Published in final edited form as:

J Diabetes Complications. 2016 ; 30(8): 1513–1518. doi:10.1016/j.jdiacomp.2016.08.010.

Associations between Recent Severe Hypoglycemia, Retinal Vessel Diameters, and Cognition in Adults with Type 1 Diabetes

Christopher M. Ryan, PhD¹, Barbara E.K. Klein, MD, MPH², Kristine E. Lee, MS², Karen J. Cruickshanks, PhD^{2,3}, and Ronald Klein, MD, MPH²

¹Department of Psychiatry, University of Pittsburgh School of Medicine, Pittsburgh, PA

²Department of Ophthalmology and Visual Sciences, University of Wisconsin-Madison School of Medicine and Public Health, Madison, WI

³Department of Population Health Sciences, University of Wisconsin-Madison School of Medicine and Public Health, Madison, WI

Abstract

Aims—Mild cognitive dysfunction has been identified in children and adults with type 1 diabetes, but most studies have failed to find a relationship between severe hypoglycemia and cognition, despite reports of such associations in older adults with type 2 diabetes. Focusing on older adults with type 1 diabetes, we examined associations between cognitive performance and recent episodes of severe hypoglycemia, retinal vessel diameters and the presence of micro- and macrovascular complications.

Methods—Cognitive functioning was assessed in 244 participants enrolled in the Wisconsin Epidemiologic Study of Diabetic Retinopathy. The mean (SD; range) age at assessment in 2012 – 14 was 55.2 (8.3; 37 – 82) years and the mean (SD) duration of diabetes was 41.1 (5.6) years. Three cognitive domains were assessed in this cross-sectional study: mental efficiency and executive function, nonverbal memory, and verbal memory.

Results—Multivariate modeling demonstrated that although age and/or education are most strongly associated with performance on measures of mental efficiency, three diabetes-related variables were also associated with poorer test scores: an episode of severe hypoglycemia in the past year ($\beta = -0.360$ [95% CI, $-0.672, -0.047$]), retinal arteriolar and venular diameters ($\beta = 0.140$ [95% CI, $0.062, 0.219$]; $\beta = -0.127$ [95% CI $-0.207, -0.047$]), and carotid artery plaque ($\beta = -0.372$ [95% CI $-0.741, -0.003$]). In addition, recent severe hypoglycemia was associated with poorer nonverbal memory ($\beta = -0.522$ [95% CI, $-0.849, -0.194$]).

Address Correspondence to: Christopher M. Ryan, Ph.D., University of California, San Francisco, 3333 California Street, San Francisco, CA 94118, christopher.ryan@ucsf.edu, 415.476.9840.

Now at the Department of Psychiatry, University of California, San Francisco, CA

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Contribution Statement

C.R. designed study, interpreted data, and wrote manuscript, B.E.K.K. designed study, interpreted data, and reviewed/edited manuscript, K.L. analyzed data and reviewed/edited manuscript, C.K. reviewed/ edited manuscript, and R.K. designed study, interpreted data, and reviewed/edited manuscript.

Conclusions—For middle-aged and older adults with long-duration type 1 diabetes, poorer cognition was associated with a recent episode of severe hypoglycemia as well as with the presence of micro- and/or macrovascular conditions. Given the increasing numbers of aging adults with type 1 diabetes, future longitudinal studies are needed to identify causality and to determine whether diabetes management techniques that reduce the onset or severity of vascular complications and hypoglycemia can also reduce the risk of cognitive dysfunction in this population.

1. Background

Neurocognitive dysfunction is now a well-established complication of diabetes (Biessels, Deary, & Ryan, 2008). Adults with type 1 diabetes perform more poorly than healthy peers on tasks requiring sustained and focused attention, rapid responding and eye-hand coordination, and planning and problem solving (Brands, Biessels, De Haan, Kappelle, & Kessels, 2005). Modest reductions in brain volume in frontal regions are also present (Hughes et al., 2013), as are microstructural lesions in white matter (Biessels & Reijmer, 2014). The strongest predictors of cognitive dysfunction include a history of chronic hyperglycemia, indexed by elevated glycosylated hemoglobin (HbA1c) values, and retinal and renal microvascular complications (Jacobson et al., 2011; Ryan, Geckle, & Orchard, 2003). In contrast, episodes of recurrent severe hypoglycemia have not been found to be associated with cognitive changes – at least in the large cohorts of young and middle-aged adults who participated in the Diabetes Control and Complications Trial (DCCT) (DCCT/EDIC Research Group, 2007) or the Epidemiology of Diabetes Complications study (Nunley et al., 2015). These null results are puzzling, given recent reports that hypoglycemia is associated with an increased risk of cognitive dysfunction and dementia in older adults with type 2 diabetes (Lin & Sheu, 2013; Whitmer, Karter, Yaffe, Quesenberry, & Selby, 2009).

To date, virtually all large neurocognitive studies of adults with type 1 diabetes have focused on groups of subjects who were less than 50 years old, on average, as compared to most studies of people with type 2 diabetes, who tended to be 65 years of age or older. Little is known about the role of metabolic and vascular factors on the aging brain in people with type 1 diabetes, but as part of the normal aging process, marked reductions in brain volume and white matter integrity begin to appear around the age of 50 years and accelerate thereafter. If these age-related changes increase the vulnerability of the brain to further cognitive decline as a consequence of age-related vascular, metabolic, and environmental changes (Drachman, 2006), we would expect to see more robust relationships between hypoglycemic events, micro- and macrovascular changes, and increased cognitive dysfunction as adults with type 1 diabetes grow older.

