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The Relationship of Blood Glucose Control Level and Memory in Type II Diabetic Patients

Michelle E. Lewis
Pacific University

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Abstract
Background: Diabetes is a prevalent chronic illness, affecting up to 23.6 million people in the United States. The association of diabetes and cognitive dysfunction is well recognized, and many have suggested memory to be among the cognitive functions most affected. The proposal of chronic hyperglycemia having a negative effect on cognition independent of other risk factors has yet to be determined.

Methods: An extensive literature search was performed using Medline, CINAHL, and Web of Science databases. Titles and abstracts were screened for relevancy and discarded if clearly not eligible. The full text of potential studies was reviewed for at least one objective measurement of memory in type II diabetic participants with correlation to level of control as measured by HbA1c. The references of selected studies and review articles were evaluated for additional publications.

Results: The majority of reviewed studies did not find a significant association between HbA1c and performance on tests of verbal and visual memory. Extensive variation in study design was found including control over confounding factors and selection of cognitive testing.

Conclusion: Studies on the relationship between level of control of diabetes and cognition are both limited and confounded by lack of control of comorbitities within study designs. Further research within carefully designed longitudinal studies is necessary to better understand any existing relationship between level of glucose control and cognition, and may spotlight the need for specialized education and support regarding disease self-management for people with type II diabetes.

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First Advisor
Anya Hill, PA-C, MS

Second Advisor
Annjanette Sommers MS, PAC

Third Advisor
Rob Rosenow PharmD, OD

Keywords
glycosylated hemoglobin, HbA1c, diabetes mellitus, type II diabetes, cognition, cognitive, chronic, hyperglycemia

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The Relationship of Blood Glucose Control Level and Memory in Type II Diabetic Patients

Michelle E. Lewis

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Faculty Advisor: Anya Hill, PA-C, MS

Clinical Graduate Project Coordinators: Annjanette Sommers MS, PAC & Rob Rosenow PharmD, OD

BIOGRAPHY

[Redacted for privacy]

ABSTRACT

Background: Diabetes is a prevalent chronic illness, affecting up to 23.6 million people in the United States. The association of diabetes and cognitive dysfunction is well recognized, and many have suggested memory to be among the cognitive functions most affected. The proposal of chronic hyperglycemia having a negative effect on cognition independent of other risk factors has yet to be determined.
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Results: The majority of reviewed studies did not find a significant association between HbA1c and performance on tests of verbal and visual memory. Extensive variation in study design was found including control over confounding factors and selection of cognitive testing.
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To *Ryan Lewis*, my husband: Thank you for your love, support, and encouragement through one of the most challenging times of our life together.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF ABBREVIATIONS

HbA1c- Hemaglobin A1c or glycosylated hemoglobin

The Relationship of Blood Glucose Control Level and Memory in Type II Diabetic Patients

BACKGROUND

Diabetes is a prevalent, progressive, and often disabling disease; affecting up to 23.6 million people in the United States.[1,2] The number of Americans with diagnosed diabetes mellitus (types I and II) is projected to increase 165%, from 11 million people in the year 2000 to 29 million in 2050.[3] Numerous literature reviews reviewing dozens of published studies have found considerable support for an association of type II diabetes and cognitive dysfunction, specifically that diabetics seem to show the most impairment in the cognitive domain memory.[4,5] However, because the lack of control over confounding factors in most if not all of the currently published studies, it is less clear on which and to what extent the comorbidities associated with this disease may be attributing to these deficits. Determining the independent role of chronic high blood glucose on brain functioning will provide more insight to the pathophysiology of the disease, potentially modify guidelines for disease management, and give direction for further research in this field. Particularly, if hyperglycemia has a negative impact on cognition, this will have significant implications for the ability of type II diabetic patients to effectively self-manage their disease. The primary purpose of this study is to determine whether poor control of diabetes is a risk factor for memory impairment in type II diabetic patients independent of other conditions commonly associated with this disease including depression, hyperlipidemia, hypertension, and vascular disease. Secondly, an attempt to describe the ideal study on the relationship of HbA1c and cognition was made

to best contribute to our understanding of this disease. The review was also designed to easily incorporate the evaluation of other domains of cognition within the selected studies.

