Published in final edited form as:

J Clin Exp Neuropsychol. 2009 October ; 31(7): 809–822. doi:10.1080/13803390802537636.

Short-term longitudinal trends in cognitive performance in older adults with type 2 diabetes

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Abstract

Type 2 diabetes is associated with cognitive deficits, although inconsistently across neuropsychological domains. We examined 3-year longitudinal data from the Victoria Longitudinal Study, comparing diabetes ($n = 28$) and control ($n = 272$) older adults on a comprehensive neuropsychological battery. Assessing potential change and stability, we found that (a) baseline diabetes group deficits in semantic speed and speed-intensive executive function were preserved, (b) new average deficits for reaction time and nonspeeded executive function appeared, and (c) no differential short-term change was observed. It is clinically and theoretically important to examine sequential change in multiple domains over time.

Keywords

Aging; Cognition; Type 2 diabetes; Longitudinal; Speed

Type 2 diabetes is a chronic, aging-related disease with documented deleterious effects on cognitive performance in older adults. Effects of diabetes on the aging brain are of particular interest given its relationship to increased risk of stroke, cerebrovascular disease, and dementia (e.g., Ott et al., 1996; Reunanen, Kangas, Martikainen, & Klaukka, 2000; Stegmayr & Asplund, 1995; Xu, Qiu, Wahlin, Winblad, & Fratiglioni, 2004). Recent estimates on the prevalence of type 2 diabetes in adults over the age of 60 are as high as 18–20% in North America (National Institute of Health, 2005; Public Health Agency of Canada, 2007)—a rate that may increase dramatically in the near future (Wild, Roglic, Green, Sicree, & King, 2004). Although many studies have reported that type 2 diabetes is related to overall cognitive dysfunction, the patterns of results are mixed regarding affected cognitive domains, potentially moderating comorbidities, and suspected underlying neural mechanisms. In fact, studies have reported contrasting effects for some cognitive domains, including the absence of any diabetes-related deficits (e.g., Robertson-Tchabo, Arenberg, Tobin, & Plotz, 1986; Vanhanen et al., 1999).

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Perhaps the two most pervasive challenges in the current neuropsychology of diabetes literature are to (a) clarify the concurrent cognitive profiles of aging type 2 diabetes adults and (b) explore the extent to which short- and long-term changes are characterized by stability or decline trajectories.

Some concurrent cross-sectional studies have reported diabetes-related deficits in episodic memory and speed-intensive measures (e.g., Arvanitakis, Wilson, & Bennett, 2006a; Awad, Gagnon, & Messier, 2004; Coker & Shumaker, 2003; Messier, 2005; Ryan & Geckle, 2000; Wahlin, Nilsson, & Fastbom, 2002), but discrepancies are common in these and other cognitive domains (Nilsson, 2006). For example, several studies focusing on diabetes-related deficits in global cognitive performance have produced both supporting (Hassing et al., 2003) and contrasting (Arvanitakis et al., 2006a; Fontbonne, Berr, Ducimetiere, & Alperovitch, 2001) evidence. Findings on the broad and multidimensional construct of executive function are similarly mixed in the diabetes literature and are likely related to the fact that single tests may represent different aspects of the domain for both healthy and special populations of older adults (Awad et al., 2004; de Frias, Dixon, & Strauss, 2006; de Frias, Dixon, & Strauss, 2008; Messier, 2005; Ryan & Geckle, 2000; Stewart & Liolitsa, 1999). Three main conclusions relevant to the present study can be noted: (a) when cognitive neuropsychological differences appear, older controls typically perform better than diabetes participants, (b) frequent discrepancies (including null findings) are observed within cognitive domains and across tasks, and (c) future research recommendations include both broad-based measurement batteries and longitudinal tracking of diabetes-related cognitive effects (e.g., Nilsson, 2006; Yeung, Fischer, & Dixon, in press). Our present research is designed to contribute to specific aspects of these recommendations.

