The Action to Control Cardiovascular Risk in Diabetes Memory in Diabetes Study (ACCORD-MIND): Rationale, Design, and Methods

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Type 2 diabetes mellitus and cognitive impairment are 2 of the most common chronic conditions found in persons aged ≥60 years. Clinical studies have shown a greater prevalence of global cognitive impairment, incidence of cognitive decline, and incidence of Alzheimer disease in patients with type 2 diabetes. To date, there have been no randomized trials of the effects of long-term glycemic control on cognitive function and structural brain changes in patients with type 2 diabetes. The primary aim of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Memory in Diabetes Study (ACCORD-MIND) is to test whether there is a difference in the rate of cognitive decline and structural brain change in patients with diabetes treated with standard-care guidelines compared with those treated with intensive-care guidelines. This comparison will be made in a subsample of 2,977 patients with diabetes participating in the ongoing ACCORD trial, a clinical trial sponsored by the National Heart, Lung, and Blood Institute (NHLBI) with support from the National Institute on Aging (NIA). Data from this ACCORD substudy on the possible beneficial or adverse effects of intensive treatment on cognitive function will be obtained from a 30-minute test battery, administered at baseline and 20-month and 40-month visits. In addition, full-brain magnetic resonance imaging will be performed on 630 participants at baseline and at 40 months to assess the relation between the ACCORD treatments and structural brain changes. The general aim of ACCORD-MIND is to determine whether the intensive treatment of diabetes, a major risk factor for Alzheimer disease and vascular dementia, can reduce the early decline in cognitive function that could later evolve into more cognitively disabling conditions. This report presents the design, rationale, and methods of the ACCORD-MIND substudy. **(Am J Cardiol 2007;99[suppl]:112i–122i)**

The prevalence and incidence of type 2 diabetes mellitus increases with age.[1,2] Similarly, cognitive impairment is prevalent in older persons and increases with age. Cognitive impairment lowers the quality of life and can advance to dementia, a leading cause of long-term care placement.[3–5]

Recent studies suggest that type 2 diabetes is a risk factor for cognitive impairment in older persons. Clinical studies have shown that patients with diabetes have impaired neuropsychological function.[6,7] Diabetes has also been associated with a greater prevalence of global impairment in cognition,[8] as well as a higher incidence of cognitive de-

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cline[9] in community-based studies. For example, data from the Cardiovascular Health Study (CHS) showed that compared with those who were normoglycemic, patients with diabetes or elevated levels of serum glucose were more likely to exhibit cognitive decline over the next 7 years of follow-up.[10] In addition, recent studies have shown that diabetes is a risk factor for Alzheimer disease[11,12] and vascular dementia,[13] the 2 most common forms of dementia. Furthermore, data suggest that patients with diabetes and hypertension are more likely to have prevalent cognitive impairment than those with diabetes or hypertension alone.[14]

More sensitive radiologic tools, such as magnetic resonance imaging (MRI), have enhanced the ability to detect changes in brain structure and function, providing new opportunities for evaluating brain anatomic correlates of cognitive changes. MRI studies within the past decade have shown that patients with diabetes have an increased risk for brain atrophy[15] and lacunar infarcts.[16] As with cognitive impairment, patients with diabetes and hypertension have been shown to be at greater risk for brain atrophy than those with none or only 1 of the risk factors.[17]

A number of mechanisms are proposed by which type 2 diabetes may increase the risk for cognitive impairment. Metabolic changes in the brain associated with diabetes may affect endothelial function, protein synthesis, DNA, mitochondrial function, and the degree of free radical and inflammatory response.[18,19] At the other extreme of the glycemic-control continuum, hypoglycemic events may have the potential for a significant adverse impact on brain metabolism, which is highly glucose dependent. Hypertension, a common comorbidity with type 2 diabetes, increases the risk for vascular and endothelial damage and is associated with cognitive impairment and brain lesions. Although theoretical considerations suggest that lipid-lowering therapy may have a role in maintaining neuronal viability,[20] the relation between hyperlipidemia and cognitive impairment remains unproved.[21]

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial is designed to test whether 3 complementary medical treatment strategies for type 2 diabetes reduce the very high rate of major cardiovascular disease morbidity and mortality in this disease. The treatment strategies tested in ACCORD are (1) intensive glycemic control, (2) treatment to increase high-density lipoprotein (HDL) cholesterol and lower triglycerides (in the context of good low-density lipoprotein [LDL] cholesterol and glycemic control), and (3) intensive treatment of systolic blood pressure (in the context of good glycemic control). The overall ACCORD trial design is a double 2 × 2 factorial design in 10,251 participants with type 2 diabetes, with all participants in the overarching glycemia trial. In addition, one 2 × 2 component of the trial addresses the lipid question in 5,518 participants, while the other 2 × 2 component addresses the blood pressure question in 4,733 participants.[22] Thus, the ACCORD trial provides a unique opportunity, in the context of a randomized clinical trial, to address further the relation between cognitive impairment and type 2 diabetes, associated risk factors, and their treatment.