METHODS

An extensive literature search using Medline, CINAHL, and Web of Science databases was performed using the following search terms: glycosylated hemoglobin, HbA1c, diabetes mellitus, type II diabetes, cognition, cognitive, chronic, and hyperglycemia. The references of selected studies and review articles were evaluated for additional publications. Titles and abstracts were screened for relevancy and discarded if clearly not eligible. The full text of the remaining references were reviewed and selected for inclusion based on the following inclusion and exclusion criteria. Studies included in this review were required to involve a population of participants with adult type II diabetes, use HbA1c as an indicator for diabetes level of control, at least one objective test of cognition, and have the relationship of glycemic control and cognition as a primary focus. Only studies published in English were selected. Exclusion criteria included pediatric populations, cognitive testing performed under and correlated with acute hyperglycemic episodes, no distinctly examined type II diabetic population, or studies published prior to 2000. The date for exclusion was chosen due to the abundance of relevant articles and because of the advances in diabetes understanding and treatment in the last decade, to review the latest research with potentially higher quality studies. Sixteen studies were found and further analyzed for testing of the cognitive domain memory.

Measures of Cognitive Function

Forty-three different cognitive tests were administered among the sixteen studies meeting the inclusion and exclusion criteria. Due to the lack of congruency between studies on the type of cognition sensitive to each test, and consistency between similar review articles, the classification of cognitive abilities according to Lezak described in "Neuropsychological Assessment" was used.[6] Although many tests call upon several major cognitive functional activities making the assignment to a single cognitive domain arbitrary, eight broad categories of cognition were found to be assessed in these studies: overall mental status; verbal function and language skills; construction; motor performance; attention, concentration and tracking; concept formation and reasoning; perception; and memory.[6] Table 1 illustrates the categorization and study references using each cognitive test. If a particular test was not found under Lezak's classifications, the test description was evaluated and correlated with a similar classified test and placed under the respective category. If a particular test was insufficiently described, without a locatable reference published in English using the above databases, and not described by Lezak, the test was excluded from review (see Table 1). Studies assessing memory with no mention of results[7] or explicit memory result as a part of an overall cognition test,[8-16] were excluded. Tests classified as working memory were not included in this review due to its categorization as tracking, and as so are classified under the attention, concentration, and tracking category. If a study provided only an overall statistical score for a group of memory tests including a test not assigned as memory by this study's classification method[17-19] or did not correlate memory with HbA1c,[14] the data could not

be analyzed for inclusion in this review. Six studies including seven memory tests were found by the described classification method and were included in this review.[8,11,16,18,20,21] Data was then abstracted from the articles and analyzed.

Data Abstraction

The selected studies can be found listed with population characteristics in Table 2. Information recorded from each study included diabetic population characteristics (number of participants, mean age, percent male, duration of diabetes, mean HbA1c), and study type.

Validity Assessment

Validity was assessed using a subjective quality scale based on a number of individual quality components and scored numerically to provide a quantitative estimate of overall study quality. This was assembled using quality criteria presented in the Centre for Reviews and Dissemination Report[22] and the Data Collection Instrument and Procedure for Systematic Reviews in the *Guide to Community Preventive Services*[23] tailored to fit this study.[22,23] The individual quality components include specific aspects of study methodology that have a potential relation to bias.[22] Because type II diabetes is associated with numerous comorbidities that may independently contribute to cognitive decline, each potentially confounding variable was assigned one point to provide greater weight in determining validity. A total score for each study was determined by assigning each quality component one point for "Yes" and zero points for "No" and calculating a total sum (Table 3). The validity of methods diagnosing or scoring confounding variables

and cognitive tests themselves was not assessed for this review as this reaches beyond the scope of this article.