A brief cognitive assessment battery was administered to 244 subjects with type 1 diabetes (current mean age = 56 years; range: 37 to 82) in the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) at the 2012–2014 examination, along with an extensive biomedical examination that included measures of micro- and macrovascular disease, metabolic control, severe hypoglycemia, blood pressure, serum lipids, and depression. This report describes the metabolic and biomedical risk factors associated with poorer cognitive

performance in this cohort of middle-aged and older adults with a long history of type 1 diabetes.

2. Methods

2.1. Participants

The population-based WESDR identified 1,210 persons with type 1 diabetes living and receiving care in an 11-county area of south central Wisconsin in 1979–1980. There were no exclusions to eligibility in the study, so the WESDR included all ages and disease severity and complications. Detailed descriptions of the WESDR cohort, participation statistics, and reasons for nonparticipation have appeared elsewhere (Klein, Knudtson, Lee, Gangnon, & Klein, 2008). In brief, the first examination in 1980–1982 included 996 persons 3 to 79 years of age with 1 to 59 years of type 1 diabetes. Further follow-up examinations were conducted periodically, with the most recent occurring in 2012–2014 ($n = 414$).

2.2. Clinical and Laboratory Assessments

Examinations in 2012–2014 were performed in a mobile examination van or clinic by trained examiners. Written informed consent was obtained prior to initiating assessments using consent forms and processes that conformed to the tenets of the Declaration of Helsinki and were approved by the University of Wisconsin Institutional Review Board.

Ocular and physical examinations included measuring visual acuity, height, weight, and blood pressure, dilating the pupils, and taking stereoscopic color fundus photographs of 7 standard fields. For each eye, the maximum grade of diabetic retinopathy in any of the 7 standard photographic fields was determined for each lesion. Proliferative diabetic retinopathy (PDR) was defined as having an ETDRS severity level of 60 or higher in either eye. Clinically significant macular edema was defined as retinal thickening in the macular area in either eye (ETDRS Research Group, 1985). Computer-assisted measurements of individual retinal arterioles and venules were each combined according to formulas that provide the average diameters of retinal arterioles (central retinal arteriolar equivalents [CRAE] and central retinal venular equivalents [CRVE]) (Knudtson et al., 2003).

Hypertension was defined as a mean systolic blood pressure ≥ 140 mmHg and/or a mean diastolic blood pressure ≥ 90 mmHg and/or a history of antihypertensive medication at the time of the assessment (Chobanian et al., 2003). Intima-media thickness (IMT) and plaque in the common carotid artery were used as surrogates for preclinical atherosclerotic disease and were assessed with high resolution B-mode carotid artery ultrasound images using a modification of the Atherosclerotic Risk in Communities (ARIC) study ultrasound scanning protocol (Riley et al., 1991). HbA_{1c} was measured in EDTA whole blood on the Tosoh HPLC Glycohemoglobin Analyzer (Tosoh Medics, Inc., San Francisco CA 94080) using an automated high performance liquid chromatography method (DCCT Research Group, 1993). Serum total and HDL cholesterol was measured by reflectance spectrophotometry. Serum creatinine was measured and estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI formula (Levey et al., 2009). Protein in the urine was measured by Labstix (Ames) and proteinuria defined as a urine protein concentration of 30 mg/dL or

more. Abnormal renal function was defined as $\text{eGFR} < 60 \text{ mL/min/1.73 m}^2$ or the presence of proteinuria. Obesity was defined as a body mass index (BMI) $\geq 30 \text{ kg/m}^2$. A structured interview provided data on medication use, history of kidney transplant and dialysis, cardiovascular disease, peripheral neuropathy, smoking, drinking, physical activity, and diabetes management (e.g., history of ketoacidosis; hypoglycemia; pump use). Occurrence of hypoglycemic events were assessed with two questions: (1) 'In the past year, how many times did hypoglycemia cause you to lose consciousness?' (2) 'In the past year, how many times were you hospitalized overnight or longer for hypoglycemia?' Severe hypoglycemia was considered present if either of these questions indicated a frequency of 1 or more times in the past year. Depressive symptomatology was assessed with the CES-D questionnaire (Radloff, 1977).

2.3. Cognitive Assessments

Three broad cognitive domains were assessed with well-validated psychometrically sound tasks previously used by us (Nunley et al., 2015). **Mental Efficiency and Executive Function** was measured with 7 tests: Trail Making Test, Parts A and B; Stroop Word and Interference Test; Grooved Pegboard; Digit Symbol Substitution Test (DSST); Verbal Fluency using the letters F, A, and S. **Nonverbal Memory** was assessed with the Rey Complex Figure Test (copy, immediate and delayed recall) and with recall of DSST number-symbol pairs (DSST Recall). **Verbal Memory** was measured with the Immediate and Delayed recall of a brief story. Detailed descriptions of these widely used tests are provided elsewhere (Strauss, Sherman, & Spreen, 2006). Participants were allowed to skip any test because of physical limitations but were encouraged to complete as many as they were able.

2.4. Statistical Analyses

All analyses were performed with SAS version 9.3 (SAS Institute). The grouping of the cognitive tests was done based on factor analysis with varimax rotation, but no other restrictions. Factor analysis identified 3 principal components (based on the mineigen criteria in SAS). Individual cognitive tests were assigned to the factor with the strongest loading score (always > 0.5). Normality assumptions were tested for all variables and z-scores were calculated by subtracting the population mean and dividing by the standard deviation (based on those participants who completed all tests). Z-scores for those tests loading on a specific cognitive domain were averaged together (flipping signs where needed to maintain a consistent directionality for the association). Analyses were performed separately for each domain as well as for each cognitive test and began with examination of the association of each possible risk characteristic in a simple model, with adjustment for age, duration of diabetes, gender, education and visual impairment.

