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The influence of subclinical cardiovascular disease and related risk factors on cognition in type 2 diabetes mellitus: The DHS-Mind study

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Abstract

We hypothesized that measures of coronary artery calcified plaque (CAC) collected at baseline from the Diabetes Heart Study (DHS) would explain associations between cognition and diabetes collected at follow-up approximately 7 years later. The DHS is a sibling study of cardiovascular disease (CVD) in a cohort with a high prevalence of type 2 diabetes (~80%). Associations between baseline CAC and cognitive performance were tested using generalized estimating equations and mixed effects models to adjust for familial relationships. Diabetes status was associated ($p < 0.05$) with poorer performance on tests of verbal memory, processing speed, and semantic fluency adjusting for age, sex, education, and hypertension status. As hypothesized, including CAC in the statistical model attenuated this association. Additionally, CAC and fasting glucose predicted performance in tasks not associated with diabetes status in this study (Stroop Task, Phonemic

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Duality of Interest

The authors report no conflicts of interest.

Contribution Statement

C.E.H. wrote the manuscript and completed the analyses. F.C.H. and S.H. supervised the analyses, gave statistical support, and contributed to the manuscript. J.J.C. is responsible for acquisition and processing of the measures of subclinical CVD and contributed to the manuscript. B.I.F. oversaw subject recruitment and clinical visits and contributed to the manuscript. D.L.N. consulted on neuropsychological testing and contributed to the manuscript. J.D.W. oversaw cognitive testing and contributed to the manuscript. D.W.B. oversaw the DHS studies, contributed to the manuscript, and is the guarantor of the data.

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Fluency). These results confirm work attributing the heterogeneity of cognitive outcomes in type 2 diabetes to subclinical risk factors that combine to affect different aspects of brain function. Importantly, these results imply that risk factor intervention should begin before comorbidities, particularly CVD, become clinically apparent.

Keywords

type 2 diabetes; cardiovascular disease; atherosclerosis; cognition

Introduction

Type 2 diabetes mellitus (T2DM) is a complex disorder that affects multiple organ systems, including the brain. Risk factors associated with T2DM are linked to cognitive performance in non-diabetic subjects, most prominently glucose regulation (Lamport, Lawton, Mansfield and Dye, 2009), hypertension (Novak and Hajjar, 2010) and cardiovascular disease (CVD) (Warsch and Wright, 2010). There is evidence that even subclinical variations in these factors in non-diabetic people may be linked to cognitive decline (Dahle, Jacobs and Raz, 2009).

T2DM increases the risk for dementia (Leibson, et al., 1997, Ott, et al., 1999, Peila, Rodriguez and Launer, 2002). It is also associated with poorer functioning in a variety of cognitive domains (Arvanitakis, et al., 2006, Awad, Gagnon and Messier, 2004, Brands, et al., 2007, Cukierman-Yaffe, et al., 2009, Nguyen, et al., 2010) comparable to the cognitive deterioration associated with normal aging (Reijmer, et al., 2010). While there is consensus that T2DM negatively contributes to cognitive function, there is significant variability across studies in the cognitive domains affected by diabetes, and some question whether a specific association exists at all [for review, see (Awad, Gagnon and Messier, 2004, Reijmer, et al., 2010)].

Multiple studies have observed that when clinically evident CVD is included in models of cognition in T2DM, it explains much of the variation in cognitive performance associated with T2DM (Manschot, et al., 2007, Ruis, et al., 2009, van den Berg, et al., 2006). Individuals with T2DM also have an increased risk for subclinical markers of CVD, such as greater carotid artery intima media thickness (IMT) (Mykkanen, et al., 1997) and increased amounts of calcified atherosclerotic plaque in coronary and carotid arteries (Hoff, et al., 2003, Schurgin, Rich and Mazzone, 2001). In non-diabetic subjects, CAC has been associated with poorer cognition (Rosano, et al., 2005, Vidal, et al., 2010). However, the association between vascular calcification and cognition in people with T2DM is not well studied.

The Diabetes Heart Study-Mind (DHS-Mind), a follow-up study to the Diabetes Heart Study (DHS), provides a unique opportunity to examine relationships between cognitive function, vascular calcified plaque and other major diabetes risk factors associated with cognition. The DHS investigated CVD in siblings with a high incidence and prevalence of T2DM, where extensive measurements of CVD risk factors were obtained during exams that occurred from 1998 – 2006. Measures included CAC, carotid artery calcium (CarCP), and carotid artery IMT. The ongoing DHS-Mind study is a follow-up study that began in 2008. The DHS-Mind added cognitive testing to existing measures with the express purpose of exploring the relationships between measures of atherosclerosis and cognition in a population enriched for diabetes, a novel approach given that previous studies have focused on diabetes and cognition in the context of clinically evident CVD. In addition, unlike a typical case-control study, elements of genetic and environmental background, which are

common confounds in case-control studies of T2DM, are shared between affected and unaffected siblings in this population. Therefore, we examined associations between cognition and T2DM risk factors in the DHS-Mind cohort.

Methods

Subjects

The DHS Mind is a follow-up to the DHS, a family-based genetic study that began in 1998 and included 1443 subjects of European American and African American descent. The DHS Mind aimed to re-recruit as many of these participants as possible, with a focus on those of European descent, and then recruit from the community to complete enrollment. The DHS Mind is currently ongoing, but the portion of the study re-recruiting DHS participants is complete. The study sample for the analyses reported here consisted of 516 European American participants who completed the DHS and follow-up DHS-Mind and had both coronary calcification and cognitive testing data. Of these, 422 were affected with T2DM and 94 were unaffected.

Recruitment and ascertainment of these subjects has been described in detail (Bowden, et al., 2010, Wagenknecht, et al., 2001). Briefly, this family study examining genetic contributions to CVD and T2DM recruited siblings concordant for diabetes without evidence of advanced renal insufficiency. Potential subjects were excluded if they were on dialysis. Individuals were considered to have T2DM if they developed diabetes after the age of 34 years and were treated with insulin and/or oral agents without historical evidence of ketoacidosis. To complement these diagnostic criteria, fasting glucose and glycosylated hemoglobin (HbA_{1c}) were measured at baseline and the follow-up DHS Mind visit.