RESULTS

Studies Reporting a Negative Correlation of HbA1c and Memory

Of the six studies reviewed, two reported a negative correlation with memory deficits and HbA1c in participants with type II diabetes (see Table 4). Cukierman-Yaffe et al[8] performed a large cross-sectional study of participants in the ongoing Action to Control Cardiovascular Risk in Diabetes- Memory in Diabetes (ACCORD-MIND) trial, a substudy of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. Using baseline data from the MIND study, the relationship between the degree of hyperglycemia and cognitive status was assessed in 2,977 diabetic men and women. A statistically significant age-adjusted association was found between HbA1c level and the verbal memory test score, specifically a 0.11 point lower score (-0.02 to -0.19, P = 0.0142) per 1% rise in HbA1c.[8]

A study by Umegaki et al[11] evaluated 77 patients with relatively well-controlled type II diabetes for an association of HbA1c, hyperinsulinemia, and ischemic brain changes with diabetes-related cognitive dysfunction. HbA1c was found to be associated with decreased performance on the memory test administered (correlation coefficient -0.194, $P = < 0.05$).[11]

Studies Reporting no Correlation of HbA1c and Memory

The majority of the remaining studies evaluating memory did not find significant associations between HbA1c and memory function. Van Harten et al[16] described the neuropsychological profile of 92 participants with diabetes and 44 control subjects without diabetes, and studied the correlations of cognitive impairment and brain lesions on MRI and influence of relevant disease variables of diabetes including HbA1c on cognition. Although significant differences in cognition between groups were found and overall cognition was associated with HbA1c, the results of memory determined by scores of two verbal memory tests was similar between groups and not independently associated with HbA1c.[16]

Ryan et al[18] evaluated 50 middle aged adults between 34-65 years old with diabetes and 50 demographically similar control subjects without diabetes to determine the extent to which demographic and biomedical variables contributed to performance on each of four cognitive domains. Performance on the domain memory, consisting of one memory test, was not found to be influenced by HbA1c.[18] A similarly small study by Cosway et al[20] of 38 uncomplicated type II diabetic and 38 non-diabetic control participants 40-75 years old aimed to compare cognitive function and information processing of diabetic persons with non-diabetic persons and determine if factors within the group of diabetics correlated with cognitive function. HbA1c was determined by averaging up to three levels obtained at prior clinic visits, and not drawn at the time of cognitive testing. The performance on two memory tests in this study also displayed no correlation with HbA1c.[20]

Finally, Saczynski et al[21] used data from the Age, Gene/Environment Susceptibility-Reykjavik Study examining the association of specific measures of cognitive function to four categories of glycemic status: normoglycemic, impaired fasting glucose, undiagnosed diabetes, and diagnosed diabetes. The relation of cognitive performance to HbA1c levels, duration of clinically recognized type II diabetes, and medication use was also examined. Of the 1,917 subjects, 163 had diagnosed type II diabetes mellitus and 55 had undiagnosed type II diabetes mellitus, with both groups having relatively well controlled diabetes as measured by HbA1c. The level of control, however, was not related to performance in memory determined by the score of one memory test.[21]

DISCUSSION

This literature review of cross-sectional studies draws a mixed conclusion in respect to the relationship between HbA1c and memory in people with type II diabetes. Four of six studies reviewed found no relationship between level of control of diabetes and performance on memory testing.[16,18,20,21] However, one of the studies supporting a relationship was a large cross-sectional study using data from participants enrolled in a randomized control trial. The study had the highest rating of validity among the studies, and by far had both the most control over confounding factors and largest diabetic sample size of 2,977 participants (others ranged from 38-163 participants).[8] The other study reporting an HbA1c and memory correlation did so despite a relatively well controlled diabetic population (mean HbA1c 6.6 ± 0.8), but had a low validity score due to lack of controlling for many confounding factors.[11] Both studies exhibited a relatively long

duration of diabetes and high level of education in their population sample. Interestingly, these two studies supporting a relationship between HbA1c and memory performance were the only studies in the review stating that the relationship of HbA1c and cognitive function was their primary focus of research.

Study Limitations

Of more significant importance than the actual results of the studies is the issue of inconsistency in the research of this topic. A number of factors may account for the difference in findings among studies of HbA1c and cognition. The study designs are considerably different, making it extremely difficult to make any useful comparisons between them. The most common discrepancies are discussed below, and therefore assist in defining the ideal study on the effect of level of control of diabetes on cognition.