Some variables included in the population description were not carried forward into the final analyses based on distribution in population and collinearity with other included factors. All risk characteristics were considered in the multivariate models. Stepwise selection was used with both the entry and exit significance criteria set at 0.10. Interactions were examined for reasonable biologic mechanisms present among factors retained in the final multivariate model, but no significant interactions were identified. With the extensive longitudinal data available for most risk characteristics, additional analyses were performed to determine if

information from prior examinations contribute to the models. Inclusion of the past data did not alter conclusions from the final multivariate models, and will not be presented.

3. Results

3.1. Participant Characteristics

Of the 414 persons who participated in the 2012–2014 physical examinations, 244 completed at least one of the cognitive tasks and 198 completed all cognitive tasks. Eighty-six refused (most commonly reporting that they did not have the time to complete the cognitive tests), 15 had significant physical disabilities that prevented them from participating, and 69 were not seen at the examination site.

The numbers included in each analysis vary for each test since we included people for analyses regardless of whether they completed other tests. Analyses for each domain were limited to those participants who completed all tests that contributed to that domain: 210 for the mental efficiency domain, 220 for non-verbal memory, and 234 for verbal memory. Characteristics of WESDR Examination 7 study participants who agreed, and did not agree to attempt the cognitive assessment battery, respectively, are summarized in Table 1. Subjects who completed the cognitive study and had experienced an episode of severe hypoglycemia ($n = 24$) within the previous year were younger, leaner, and less likely to drink alcohol, but were more likely to be a current smoker, have cardiovascular disease, and/or have an amputation as compared to those without a recent hypoglycemic event (all p values $< .05$).

3.2. Cognitive Findings

Cognitive test results for the entire sample are summarized in Supplementary Table S1. Scores on all measures are well within the ‘normal’ range for this age group. Consistent with previous studies of adults with type 1 (Brands et al., 2005; DCCT/EDIC Research Group, 2007) or type 2 (Palta, Schneider, Biessels, Touradji, & Hill-Briggs, 2014) diabetes, tests measuring mental efficiency and executive function were most strongly associated with diabetes-related variables.

3.3. Associations between biomedical variables and cognitive outcomes

Associations between each biomedical variable and each cognitive domain are shown in Table 2. Of the 3 domains, mental efficiency was most sensitive to both demographic and biomedical variables. Supplementary Table S2 summarizes test-specific associations with each predictor variable. Of the individual cognitive tests administered, performance on the Grooved Pegboard – which requires participants to insert notched pegs into a pegboard as quickly as possible – was particularly sensitive to demographic variables (age, duration, gender, years of education) as well as to psychosocial and biomedical variables (depression, visual impairment, HbA1c, waist circumference, history of ketoacidosis, signs of microvascular disease).

Multivariate modeling for each cognitive domain (Table 3) demonstrates that although the strongest predictors of performance tended to be age and/or education, a recent episode of

severe hypoglycemia was associated with poorer performance on measures of mental efficiency ($p < .05$) and nonverbal memory ($p < .002$). Narrower central retinal arterioles and wider retinal venules equivalents (CRAE; CRVE, respectively) were associated with poorer performance on measures of mental efficiency ($p < .001$; $p = 0.002$); associations with verbal memory were marginally significant (CRAE; $p = .06$). Common carotid artery plaque was also associated with reduced mental efficiency ($p = .05$), but history of cardiovascular disease failed to reach statistical significance ($p = .07$) as did measures of blood pressure ($p > .10$).

4.0 Discussion

In our sample of older adults with type 1 diabetes, poorer performance on measures of mental efficiency and executive functioning was associated with a recent history of severe hypoglycemia, the presence of subclinical atherosclerosis (indexed by carotid artery plaque) and subtle variations in retinal microvasculature (narrower central arterioles and wider central venules). To the best of our knowledge, this is the first demonstration that a recent episode of severe hypoglycemia is associated with cognitive outcomes in older adults (median age = 54.4 years) who have a long history of type 1 diabetes (median duration = 40.3 years).

Previous studies of adults with type 1 diabetes have demonstrated repeatedly that the development of microvascular complications like retinopathy or nephropathy may adversely affect mental efficiency (Ferguson et al., 2003; Jacobson et al., 2011; Ryan et al., 2003). Associations between poorer cognition and microvascular changes in the retina, whether indexed by the presence of retinopathy or by more subtle alterations in retinal arterioles and venules, have also been observed in adults with, and without type 2 diabetes (Heringa et al., 2013). However, until our study, relationships between CRAE, CRVE and cognition had not been examined in people with type 1 diabetes.

Our findings are consistent with the hypothesis that both retinal vascular characteristics and cognitive dysfunction may be manifestations of a similar underlying microvascular pathophysiological process ("systemic arteriole dysfunction") that affects the brain as well as multiple extracranial systems (Thompson & Hakim, 2009). In older adults with, or without, type 2 diabetes, narrower retinal arterioles and wider venules are associated with brain atrophy (primarily white matter atrophy) (Ikram et al., 2013) and cerebral microbleeds (Hilal et al., 2014). These, in turn, are associated with poorer mental efficiency and executive function (Qiu et al., 2010). Retinal arteriolar narrowing is also associated with peripheral neuropathy (Ding et al., 2012) and chronic kidney disease (Wong, Wong, Cheng, & Sabanayagam, 2014) in older adults. In children with type 1 diabetes, its presence predicts the subsequent development of microvascular complications (peripheral neuropathy, retinopathy, and nephropathy) 16 years later (Broe et al., 2014). Ours is the first demonstration that narrower retinal arteriolar diameters are associated with mental slowing in middle-aged adults with type 1 diabetes. The fact that narrower arterioles in our cohort is more strongly associated with lower mental efficiency scores than a diagnosis of PDR may reflect the greater sensitivity of continuous measures of vascular caliber to subtle alterations in the cerebral microvasculature and white matter integrity, as compared to a dichotomous

variable like PDR. Retinal arteriolar diameter may also serve as a marker of transient, but unobserved, blood pressure elevations occurring at times of the day other than when measured during this study.