Siblings without T2DM were included if they had at least two enrolled diabetes-affected siblings meeting the above criteria. Participants who self-reported being unaffected were coded as affected if they reported taking insulin or oral agents, or presented with HbA_{1c} greater than or equal to 6.5%. Participants classified as unaffected were unaffected at both visits. In order to avoid problems with diabetes classification, participants (n = 30) were excluded from this analysis if they were not affected with diabetes at the baseline visit when CAC was measured, but were affected at the follow-up visit when cognition was tested, as determined by self-report of diagnosis of diabetes or HbA_{1c} greater than or equal to 6.5%.

All subjects provided written informed consent. Study protocols were approved by the Wake Forest School of Medicine Institutional Review Board and conducted in accordance with the Declaration of Helsinki.

Study Design

The parent DHS consisted of one study visit during which a medical history, demographic information, standard laboratory measures (e.g., fasting cholesterol, triglycerides) and multiple measures of cardiovascular health were collected. Measures of vascular calcified plaque included Agatston scores derived from computed tomography (CT) measures of coronary (CAC) and carotid (CarCP) arteries. In addition, IMT of the wall of the common carotid artery was measured using B-mode ultrasonography. Detailed methods have been described (Bowden, et al., 2008). This cohort is being re-examined in the DHS-Mind study, which began in 2008. Participants returned an average of 6.7±1.6 years after their initial visit.

In the DHS-Mind, participants were administered a battery of cognitive tests including the Digit Symbol Substitution Task (DSST) (Wechsler, 1981), the Modified Mini-Mental State Examination (3MSE) (Teng and Chui, 1987), Phonemic Fluency via the Controlled Oral

Word Association Task (COWA), Semantic Fluency (Benton, Hamsher and Sivan, 1994, Strauss, Sherman and Spreen, 2006), the Stroop test (Houx, Jolles and Vreeling, 1993), and the Rey Auditory-Verbal Learning Task (RAVLT) (Lezak, Howieson and Loring, 2004).

DSST performance was defined as the number of correct responses within 2 minutes. In this analysis, the measure derived from the Stroop test was the ratio of response times for subtest 1 to subtest 3. The metric of Phonemic Fluency was the sum of words generated for three different letters (F, A, S). Semantic Fluency was measured as the sum of words generated for two different categories (kitchen, animals). The RAVLT measure employed was the sum of words remembered across the first 5 trials.

Although most subjects completed all the cognitive tasks, there were a small number who did not. Forty-two participants were part of a pilot feasibility study and did not complete the Phonemic or Semantic fluency tasks. In addition, participants who reported being color-blind or missed a significant number of questions on the color-naming portion of the task were excluded from analysis of the Stroop test (n=6). DSST scores were missing for 3 subjects due to problems with writing (n=1) and vision (n=2). The RAVLT and MMSE were not completed by one subject each. One subject had an extremely low score on the 3MSE and was unable to complete the other tasks, in part due to vision problems. 3MSE models were computed with and without this subject. Inclusion of the subject did not change the statistical results, so the data were included.

Analyses

Statistical analysis was completed using SAS software version 9.2 implemented with SAS Enterprise Guide 4.3 software (SAS Institute, Cary, NC, USA). Statistical significance was defined as a p-value ≤ 0.05 . Summary statistics such as means and standard deviations were computed for the normally distributed continuous characteristics; medians and interquartile ranges were computed for non-normally distributed continuous characteristics; and counts and frequencies were computed for discrete characteristics separately for those with and without diabetes (Table 1). Average differences between those affected and unaffected with diabetes were assessed using generalized estimating equations (GEE) (Liang and Zeger, 1986) to account for the familial correlation, but were otherwise unadjusted. Data from the Stroop test and measures of CAC, CarCP, IMT, and fasting glucose were transformed with a natural log to approximate a normal distribution.

A mixed effects model was used to test for associations between risk factors associated with T2DM and cognitive performance. The covariance arising from sibling relationships was accounted for by including family as a random effect. Cognitive tests including 3MSE, DSST, Stroop, Phonemic Fluency, Semantic Fluency, and RAVLT were treated as dependent variables. Cognitive test scores were standardized by calculating z-scores for each measure to facilitate comparison across tasks.

Covariates of interest included presence of diabetes, CAC, CarCP, IMT, fasting glucose, HbA_{1c}, BMI, smoking, and hypertension. All variables except those for subclinical CVD (CAC, CarCP, IMT) were collected at both baseline and follow-up. Follow-up measures that were contemporaneous with cognitive testing were used as covariates unless otherwise noted. Age, sex, and educational attainment were included in all models.

In cross-sectional studies hypertension is associated with poorer cognitive performance, white matter lesions, and brain atrophy [see (Novak and Hajjar, 2010) for review], and hypertension at baseline has been observed to correlate with cognitive performance at follow-up (van den Berg, et al., 2009). Presence of hypertension was defined as self-report of diagnosis, observed diastolic blood pressure > 90 mmHg or systolic blood pressure > 140

mmHg, or use of antihypertensive medication. Presence of hypertension at follow-up was selected empirically for use in these models instead of systolic blood pressure, diastolic blood pressure, pulse pressure, or presence of baseline hypertension because hypertension status achieved significance in preliminary models, while the other variables did not.

Microvascular disease has also been associated with cognitive performance and brain lesions, particularly renal insufficiency (de Bresser, et al., 2010, Jacobson, et al., 2011, Murray, 2008, Murray, et al., 2011, Seliger, et al., 2004) and retinopathy (Ding, et al., 2008, Kim, et al., 2011, Longstreth, et al., 2007, Manschot, et al., 2007, Qiu, et al., 2010). Collecting data on microvascular disease was not a primary aim of the DHS Mind, but data were collected on renal insufficiency (albumin/creatinine ratio, estimated glomerular filtration rate (eGFR)) and self-reported retinopathy). A microvascular disease composite was constructed where 1 point was given for self-reported laser eye surgery for retinopathy and 1 point was given for an eGFR less than or equal to 60 ml/min.

