84–1·35]). There were no other treatment differences across baseline subgroups (previous cardiovascular disease p=0·35, sex p=0·82, clinical centre network p=0·3401, diabetes duration p=0·7496, and DSST p=0·8073). There was no evidence that measures of peripheral oedema or weight gain could explain the differences in TBV or AWM between treatment groups.

Discussion

To our knowledge, ACCORD MIND is the first randomised study in older people with type 2 diabetes to test the effect of intensive compared with standard glycaemic lowering strategies on cognitive domains and on structural changes in the brain (panel). Overall, there is no evidence in this patient group, which had longstanding type 2 diabetes, a high risk of cardiovascular disease, and mean age of 62 years, that an intensive glycaemic treatment strategy provides benefit to cognitive function. There was a significant but small difference in TBV favouring the intensive strategy. However, this difference does not support the use of intensive treatment to reduce brain atrophy in view of the effects of this intervention in the main ACCORD trial: raised mortality, no overall benefit on cardiovascular disease events, an increase in hypoglycaemic events, and weight gain.[7]

In the 30% of ACCORD participants who entered the MIND substudy, the separation in HbA_{1c} concentrations, and differences in mortality rates between the treatment strategy groups, were similar to those in the main trial. There was reasonable balance of baseline characteristics between treatment groups. Adherence to the cognitive assessment protocol and retention of patients in the study was high, minimising the likelihood of bias. The cognitive battery was successfully administered in a standardised manner in many geographically and demographically diverse clinics; fewer 40-month DSST assessments than expected were missing (11% [n=333] actual *vs* 15% expected), and these were distributed similarly across the treatment groups (11% [n=165] intensive *vs* 11% [n=168] standard). Our overall conclusions did not change with different assumptions about the missing 40-month scans.

Several factors might have attenuated treatment differences in cognitive scores. Not all participants completed 40 months on intensive treatment, but most had at least 34 months. Methodological factors, such as practice effects, might contribute, but these effects should be similar in both treatment groups. The tests might not have measured appropriate functions, but those functions have been repeatedly shown to be affected in people with type 2 diabetes[10] and the tests are appropriate for a large-scale heterogeneous study population. For the deaths to have affected our conclusion in favour of intensive treatment, substantially higher follow-up cognitive scores would have been needed from the 47 people who died in the intensive group than from the 39 in the standard group. We think this would be unlikely, because it assumes that those on intensive therapy who died would have experienced a greater treatment-group effect than those who survived.

Several other explanations are possible. High patient motivation and the optimum diabetes care provided to all participants might have brought glucose into sufficient control to have mitigated some cerebral pathology caused by type 2 diabetes.[3] Optimum treatment has been raised as a reason for the null effect on cognition in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications trial.[33] Age might also be a factor in that treatment differences might have been more apparent if the intervention had been given during a period when participants were experiencing more rapid decline in cognition.[35] It has been suggested that up to age 70 years there is little measurable cognitive decline in people with type 2 diabetes, although after that the rates of decline begin to diverge between those who remain cognitively stable and those who will develop mild cognitive impairment or Alzheimer's disease. It is also possible that an intensive treatment strategy does not improve outcomes in the group of patients targeted by ACCORD.

The annualised decline in TBV (3·9 cm³) in the intensive-treatment group is 26% less than that in the standard-treatment group (5·31 cm³). From another perspective, a study of people with a mean age of 76 years recorded that TBV of cognitively stable people declined 0·4% per year compared with 0·8% per year in those who converted to mild cognitive impairment or dementia.[36] This is compared with an annual decline of 0·41% in the intensive-treatment group and 0·57% in