Multivariate analyses also indicated that plaque in the common carotid artery were associated with lower mental efficiency scores in our cohort. This observation is similar to that reported in the DCCT/EDIC cognitive follow-up study (Jacobson et al., 2011), which found a marginally significant relationship between carotid intima-media thickness and changes in mental efficiency over time. Decreases in white matter integrity as well as poorer cognitive functioning have also been associated with larger intima media thickness in middle-aged adults with type 1 diabetes, but effects were limited to subjects without retinopathy (Van Duinkerken et al., 2015). Those authors speculated that in subjects with PDR, subclinical carotid artery disease may have little or no impact on brain structure or function because more extensive damage may have already occurred in these individuals secondary to the development of PDR-associated generalized microangiopathy (Woerdeman et al., 2014).

Longitudinal studies of community-dwelling adults have also reported that the multiple cardiovascular risk factors (Qiu & Fratiglioni, 2015; Yaffe et al., 2014) and/or carotid artery changes measured at midlife (Arntzen, Schirmer, Johnsen, Wilsgaard, & Mathiesen, 2012) were associated with accelerated cognitive decline 7 to 25 years later. Those findings provide additional support for the hypothesis that diabetes-related cognitive dysfunction is largely vascular in origin, and are consistent with a cumulative exposure model that posits that earlier exposure to more vascular risk characteristics leads to poorer cognition over time (Yaffe et al., 2014). Unfortunately, we do not have information on plaque from all previous examinations, so were unable to evaluate the impact of earlier exposures from vascular risk characteristics in this analysis.

The relationship between severe hypoglycemia and cognitive impairment in adults with diabetes continues to be controversial. Within our cohort, an episode of severe hypoglycemia within the past year was associated with lower mental efficiency scores. Our findings are consistent with data demonstrating that older adults (mean age = 68 years) with type 1 diabetes who experienced severe hypoglycemia in the past 12 months performed poorer on measures of mental efficiency than age-matched diabetic patients who had not experienced hypoglycemia (Weinstock et al., 2016). These observations are at variance with most other large studies of adults with type 1 diabetes, which have failed to find any relationship between severe hypoglycemia and cognition (Austin & Deary, 1999; Brands et al., 2006; Ferguson et al., 2003; Jacobson et al., 2011). Differences among study populations and in ascertainment of hypoglycemia may account for this discrepancy. For example, our subjects were more likely to be diagnosed in childhood as compared to others, had a longer duration of diabetes (Brands et al., 2006; DCCT/EDIC Research Group, 2007), and tended to be older than all but one cohort (Brands et al., 2006). Furthermore, we included only those hypoglycemic events that occurred in the year prior to the cognitive assessment, whereas other studies included all hypoglycemic events either estimated across the subject's lifetime (Brands et al., 2006; Ferguson et al., 2003) or occurring during the study follow-up period (DCCT/EDIC Research Group, 2007). In this population, information about hypoglycemic

events from earlier exam phases did not significantly add to the model (data not shown). Previous studies that combined data across the subject's lifetime or across the entire study period may have diluted potential associations, thereby leading to null results. It may be that the association between cognitive dysfunction and severe hypoglycemia identified in our study reflects the effects of a moderately severe neuroglycopenic event on the aging brain.

Indeed, two very large medical record review studies have reported that even a single episode of clinically significant hypoglycemia in older adults with type 2 diabetes increases their risk of subsequently developing dementia or cognitive dysfunction (Lin & Sheu, 2013; Whitmer et al., 2009). Although it may be tempting to conclude that those data support the view that hypoglycemia-associated neuroglycopenia causes structural changes to the brain, as demonstrated in animal studies (Bree, Puente, Daphna-Iken, & Fisher, 2009), results from prospective cohort studies do not support that position. In those studies, subjects who performed poorly at study entry were subsequently more likely to experience one or more hypoglycemic events that could, in turn, further accelerate the rate of cognitive decline (Feinkohl et al., 2014; Punthakee et al., 2012; Yaffe et al., 2013). Whether those findings are a consequence of poorer diabetes management secondary to cognitive dysfunction (Duke & Harris, 2014), or whether the development of cognitive dysfunction and severe hypoglycemia have a common, and as yet unidentified, etiology, remains to be determined. Because we assessed cognitive function at a single time point, we cannot determine whether the presence of poorer cognition at study entry is associated with subsequent episodes of severe hypoglycemia. However, we found no difference in level of education (a surrogate measure of intelligence) between our subjects who did, and did not, experience a recent hypoglycemic episode, unlike studies of adults with type 2 diabetes (Punthakee et al., 2012). Moreover, in the single longitudinal study that examined the effects of intelligence at study entry and subsequent episodes of severe hypoglycemia, no relationship was found for the young adults with type 1 diabetes who participated in the DCCT (Austin & Deary, 1999).