Study Sample

From within the overall ACCORD study population, a sample of 2,977 participants were recruited into the ACCORD Memory in Diabetes (ACCORD-MIND) substudy. ACCORD-MIND will seek to determine whether the intensity of diabetes treatment affects cognitive function and MRI-assessed brain structure. The collection of longitudinal cognitive data is planned on 3 occasions (at baseline and at 20 and 40 months) from the 2,977 participants, and the acquisition of 2 MRI brain scans (at baseline and at 40-month follow-up) is planned for 630 of these participants.

Of 7 ACCORD clinical center networks (CCNs), which provide oversight of clinics in specific regions of the United States and Canada, 6 are participating in ACCORD-MIND. These 6 networks include 54 individual clinics that recruit and provide care to patients. Clinics located within 2 hours' driving time of 1 of the 4 MRI centers are participating in the MRI substudy.

Participants eligible for ACCORD-MIND must have been randomized to glycemia control and to either the blood pressure arm or the lipid treatment arm in the overall ACCORD trial, as described elsewhere in this supplement.[22] Recruitment into, and consent for, ACCORD-MIND had to take place <45 days after randomization into the overall ACCORD trial. The collection of longitudinal cognitive data was planned in a minimum of 350 participants in each of the glycemia, lipid, and blood pressure cells of the ACCORD-MIND study (Table 1). Similarly, the MRI component of ACCORD-MIND (Table 2) planned the recruitment of 640 participants who received the cognitive evaluation. Recruitment into this component of MIND was initially confined to the blood pressure trial[14] but was opened to participants in the lipid trial when MRI recruitment lagged. The effect of the glycemia intervention will be tested across the blood pressure and lipid trials.

The overall ACCORD inclusion criteria, in addition to the following criteria, are confirmed in all participants in the ACCORD-MIND study: (1) willingness to participate in the average 5-year follow-up of the ACCORD trial and this substudy, (2) age ≥55 years, (3) English or Spanish as the usual language (for testing purposes), and (4) informed consent provided.

The exclusion criteria for ACCORD-MIND are similar to those for the overall ACCORD trial, including (1) diagnosis and treatment for cancer within the past 5 years that, in the judgment of clinical study staff members, would compromise a participant's ability to adhere to the protocol and complete the trial (exceptions could include nonmelanoma skin cancer and early-stage prostate cancer), and (2) any condition that, in the judgment of clinical study staff

Table 1
Study design for the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Memory in Diabetes Study (ACCORD-MIND) cognition substudy: 6 centers (N = 2,977)*

	Lipid Trial		BP Trial	
Glucose+	Fibrate–active drug n = 383 (n = 350)	Fibrate-placebo n = 381 (n = 350)	BP+ n = 362 (n = 350)	BP− n = 343 (n = 350)
Glucose−	Fibrate–active drug n = 399 (n = 350)	Fibrate-placebo n = 375 (n = 350)	BP+ n = 383 (n = 350)	BP− n = 351 (n = 350)

BP = blood pressure; + = intensive; – = standard
* Targeted sample sizes are in parentheses.

Table 2
Study design for the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Memory in Diabetes Study (ACCORD-MIND) magnetic resonance imaging substudy: 4 centers (n = 630)*

	Lipid Trial		BP Trial	
Glucose+	Fibrate–active drug n = 53 (n = 60)	Fibrate-placebo n = 59 (n = 60)	BP+ n = 90 (n = 100)	BP− n = 99 (n = 100)
Glucose−	Fibrate–active drug n = 62 (n = 60)	Fibrate-placebo n = 64 (n = 60)	BP+ n = 112 (n = 100)	BP− n = 91 (n = 100)

BP = blood pressure; + = intensive; – = standard.
* Targeted sample sizes are in parentheses.

members, would preclude full participation in the study (eg, preexisting clinical evidence of dementia, substance abuse).