	Intensive-treatment group	Standard-treatment group
Participants	294 (48%)	320 (52%)
Age (years)	62·1 (5·7)	62·7 (5·8)
Women	130 (44%)	143 (45%)
Education		
Less than high school graduate	32 (11%)	30 (9%)
High school graduate or GED	69 (24%)	79 (25%)
Some college/technical school	103 (35%)	107 (33%)
College graduate or more	90 (31%)	104 (33%)
Clinical centre network		
Minnesota and Iowa	129 (44%)	145 (45%)
Ohio and Michigan	46 (16%)	53 (17%)
Northeast	48 (16%)	38 (12%)
Southeast	71 (24%)	84 (26%)
Ethnic origin		
White	192 (65%)	228 (71%)
Black	53 (18%)	50 (16%)
Hispanic	22 (8%)	17 (5%)
Other	27 (9%)	25 (8%)
Smoking status		
Current	38 (13%)	42 (13%)
Former	123 (42%)	135 (42%)
Never	132 (45%)	143 (45%)
Systolic blood pressure (mm Hg)	133·5 (16·3)	136·0 (19·2)
Diastolic blood pressure (mm Hg)	74·5 (9·8)	74·5 (10·6)
Duration of diabetes (years)	8 (5–13)	8 (5–13)
HbA_{1c} (mmol/mol)	8·2% (1·0); 66 (10·9)	8·1% (1·1); 65 (10·9)
Total cholesterol (mmol/L)	4·71 (1·00)	4·75 (1·16)
Low-density lipoprotein (mmol/L)	2·62 (0·82)	2·65 (0·90)
High-density lipoprotein (mmol/L)		
Women	1·28 (0·35)	1·24 (0·32)
Men	1·01 (0·28)	1·04 (0·24)
Body-mass index (kg/m²)	33·1 (5·1)	32·2 (5·0)
History of cardiovascular disease	82 (28%)	78 (24%)
Total brain volume (cm³)	928·3 (101·2)	926·8 (91·5)
Depression (patient health questionnaire >10*)	45 (15%)	48 (15%)
DSST†	52·5 (15·9)	54·2 (16·2)
RAVLT‡	7·4 (2·5)	7·5 (2·5)
Stroop§	32·1 (17·1)	29·9 (13·8)
MMSE¶	28 (26–29)	28 (27–29)

Data are n (%), mean (SD), or median (IQR). GED=general educational development test. DSST=Digit Symbol Substitution Test. RAVLT=Rey Auditory Verbal Learning Test. MMSE=Mini-Mental State Examination. *Possible range 0–27. †Number of correct cells (possible range 0–133). ‡Total number of words recalled (possible range 0–15). §Possible range −160 to 220. ¶Possible range 0–30.

Table 3: **Baseline characteristics of the MRI cohort**

Panel: Research in context

Systematic review

We reviewed PubMed from 1970 to July 29, 2011, with the search terms "diabetes", "type 2 diabetes", and "glycaemic intensive therapy" in combination with "cognition", "neuropsychological function", "neuroimaging", "MRI", and "MCI or Alzheimer's disease", and limited to observational studies and clinical trials. Recent review articles emerging in this search were also examined for relevant studies. We identified one published randomised, therapeutic trial comparing intensive with conventional treatments in patients with type 1 diabetes.[32,33] The authors did not identify treatment-related differences in cognitive function, but did identify a significant association of higher HbA_{1c} with psychomotor function and mental efficiency after 18 years of follow-up. There were no early intervention trials comparing therapeutic strategies in a target patient group of older people with longstanding type 2 diabetes and at high risk of cardiovascular events.

Interpretation

Our study is the first reported randomised, controlled clinical trial in this target population that assessed multiple measures of brain structure and function. Over a 40-month period, we showed no significant difference between treatments in cognitive function, but there was a significantly higher total brain volume in the group receiving the intensive glycaemic intervention versus standard treatment. Structural changes might happen earlier than functional changes and both should be measured to have a more complete assessment of the efficacy of a treatment. Better understanding of the progression of decline in people in the same age range as included in this study, when disease processes in the brain begin to accelerate, is necessary for the development of effective prevention strategies. Although we identified that intensive treatment strategies might reduce the rate of brain atrophy, the overall benefit of intensive therapy for type 2 diabetes is being widely debated.[34] This debate centres on the type, severity, burden of comorbidity, stage of macrovascular disease, and treatment side-effects of intensive compared with standard therapy. Additional follow-up is needed to establish whether the different treatment strategies result in different rates of cognitive change beyond what is obtained by following standard therapy guidelines.

the standard-treatment group in ACCORD MIND. The increase in AWM volume in participants younger than 60 years in the intensive group needs further study. We did not identify evidence that major factors such as oedema or weight gain affected the results, although another unknown or unmeasured side-effect might have resulted in TBV treatment differences.