Our study has many strengths. The sample is comprised of a large, well-characterized cohort of middle-aged adults with type 1 diabetes for more than 41 years, on average. Cognitive functioning was evaluated with a battery of widely used tests that have been shown previously to be sensitive to diabetes-associated variables, and standard protocols were followed to measure multiple micro- and macrovascular complications and risk factors – including retinal vessel caliber, metabolic control, and severe hypoglycemia. Limitations include the fact that cognitive measures were only available at a single examination. Also, some subjects with visual and/or sensory/motor problems were unable to complete certain tasks. This may have led to an underestimate of the degree of such impairment in the cohort. The IMT and plaque variables may have underestimated the severity of atherosclerosis, since the ultrasound scan did not include the internal carotid artery and the bulb. Finally, because our cohort includes, by design, persons with long term type 1 diabetes, we report findings on relatively healthy survivors. While this may be viewed as a limitation, it is also a strength because our purpose was to examine relationships between hypoglycemia, vascular characteristics and cognitive function in such individuals.

In summary, our study showed that poorer mental efficiency is associated with not only microvascular (narrower retinal arterioles, wider retinal venules) characteristics, but also

with recent episodes of severe hypoglycemia. Our results emphasize the potentially harmful effects of severe hypoglycemia in older adults with type 1 diabetes, particularly when they also show evidence of micro- and macrovascular characteristics. Future research is needed to determine whether diabetes management techniques that reduce the onset or severity of diabetes-associated complications, including reduction of severe hypoglycemic events, can lead to corresponding improvements in cognitive functioning in the growing population of aging adults with type 1 diabetes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding

This research was supported in part by funding from the National Institutes of Health: EY016379 (R.K.) and an unrestricted grant from Research to Prevent Blindness (R.K.).

References

- Arntzen KA, Schirmer H, Johnsen SH, Wilsgaard T, Mathiesen EB. Carotid artery plaque progression and cognitive decline: the Tromso Study 1994–2008. *Eur J Neurol*. 2012; 19(10):1318–1324. [PubMed: 22537454]
- Austin EJ, Deary IJ. Effects of repeated hypoglycemia on cognitive function: A psychometrically validated reanalysis of the Diabetes Control and Complications Trial Data. *Diabetes Care*. 1999; 22:1273–1277. [PubMed: 10480770]
- Biessels GJ, Deary IJ, Ryan CM. Cognition and diabetes: A lifespan perspective. *Lancet: Neurology*. 2008; 7:184–190. [PubMed: 18207116]
- Biessels GJ, Reijmer YD. Brain changes underlying cognitive dysfunction in diabetes: what can we learn from MRI? *Diabetes*. 2014; 63(7):2244–2252. [PubMed: 24931032]
- Brands AMA, Biessels G-J, De Haan EHF, Kappelle LJ, Kessels RPC. The effects of type 1 diabetes on cognitive performance: A meta-analysis. *Diabetes Care*. 2005; 28:726–735. [PubMed: 15735218]
- Brands AMA, Kessels RPC, Biessels GJ, Hoogma RPLM, Henselmans JML, van der Beek Boter JW, De Haan EHF. Cognitive performance, psychological well-being, and brain magnetic resonance imaging in older patients with type 1 diabetes. *Diabetes*. 2006; 55:1800–1806. [PubMed: 16731845]
- Bree AJ, Puente EC, Daphna-Iken D, Fisher SJ. Diabetes increases brain damage caused by severe hypoglycemia. *American Journal of Physiology - Endocrinology and Metabolism*. 2009; 297:E194–E201. [PubMed: 19435850]
- Broe R, Rasmussen ML, Frydkjaer-Olsen U, Olsen BS, Mortensen HB, Hodgson L, Grauslund J. Retinal vessel calibers predict long-term microvascular complications in type 1 diabetes: the Danish Cohort of Pediatric Diabetes 1987 (DCPD1987). *Diabetes*. 2014; 63(11):3906–3914. [PubMed: 24914239]
- Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL. National High Blood Pressure Education Program Coordinating Committee. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension. 2003; 42:1206–1252. [PubMed: 14656957]
- DCCT Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *New England Journal of Medicine*. 1993; 329:977–986. [PubMed: 8366922]
- DCCT/EDIC Research Group. Long term effects of diabetes and its treatment on cognitive function. *New England Journal of Medicine*. 2007; 356:1842–1852. [PubMed: 17476010]