Additional (MRI only) exclusion criteria are the following: (1) the presence of a pacemaker, cerebral aneurysm clips or other clips from previous brain surgery, metal fragments in the eyes, a neurostimulator, a Starr-Edwards heart valve (implanted before 1970), other metallic valves, severe head tremor or other problems resulting in a participant's being unable to lie supine, participant weight exceeding the limit set by the MRI manufacturer (150 kg), cochlear implants, participant size exceeding the gantry size limits, epidural catheters, or shunts with flow valves; and (2) known previous inability to complete an MRI scan because of claustrophobia.

Study Design

The ACCORD-MIND study is designed to test the primary hypothesis that, over a 40-month period, the rate of decline in cognitive function (as measured by the Digit Symbol Substitution Test [DSST] from the Wechsler Adult Intelligence Scale–Third Edition; Harcourt Assessment, Inc., San Antonio, TX)[23] and total brain volume (on the basis of MRI) will be lower in the group randomized to intensive glycemic control (target glycosylated hemoglobin [HbA_{1c}] <6.0%) compared with the group randomized to standard glycemic control (target HbA_{1c}, 7.0%–7.9%; expected median HbA_{1c}, 7.5%).

In addition, several secondary hypotheses are addressed. Specifically, in the context of good glycemic control, over a 40-month period:

- The rate of decline in cognitive function (as measured by the DSST) and MRI-based total brain volume will be lower in the group randomized to intensive blood pressure control (target systolic blood pressure <120 mm Hg) compared with the group randomized to standard blood pressure control (target systolic blood pressure <140 mm Hg).
- The rate of decline in cognitive function (as measured by the DSST) will be lower in the group randomized to receive fibrate to increase HDL cholesterol and lower triglyceride levels compared with the group randomized to receive placebo (in a double-blind context), in the presence of equivalent 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor (statin) therapy for the treatment of LDL cholesterol. Within the lipid trial, the MRI sample size will not be sufficient to address the effect of the lipid intervention on brain volume.

Additional tertiary hypotheses will be tested in ACCORD-MIND. One hypothesis is that the ability to manage diabetes and adhere to the ACCORD protocol, as measured by a 4-item questionnaire, will be better in patients in the intensive glycemic intervention arm because of less decline in cognitive function compared with those in the standard-treatment arm. In addition, MRI data from ACCORD-MIND will be analyzed for the effects of treatment on specific regions of the brain, such as the hippocampus, and on the incidence and progression of regional and total brain abnormal white matter content.

Action to Control Cardiovascular Risk in Diabetes Memory in Diabetes Study Outcomes

Cognitive outcomes: The already high participant and staff member burden within the main ACCORD trial, the large ACCORD-MIND sample size, and the multiple cen-

Table 3
The Action to Control Cardiovascular Risk in Diabetes (ACCORD) Memory in Diabetes Study (ACCORD-MIND) test battery and order of administration

Domain	Time (min)	Usual Language		Outcome Score
		English	Spanish	
Global mental status	5	MMSE	MMSE (Spanish version)	Total score
Memory I	7	RAVLT	Spanish English Verbal Learning Test	Total no. of words recalled
Psychomotor speed	2	DSST	Symbol-Digit	No. of correct entries
Executive function	7	Stroop test	Stroop test (Spanish version)	Time to complete
Depression	3	PHQ	PHQ	Total score
Memory II	4	RAVLT–Delayed Recall	Spanish English Verbal Learning Test	Total no. of words recalled

DSST = Digit Symbol Substitution Test (from the Wechsler Adult Intelligence Scale–Third Edition; Harcourt Assessment, Inc., San Antonio, TX); MMSE = Mini-Mental State Examination (Psychological Assessment Resources, Inc., Lutz, FL); PHQ = Patient Health Questionnaire (Pfizer, Inc., New York, NY); RAVLT = Rey Auditory Verbal Learning Test.

ters participating in ACCORD-MIND (n = 54) required that we design a focused cognitive battery targeted to the cognitive functions of interest, that it be easy to score, and that it could be administered within a 30-minute period. The test battery also had to be sensitive to early or mild cognitive changes that could affect daily functioning. Thus, the final ACCORD-MIND test battery was formulated to meet several objectives: (1) sensitivity to changes in memory and in information-processing speed and executive function, (2) standardization and good validation in the target age groups, (3) ease of administration, and (4) the availability of a comparable Spanish version. The test selection was based on a battery used previously as a part of a multicenter MRI study.[24]

The primary cognitive outcome of ACCORD-MIND is the score on the DSST.[23] An omnibus instrument, the DSST is designed primarily to measure psychomotor speed, but performance is also affected by memory and attention. Therefore, we expect it to be sensitive to the array of cognitive changes previously shown to be affected by diabetes. In addition, many clinical and epidemiologic studies have used the test because it has a wide distribution of scores in the target population, avoiding ceiling or floor effects. Secondary cognitive outcomes will incorporate data from of all the tests (see later) and include analyses of composite scores for memory and executive function. Executive function includes skills necessary for complex, goal-directed behavior and adaptation to environmental conditions.