Sample selection

One of the most important factors relevant to the study of HbA1c and cognition is the use of strict exclusion criteria and statistical adjustment regarding important confounding variables. Type II diabetes is a complex disease process as it is associated with numerous multisystem complications and other significant disorders and conditions that may each contribute independently to cognitive dysfunction. These confounding variables are numerous and include hypertension, hyperlipidemia, cerebrovascular disease, cardiovascular disease, HPA (hypothalamic-pituitary-adrenal) axis abnormalities, metabolic syndrome, severe hypoglycemic episodes, hyperinsulinemia, and depression. Other confounding variables include age-associated cognitive decline,

gender, education level, previous occupation, functional disorders (visual, hearing and movement) that could interfere with testing, significant alcohol and drug use, smoking, exercise, psychiatric and neurological disorders including dementia and head injury, medications, and premorbid intelligence. An overview of how well each of the articles in this review accounted for these variables can be found in table 3. Only three of the six articles accounted for at least five confounding factors listed above; clearly not nearly enough to accurately propose causality of cognitive impairment in diabetic patients.[8,16,18]

As only some of the above factors are those that could be excluded from a sample selection, others such as education level, premorbid intelligence, gender, age, and duration of diabetes must be similar or adjusted for within the population sample. Only one study divided the population in terms of education level and gender and made respective adjustments in their statistical analysis.[8] One study attempted to select and analyze participants in a similar point of their disease progression by creating a population of undiagnosed diabetic participants, defined as participants with no self-report of diabetes, no use of diabetes medication, and a fasting blood glucose level greater than or equal to 7.0 mmol/L at the baseline examination. This study also categorized disease duration among diagnosed diabetic participants into four relatively equal-sized groups and compared them to the undiagnosed diabetes group; however no attempt was made to use this data to evaluate HbA1c and cognition within each group.[21] Intelligence was estimated in two of six studies.[18,20] Evidently many of the studies considered important confounding variables however many of them were used for adjustment and comparison between groups and not specifically applied to the HbA1c and cognition analyses.

There are several further aspects worth discussing regarding the sample population and study of cognition. Firstly, the potential bias introduced by selective recruitment may significantly affect the outcomes of the studies. Persons with more severe cognitive impairment would be less likely to participate in a study of cognition. This would underestimate the effect of level of control of diabetes on cognition if those participants were among those with very poorly-controlled diabetes. Secondly, the majority of studies based their results on very small populations, eliciting another possible reason for discrepancy among the study results. The findings from studies finding no association between level of control of diabetes and cognition may therefore result from a lack of appropriate numbers of participants to compare. Finally, the universe of selection of the diabetic participants may yield different results between studies. Two studies selected diabetic samples from the general population,[8,21] two from diabetic clinics,[11,20] one from a hospital internal medicine department,[16] and one from a diabetes research subject registry.[18] Participants selected from a diabetes clinic or internal medicine department are more likely to have additional and worse confounding conditions compared with those from the general diabetic population. If rigorous exclusion criteria or statistical adjustment were not used, participants selected from a sicker population would be more likely to show a decrease in cognition compared to a healthier sample, confounding any association found with HbA1c. If the majority of confounding variables are not accounted for, this would also pose a problem for comparing study results of participants from the general diabetic population to those from a diabetes clinic.

Study design and methodology

Several important details regarding the study of diabetes and cognition were inconsistently evaluated among the studies, effecting the interpretation of results. Only two of the studies explicitly stated a valid method of diagnosing diabetes by laboratory measurement, one only doing so for the undiagnosed diabetes sample.[8,21] The remaining diagnosed diabetes samples were based on self-reported doctor's diagnosis, use of diabetic medications, standardized questionnaires,[21] or the method of diagnosis was not mentioned at all.[11,16,18,20] Three of the four studies not stating the method of diagnosis were those whose sample was selected from an already established diabetic population, including the two diabetes clinics[11,20] and diabetes research subject registry.[18] Along the same lines, only five of the six studies provided a description of the method of obtaining HbA1c levels,[8,11,18,20,21] with only one specifying the time period in which the laboratory and cognitive testing was performed.[21] As time passes between HbA1c and cognitive testing, the more inaccurate the result of comparisons become; therefore the results of the studies not providing this piece of pertinent information have reduced validity. Lastly, of the four studies evaluating diabetic versus non-diabetic populations,[16,18,20,21] and two studies evaluating diabetics only[8,11] only one study specified that the examiner was blind to the diabetic status of the participants.[16]