To fairly contrast different models, model building was performed on a subset of 335 participants (252 affected, 83 unaffected,) who had complete data for all variables of interest. Variables that were missing data in more than 5 individuals included, fasting glucose and HbA_{1c} (n=45), Stroop task (n=6), Phonemic and Semantic Fluency (n=46), CarCP (n=7), and IMT (n=55). Participants who were part of the pilot study for the DHS Mind (n=42) were missing Phonemic Fluency, Semantic Fluency, HbA_{1c} and fasting glucose. Missing data occurred equally in men and women, and there was no significant difference in age or diabetes duration between those included in the 335 and those not. The following variables were included in the model with basic covariate adjustment one at a time: presence of T2DM, fasting glucose, HbA_{1c}, BMI, smoking, CAC, CarCP, and IMT. The model with the minimum value for Akaike's information criterion (AIC) was identified as the optimal model for the specific outcome measure. Final analyses aimed to maximize the available data by using all available data points for each measure and were applied to the full data set.

Results

Characteristics of the study sample are shown in Table 1, which summarizes and compares T2DM-affected and unaffected subjects adjusting for family relationships only. The two measures of calcified atherosclerotic plaque (CAC, CarCP) and carotid artery IMT were significantly higher in those with diabetes ($p < 0.0001$). On the cognitive tests, siblings affected with T2DM performed worse than the group who were unaffected with T2DM on the DSST ($p = 0.003$), RAVLT ($p = 0.0003$), 3MSE ($p = 0.001$), and Semantic Fluency ($p = 0.007$). Scores were lower in those with diabetes on the Stroop test and Phonemic Fluency, but these comparisons failed to reach statistical significance. Next, the relationships between the cognitive measures and T2DM status were tested using progressive models, beginning with the covariates age, sex, and education.

Associations between cognitive performance, T2DM status, and CAC

All cognitive variables were tested for association with T2DM after adjusting for age, sex, and education using a mixed models analysis. Performance on the DSST ($\beta = -0.18$, $p = 0.04$), RAVLT ($\beta = -0.22$, $p = 0.01$), and Semantic Fluency ($\beta = -0.21$, $p = 0.04$) were modestly associated with T2DM status (Table 2, Model 1). After adjusting for age, sex, and education, T2DM status was not associated with performance on the 3MSE, Stroop test, or Phonemic Fluency.

Coronary Artery Calcium burden was highly associated with cognitive performance areas that are typically affected in persons with T2DM (Table 2, Model 2). Poorer performance on

the DSST ($\beta = -0.05$, $p = 0.002$), RAVLT ($\beta = -0.05$, $p = 0.0003$), and Semantic Fluency ($\beta = -0.05$, $p = 0.007$) was associated with increased CAC burden after adjusting for age, sex, and education.

The association between T2DM status and cognitive performance disappeared when we included CAC burden in the analysis. These results are seen in Model 3, Table 2 where CAC and T2DM status were modeled together, also adjusting for age, sex, and education. For all three cognitive tests, inclusion of CAC reduced the association with T2DM status to non-significance. The percent change in the regression coefficient for T2DM status was calculated between Models 1 and 3. Addition of CAC to Model 1 for the DSST resulted in a 38.9% decrease in the magnitude of the coefficient for T2DM status, for the RAVLT it led to a 36.4% decrease, and a 33.3% decrease for Semantic Fluency.

Best fit models

Table 2 shows the analytic models found to be the best fit for explaining variance in the three cognitive tests associated with T2DM status (Models 4 and 5). For model fitting, we included in the “base” model age, sex, education and hypertension, factors that have been reliably associated with cognitive performance. Additionally, the best fit model for both the RAVLT and Semantic Fluency was the base model + CAC (Model 4, Table 2). Finally, the best fit model for the DSST was the base model + CAC and IMT. BMI and smoking were not associated with cognition in any model.

Associations with other relevant factors: hypertension and microvascular disease

The above results show that vascular calcification is an important predictor of cognitive performance. However, they do not address hypertension or microvascular disease, important vascular risk factors associated with T2DM and cognitive performance.

The DSST was the only cognitive test that showed significant associations with hypertension. Scores on the DSST were associated with hypertension ($\beta = -0.33$, $p = 0.001$) after adjusting for age, sex, and education. When hypertension and T2DM status were modeled together, the association with hypertension remained significant ($\beta = -0.30$, $p = 0.005$), but the association between DSST and T2DM status was reduced to non-significance ($\beta = -0.12$, $p = 0.19$), a 33.3% decrease in the magnitude of the regression coefficient for T2DM status. Adding hypertension to Model 3 did not affect the magnitude of the regression coefficient for CAC, but did reduce the regression coefficient for hypertension by 13.3% ($\beta = -0.26$, $p = 0.01$) relative to the model including hypertension and T2DM.

Microvascular disease was included as a composite variable that included observed eGFR less than 60 ml/min and self-reported laser surgery for retinopathy. The DSST was the only cognitive test associated with the microvascular composite after adjusting for age, sex, and education ($\beta = -0.62$, $p = 0.0005$ for a composite score of 2 relative to 0). The association remained when the microvascular composite was included in the best fit model ($\beta = -0.49$, $p = 0.01$), although its magnitude was attenuated by 21.0% by inclusion of the other variables. Addition of the microvascular composite slightly attenuated the associations with IMT ($\beta = -0.62$, $p = 0.008$, 11.4% decrease in regression coefficient) and CAC ($\beta = -0.034$, $p = 0.04$, 8.1% decrease in regression coefficient).

Associations with the 3MSE, Stroop test and Phonemic Fluency

Performance on the 3MSE, Stroop test, and Phonemic Fluency did not show significant associations with diabetes status after adjusting for age, sex, and education. However, performance on both the Stroop test and Semantic Fluency was associated with fasting plasma glucose (Supplementary Table 1). Performance on the 3MSE was only associated

with age, sex, and education, and was not significantly associated with any of the tested risk factors in this cohort.