Table 3 lists the composition of the cognitive test battery. In addition to the DSST, the battery includes a brief self-report questionnaire (4 questions) on cognitive ability to manage diabetes, the Mini-Mental State Examination (MMSE) (Psychological Assessment Resources, Inc., Lutz, FL),[25] the Rey Auditory Verbal Learning Test (RAVLT),[26] the Stroop test,[27,28] and a measure of depression, the Patient Health Questionnaire (PHQ) (Pfizer Inc, New York, NY).[29]

Global mental status is assessed by the 30-point MMSE. This measure, administered in about 5 minutes, has been shown to have adequate sensitivity for moderate cognitive changes. Because many studies use this instrument, we will be able to compare the levels of ACCORD-MIND participants with those of other samples.[30,31]

Verbal memory is evaluated using the RAVLT (English) and the Spanish English Verbal Learning Test (SEVLT). The study participant is read a list of 15 words 5 times. After each time the list is given, the participant is asked to immediately recall as many words as possible. After the fifth recall, an interference list is presented, after which the participant is asked to spontaneously recall words from the original list. After a 10-minute interval has passed, the participant is asked again to remember as many words as possible from the list (with a 7-minute time limit).[26]

The DSST is a symbol substitution task in which a key is presented at the top of a page showing the numbers 1–9, with each number paired with a different symbol. Below the key are paired rows of blank squares with randomly assigned displayed numbers (1–9) printed in the upper square and a blank square below each number. As rapidly as possible, the participant fills in the blanks with the symbols that correspond to the numbers in the key. The score is the total number of correctly entered symbols completed in 2 minutes.[23]

The Stroop test evaluates the ability to view complex visual stimuli and to respond to one stimulus dimension while suppressing response to another competitive stimulation. The study participant first reads aloud words denoting colors printed in black ink, then names aloud colored bars, and finally has to read aloud words denoting colors, each of which is printed in an incongruent color ink (eg, "blue" in red letters). In this modified version, 40 words and bars are used. The amount of time for the participant to perform the readings and the number of errors are recorded. A limit of 120 seconds is set for subtests I and II and 180 seconds for subtest III.[27,28]

Depression is an important covariate of cognitive function. The PHQ,[29] a simple instrument that is sensitive to specific symptoms of depression in older subjects, is administered during the prescribed 10-minute interval between the Stroop and RAVLT delayed-recall tests.

Finally, all participants will be administered 4 questions designed to assess self-reported ability to manage therapy

Table 4
Magnetic resonance imaging scan protocol and times

Step	Procedure Component	Time (min)
1	Participant preparation	9:00
2	Participant setup and positioning	2:50
3	3-plane localizer	0:14
4	Sagittal T1-W midslice image	1:03
5	Axial FSE PD T2-W image	5:20
6	Axial FLAIR T2-W image	6:24
7	Axial 3D FSPGR image	10:16
8	Remove participant from scanner	3:00
Total		38:12

FLAIR = fluid-attenuated inversion-recovery; FSE = fast spin-echo; FSPGR = fast spoiled gradient-echo; PD = proton-density; 3D = 3-dimensional; T1-W = T1-weighted; T2-W = T2-weighted.

for diabetes. These questions address areas such as difficulty remembering to monitor glucose and taking medication at the prescribed time.

The maintenance of quality control for the cognitive assessment portion of the protocol is ensured through training, certification, and monitoring. A 1-day training session on the ACCORD-MIND cognitive battery was provided at each of the network sites by the ACCORD-MIND Coordinating Center. Training included a presentation on each test in the cognitive battery, detailed instruction on the administration and scoring of each test, discussion of challenges to data fidelity, direct observation of the ACCORD-MIND battery test administration, and practice test administrations with feedback. All trainees were certified for administration of the ACCORD-MIND battery by direct observation or submitting to the Coordinating Center an audiotape of their practice administrations. Certification, with feedback, is repeated at 6 months, 1 year, and then yearly over the course of the study. Thus, each field site technician demonstrates adequate skills to administer the cognitive battery accurately and consistently. These training and certification measures were used and found to be effective in the Women's Health Initiative Memory Study (WHIMS)[30] and the Women's Health Initiative Study of Cognitive Aging (WHISCA).[31]

