Type 2 diabetes and cognitive impairment are 2 of the most common chronic conditions found in persons 60 years and older. After that age, approximately 18% to 20% of older persons have diabetes,1 approximately 19% suffer from mild cognitive impairment in multiple domains,2 and approximately 6% of community-dwelling individuals have some dementia.3 The prevalence of mild cognitive impairment and dementia increases with age as does the prevalence of diabetes; there is also an alarming trend toward a younger age of diabetes onset.4 Several lines of investigation suggest a link among diabetes, cognitive impairment, and dementia, described briefly subsequently. Thus, the age-related trends in diabetes and cognitive disorders indicate a further increase in the number of persons with mild cognitive impairment and dementia, beyond the increase that is expected as the population ages.

**What Is the Evidence Linking Diabetes to Late-Age Cognitive Disorders?**

Clinical studies have shown impaired neuropsychological functioning in patients with diabetes.5 Compared with community-dwelling normoglycemic persons, those with diabetes have a higher prevalence of global cognitive impairment6 and a higher incidence of cognitive decline.7 Population-based studies have also shown that diabetes is a risk factor for Alzheimer disease (AD),8–11 the most common form of dementia.

The association of diabetes to cognitive disorders may be moderated by a spectrum of factors that range from healthcare access to genetic susceptibility. For example, data from several studies suggest those with diabetes and who are apolipoprotein E ε4 allele (a genetic susceptibility risk factor for AD) carriers are at higher risk for a cognitive disorder than those with no diabetes and no ε4 allele, or either one alone.12–14 Wu15 showed in the SALSA study of Hispanics that characteristics of diabetes, including treatment and duration, were associated with global cognitive function: longer duration was associated with lower cognitive function and treatment with higher function. Additional modulation of risk may come from comorbidities of diabetes. For instance, between diabetes and hypertension has been reported to increase the risk for global atrophy16 and performing poorly on a test of visual memory.17

The metabolic and hemodynamic profile of diabetes, including comorbidities such as hypertension, hyperinsulinemia, and obesity,18 modulates vascular health and neuronal survival through multiple mechanisms. Pathophysiological mechanisms that have been identified include inflammation, oxidative stress, energy imbalance, protein misfolding, glucocorticoid-mediated effects, and differences in gene expression.19–24 More recently, several endocrine proteins, angioteins (ie, vascular endothelial growth factor) have been shown to modify both vascular health and neuronal survival.25 Finally, genetic findings may identify new pathways contributing to diabetes that may also contribute to cerebral disease.26

In the context of rapidly increasing evidence that diabetes can have a critical role in disease causing mixed cerebral brain pathophysiology, type 2 diabetes cerebral disease is still largely considered to be large vessel infarction. It is notable from recent reviews27 that little is known about the prevalence and incidence of brain changes or the functional sequelae of small and microvascular cerebral disease in persons with diabetes. For instance, does microvascular disease, common in diabetes-related peripheral neuropathy, nephropathy, and retinopathy, extend to the brain?

**Integrated Community-Based Studies of Diabetes and the Brain**

Despite major gaps in our knowledge of the interaction of diabetes and cerebral disease, an increasing body of data suggest the hypothesis that diabetic pathologies lead to both the AD-type neurodegeneration as well as vascular damage, and it is this mix of these diseases that forms the anatomical basis for clinical and subclinical cognitive impairment in diabetes. To test this hypothesis, an integrated vertical approach is needed that is based on multiple measures of brain structure/function. The Honolulu Asia Aging Study (HAAS),9 the Age Gene/Environment Susceptibility–Reykjavik Study (AGES-Reykjavik Study),28 and the Memory in Diabetes (MIND)29 substudy embedded in the ACCORD trial30 provide the opportunity to take this approach.
The HAAS began in 1991 as a continuation of the Honolulu Heart Program, a population-based longitudinal study of Japanese-American men born between 1900 and 1919 and living in Oahu, Hawaii, when the study began in 1965. Participants were seen at 3 midlife examinations (1965 to 1968, 1968 to 1970, 1971 to 1974) and at 4 examinations in late life (1991 to 1993, 1994 to 1996, 1997 to 1999; 2001 to 2002). Clinical measurements, demographic information, and medical information were collected at each examination. Starting in 1991, global cognitive function was measured in the total sample and cases of dementia ascertained. An autopsy study nested within the cohort was also started in 1991; an MRI substudy of 575 men was performed in 1995 to 1996.