Discussion

New approaches to preventing the cognitive complications of T2DM are urgently needed as recent results targeting aggressive treatment of glycemia have not shown benefit in reducing cognitive decline in persons with T2DM (Launer, et al., 2011). The present analyses revealed differences in cognitive function between people affected and unaffected by T2DM in a sibling cohort, and refines prior work identifying associations between cognition and risk factors associated with T2DM. Results from this group of investigators and others have shown the importance of CAC in predicting complications outside the brain in persons with T2DM (Agarwal, et al., 2011, Agarwal, et al., 2012, Carr, et al., 2008, Divers, et al., 2011, Nelson, et al., 2008, Wagenknecht, et al., 2011) and therefore we hypothesized that CAC would explain much of the variance in cognition associated with diabetes, which was true for the three tasks associated with diabetes status (DSST, RAVLT, Semantic Fluency). The magnitude of the effects of diabetes on the cognitive tests was relatively small. This is not an uncommon finding in the literature on cognition and T2DM (Reijmer, et al., 2010). While relatively small effects may not be clinically evident, awareness of subtle cognitive changes is important for health care providers as they explain detailed care regimens to patients and monitor them for adherence.

Benefits and limitations of these results

These results show the contributions of diabetes comorbidities to decrements in cognition using a family-based (genetically related) sample. The unique family design of this study is a strength, but requires thoughtful interpretation. Most studies of cognition in T2DM use a case-control design. One weakness of any case-control design is the potential for cohort effects, such as underlying differences in environment between affected and unaffected groups that may act as confounders. By using a related comparison group, this study highlights the influence of T2DM-related comorbidity when genetic and environmental background is similar. In addition, while p-values for the relationship between CAC and cognition were strong, and make sense in the context of existing literature, many models were tested, which can inflate the risk of a false positive result.

Examination of Table 1 shows that unaffected siblings are not necessarily healthy. Although they do not have diabetes, many have elevated BMI, hypertension, and significant presence of atherosclerosis. In spite of this, the presence of T2DM is detrimental for performance of verbal memory and processing speed tasks. One weakness of this design is that the results quite likely underestimate the effects of T2DM on cognition relative to what would be seen if the comparison group was age-matched healthy controls. While the comparison group in this study is not traditional, the unique design provides an important foundation for understanding the potential importance of early intervention to prevent the devastating brain complications of T2DM and its associated risk factors, which are increasingly prevalent in older adults.

The relationship between subclinical cardiovascular disease and cognition

CAC was an important predictor of cognitive function and reduced the association between cognitive function and presence of T2DM by over 30% for the DSST, RAVLT, and Phonemic Fluency. Previous studies observed that including clinically evident CVD in models of cognition and diabetes status attenuates, but does not eliminate, the relationship between diabetes and cognitive performance (Manschot, et al., 2007, Ruis, et al., 2009, van

den Berg, et al., 2009). Using CAC, we were able to capture subclinical as well as clinically-evident atherosclerosis.

One recent study (Reijmer, et al., 2011) concluded that while metabolic syndrome and IMT were associated with cognition, neither IMT nor clinically manifest vascular disease mediated the relationship between metabolic syndrome and cognition. Although the conclusion of this paper diverges from ours, we also did not observe that IMT mediated the effects of any task but the DSST. In this sample, CAC was more predictive of cognitive decline than CarCP or IMT for the RAVLT and Semantic Fluency. Inclusion of IMT in the DSST model improved the model fit, but did not replace CAC. Therefore, it might be inferred that CAC and IMT, while related, are measuring subtly different aspects of cardiovascular disease that are differently related to cognition. While our results require replication, they suggest that the cardiovascular risk conferred by T2DM, even before it is clinically evident, may explain diabetes-associated cognitive decrements in some domains. Further, early intervention to prevent mild or subclinical CVD may be important avenues to reducing the burden of cognitive decrements in certain cognitive domains for persons with T2DM.

Associations with hypertension and microvascular disease

Associations with hypertension and microvascular disease were only observed for the DSST, and persisted after including subclinical CVD variables. This observation is in line with results from Raz and colleagues (Dahle, Jacobs and Raz, 2009) who observed that elevated pulse pressure was not associated with memory performance, but did correlate with perceptual-motor processing, a component of DSST performance. It is also likely that the high rate of hypertension in this population (diabetes-affected = 91.18%, diabetes-unaffected = 72.55%) interfered with our ability to assess its relative impact on specific domains of cognitive function. Rates of hypertension in cohorts with T2DM are often high, and other studies also observed no significant relationship between hypertension and cognition, even when more stringent criteria for hypertension were employed (Manschot, et al., 2006, Manschot, et al., 2007).

Lack of associations with 3MSE and HbA1c

While performance on the 3MSE was significantly better in siblings unaffected with diabetes, it was not associated with diabetes status or any tested diabetes risk factors after basic demographic factors were included in the model. This result is likely due to the psychometric properties of the 3MSE; it is a test of general cognitive function that includes items representing an array of different cognitive domains. As such, it may not be sensitive or specific enough for detecting associations with diabetes risk factors.

We found no association between HbA1c and cognitive performance. Results from studies assessing associations of cognitive performance with fasting glucose or HbA1c levels have been inconsistent [for review see (Lamport, Lawton, Mansfield and Dye, 2009)]. Other researchers suggested that postprandial glucose levels (Abbatecola, et al., 2006) or variation in glucose control over extended periods of time (Rizzo, et al., 2010) might be more sensitive than FPG or HbA1c.

Associations of T2DM with different cognitive domains

These results also demonstrate that affected domains of cognitive function differ according to the presence of various diabetes comorbidities. The literature on the relationship between diabetes and cognition has reached the consensus that diabetes negatively affects a broad range of cognitive performance. However, the particular cognitive domains affected by T2DM vary by study. For example, some investigators observed that those with diabetes

have poorer performance in the domain of executive function (Gunstad, et al., 2007, Manschot, et al., 2006), while others have not (Bruehl, et al., 2009, Gold, et al., 2007). This variability arises in part because investigators use a variety of tasks testing different cognitive domains. However, our results suggest that part of the variability arises from the heterogeneity of underlying risk factors and comorbidities of T2DM, especially subclinical CVD, and this effect may originate before clinically apparent disease. This study used a more limited range of cognitive tests than some previous studies e.g., (Manschot, et al., 2006) due to feasibility given the size and time limitations of the DHS Mind. A broader battery of tests could be more informative about difference across cognitive domains.