Another important consideration of study design is to account for conditions that may interfere with cognitive testing including deficits of perception and aspects of acute blood glucose. An inability to sufficiently hear or see a portion of a cognitive test may markedly alter the performance measured for a particular domain and not test a person's true cognitive functionality. Only one study ensured adequate visual perception by

applying a minimum visual acuity to participate, and one study simply stated there were no audio-visual deficits among the participants.[11,20] Abnormalities in blood glucose during testing may also acutely affect the results of a particular cognitive test. Numerous studies have demonstrated the negative impact of hypoglycemia on cognitive dysfunction,[24] however only three of six studies took this into account or ensured blood glucose to be ≥ 60 mg/dl prior to testing.[8,18,20] Acute hyperglycemia has also been shown to impair cognitive function in type II diabetics in recent studies[25,26] and was not addressed in any of the studies reviewed. This is a potentially significant detail in the study of the effect of HbA1c on cognition in that it may help distinguish whether or not any deficits in cognition associated with HbA1c are due to the chronic effects of hyperglycemia or acute hyperglycemia itself. There is also evidence to suggest the utilization of blood glucose rather than the actual glucose level may be associated with performance on cognitive tests among participants with type II diabetes.[27]

Additional features absent from the majority of studies are measures taken to ensure accuracy of the cognitive test scores and consistency between test givers. No study in this review repeated cognitive testing to obtain an average and more accurate score, which would help adjust for the possibility of unknown factors influencing performance at that particular time of testing. However, some of the studies attempted to provide consistency of scoring between participants by indicating that they administered the tests in the same order,[11,18] used certified technicians to administer the tests,[8] or calculated high inter-rater reliability.[21]

Selection and reporting results of cognitive testing

One of the most significant issues regarding consistency between studies is the selection of cognitive tests. There is currently no consensus regarding a standard neuropsychological test battery, leaving authors to choose among hundreds of tests to assess cognition. According to this review and other recent reviews of diabetes and cognitive function, memory and attention/concentration tests seem to be the most widely used.[4,28,29] Forty-three different tests of cognitive function were used among the sixteen studies meeting the primary inclusion criteria in this review. The measure of cognitive function for each study ranged from a single neuropsychological test[10,15] to a battery of 14 tests,[19] with an average of 5-6 tests administered among the studies.

The method of analyzing the studies in this review using an independent classification system for tests was chosen for several reasons. A number of studies were found to show discrepancies in classifying cognitive tests. For example, both Manschot et al[17] and Ruis et al[19] assessed memory based on several tests including the forward and backward Digit Span.[17,19] Saczynski et al[21] also used the forward and backward Digit Span test, except classified as a test of executive function.[21] Another reason for choosing to compare results of cognitive domains to HbA1c is that the alternative, individual test performance could not effectively be compared among the studies without omitting a large proportion of relevant articles. Evaluating over forty cognitive tests with no two studies using the same tests would create far too many variables to effectively assess HbA1c and cognition relation in one literature review. Also, if one were to include only the most common tests administered, potentially relevant information attained by other studies would be excluded. Finally, many studies do not analyze the relationship between

individual test scores and HbA1c. They alternatively evaluate the relationship of HbA1c and result of performance in a particular domain, derived from tests they defined as testing that domain.[7,17-19,21,30] Excluding these studies from review would contribute to the loss of further potentially relevant data.

Implications for Diabetes Self-Management

After further and more comprehensive studies are done, data continuing to support a negative correlation of chronic hyperglycemia on cognition would promote interest on whether or not patients fitting within this category are able to effectively manage their own disease. It is important to consider the possibility that patients with relatively high HbA1c levels may be less well-controlled due to established cognitive impairment. Studies examining the association between impaired cognition and diabetes self-care have shown that diabetic subjects with lower cognitive test scores were less likely to be involved in self-care.[31,32] These findings imply that whether due to age-associated or other causes of cognitive decline, people with type II diabetes may require additional teaching and support in order to manage this condition. In fact, there is evidence to support patients with type II diabetes and impaired cognitive function benefit from specialized structured treatment and teaching programs by demonstrating better diabetes self-management compared to those in standard diabetes treatment and teaching programs.[33]

CONCLUSION

Over the last decade, a number of studies have evaluated the association of HbA1c levels and memory in people with type II diabetes, with the majority indicating no significant relationship between them. However, the wide variation in methodology, selection of cognitive tests, and control for confounding factors obscures both the conclusions of the individual studies and any meaningful comparisons between them. Studies primarily evaluating this relationship are also few and far between. Further research within carefully designed longitudinal studies is necessary to better understand any existing relationship between level of glucose control and cognition, and may spotlight the need for specialized education and support regarding disease self-management for people with type II diabetes.