- Ding J, Cheung CY, Ikram MK, Zheng YF, Cheng CY, Lamoureux EL, Wong TY. Early retinal arteriolar changes and peripheral neuropathy in diabetes. *Diabetes Care*. 2012; 35(5):1098–1104. [PubMed: 22374638]
- Drachman DA. Aging of the brain, entropy, and Alzheimer disease. *Neurology*. 2006; 67:1340–1352. [PubMed: 17060558]
- Duke DC, Harris MA. Executive function, adherence, and glycemic control in adolescents with type 1 diabetes: a literature review. *Curr Diab Rep*. 2014; 14(10):532. [PubMed: 25142717]
- ETDRS Research Group. Photocoagulation for diabetic macular edema. *Archives of Ophthalmology*. 1985; 103:1796–1806. [PubMed: 2866759]
- Feinkohl I, Aung PP, Keller M, Robertson CM, Morling JR, McLachlan S. Edinburgh Type 2 Diabetes Study, I. Severe hypoglycemia and cognitive decline in older people with type 2 diabetes: The Edinburgh type 2 diabetes study. *Diabetes Care*. 2014; 37(2):507–515. [PubMed: 24103900]
- Ferguson SC, Blane A, Perros P, McCrimmon RJ, Best JJK, Wardlaw JM, Frier BM. Cognitive ability and brain structure in type 1 diabetes: Relation to microangiopathy and preceding severe hypoglycemia. *Diabetes*. 2003; 52:149–156. [PubMed: 12502506]
- Heringa SM, Bouvy WH, van den Berg E, Moll AC, Kappelle LJ, Biessels GJ. Associations between retinal microvascular changes and dementia, cognitive functioning, and brain imaging abnormalities: a systematic review. *Journal of Cerebral Blood Flow and Metabolism*. 2013; 33(7):983–995. [PubMed: 23591648]
- Hilal S, Ong YT, Cheung CY, Tan CS, Venketasubramanian N, Niessen WJ, Ikram MK. Microvascular network alterations in retina of subjects with cerebral small vessel disease. *Neuroscience Letters*. 2014; 577:95–100. [PubMed: 24937268]
- Hughes TM, Ryan CM, Aizenstein HJ, Nunley K, Gianaros PJ, Miller R, Rosano C. Frontal gray matter atrophy in middle aged adults with type 1 diabetes is independent of cardiovascular risk factors and diabetes complications. *Journal of Diabetes and Its Complications*. 2013; 27(6):558–564. [PubMed: 23994432]
- Ikram MK, De Jong FJ, Vernooij MW, Hofman A, Niessen WJ, Van der Lugt A, Ikram MK. Retinal vascular calibers associate differentially with cerebral gray matter and white matter atrophy. *Alzheimer Disease and Associated Disorders*. 2013; 27:351–355. [PubMed: 23632264]
- Jacobson AM, Ryan CM, Cleary PA, Waberski BH, Weinger K, Musen G. The DCCT/EDIC Research Group. 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]
- Klein R, Knudtson MD, Lee KE, Gangnon R, Klein BE. The Wisconsin Epidemiologic Study of Diabetic Retinopathy: XXII the twenty-five-year progression of retinopathy in persons with type 1 diabetes. *Ophthalmology*. 2008; 115(11):1859–1868. [PubMed: 19068374]
- Knudtson MD, Lee KE, Hubbard LD, Wong TY, Klein R, Klein BE. Revised formulas for summarizing retinal vessel diameters. *Current Eye Research*. 2003; 27:143–149. [PubMed: 14562179]
- Levey AS, Stevens LA, Schmidt CH, Zhang Y, AF C, Feldman HI. CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A new equation to estimate glomerular filtration rate. *Annals of Internal Medicine*. 2009; 150:604–612. [PubMed: 19414839]
- Lin CH, Sheu WH. Hypoglycaemic episodes and risk of dementia in diabetes mellitus: 7-year follow-up study. *Journal of Internal Medicine*. 2013; 273(1):102–110. [PubMed: 23003116]
- Nunley KA, Rosano C, Ryan CM, Jennings JR, Aizenstein HJ, Zgibor JC, Saxton JA. Clinically relevant cognitive impairment in middle-aged adults with childhood-onset type 1 diabetes. *Diabetes Care*. 2015; 38:1768–1776. [PubMed: 26153270]
- Palta P, Schneider AL, Biessels GJ, Touradji P, Hill-Briggs F. Magnitude of cognitive dysfunction in adults with type 2 diabetes: a meta-analysis of six cognitive domains and the most frequently reported neuropsychological tests within domains. *J Int Neuropsychol Soc*. 2014; 20(3):278–291. [PubMed: 24555960]
- Punthakee Z, Miller ME, Launer LJ, Williamson JD, Lazar RM, Cukierman-Yaffe T. Accord MIND Investigators. Poor cognitive function and risk of severe hypoglycemia in type 2 diabetes: Post hoc epidemiologic analysis of the ACCORD trial. *Diabetes Care*. 2012