Implications for brain health

Current consensus is that T2DM is associated with negative outcomes for the brain, but it is not yet clear what brain regions and networks are primarily affected (Bruehl, et al., 2009, Gold, et al., 2007, Last, et al., 2007, Manschot, et al., 2006) nor is the underlying pathophysiology that adversely impacts cognition clear. Most associations between neuropsychological tests and individual brain regions are based on lesion studies. However, functional neuroimaging studies over the past 20 years have made it clear that all cognitive tasks rely on brain networks.

The neuroimaging of T2DM thus far broadly supports the idea that different brain regions and cognitive domains may be affected differentially by T2DM, and our cognitive observations are in line with this. DSST performance is associated with hypertension and white matter lesions (Hajjar, et al., 2011, Mosley, et al., 2005), and white matter lesion burden is likely increased in those with T2DM (Manschot, et al., 2006, Manschot, et al., 2007). We observed that hypertension and microvascular disease were only associated significantly with the DSST.

The RAVLT and Semantic Fluency tasks test different cognitive domains, but lesion studies suggest RAVLT and Semantic Fluency rely on the hippocampus, a complex brain region involved in higher order cognition that is important for episodic memory and establishing context (Strauss, Sherman and Spreen, 2006). Hippocampal atrophy in those with T2DM has been documented multiple times. Factors that have been implicated include glucose regulation (Gold, et al., 2007) and BMI (Bruehl, et al., 2009), but there are currently no studies that show an association with macrovascular variables and hippocampal size in T2DM (Brundel, et al., 2010, den Heijer, et al., 2003, Korf, White, Scheltens and Launer, 2006, Korf, et al., 2007). Nevertheless, the complexities of this observation would be interesting to test further using neuroimaging methods and potentially examining the role of physical fitness, which has been associated with hippocampal volume (Erickson, et al., 2009).

Neuroimaging and lesion studies suggest the Stroop test and Phonemic Fluency depend heavily on a network that includes the prefrontal cortex (Milham, et al., 2002, Strauss, Sherman and Spreen, 2006), another brain region important for higher cognitive function that is strongly implicated in executive function. The association between fasting glucose and frontally-mediated tasks is supported by the observation that poor glycemic control is associated with grey matter atrophy in the prefrontal cortex in middle-aged and older adults with T2DM (Bruehl, et al., 2009) and a recent observation that resting state functional connectivity between frontal cortex and the posterior cingulate is associated with HOMA-IR (Musen, et al., 2012).

Future directions

These results strongly suggest that the heterogeneity of risk factors and comorbidities associated with metabolic disease may differentially affect specific brain regions and the networks in which they participate. They also imply that additional CVD factors, especially CAC and vascular status and not diabetes status alone are major contributors to T2DM-related cognitive decline. The clinical importance of these results is that they begin to assist clinicians in identifying the subgroups of patients with T2DM who are also at highest risk for the devastating cognitive complication that occur in some persons with T2DM. Future analyses will build on these epidemiological findings by using the genetic, brain imaging, and serum biomarker data collected as part of the ongoing DHS-Mind study to explore the genetic and neural underpinnings of the effects of T2DM on cognition.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

- Abbatecola AM, Rizzo MR, Barbieri M, Grella R, Arciello A, Laieta MT, et al. Postprandial plasma glucose excursions and cognitive functioning in aged type 2 diabetics. *Neurology*. 2006; 67:235–240. [PubMed: 16864814]
- Agarwal S, Morgan T, Herrington DM, Xu J, Cox AJ, Freedman BI, et al. Coronary calcium score and prediction of all-cause mortality in diabetes: the diabetes heart study. *Diabetes Care*. 2011; 34:1219–1224. [PubMed: 21398528]
- Agarwal S, Cox AJ, Herrington DM, Jorgensen NW, Xu J, Freedman BI, et al. Coronary Calcium Score Predicts Cardiovascular Mortality in Diabetes: Diabetes Heart Study. *Diabetes Care*. 2012
- Arvanitakis Z, Wilson RS, Li Y, Aggarwal NT, Bennett DA. Diabetes and function in different cognitive systems in older individuals without dementia. *Diabetes Care*. 2006; 29:560–565. [PubMed: 16505506]
- Awad N, Gagnon M, Messier C. The relationship between impaired glucose tolerance, type 2 diabetes, and cognitive function. *J Clin Exp Neuropsychol*. 2004; 26:1044–1080. [PubMed: 15590460]
- Bowden DW, Lehtinen AB, Ziegler JT, Rudock ME, Xu J, Wagenknecht LE, et al. Genetic epidemiology of subclinical cardiovascular disease in the diabetes heart study. *Ann Hum Genet*. 2008; 72:598–610. [PubMed: 18460048]
- Bowden DW, Cox AJ, Freedman BI, Hugenschmidt CE, Wagenknecht LE, Herrington D, et al. Review of the Diabetes Heart Study (DHS) Family of Studies: A Comprehensively Examined Sample for Genetic and Epidemiological Studies of Type 2 Diabetes and its Complications. *Rev Diabet Stud*. 2010; 7:188–201. [PubMed: 21409311]
- Brands AM, Van den Berg E, Manschot SM, Biessels GJ, Kappelle LJ, De Haan EH, et al. A detailed profile of cognitive dysfunction and its relation to psychological distress in patients with type 2 diabetes mellitus. *J Int Neuropsychol Soc*. 2007; 13:288–297. [PubMed: 17286886]
- Bruehl H, Wolf OT, Sweat V, Tirsi A, Richardson S, Convit A. Modifiers of cognitive function and brain structure in middle-aged and elderly individuals with type 2 diabetes mellitus. *Brain Res*. 2009; 1280:186–194. [PubMed: 19463794]