The AGES-Reykjavik Study is a population-based follow-up study of men and women born from 1907 to 1934. The cohort was established in 1967 by the Icelandic Heart Association; participants were examined up to 6 times. From 2002 to 2006, 5764 cohort members were re-examined as a part of the AGES-Reykjavik Study. All participants were administered a battery of cognitive tests of speed, memory, and working memory; and all eligible participants underwent a brain MRI. Retinal photographs, which provide a measure of microvessels, were also acquired.

HAAS has provided valuable insights on the association of diabetes and related risk factors, high blood pressure and hyperinsulinemia, to clinical disease and brain pathology. In this cohort, diabetes is associated with both vascular disease, ie, infarcts, and neurodegenerative changes, ie, hippocampal atrophy, which are frequently seen in AD. Consistent with the findings on clinical AD, we found those with diabetes and an apolipoprotein E ε4 allele, compared with those with neither, had an increased risk for cerebral amyloid angiopathy, neuritic plaques, and neurofibrillary tangles, all common markers in AD.

To further address the question of microvascular disease in older persons with diabetes, we examined the association of cerebral microbleeds to retinal lesions in the AGES-Reykjavik Study. We found an increased risk for multiple microbleeds in the presence of arteriovenous nicking (2.47; 95% CI, 1.42 to 4.31) and retinal hemorrhages (2.28; 95% CI, 1.24 to 4.18). These associations were stronger in diabetic subjects compared with nondiabetic subjects, suggesting microvascular disease may extend to the brain of persons with diabetes.

These brain structure studies establish an association of diabetes to neurodegenerative and vascular brain pathology. Experimental data are needed to articulate mechanisms (ie, see ). From an epidemiological perspective, longitudinal assessments of macro- and microstructural changes are needed to better understand the trajectory and functional consequences of diabetes-related cerebral disease.

In addition to studying the possible physiological contribution of diabetes to late-age brain pathology, studies of diabetes disease management and cognitive disorders are needed.

ACCORD MIND is a substudy embedded in the clinical trial ACCORD, which is designed to investigate the efficacy of intensive (to reduce HbA1C to <6.0%) versus standard treatment (to obtain HbA1C of 7% to 7.9%) of hyperglycemia to reduce cardiovascular events. MIND aims to test the effect on brain structure and function of intensive treatment compared with standard treatment. This comparison takes on new dimensions because the intensive glycemic arm of ACCORD was recently stopped for safety reasons. Analyses are in progress to understand the effect of treatment strategy on brain outcomes. In addition, several other important questions will be addressed such as how cognitive disorders influence an individual’s ability to follow a disease management protocol and whether frequent hypoglycemia events contribute to cognitive dysfunction.

In summary, data suggest, compared with nondiabetic individuals, those with diabetes have brain structural changes that reflect neuronal degeneration as well as vascular damage, and it is likely diabetes leads to microstructural changes not seen on standard MRI. Many factors modulate the strength of the association between diabetes and brain structure/function. Areas of interest to further investigate include pathophysiology of diabetes and the brain, genetic contributions to the associations of diabetes and brain, and the clinical and functional consequences of diabetes.

Sources of Funding
AGES-Reykjavik is supported by the National Institutes of Health contract N01-AG-12100, the National Institute on Aging Intramural Research Program, Hjartavernd (the Icelandic Heart Association), and the Althingi (the Icelandic Parliament). Components of the study were also supported by the National Eye Institute, the National Institute on Deafness and Other Communication Disorders, and the National Heart, Lung, and Blood Institute. HAAS has been supported by the Intramural Research Program of the National Institutes of Health, the National Institute on Aging (grants U01 AG019349 and R01 AG0-17155 S1), and the National Heart, Lung, and Blood Institute (grant N01 HC05102).

Disclosures
None.

References
7. Gregg EW, Yaffe K, Cauley JA, Rolka DB, Blackwell TL, Narayan KM, Cummings SR. Is diabetes associated with cognitive impairment and

**KEY WORDS:** diabetes ■ vascular dementia
Diabetes: Vascular or Neurodegenerative: An Epidemiologic Perspective
Lenore J. Launer

Stroke. 2009;40:S53-S55; originally published online December 8, 2008;
doi: 10.1161/STR0039-2499.108.533075
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2008 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://stroke.ahajournals.org/content/40/3_suppl_1/S53

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published
in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office.
Once the online version of the published article for which permission is being requested is located, click
Request Permissions in the middle column of the Web page under Services. Further information about this
process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org/subscriptions/