In our previous cross-sectional study we examined group differences in performance across five cognitive domains (spanning 17 cognitive tests), comparing otherwise-healthy type 2 diabetes older adults with nondiabetes control participants (Yeung et al., in press). One feature of our comprehensive cognitive neuropsychological battery is that we were able to examine and compare performances on a broad range of tasks. Notably, we found that diabetes-related performance deficits were concentrated on complex and demanding speed-intensive tasks of executive function and semantic speed of processing, but not on tasks representing such domains as episodic memory, semantic memory, verbal fluency, less speed-reliant tests of executive function (e.g., Brixton), or simple reaction time (e.g., Nilsson, 2006; Ryan & Geckle, 2000; Wahlin et al., 2002). Because the initial age range of our participants was broad (53 to 90 years old), we speculated in our discussion that the complex and speed-intensive tasks may be sensitive to relatively early-appearing group differences. In general, our baseline results highlighted the potential selectivity of effects within and across study samples, and our recommendations emphasized the importance of follow-up assessments to examine potentially varying decline patterns in relation to diabetes and neuropsychological domain. To date, relatively little is known about the diabetes-related pattern of cognitive change in older adults, or about the tasks that might be affected by, or sensitive to, short-term changes or instability. Examining temporal trajectories for all cognitive domains—and perhaps especially semantic speed and speed-intensive executive functioning—will provide insight into the extent to which baseline group effects are maintained, diminished, emerging, or exacerbated over time. The clinically important questions regarding the temporal ordering of cognitive changes with diabetes and early markers of cognitive decline may also be approached with longitudinal data. In the present article, we report our first effort to examine newly available short-term longitudinal data in a sample of healthy controls and type 2 diabetes participants.

What does the emerging literature on longitudinal changes in cognition for diabetes patients reveal so far? In concordance with cross-sectional findings, some prospective studies on diabetes and cognition suggest an earlier or accelerated decline in cognitive performance for

older diabetes participants (e.g., Coker & Shumaker, 2003; Cukierman, Gerstein, & Williamson, 2005; Hassing et al., 2004a). A systematic overview of prospective studies found that individuals with diabetes had a 1.2- to 1.5-fold higher change in cognitive performance over long-term intervals compared to healthy controls (Cukierman et al., 2005). In several studies assessing disease severity, a longer duration of type 2 diabetes was associated with greater cognitive decline (e.g., M. F. Elias, Elias, Sullivan, Wolf, & D'Agostino, 2005; Gregg et al., 2000; Okereke et al., 2008). However, like the cross-sectional literature, longitudinal research is limited by the few and varying cognitive neuropsychological indicators used within and across studies and by the consequent discrepant patterns of observed change. Longitudinal trends in global cognition generally indicate that diabetes groups show accelerated decline in comparison to healthy controls, whether or not significant group differences were observed at baseline (Hassing et al., 2004a; Logroscino, Kang, & Grodstein, 2004; Okereke et al., 2008). However, across all other domains of function, prospective results remain mixed. Among the studies that found lower episodic memory performance at baseline in diabetes groups, most observed no significant changes over various longitudinal follow-up intervals (Arvanitakis, Wilson, Bienias, Evans, & Bennett, 2004; Fontbonne et al., 2001; Knopman et al., 2001). Research with semantic memory tasks has generally found group differences in favor of healthy controls at baseline or a diabetes-related accelerated decline (Arvanitakis et al., 2004; Hassing et al., 2004b; Strachan, Deary, Ewing, & Frier, 1997), although null results (i.e., no differential change) have also been reported (Aberle, Kliegel, & Zimprich, 2008). Verbal fluency has been examined in several studies with mixed results (Grodstein, Chen, Wilson, & Manson, 2001; Hewer, Mussell, Rist, Kulzer, & Bergis, 2003; Knopman et al., 2001). Performance on executive function tests has been evaluated primarily with tasks of rule switching (i.e., Trails B) and speeded accuracy (e.g., digit symbol substitution, DSS). Several studies have noted diabetes-related deficits at baseline and differential decline at follow-up on the Trails B task (e.g., Fontbonne et al., 2001; Gregg et al., 2000). The majority of studies examining executive functioning used the DSS, finding significantly lower performance in diabetes participants than in nondiabetes controls, combined with an accelerated trajectory of decline (e.g., Cukierman et al., 2005; Fontbonne et al., 2001; Gregg et al., 2000). Similarly, diabetes participants (M age = 63 years) performed worse than controls over a 4-year interval on a speeded measure of psychomotor sequencing (e.g., Aberle et al., 2008). However, as noted previously (Aberle et al., 2008; Cukierman et al., 2005), few studies have used comprehensive test batteries, with multiple indicators of speed and executive functions notably lacking in the literature. Given the theoretical and clinical relevance of these domains in healthy and impaired aging, as well as the potential multidimensionality of executive functioning, more comprehensive cognitive batteries are recommended.