- Brundel M, van den Heuvel M, de Bresser J, Kappelle LJ, Biessels GJ. Utrecht Diabetic Encephalopathy Study G. Cerebral cortical thickness in patients with type 2 diabetes. *J Neurol Sci*. 2010; 299:126–130. [PubMed: 20869085]
- Carr JJ, Register TC, Hsu FC, Lohman K, Lenchik L, Bowden DW, et al. Calcified atherosclerotic plaque and bone mineral density in type 2 diabetes: the diabetes heart study. *Bone*. 2008; 42:43–52. [PubMed: 17964237]
- Cukierman-Yaffe T, Gerstein HC, Williamson JD, Lazar RM, Lovato L, Miller ME, et al. Relationship between baseline glycemic control and cognitive function in individuals with type 2 diabetes and other cardiovascular risk factors: the action to control cardiovascular risk in diabetes-memory in diabetes (ACCORD-MIND) trial. *Diabetes Care*. 2009; 32:221–226. [PubMed: 19171735]
- Dahle CL, Jacobs BS, Raz N. Aging, vascular risk, and cognition: blood glucose, pulse pressure, and cognitive performance in healthy adults. *Psychol Aging*. 2009; 24:154–162. [PubMed: 19290746]
- de Bresser J, Reijmer YD, van den Berg E, Breedijk MA, Kappelle LJ, Viergever MA, et al. Microvascular determinants of cognitive decline and brain volume change in elderly patients with type 2 diabetes. *Dement Geriatr Cogn Disord*. 2010; 30:381–386. [PubMed: 20962529]
- den Heijer T, Vermeer SE, van Dijk EJ, Prins ND, Koudstaal PJ, Hofman A, et al. Type 2 diabetes and atrophy of medial temporal lobe structures on brain MRI. *Diabetologia*. 2003; 46:1604–1610. [PubMed: 14595538]
- Ding J, Patton N, Deary IJ, Strachan MW, Fowkes FG, Mitchell RJ, et al. Retinal microvascular abnormalities and cognitive dysfunction: a systematic review. *Br J Ophthalmol*. 2008; 92:1017–1025. [PubMed: 18614569]
- Divers J, Register TC, Langefeld CD, Wagenknecht LE, Bowden DW, Carr JJ, et al. Relationships between calcified atherosclerotic plaque and bone mineral density in African Americans with type 2 diabetes. *J Bone Miner Res*. 2011; 26:1554–1560. [PubMed: 21437982]
- Erickson KI, Prakash RS, Voss MW, Chaddock L, Hu L, Morris KS, et al. Aerobic fitness is associated with hippocampal volume in elderly humans. *Hippocampus*. 2009; 19:1030–1039. [PubMed: 19123237]
- Gold SM, Dziobek I, Sweat V, Tirsi A, Rogers K, Bruehl H, et al. Hippocampal damage and memory impairments as possible early brain complications of type 2 diabetes. *Diabetologia*. 2007; 50:711–719. [PubMed: 17334649]
- Gunstad J, Paul RH, Cohen RA, Tate DF, Spitznagel MB, Gordon E. Elevated body mass index is associated with executive dysfunction in otherwise healthy adults. *Compr Psychiatry*. 2007; 48:57–61. [PubMed: 17145283]
- Hajjar I, Quach L, Yang F, Chaves PH, Newman AB, Mukamal K, et al. Hypertension, white matter hyperintensities, and concurrent impairments in mobility, cognition, and mood: the Cardiovascular Health Study. *Circulation*. 2011; 123:858–865. [PubMed: 21321150]
- Hoff JA, Quinn L, Sevrakov A, Lipton RB, Daviglus M, Garside DB, et al. The prevalence of coronary artery calcium among diabetic individuals without known coronary artery disease. *J Am Coll Cardiol*. 2003; 41:1008–1012. [PubMed: 12651050]
- Houx PJ, Jolles J, Vreeling FW. Stroop interference: aging effects assessed with the Stroop Color-Word Test. *Exp Aging Res*. 1993; 19:209–224. [PubMed: 8223823]
- Jacobson AM, Ryan CM, Cleary PA, Waberski BH, Weinger K, Musen G, et al. Biomedical risk factors for decreased cognitive functioning in type 1 diabetes: an 18 year follow-up of the Diabetes Control and Complications Trial (DCCT) cohort. *Diabetologia*. 2011; 54:245–255. [PubMed: 20803190]
- Kim DH, Newman AB, Hajjar I, Strotmeyer ES, Klein R, Newton E, et al. Retinal microvascular signs and functional loss in older persons: the cardiovascular health study. *Stroke*. 2011; 42:1589–1595. [PubMed: 21493913]
- Korf ES, White LR, Scheltens P, Launer LJ. Brain aging in very old men with type 2 diabetes: the Honolulu-Asia Aging Study. *Diabetes Care*. 2006; 29:2268–2274. [PubMed: 17003305]
- Korf ES, van Straaten EC, de Leeuw FE, van der Flier WM, Barkhof F, Pantoni L, et al. Diabetes mellitus, hypertension and medial temporal lobe atrophy: the LADIS study. *Diabet Med*. 2007; 24:166–171. [PubMed: 17257279]