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TABLES

Table 1 Classification of Tests by Categories of Cognition

Memory		**Construction**	
Test	Reference	Test	Reference
Rey Auditory Verbal Learning Test (immediate; delayed)	8,16,17,19,20	Clock-in-a-box	13
Location Learning Test (immediate; delayed)	17,19	Clock Drawing Test	7,13
Rey-Osterreith Complex Figure Test (delayed)	19	Mosaic Test	30
Logical Memory Test of the Rivermead Behavioral Memory Test (immediate; delayed)	16	Copy Trial of the Rey-Osterreith Complex Figure Test	17,19
Word List subtest of Alzheimers Disease Assessment Scale	11,14	Object Assembly Subtest of Wechsler Adult Intellegence Scale-Revised	18
Verbal Pairs of the Wechsler Memory Scale-Revised	20		
Visual Pairs of the Wechsler Memory Scale-Revised	20	**Concept Formation and Reasoning**	
Logical Memory Test of the Wechsler Memory Scale- Revised	20	Raven Advanced Progressive Matrices	17,19,20
Verbal Paired-Associate Learning Test (immediate; delayed)	18	Brixton Spatial Anticipation Test	17,19
Four Word Short Term Memory Test	18	Halstead Category Test	18
California Verbal Learning Test (immediate;delayed)	21	Problem Solving Test	7
Attention, Concentration, and Tracking		**Verbal Function / Language Skills**	
Digit Symbol Substitution Test	8,11,12,14,19,30	Category Fluncy	7,9,16,17,19
Stroop Tests	8,16,19	Lexical Fluency Test	19
Digit Span (forward; backward)	17,19,21	Token Test	19
Corsi Block-Tapping Test	17,19	Controlled Oral Word Association Test	16
Trail Making Test	9,16-19,30	Mehrfachwahl-Wortschatz Test	30
Binary Choice Reaction Time of FEPSY	16	The Borkowski Verbal Fluency Test	20
Symbol-Digit Paired Associate Learning Test (immediate; delayed)	18		
Spatial Working Memory Test of the Cambridge Neuropsychological Test Battery	21		
Overall Mental Status		**Perception**	
Mini-Mental Status Examination or Teng Modified Mini-Mental Status Examination	8-14	Tactual Performance Test	18
Cambridge Cognitive Examination	16	Embedded Figures Test	18
HIV Dementia Scale	16	Digit Vigilance Test	18
Health and Retirement Study Cognitive Scale	15		
		Motor Performance	
		Grooved Pegboard Test	16,18

Other Tests: Figure Comparison Test [21] was excluded due to lack of sufficient written description, and referenced article could not be located.

Table 2 Diabetic population characteristics in selected studies

Study	Year Published	Diabetic Subjects (n, % male)	Age (years)	Diabetes Duration (Years)	Education (Years)	HbA1c (%)	Study Type	Validity Score (n/25)
Cosway et al.	2001	38, 42%	57.7 ± 10.3	6.0 (3.0, 11.3) ♦	11.2 ± 2.7	7.6 (6.6, 9.5) ♦	Cross-sectional	11
Cukierman-Yaffe et al.	2009	2,997, 53%	62.5 ± 5.8	10.4 ± 7.3	○	8.3 ± 1.1	Cross-sectional	20
Ryan et al.	2000	50, 30%	50.8 ± 7.7	8.1 ± 5.9	14.4 ± 3.1	10.2 ± 2.4	Cross-sectional	11
Saczynski et al.	2008	163, 66% †	75.6 ± 5.4 †	9 (3-19) † ■	21.5 † ▲	6.4 (6.0 -7.1) † ■	Cross-sectional	16
		55, 55% ‡	75.9 ± 4.9 ‡	– ‡	10.9 ‡ ▲	6.2 (5.8-6.5) ‡ ■		
Umegaki et al.	2008	77, 40%	74.5 ± 5.5	15.5 ± 8.9	9.4 ± 2.4	6.6 ± 0.8	Cross-sectional	8
van Harten et al.	2007	92, 43%	73.2 ± 5.7	13.8 ± 10.8	4.0 (1.6) ●	7.7 ± 1.0	Cross-sectional	11

