ELSEVIER

Alzheimer's & Dementia ■ (2017) 1-10

Alzheimer's & Dementia

Featured Article

# Brain function and structure and risk for incident diabetes: The Atherosclerosis Risk in Communities Study

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**Abstract**

**Introduction:** Diabetes is prospectively associated with cognitive decline. Whether lower cognitive function and worse brain structure are prospectively associated with incident diabetes is unclear.
**Methods:** We analyzed data for 10,133 individuals with cognitive function testing (1990–1992) and 1212 individuals with brain magnetic resonance imaging (1993–1994) from the Atherosclerosis Risk in Communities cohort. We estimated hazard ratios for incident diabetes through 2014 after adjustment for traditional diabetes risk factors and cohort attrition.
**Results:** Higher level of baseline cognitive function was associated with lower risk for diabetes (per 1 standard deviation, hazard ratio = 0.94; 95% confidence interval = 0.90, 0.98). This association did not persist after accounting for baseline glucose level, case ascertainment methods, and cohort attrition. No association was observed between any brain magnetic resonance imaging measure and incident diabetes.
**Discussion:** This is one of the first studies to prospectively evaluate the association between both cognitive function and brain structure and the incidence of diabetes.


*Keywords:* Cognitive function; Brain magnetic resonance imaging; Incident diabetes; Epidemiology; Prospective

## 1. Introduction

Diabetes is an established risk factor for cerebrovascular disease [1], cognitive decline [2], increased risk of dementia [3], and greater burden of degenerative and vascular brain pathology [4,5]. This suggests that hyperglycemia precedes cognitive decline or structural changes to the brain. However, diabetes, dementia, and neurodegeneration share similar risk factors and may have long overlapping preclinical phases [6–10]. Diabetes is shown to have complex associations with other conditions of the brain; for example, diabetes and depression are shown to independently predict the incidence of the other [10,11]. Mouse models of Alzheimer's disease (AD) suggest cerebral amyloidosis may produce subsequent metabolic dysfunction [12]. Therefore, it may be informative to investigate whether brain structure and cognitive function influence glucose metabolism over time.

Recent epidemiological evidence suggests an association between baseline level of cognitive function and subsequent development of impaired fasting glucose and diabetes [13–15]. However, determination of baseline brain health in these studies is limited to cognitive assessment only.

The authors have declared that no conflict of interest exists.

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http://dx.doi.org/10.1016/j.jalz.2017.04.006
1552-5260/

Wechsler noted that factors not indicative of cognitive function per se, such as experience and familiarity with testing and socioeconomic structures, may influence performance on cognitive assessments [16]. Magnetic resonance imaging (MRI) may provide a complementary method to characterize brain health where the method of measurement is less subject to these factors. Structural characterization of the health of the brain is needed to identify the underlying cerebral pathophysiology of this potential association and provides a biological anatomic marker for measurement and intervention. Investigation of this relationship may help clarify the natural history, changes in brain structure, and risk factors for cognitive dysfunction in diabetes [17].

Our first aim (aim 1) was to assess the association between cognitive function in middle adulthood and the development of diabetes in later adulthood. The second aim (aim 2) was to evaluate the association between three structural measures obtained from brain imaging in middle adulthood and the development of diabetes in later adulthood. We hypothesized that lower cognitive function and greater brain atrophy and white matter hyperintensity (WMH) volume would be associated with an increased incidence of diabetes after taking into account traditional diabetes risk factors.

## 2. Methods

The Atherosclerosis Risk in Communities (ARIC) study, initiated in 1987, used probability sampling to select, recruit, and enroll individuals drawn from four US communities: Forsyth County, NC; the City of Jackson, MS; seven suburbs of Minneapolis, MN; and Washington County, MD [18]. Each field center enrolled men and women aged 45 to 64 years reflecting the racial/ethnic makeup of the community, with the exception of the Jackson cohort, which only enrolled blacks, for a cohort total of 15,792 study participants in 1987 to 1989. Participants have been invited to participate in five clinical examinations in 1987 to 1989, 1990 to 1992, 1993 to 1995, 1996 to 1998, and 2011 to 2013 and receive annual follow-up telephone calls to update health-related developments occurring since the last contact. Participants gave written informed consent, and the ARIC study procedures were reviewed and approved by each institution's review board.

### 2.1. Assessment of cognitive function

Cognitive function was first assessed on all ARIC participants present at visit 2 (1990–1992). Cognitive function was measured with three neuropsychological tests: Delayed Word Recall (DWR), Digit Symbol Substitution Test (DSST), and first-letter Word Fluency Test (WFT). The DWR assesses memory and is composed of a set of 10 common nouns presented to participants and asked to recall after a 5-minute interval. The test shows fair test-retest reliability reassessed at 6 months over a 6 month period ($r = 0.75$), with high specificity and sensitivity for dementia at a cutoff of 3 or more correct words recalled (specificity = 0.98; sensitivity = 0.89) [19]. The DSST is a test requiring the participant to associate numbers with unique symbols, testing sustained attention and psychomotor speed [16,20]. Test-retest reliability in middle-aged adults is 0.82 [20]. The WFT requires participants to produce as many words as possible that begin with three different letters of the alphabet [21]. This test measures verbal function and mental agility in retrieving words, scored as the sum of all three trials [22]. Forms of this test have high test-retest reliability reassessed between 19 to 42 days in normal middle–aged adults ($r = 0.81$–$0.88$) [23].

### 2.2. Brain MRI

Basic details of MRI measurement and imaging analysis have been described previously [24,25]. Briefly, during the first 2 years of the ARIC visit 3 wave (1993 and 1994), 1.5-T MRI scanners (GE Signa or Picker) were used to capture brain images for selected participants at the Mississippi (MS) and North Carolina (NC) field centers. ARIC participants at the MS and NC field centers who were aged $\geq$55 years at the time of their visit 3 examination were eligible for the cerebral MRI examination. Participants were screened for the MRI evaluation and individuals with contraindications were ineligible for MRI. A total of 2891 participants were screened for eligibility and after excluding ineligible participants and those who declined participation, 1949 participants underwent cerebral MRI [26].

Scans were interpreted at the ARIC MRI Reading Center at Johns Hopkins Medical Institutions and assigned a grade using a validated scoring protocol [24,25]. Each image had a primary and secondary interpretation adjudicated by different board-certified radiologists, blinded to a participant's characteristics. Brain MRI measures included ventricular size (VS), sulcal size (SS), and WMHs. Each MRI measure was evaluated according to a semiquantitative 10-point scale with visual pattern matching. For example, each image for VS was compared with a series of eight images of successively increasing VS ranging from "small and presumably normal" (grade 1) to "severe atrophy" (grade 8). Images with ventricles smaller than those in grade 1 received a grade of 0 and those worse than a grade 8 received grade 9. Images for SS were graded in a similar fashion. WMHs were estimated as the total volume of periventricular and subcortical white matter signal abnormality, similarly by visual comparison with eight images that successively increased from "barely detectable white matter changes" (grade 1) to "extensive, confluent changes" (grade 8). Images interpreted as no white matter change received grade 0 and those with changes more significant that grade 8 received grade 9. This grading system is shown to have high intrareader reliability for VS ($\kappa = 0.89$) and WMH ($\kappa = 0.81$) and moderate reliability for SS ($\kappa = 0.66$) [27].