- Qiu C, Cotch MF, Sigurdsson S, Jonsson PV, Jonsdottir MK, Sveinbjörnsdottir S, Launer LJ. Cerebral microbleeds, retinopathy, and dementia: the AGES-Reykjavik Study. *Neurology*. 2010; 75:2221–2228. [PubMed: 21172845]
- Qiu C, Fratiglioni L. A major role for cardiovascular burden in age-related cognitive decline. *Nat Rev Cardiol*. 2015; 12(5):267–277. [PubMed: 25583619]
- Radloff LS. The CES-D scale: A self report depression scale for research in the general population. *Applied Psychological Measurement*. 1977; 1:385–401.
- Riley WA, Barnes RW, Bond MG, Evans GW, Chambless LE, Heiss G. High resolution b-mode ultrasound reading methods in the Atherosclerosis Risk in Communities (ARIC) cohort. *Journal of Neuroimaging*. 1991; 1:168–172. [PubMed: 10149810]
- Ryan CM, Geckle MO, Orchard TJ. Cognitive efficiency declines over time in adults with Type 1 diabetes: Effects of micro- and macrovascular complications. *Diabetologia*. 2003; 46:940–948. [PubMed: 12819900]
- Strauss, E.; Sherman, EMS.; Spreen, O. A Compendium of Neuropsychological Tests. 3. Oxford, UK: Oxford University Press; 2006.
- Thompson CS, Hakim AM. Living beyond our physiological means: Small vessel disease of the brain is an expression of systematic failure in arteriolar function: A unifying hypothesis. *Stroke*. 2009; 40:e322–e330. [PubMed: 19228835]
- Van Duinkerken E, Ijzerman RG, van der Zijl NJ, Barkhof F, Pouwels PJW, Schoonheim MM, Diamant M. Differential impact of subclinical carotid artery disease on cerebral structure and functioning in type 1 diabetes patients with versus those without proliferative retinopathy. *Cardiovascular Diabetology*. 2015; 13:1–8.
- Weinstock RS, DuBose SN, Bergenstal RM, Chaytor NS, Peterson C, Olson BA. T1D Exchange Severe Hypoglycemia in Older Adults with Type 1 Diabetes Study Groups. Risk factors associated with severe hypoglycemia in older adults with type 1 diabetes. *Diabetes Care*. 2016; 39:603–610. [PubMed: 26681721]
- Whitmer RA, Karter AJ, Yaffe K, Quesenberry CP, Selby JV. Hypoglycemic episodes and risk of dementia in older patients with type 2 diabetes mellitus. *Journal of the American Medical Association*. 2009; 301:1565–1572. [PubMed: 19366776]
- Woerdeman J, Van Duinkerken E, Wattjes MP, Barkhof F, Snoek FJ, Moll AC, Diamant M. Proliferative retinopathy in type 1 diabetes is associated with cerebral microbleeds, which is part of generalized microangiopathy. *Diabetes Care*. 2014
- Wong CW, Wong TY, Cheng CY, Sabanayagam C. Kidney and eye diseases: common risk factors, etiological mechanisms, and pathways. *Kidney Int*. 2014; 85(6):1290–1302. [PubMed: 24336029]
- Yaffe K, Falvey CM, Hamilton N, Harris TB, Simonsick EM, Strotmeyer ES. Health ABC Study. Association between hypoglycemia and dementia in a biracial cohort of older adults with diabetes mellitus. *JAMA Intern Med*. 2013; 173(14):1300–1306. [PubMed: 23753199]
- Yaffe K, Vittinghoff E, Pletcher MJ, Hoang TD, Launer LJ, Whitmer R, Sidney S. Early adult to midlife cardiovascular risk factors and cognitive function. *Circulation*. 2014; 129(15):1560–1567. [PubMed: 24687777]

Table 1

Characteristics of Study Sample

	Cognitive Assessment	No Cognitive Assessment	P
Number	244	107	
Age (years)	55.2 ± 8.3	57.9 ± 9.9	0.009
Diagnosed before 8 years of age (%)	21%	24%	0.54
Age at diagnosis (years)	14.0 ± 6.9	13.9 ± 7.8	0.87
Diabetes Duration (years)	41.1 ± 5.6	44.0 ± 8.1	<0.001
Male (%)	53%	46%	0.20
HbA1c (%)	7.8 ± 1.2	7.8 ± 1.2	0.78
Education (years)	14.6 ± 2.4	13.4 ± 3.0	<0.001
Depressive Symptomatology Present (%)	21%	27%	0.25
Impaired visual acuity (%)	5%	25%	<0.001
Hypertension (%)	71%	74%	0.57
Mean Arterial Blood Pressure (mmHg)	94.8 ± 10.6	91.5 ± 11.7	0.008
Body Mass Index (kg/m ²)	29.2 ± 5.5	28.1 ± 5.9	0.12
Obese (BMI > 30) (%)	37%	32%	0.40
Ever Smoker (%)	35%	41%	0.31
Current Drinker (%)	90%	78%	0.004
Proliferative Diabetic Retinopathy (%)	47%	55%	0.14
Clinically Significant Macular Edema (%)	7%	2%	0.06
Cardiovascular Disease (%)	17%	20%	0.46
Common carotid artery plaque	7%	7%	0.99
IMT (Common carotid artery, mm)	0.6 ± 0.1	0.6 ± 0.1	0.91
Abnormal Renal Function (%)	25%	41%	0.006
Amputation (%)	6%	13%	0.02
Peripheral Neuropathy Present (%)	36%	43%	0.22
History of Ketoacidosis (%)	16%	18%	0.77
CRAE (μm)	146 ± 19.9	145 ± 23.7	0.58
CRVE (μm)	217 ± 29.3	214 ± 38.2	0.40
Severe Hypoglycemia in past year (%)	11%	19%	0.04

HbA1c = glycosylated hemoglobin A1c; IMT = intima media thickness; CRAE = central retinal arteriolar equivalent; CRVE = central retinal venular equivalent