Although most clinical and population-based literature confirm an overall diabetes-related deficit in cognitive neuropsychological performance, the variability of results within and across cognitive domains qualifies interpretations and signals the need for testing domain-specific effects observed in aging individuals with type 2 diabetes. For example, a substantial proportion of recent longitudinal studies utilized smaller batteries of tests that sampled only a restricted range of cognitive abilities and even limited aspects of such cognitive domains as executive function (e.g., Aberle et al., 2008; Gregg et al., 2000; Logroscino et al., 2004). In addition, many neuropsychological studies have examined either young-old (typically, 60–65 years; e.g., Aberle et al., 2008) or old-old (typically, 80+ years; e.g., Hassing et al., 2004b) adults, but rarely in the same study. The present study adds to the literature by exploring diabetes effects across a broad range of both cognitive neuropsychological measures (as recommended by Allen, Frier, & Strachan, 2004; Stewart & Liolitsa, 1999) and age ranges of older adults (initially 53–90 years), all measured at two longitudinal waves (3-year interval). Based on previous literature, as well as conceptual and empirical associations, we organize the range of measures into four cognitive domains reflecting both products and processes of functioning relevant to aging (Hertzog, Dixon, Hultsch, & MacDonald, 2003). The main objective was to

extend our previously observed selective cross-sectional group differences by examining the neuropsychological battery on participants returning for retesting after a 3-year interval. The key research questions concerned stability and change over the 3-year interval: (a) whether previously observed group differences in baseline cognitive performance would continue over the period, (b) whether other cognitive performance differences would emerge over the period, and (c) whether differential change would be observed across waves (i.e., Group $\times$ Wave interactions). Given previously observed longitudinal trends and our earlier baseline findings (see Yeung et al., in press), we expected to find significant diabetes-related group differences in complex and speed-intensive indicators of executive function and semantic speed. As it has been suggested that the aging brain may be increasingly sensitive to diabetes sequelae (see Gispen & Biessels, 2000), we expected to find a trend for declining cognitive performance over time, especially in speed-intensive measures.

METHOD

Participants and sample selection

Source sample—All participants were drawn from the Victoria Longitudinal Study (VLS), an ongoing multicohort study involving three independent volunteer samples of initially healthy older adults. Participants were followed for 3 years and were assessed on numerous biomedical, cognitive, health, and neurocognitive measures (Dixon & de Frias, 2004). The present participants were from VLS Sample 3 and completed baseline testing in 2002–2003 (Wave 1 or W1; initial $n = 577$, range = 53–90 years; M age = 68.29 years, $SD = 8.60$) and at follow-up 3 years later (Wave 2 or W2; returning $n = 402$, range = 57–93 years; M age = 72.08 years, $SD = 8.37$). A total of 7 participants were removed from the baseline sample (6 with missing information on diabetes status, 1 with type 1 diabetes), for an initial W1 sample of $n = 570$. Participants were further examined and were selected into appropriate diabetes and control groups based on defined diagnosis information and exclusionary criteria.

Diabetes classification—The presence of type 2 diabetes was determined by a multiple-stage diagnostic procedure involving a series of self-report, objective medication information, and validity checks at both W1 and W2. We utilized a previously developed sequence of strict diagnostic criteria for selection into the type 2 diabetes or the control group (see Yeung et al., in press). Specifically, inclusion into the diabetes group required that all of the following five conditions be met: (a) self-report of formal diabetes diagnosis (by a physician) and severity rating at W1; (b) W1 report of onset over the age of 31; (c) W1 report of method of treatment (i.e., oral medication, insulin, diet and exercise, no control, or any combination); (d) W1 presence of objective prescription and nonprescription medications for those diabetes participants who reported this form of treatment; and (e) W2 report confirming diabetes-related diagnosis, severity rating, and treatment method. (Additional medical information pertaining to diabetes diagnosis such as blood glucose levels or glycated hemoglobin A1c (HbA1c) levels is unavailable in the VLS.) Based on initial self-reports at W1, the first pool of potential diabetes participants was $n=48$; these participants were selected for the full diagnostic evaluation (see below).