In addition to the training and certification of ACCORD-MIND site technicians, quality assurance of the ACCORD-MIND data will be monitored by random review of 10% of the test administrations, with feedback to the technicians, the ACCORD-MIND network coordinator, and the ACCORD-MIND CCN principal investigator. All participants are asked to provide consent for the audiotaping of ACCORD-MIND test administrations to allow ongoing review of every clinic technician's skills. Quality assurance will be conducted on administrations of the ACCORD-MIND battery conducted in English and Spanish.

MRI outcome: The primary MRI outcome is total brain volume. This measure is sensitive to multiple sources of brain pathology, including neurodegeneration and vascular injury secondary to mechanisms such as ischemia or inflammation.

MRI is a safe, noninvasive method to assess the structural characteristics of the brain. The MRI analysis protocol and sequences in ACCORD-MIND are designed to identify vascular lesions and brain atrophy that form the anatomic basis for cognitive changes and that may be associated with type 2 diabetes or the ACCORD treatments. Because differential changes in white and gray matter are hypothesized, MRI will be used to obtain longitudinal measures of infarction, lacunae, white-matter lesions, atrophy in the different lobes of the brain, and total brain volume.

The MRI scanning protocol is described in Table 4. Initially, axial, coronal, and sagittal gradient echo scout views are obtained to serve as localizers; these are important for longitudinal studies. The main sequences are an axial 3-dimensional fast spoiled gradient-echo T1-weighted sequence and a fast spin-echo proton-density T2-weighted sequence. In general, the fast spoiled gradient-echo sequence is used to study brain morphology, including volume, and the fluid-attenuated inversion-recovery and proton-density T2-weighted sequences are used to study pathology reflected by magnetic resonance signal changes. These sequences also provide the data needed to quantify total brain, gray matter, and white matter. As a result, the scan protocol will afford region-specific imaging data to identify areas in the brain that may be particularly vulnerable to diabetes, as well a comparison between treatment arms of the prevalence of white-matter lesion load and infarct-like lesions.

The ACCORD-MIND MRI Reading Center is located in the Department of Radiology at the University of Pennsylvania School of Medicine (Philadelphia, PA). The MRI Reading Center is primarily responsible for MRI Quality Control (QC), on the basis of the American College of Radiology's (ACR) MRI QC Program, which incorporates the monthly analysis of scans of an ACR–National Electrical Manufacturers Association (NEMA) QC phantom. Specific components of MRI QC include magnetic field homogeneity evaluation; slice position accuracy; slice thickness

accuracy; radiofrequency coil checks, including signal–noise ratio and image-intensity uniformity; interslice radiofrequency interference; and MRI phase stability. Each MRI field center (FC) sends monthly to the ACCORD MRI QC Center digital images of its phantom QC data for in-house review. Each FC will be responsible for keeping its ACCORD scanners within ACR performance specifications. The MRI QC Center will monitor FC adherence with the MRI QC protocol.

In addition to the phantom-based QC, a contingency QC program for major equipment changes will be done. Whenever a major equipment change (such as the installation of a new scanner) is made at an FC, not only will ACR QC phantom evaluation be made shortly before and after equipment modifications, but 10 normal participants will be scanned before and after the modification. These additional QC studies will be performed and reviewed by the MRI QC Center before any further ACCORD-MIND studies are performed. On the basis of the phantom and human studies, every effort will be made by the MRI QC Center and the FC to duplicate scanner performance before equipment modification. These data may also be used by any subsequent image analysis program to correct for any effects due to equipment change.

Analysis and Sample Size Considerations

Primary cognitive outcome: The sample size for ACCORD-MIND was based on estimates of the mean ± SD of DSST scores collected in the CHS.[32] The analysis of ACCORD-MIND will be performed as a contrast of the 40-month mean DSST scores within the framework of a repeated-measures analysis of covariance. DSST scores collected at 20 and 40 months will be used as outcomes, and the baseline DSST measurement will be a covariate. Indicators of CCNs and main effects for treatment groups will be included in the model. The sensitivity of conclusions to assumptions about missing outcomes will be assessed using pattern-mixture models.[33,34]

The sample size for the cognitive portion of ACCORD-MIND was calculated to obtain adequate power for comparing average DSST scores between randomized groups. On the basis of progression rates of DSST scores in CHS,[32] we estimated that the glycemia intervention should result in a difference of approximately ≤1.08 in mean cognitive function between the standard and intensive groups at the 40-month follow-up. The standard deviation of the follow-up means was estimated to be 12.5 and the correlation between baseline and follow-up measurements to be approximately 0.80.