Data are the mean ± standard deviation unless otherwise indicated.
♦ Mean with 25th and 75th percentiles in parentheses
■ Median with ranges in parentheses
● Median with standard deviation in parentheses
▲ Percent low education, study did not define

† Diagnosed diabetes participants
‡ Undiagnosed diabetes participants
◊ Insulin-treated diabetes participants
Δ Noninsulin treated diabetes participants
○ Not a high school graduate- 13%, Just high school- 26%, Some college or technical school- 35%, College graduate or more- 27%

Table 3 Validity Scores

	Cosway et al.	Cukierman-Yaffe et al.	Saczynski et al.	Ryan et al.	Umegaki et al.	van Harten et al.
Descriptions						
Was the study population well described?	1	1	1	1	1	1
Sampling						
Did the authors specify the sampling frame or universe of selection for the study population?	1	1	1	1	1	1
Did the authors specify the sample was selected from the general diabetic population?	0	1	1	1	0	0
Did the authors specify the screening criteria for study eligibility?	1	1	1	1	1	1
Are the groups assembled at a similar point in their disease progression?	0	0	1*	0	0	0
Measurement						
Did the authors specify a reliable and valid method of diagnosing diabetes?	0	1	1*	0	0	0
Did the authors specify a valid method of obtaining HbA1c measurement with blood drawn near the time of cognitive testing?	0	1	1	0	0	0
Did the authors specify that measures were taken to ensure the accuracy/consistency of the cognitive test scores obtained?	0	1	1	1	1	0
Did the authors specify that interviewers were blinded to diabetes status?	0	0	0	0	0	1
Data analysis						
Did the authors conduct appropriate analysis by conducting specified statistical testing?	1	1	1	1	1	1
Interpretation of Results						
Did at least 80% of enrolled participants complete the study?	1	1	1	1	1	1
Was the study longitudinal?	0	0	0	0	0	0
Did the authors ensure the lack of audio or visual defecits prior to cognitive testing?	1	0	0	0	1	0
Did the authors specify if blood glucose was measured prior to testing to exclude hypoglycemia?	1	1	0	1	0	0
Were important confounding variables methodologically controlled or statistically adjusted in regards to HbA1c?						
• Age	0	1	1	0	0	0
• Sex	0	1	0	0	0	0
• Neurological conditions, including head injuries	1	1	0	1	0	1
• Psychiatric conditions	1	0	0	1	0	1
• Depression/Depressive symptoms	0	1	1	0	0	0
• Alcohol and/or Substance Abuse	1	1	0	1	0	1
• Hypertension	0	1	1	0	0	0
• Hyperlipidemia	0	1	0	0	0	0
• Vascular complications, including myocardial infarction, unstable angina, nephropathy, retinopathy, cerebrovascular accidents, and/or transient ischemic attacks	1	1	1	0	1	1
• Premorbid intellegence/Education	0	1	1	0	0	0
• Dementia	0	1	1	0	0	1
Sum of Components	**11**	**20**	**16**	**11**	**8**	**11**
*This study assessed both diagnosed and undiagnosed type II diabetic participants, the latter being similar in disease progression stage and reliably diagnosed .						

Table 4 Results

Study	**Memory**	
	Verbal	Visual
Cosway et al.	NS	NS
Cukierman-Yaffe et al.	Sig *	–
Ryan et al.	NS	–
Saczynski et al.	NS	–
Umegaki et al.	Sig *	–
van Harten et al.	NS	–

NS = No significant correllation found between HbA1c and memory
Sig = Significant correllation found between HbA1c and memory
* $P \leq 0.05$