Exclusionary criteria—In addition to the diagnostic criteria, all W1 participants were evaluated on three sets of standard exclusionary criteria common in current cognitive neuropsychological literature. First, we confirmed that all participants were free of Alzheimer's disease or other dementias upon entry into the study. Second, we removed all participants scoring less than 26 on the Mini-Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975) at W1 and less than 24 at W2, as well as those who declined by 3 or more points on the MMSE in the 3-year interval between waves. Third, participants' W1 and W2 health inventories were examined on four clusters of potential comorbid conditions: (a)

neurological conditions (i.e., stroke, Parkinson's disease, epilepsy, and head injury), (b) cardiovascular complications (i.e., heart trouble, hypertension, hypotension, and atherosclerosis), (c) psychiatric conditions (i.e., depression, alcohol dependence, drug dependence, use of antidepressant or antipsychotic medication), and (d) other health-related conditions (e.g., spinal condition and thyroid complications). As previously described (Yeung et al., in press), at W1 we removed all control participants indicating a very serious case of any of the above conditions and any control participant indicating a moderate or serious case of stroke or Parkinson's disease. Diabetes participants meeting exclusionary criteria were selected for individual examination on a set of performance indicators (see Yeung et al., in press). Upon implementing the exclusionary criteria at W1, 86 control and 3 diabetes participants were excluded from the sample. An additional 12 control participants were excluded for scoring less than 26 on the MMSE at W1. Finally, of the remaining provisional diabetes participants, 4 failed to meet our stepwise diagnostic criteria for type 2 diabetes. The final W1 cross-sectional sample was $n = 465$ (diabetes: $n = 41$; controls: $n = 424$) participants. Participants' W2 health inventories were evaluated to check for developing conditions meeting our exclusionary criteria. At W2 several diabetes participants reported incidents of scattered comorbid conditions, but we opted to examine follow-up cognitive performance for possible inclusion in the longitudinal sample. Specifically, individuals who reported at W2 antidepressant ($n = 4$ diabetes; $n = 14$ controls) or antipsychotic ($n = 1$ diabetes) medication use, moderate stroke ($n = 3$ controls), or Parkinson's disease ($n = 1$ diabetes), as well as diabetes participants who self-rated moderate or severe on any of the four health clusters, were examined individually for the presence of any adverse cognitive effects; they were removed from the sample if they scored 1 standard deviation (or more) below their respective group mean for any of cognitive reference tests. From this, 11 participants were removed due to health and cognitive problems ($n = 11$ controls; $n = 0$ diabetes) or MMSE scores ($n = 11$ controls; $n = 0$ diabetes).

Initial longitudinal sample—Of the final W1 cross-sectional sample, $n = 330$ (diabetes: $n = 28$; controls: $n = 302$) participants returned 3 years later and completed the second wave of testing. The overall retention rate was 71%, with notably similar rates for diabetes participants (68.3%) and control participants (71.2%). Reasons for attrition included death (diabetes: 30.8%; controls: 12.3%), health concerns (diabetes: 7.7%; controls: 12.3%), participants who had since moved (diabetes: 7.7%; controls: 12.3%), and those who either declined or we were unable to locate (diabetes: 53.9%; controls: 63.1%). In addition to participant attrition (diabetes: $n = 13$; controls: $n = 122$) and exclusion (diabetes: $n = 0$; controls: $n = 22$, described above), we removed 8 controls with substantial missing cognitive data at W2.