For the planned comparison of cognitive function between the intensive glycemic control and standard glycemic control groups, using a 2-sided significance level of 0.05, a sample of 1,200 per group provides approximately 90% power to detect a difference of 1.0 between 40-month mean DSST scores. For the comparison of cognitive function between the intensive blood pressure control and standard blood pressure control groups (or fibrate versus placebo in the lipid trial), using a 2-sided significance level of 0.05, this sample size will provide approximately 80% power to detect a difference of 1.2 on the 40-month mean DSST scores. To account for a 15% loss to follow-up, the recruitment of ≥350 participants was planned within each cell.

Primary MRI outcome: The final analysis of the MRI data collected in ACCORD-MIND will use analysis of covariance to compare the mean total brain volume between randomized groups, controlling for the baseline MRI value as a covariate. Indicators of CCNs and main effects for treatment groups will be included in the model. The sensitivity of conclusions to assumptions about missing outcomes will be assessed using pattern-mixture models.[33]

The sample size for the MRI component was based on unpublished data from the Baltimore Longitudinal Study of Aging (BLSA) (S. Resnick, personal communication, April 23, 2002). From the data, we projected the mean 40-month volume in the standard glycemic control group to be 18.33 cm^3, the variance of follow-up measurements to be 9.200 $(cm^3)^2$, and the correlation between baseline and follow-up measurements to be 0.992. Assuming a 20% effect size for all interventions, we projected the 40-month difference in means between the intensive and standard groups to be 3.3 cm^3. After accounting for a 15% nonresponse rate, and assuming a 2-sided level of significance of 0.05, the planned sample size of 320 per glycemia-control group provides approximately 90% power to detect this 3.3-cm^3 difference between groups. With approximately 200 blood pressure trial participants in each arm, we will have approximately 70% power to detect a 20% effect of the blood pressure intervention (a 3.3-cm^3 difference between groups), assuming a 15% nonresponse rate, an underlying 20% glycemia effect size, and a 2-sided significance level of 0.05. The sample size of 120 per group in the lipid trial does not provide adequate power to test for the 3.3-cm^3 difference associated with a 20% effect size, but these data are used when testing the glycemia hypothesis.

Conclusion

Because it is nested within the ACCORD trial, ACCORD-MIND provides a unique opportunity to investigate the relations among diabetes, treatment intensity, and change in cognitive performance within a randomized clinical trial. The ACCORD sample size, interventions, core measurements, and follow-up procedures present a population and study design that could not otherwise be duplicated. ACCORD-MIND provides a new opportunity for the important health outcome of cognitive function to be incorporated into the arena of large clinical trials examining treatment for a prevalent chronic condition (other than trials involving patients with prevalent dementia).

There are a number of additional benefits to the field of diabetes research as a result of the ACCORD-MIND substudy. First, the addition of cognitive tests may provide important insights as to the reasons some patients with type 2 diabetes develop difficulties in medication adherence and management of their treatment regimens. ACCORD-MIND data may also provide additional important safety data regarding the effects of hypoglycemia. In contrast to previous studies, this study not only will allow us to test prospectively the effectiveness of the various interventions on brain outcomes but will also provide the opportunity to study in more detail which cognitive functions are affected by diabetes or its treatment (through separate analyses of the cognitive domains included in the test battery) and to explore the anatomic correlates of such impairments. We will also have data to evaluate functional correlates, including depression and medication adherence. Finally, the MRI data can be used to estimate the effect of treatment on subclinical cerebrovascular end points that may not be detected by study personnel and clinicians.

With the recent discontinuation of large clinical trials, one on whether estrogen prevents or delays dementia[30] and cognitive decline[31] and another on whether nonsteroidal anti-inflammatory drugs prevent or delay the onset of dementia,[35] ACCORD-MIND is currently one of the largest ongoing clinical trials in existence evaluating the primary prevention of cognitive dysfunction. The burden of cognitive impairment and dementia is a growing public health concern, and to date, there is no clinical trial evidence that the treatment of any risk factor is associated with the prevention or delay of cognitive decline. In this context, ACCORD-MIND has substantial potential to affect public health and expand our understanding of the biologic basis of dementia.

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