- Lamport DJ, Lawton CL, Mansfield MW, Dye L. Impairments in glucose tolerance can have a negative impact on cognitive function: a systematic research review. *Neurosci Biobehav Rev*. 2009; 33:394–413. [PubMed: 19026680]
- Last D, Alsop DC, Abduljalil AM, Marquis RP, de Bazelaire C, Hu K, et al. Global and regional effects of type 2 diabetes on brain tissue volumes and cerebral vasoreactivity. *Diabetes Care*. 2007; 30:1193–1199. [PubMed: 17290035]
- Launer LJ, Miller ME, Williamson JD, Lazar RM, Gerstein HC, Murray AM, et al. Effects of intensive glucose lowering on brain structure and function in people with type 2 diabetes (ACCORD MIND): a randomised open-label substudy. *Lancet Neurol*. 2011; 10:969–977. [PubMed: 21958949]
- Leibson CL, Rocca WA, Hanson VA, Cha R, Kokmen E, O'Brien PC, et al. Risk of dementia among persons with diabetes mellitus: a population-based cohort study. *Am J Epidemiol*. 1997; 145:301–308. [PubMed: 9054233]
- Liang KY, Zeger SL. Longitudinal data analysis using generalized linear models. *Biometrika*. 1986; 73:13–22.
- Longstreth W Jr, Larsen EK, Klein R, Wong TY, Sharrett AR, Lefkowitz D, et al. Associations between findings on cranial magnetic resonance imaging and retinal photography in the elderly: the Cardiovascular Health Study. *Am J Epidemiol*. 2007; 165:78–84. [PubMed: 17041135]
- Manschot SM, Brands AM, van der Grond J, Kessels RP, Algra A, Kappelle LJ, et al. Brain magnetic resonance imaging correlates of impaired cognition in patients with type 2 diabetes. *Diabetes*. 2006; 55:1106–1113. [PubMed: 16567535]
- Manschot SM, Biessels GJ, de Valk H, Algra A, Rutten GE, van der Grond J, et al. Metabolic and vascular determinants of impaired cognitive performance and abnormalities on brain magnetic resonance imaging in patients with type 2 diabetes. *Diabetologia*. 2007; 50:2388–2397. [PubMed: 17764005]
- Milham MP, Erickson KI, Banich MT, Kramer AF, Webb A, Wszalek T, et al. Attentional control in the aging brain: insights from an fMRI study of the stroop task. *Brain Cogn*. 2002; 49:277–296. [PubMed: 12139955]
- Mosley TH Jr, Knopman DS, Catellier DJ, Bryan N, Hutchinson RG, Grothues CA, et al. Cerebral MRI findings and cognitive functioning: the Atherosclerosis Risk in Communities study. *Neurology*. 2005; 64:2056–2062. [PubMed: 15985571]
- Murray AM. Cognitive impairment in the aging dialysis and chronic kidney disease populations: an occult burden. *Adv Chronic Kidney Dis*. 2008; 15:123–132. [PubMed: 18334236]
- Murray AM, Barzilay JI, Lovato JF, Williamson JD, Miller ME, Marcovina S, et al. Biomarkers of renal function and cognitive impairment in patients with diabetes. *Diabetes Care*. 2011; 34:1827–1832. [PubMed: 21715519]
- Musen G, Jacobson AM, Bolo NR, Simonson DC, Shenton ME, McCartney RL, et al. Resting-state brain functional connectivity is altered in type 2 diabetes. *Diabetes*. 2012; 61:2375–2379. [PubMed: 22664957]
- Mykkanen L, Zaccaro DJ, O'Leary DH, Howard G, Robbins DC, Haffner SM. Microalbuminuria and carotid artery intima-media thickness in nondiabetic and NIDDM subjects. The Insulin Resistance Atherosclerosis Study (IRAS). *Stroke*. 1997; 28:1710–1716. [PubMed: 9303013]
- Nelson MR, Daniel KR, Carr JJ, Freedman BI, Prineas RJ, Bowden DW, et al. Associations between electrocardiographic interval durations and coronary artery calcium scores: the Diabetes Heart Study. *Pacing Clin Electrophysiol*. 2008; 31:314–321. [PubMed: 18307626]
- Nguyen HT, Grzywacz JG, Arcury TA, Chapman C, Kirk JK, Ip EH, et al. Linking glycemic control and executive function in rural older adults with diabetes mellitus. *J Am Geriatr Soc*. 2010; 58:1123–1127. [PubMed: 20722846]
- Novak V, Hajjar I. The relationship between blood pressure and cognitive function. *Nat Rev Cardiol*. 2010; 7:686–698. [PubMed: 20978471]
- Ott A, Stolk RP, van Harskamp F, Pols HA, Hofman A, Breteler MM. Diabetes mellitus and the risk of dementia: The Rotterdam Study. *Neurology*. 1999; 53:1937–1942. [PubMed: 10599761]

- Peila R, Rodriguez BL, Launer LJ. Type 2 diabetes, APOE gene, and the risk for dementia and related pathologies: The Honolulu-Asia Aging Study. *Diabetes*. 2002; 51:1256–1262. [PubMed: 11916953]
- Qiu C, Cotch MF, Sigurdsson S, Jonsson PV, Jonsdottir MK, Sveinbjrnsdottir S, et al. Cerebral microbleeds, retinopathy, and dementia: the AGES-Reykjavik Study. *Neurology*. 2010; 75:2221–2228. [PubMed: 21172845]
- Reijmer YD, van den Berg E, Ruis C, Kappelle LJ, Biessels GJ. Cognitive dysfunction in patients with type 2 diabetes. *Diabetes Metab Res Rev*. 2010; 26:507–519. [PubMed: 20799243]
- Reijmer YD, van den Berg E, Dekker JM, Nijpels G, Stehouwer CD, Kappelle LJ, et al. The metabolic syndrome, atherosclerosis and cognitive functioning in a non-demented population: the Hoorn Study. *Atherosclerosis*. 2011; 219:839–845. [PubMed: 21959256]
- Rizzo MR, Marfella R, Barbieri M, Boccardi V, Vestini F, Lettieri B, et al. Relationships between daily acute glucose fluctuations and cognitive performance among aged type 2 diabetic patients. *Diabetes Care*. 2010; 33:2169–2174. [PubMed: 20573753]
- Rosano C, Naydeck B, Kuller LH, Longstreth WT Jr, Newman AB. Coronary artery calcium: associations with brain magnetic resonance imaging abnormalities and cognitive status. *J Am Geriatr Soc*. 2005; 53:609–615. [PubMed: 15817006]
- Ruis C, Biessels GJ, Gorter KJ, van den Donk M, Kappelle LJ, Rutten GE. Cognition in the early stage of type 2 diabetes. *Diabetes Care*. 2009; 32:1261–1265. [PubMed: 19366968]
- Schurigin S, Rich S, Mazzone T. Increased prevalence of significant coronary artery calcification in patients with diabetes. *Diabetes Care*. 2001; 24:335–338. [PubMed: 11213888]
- Seliger SL, Siscovick DS, Stehman-Breen CO, Gillen DL, Fitzpatrick A, Bleyer A, et al. Moderate renal impairment and risk of dementia among older adults: the Cardiovascular Health Cognition Study. *J Am Soc Nephrol*. 2004; 15:1904–1911. [PubMed: 15213280]
- Teng EL, Chui HC. The Modified Mini-Mental State (3MS) examination. *J Clin Psychiatry*. 1987; 48:314–318. [PubMed: 3611032]
- van den Berg E, de Craen AJ, Biessels GJ, Gussekloo J, Westendorp RG. The impact of diabetes mellitus on cognitive decline in the oldest of the old: a prospective population-based study. *Diabetologia*. 2006; 49:2015–2023. [PubMed: 16804671]
- van den Berg E, Dekker JM, Nijpels G, Kessels RP, Kappelle LJ, de Haan EH, et al. Blood pressure levels in pre-diabetic stages are associated with worse cognitive functioning in patients with type 2 diabetes. *Diabetes Metab Res Rev*. 2009; 25:657–664. [PubMed: 19768735]
- Vidal JS, Sigurdsson S, Jonsdottir MK, Eiriksdottir G, Thorgeirsson G, Kjartansson O, et al. Coronary artery calcium, brain function and structure: the AGES-Reykjavik Study. *Stroke*. 2010; 41:891–897. [PubMed: 20360538]
- Wagenknecht LE, Bowden DW, Carr JJ, Langefeld CD, Freedman BI, Rich SS. Familial aggregation of coronary artery calcium in families with type 2 diabetes. *Diabetes*. 2001; 50:861–866. [PubMed: 11289053]
- Wagenknecht LE, Divers J, Bertoni AG, Langefeld CD, Carr JJ, Bowden DW, et al. Correlates of coronary artery calcified plaque in blacks and whites with type 2 diabetes. *Ann Epidemiol*. 2011; 21:34–41. [PubMed: 21130367]
- Warsch JR, Wright CB. The aging mind: vascular health in normal cognitive aging. *J Am Geriatr Soc*. 2010; 58(Suppl 2):S319–324. [PubMed: 21029061]