Taking the cognitive and MRI findings together, it is reasonable to postulate that, in this age-group, structural changes in the brain happen before cognitive changes and that over time cognitive differences between treatment groups would emerge. With additional ongoing follow-up of the cohort, we will be able to establish whether, above the benefits of standard therapy, the different treatment strategies resulted in different rates of cognitive change. At present, there is little evidence to quantify the clinical effect of the recorded treatment differences. We feel it is reasonable to suggest that a larger decline in brain capacity will lead to earlier loss of function and possibly dementia—the MIND participants at an approximate mean age of 62 years are already experiencing an annual decline of TBV in the range reported for people 15 years older,[36] when the incidence of dementia increases logarithmically. Furthermore, there are few data quantifying the progression of brain changes in people with type 2 diabetes who are similar in age to MIND participants, and little is known about the functional effects of accumulating small decrements in brain structure and function or about the determinants of who, in a general population, will go on to develop dementia. Most data on people with diabetes describe patterns in younger people with type 1 diabetes,[37] or in cohorts that are at least 10 years older.[1] However, MIND participants are in the crucial age range when disease processes in the brain begin to accelerate, eventually leading to double the risk of dementia in people with type 2 diabetes compared with people without this disorder. Gaps in our knowledge of this transition phase clearly need to be filled if we are to design effective prevention strategies.

Cognitive function affects the ability of patients to follow complex disease management protocols, and impaired cognition predicts cardiovascular disease and severe hypoglycaemic events.[38] Early prevention strategies to reduce the risk of cognitive impairment are needed because, as the longevity of patients with diabetes increases, so too does the number reaching an age at which cognitive disorders become clinically apparent. Optimum treatment strategies for brain health in older people with type 2 diabetes are needed and should be assessed in the context of a comprehensive assessment of therapeutic strategies to manage type 2 diabetes and its consequences.

Contributors

LJL, JDW, RNB, and MEM designed the study. RML, HCG, AMM, MS, KRH, JD, CT, JLS, JM, and JH collected the data. LC, MEM, LCL, JL, and CD were involved in quality control and data analysis. LJL was lead author with MEM, JDW, and RNB. All authors contributed equally to the interpretation of the data and writing of the report.

Conflicts of interest

HCG has received consulting fees from Sanofi-Aventis, GlaxoSmithKline, Eli Lilly, Novo Nordisk, AstraZeneca, Bristol-Myers Squibb, Roche, Merck, Bayer, and Janssen-Ortho; institutional grant support to McMaster University from Sanofi-Aventis, GlaxoSmithKline, Novo Nordisk, Merck, Pronova, Roche, Eli Lilly, and Boehringer Ingelheim; and lecture fees from Sanofi-Aventis, GlaxoSmithKline, Eli Lilly, and Novo Nordisk. All other authors declare that they have no conflicts of interest.

Acknowledgments

ACCORD MIND was funded through an intra-agency agreement between NIA and NHLBI (AG-0002) and the NIA Intramural Research Program. ACCORD was funded by NHLBI (N01-HC-95178; N01-HC-95179; N01-HC-95180; N01-HC-95181; N01-HC-95182; N01-HC-95183; N01-HC-95184). The following companies provided study drugs, equipment, or supplies: Abbott Laboratories, Amylin Pharmaceutical, AstraZeneca, Bayer HealthCare, Closer Healthcare, GlaxoSmithKline, King Pharmaceuticals, Merck, Novartis, Novo Nordisk, Omron Healthcare, Sanofi-Aventis, and Schering-Plough.

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