Table 2

Relationships between biomedical variables and domain scores

	Mental Efficiency			Non-Verbal Memory			Verbal Memory		
	Beta	(95% CI)	p-value	Beta	(95% CI)	p-value	Beta	(95% CI)	p-value
Age, per 5 years	-0.176	(-0.242, -0.111)	<.001	-0.081	(-0.153, -0.009)	0.03	-0.062	(-0.155, 0.031)	0.19
Duration, per 5 years	-0.114	(-0.208, -0.019)	0.02	-0.103	(-0.211, 0.005)	0.06	0.045	(-0.092, 0.182)	0.52
Gender (M vs F)	-0.148	(-0.325, 0.028)	0.10	0.021	(-0.177, 0.220)	0.83	-0.052	(-0.309, 0.204)	0.69
Education, per years	0.083	(0.047, 0.118)	<.001	0.038	(-0.003, 0.079)	0.07	0.129	(0.076, 0.181)	<.001
Visual Impairment	-0.288	(-0.853, 0.276)	0.32	-0.084	(-0.555, 0.386)	0.73	-0.191	(-0.793, 0.411)	0.53
HbA1c, per %	-0.038	(-0.113, 0.037)	0.32	-0.036	(-0.116, 0.044)	0.38	-0.039	(-0.143, 0.066)	0.47
Hypertension (140/90)	-0.011	(-0.212, 0.190)	0.92	0.058	(-0.163, 0.279)	0.60	0.080	(-0.208, 0.368)	0.59
Systolic BP, per 10 mmHg	0.007	(-0.043, 0.057)	0.79	-0.026	(-0.083, 0.031)	0.38	-0.048	(-0.118, 0.023)	0.19
Diastolic BP, per 5 mmHg	-0.004	(-0.058, 0.051)	0.89	-0.026	(-0.086, 0.033)	0.39	-0.062	(-0.138, 0.013)	0.11
MABP, per 5 mmHg	0.002	(-0.042, 0.046)	0.93	-0.025	(-0.074, 0.025)	0.33	-0.052	(-0.114, 0.010)	0.10
Waist Circumference, per inch	-0.003	(-0.019, 0.013)	0.71	-0.008	(-0.026, 0.010)	0.41	-0.007	(-0.031, 0.016)	0.53
Body Mass Index, per kg/m ²	0.003	(-0.012, 0.019)	0.67	-0.002	(-0.020, 0.016)	0.84	-0.008	(-0.031, 0.015)	0.51
Obesity (BMI ≥ 30)	-0.041	(-0.223, 0.141)	0.66	-0.034	(-0.239, 0.170)	0.74	-0.005	(-0.271, 0.262)	0.97
Ever Smoked	-0.038	(-0.225, 0.149)	0.69	0.046	(-0.167, 0.258)	0.68	0.230	(-0.043, 0.503)	0.10
Proliferative Diabetic Retinopathy	-0.097	(-0.282, 0.087)	0.30	0.207	(0.000, 0.414)	0.05	0.303	(0.034, 0.572)	0.03
Clinically Significant Macular Edema	-0.196	(-0.589, 0.198)	0.33	-0.179	(-0.567, 0.209)	0.37	0.141	(-0.380, 0.663)	0.60
CVD (angina, MI, stroke)	-0.263	(-0.506, -0.021)	0.03	-0.105	(-0.381, 0.170)	0.45	0.133	(-0.219, 0.484)	0.46
Common carotid artery plaque	-0.301	(-0.665, 0.063)	0.10	0.321	(-0.134, 0.775)	0.17	-0.237	(-0.762, 0.288)	0.38
IMT, per 0.1 mm	-0.014	(-0.084, 0.057)	0.70	0.032	(-0.049, 0.113)	0.44	0.115	(0.011, 0.218)	0.03
CKD / Proteinuria	-0.094	(-0.292, 0.103)	0.35	0.169	(-0.052, 0.391)	0.13	0.155	(-0.134, 0.443)	0.29
Neuropathy (self-report)	-0.198	(-0.384, -0.013)	0.04	-0.056	(-0.262, 0.150)	0.59	0.216	(-0.050, 0.481)	0.11
Age Diagnosis (per year)	-7.421	(-15.51, 0.672)	0.07	1.743	(-7.433, 10.919)	0.71	-0.496	(-12.49, 11.497)	0.94
Ever Ketoacidosis	-0.129	(-0.365, 0.106)	0.28	-0.110	(-0.373, 0.154)	0.41	-0.037	(-0.382, 0.308)	0.83
Severe Hypoglycemic Episode	-0.442	(-0.735, -0.148)	0.003	-0.492	(-0.819, -0.165)	0.003	0.016	(-0.417, 0.449)	0.94
CRAE (μm)	0.052	(0.000, 0.103)	0.05	-0.002	(-0.057, 0.053)	0.94	-0.077	(-0.146, -0.008)	0.03
CRVE (μm)	-0.004	(-0.052, 0.045)	0.89	-0.006	(-0.061, 0.048)	0.83	-0.056	(-0.125, 0.013)	0.11

	Mental Efficiency			Non-Verbal Memory			Verbal Memory		
	Beta	(95% CI)	p-value	Beta	(95% CI)	p-value	Beta	(95% CI)	p-value
Depressed (CES-D scale > 16)	-0.178	(-0.404, 0.047)	0.12	-0.001	(-0.258, 0.257)	1.00	0.327	(-0.002, 0.655)	0.05

HbA1c = glycosylated hemoglobin A1c; BP = blood pressure; MABP = mean arterial blood pressure; CVD = cardiovascular disease; IMT = intima media thickness; CKD = chronic kidney disease; CRAE = central retinal arteriolar equivalent; CRVE = central retinal venular equivalent; CES-D = Centers for Epidemiologic Studies – Depression

Table 3

Final Multivariate Model Results for each Cognitive Domain

Variable	Mental Efficiency		Non-Verbal Memory		Verbal Memory	
	Beta (95% CI)	p-value	Beta (95% CI)	p-value	Beta (95% CI)	p-value
AGE, per 5 years	-0.222 (-0.279, -0.164)	<.001	-0.100 (-0.175, -0.026)	0.009		
DURATION, per 5 years			-0.096 (-0.206, 0.014)	0.09		
EDUCATION, per year	0.070 (0.033, 0.106)	<.001			0.133 (0.080, 0.187)	<.001
CVD (angina, MI, stroke)	-0.235 (-0.487, 0.017)	0.07				
Common carotid artery plaque	-0.372 (-0.741, -0.003)	0.05				
Severe Hypoglycemia	-0.360 (-0.672, -0.047)	0.03	-0.522 (-0.849, -0.194)	0.002		
CRAE per 10 μ m	0.140 (0.062, 0.219)	<.001			-0.062 (-0.126, 0.003)	0.06
CRVE per 15 μ m	-0.127 (-0.207, -0.047)	0.002				

CRAE = central retinal arteriolar equivalent; CRVE = central retinal venular equivalent