Table 1

Summary statistics.

		Type 2 Diabetes Affected (n=422)	Type 2 Diabetes Unaffected (n=92)	p-value
	n			
<i>General Descriptors</i>				
Sex (% male)	516	46.21%	36.17%	0.08
Age (years)	516	67.80 ± 8.60	66.99 ± 10.12	0.20
BMI (kg/m ²)	514	32.15 ± 6.55	28.44 ± 5.76	<0.0001
Education	515			0.04
< High School Diploma		19.24%	10.64%	
High School Diploma		51.54%	59.57%	
> High School Diploma		29.22%	29.79%	
<i>Diabetes</i>				
Diabetes duration (years)	508	14.64 (12.1–20.3)	0	
HbA _{1c} (% glycated hemoglobin)	471	7.3 (6.5–8.0)	5.8 (5.6–6.1)	<0.0001
Fasting plasma glucose (mg/dL)	471	133.0 (109.0–168.0)	95.5 (90.0–104.0)	<0.0001
eGFR (ml/min)	515	65.7 (57.3–77.2)	65.2 (58.7–74.5)	0.98
Self-report retinopathy	516	8.29%	0%	
<i>Cardiovascular Health</i>				
Systolic blood pressure (mm Hg)	515	132.60 ± 17.92	129.55 ± 18.67	0.20
Diastolic blood pressure (mm Hg)	515	68.79 ± 9.42	73.91 ± 11.38	0.0002
Presence of hypertension	508	92.40%	71.28%	0.0003
Use of hypertension medication	484	79.85%	58.44%	0.002
†Coronary calcified plaque	516	308.0 (38.0–1702.0)	24.5 (1.5–270.5)	<0.0001
†Carotid calcified plaque	509	35.0 (0.5–228.5)	1.0 (0.0–68.5)	<0.0001
†Carotid intima media thickness	461	0.641 (0.571–0.736)	0.610 (0.555–0.691)	0.007
<i>Lipids</i>				
†Total cholesterol (mg/dL)	516	178.0 (155.0–203.0)	192.0 (169.0–216.0)	0.01
†HDL cholesterol (mg/dL)	516			
Men	229	37.0 (32.0–43.0)	40.0 (35.0–46.0)	0.19
Women	287	44.0 (38.0–53.0)	51.0 (44.0–61.0)	0.0002
†LDL cholesterol (mg/dL)	516	93.52 ± 41.47	113.5 ± 30.28	0.0009
†Triglycerides	516	166.0 (115.0–240.0)	144.0 (101.0–192.0)	0.0003
Use of lipid lowering medication	463	54.57%	48.28%	0.55
<i>Cognitive scores</i>				
3MSE	515	92 (86.0–96.0)	93 (89.0 – 96.0)	0.001
DSST	513	46.67 ± 14.90	51.31 ± 15.42	0.003
Stroop Task	510	0.33 (0.28–0.38)	0.34 (0.28–0.41)	0.30
Phonemic Fluency	471	28.69 ± 11.58	30.04 ± 12.22	0.20
Semantic Fluency	471	29.34 ± 7.87	31.89 ± 7.68	0.007
RAVLT	515	40.72 ± 10.55	44.56 ± 9.06	0.0003

Coronary calcification is associated with cognitive performance in tasks associated with T2DM.

Table 2

		DSST		RAVLT		Semantic Fluency	
		beta	p-value	beta	p-value	beta	p-value
Model 1	Diabetes Affected	-0.18	0.04	-0.22	0.01	-0.21	0.04
Model 2	Coronary Calcification	-0.05	0.002	-0.05	0.0003	-0.05	0.007
Model 3	Diabetes Affected	-0.11	0.22	-0.14	0.12	-0.14	0.18
	Coronary Calcification	-0.04	0.009	0.05	0.003	-0.04	0.03
Model 4	Diabetes Affected	-0.06	0.48	0.15	0.10	-0.13	0.21
	Hypertension	-0.26	0.01	0.05	0.64	-0.05	0.71
	Coronary Calcification	-0.04	0.03	-0.05	0.003	-0.04	0.03
Model 5	Diabetes Affected	-0.07	0.45	0.13	0.18	-0.15	0.17
	Hypertension	-0.20	0.07	0.06	0.58	-0.05	0.67
	Coronary Calcification	-0.04	0.02	-0.05	0.004	-0.04	0.03
	Intima Media Thickness	-0.70	0.003	0.05	0.81	-0.31	0.27

Best fit models are highlighted in grey. All models are adjusted for age, sex, and education. Cognitive variables are standardized so that betas can be directly compared as described in methods. Statistically significant values are in bold. Please note that coronary calcification, IMT, and fasting glucose were log transformed.