Final longitudinal sample—The final longitudinal sample comprised a type 2 diabetes group ($n = 28$) and a corresponding group of nondiabetes controls ($n = 272$) who met our sample criteria, including participation in both waves. Characteristics of the sample are listed in Table 1. Age, education, and gender proportions were very similar between the groups. Subjective health was measured on a 5-point Likert scale (1 = *very good*, 5 = *very poor*) at both waves. At both W1, $F(1, 298) = 24.03$, $p < .001$, partial $\eta^2 = .08$, and W2, $F(1, 297) = 33.14$, $p < .001$, partial $\eta^2 = .10$, diabetes participants perceived themselves as having poorer health than controls, relative to a perfect state (i.e., absolute rating). In comparison to their peers, diabetes participants' health self-perceptions were also significantly lower than those of controls at W1, $F(1, 298) = 9.48$, $p < .01$, partial $\eta^2 = .03$, and W2, $F(1, 297) = 21.30$, $p < .001$, partial $\eta^2 = .07$. Body mass index (BMI; kg/m^2) was significantly greater for the diabetes group at W1, $F(1, 296) = 21.37$, $p < .001$, partial $\eta^2 = .07$, and W2, $F(1, 297) = 11.11$, $p < .001$, partial $\eta^2 = .04$. The average of eight blood pressure readings (mmHg) taken across four testing sessions was examined. Similar to other studies, (Hassing et al., 2004b; Yeung et al., in press), systolic blood pressure was significantly higher in diabetes participants at W1, $F(1, 293) = 16.64$, $p < .$

001, partial $\eta^2 = .05$, and $W2, F(1, 297) = 14.09, p < .001$, partial $\eta^2 = .05$, whereas no difference was observed for diastolic blood pressure. As recommended elsewhere, systolic blood pressure was used as a covariate in group difference analyses. Both diabetes and control groups had similar levels of visual (Close Vision Task: Snellen fractions) and audio acuity (dB). Global cognition (MMSE) was high and not significantly different for the two groups. Nearly all diabetes participants reported receiving treatment or another method of control at W1 (82.14%) and W2 (96.40%). Typical forms used included oral medications, insulin, and diet alone or a combination of diet and oral medication (see Table 2). Accordingly, self-reported ratings of disease severity were mild to moderate in nearly all (exactly 96.4% at each wave) diabetes participants.

Neuropsychological measures

All measures were used in our previous cross-sectional diabetes study (Yeung et al., in press) and have been used widely in VLS research (e.g., Dixon & de Frias, 2004).

Declarative memory—This domain included two indicators: one episodic memory task and a composite variable of two semantic memory tasks. The episodic task was the VLS *word recall* test, which assessed immediate free recall of two 30-word lists, each comprising 6 words from five taxonomic categories. We measured the average number of words recalled from the two lists (see Dixon et al., 2004). Two VLS tasks (combined as a composite) measured semantic memory (Hultsch, Hertzog, Dixon, & Small, 1998). The *vocabulary* test measured participants' total number of correct responses on a 54-question multiple-choice recognition vocabulary test from the Educational Testing Service (ETS) kit of factor-referenced tests (Ekstrom, French, Harman, & Dermen, 1976). *Fact recall* was measured with two different 40-item tests of general information (e.g., from history, arts, sports) derived from a normed battery (Nelson & Narens, 1980). The composite semantic memory score was the summed average score for both tests.

Verbal fluency—Because of discrepancies in the literature, we examined fluency separately from related cognitive domains. The VLS fluency *Opposites*, *Figures of Speech*, and *Similarities* subtests have been used extensively throughout the VLS and have been previously documented (Hultsch et al., 1998). The raw scores from the three subtests were summed and averaged to create a composite fluency indicator.

Neurocognitive speed—We used four standard tests in the VLS and cognitive neuropsychological literature to assess neurocognitive speed. Two of these were computerized reaction time (RT) tests, measuring the average latency over trials to attend to a signal stimulus (*Simple Reaction Time*, *SRT*, and *Four-Choice Reaction Time*, *CRT4*). The other two were computerized tasks measuring semantic speed latency (*Lexical Decision* and *Sentence Verification*). Lexical Decision scores involved the average of 60 trials with participants indicating whether a string of letters formed a plausible word. Sentence Verification required participants to judge whether a sentence was meaningful or not, recording the mean latency of all responses (within ± 3 SDs of the mean). Composite semantic speed (summed average score for Lexical Decision and Sentence Verification) and RT (summed average score for SRT and CRT4) scores were computed. All neurocognitive speed tasks have been widely used and have been previously described (e.g., Dixon et al., 2007; Hultsch et al., 1998).

Executive functioning—The VLS includes five tests reflecting the general domain of executive functioning, with two representing the subdomain of inhibition and three representing the subdomain of shifting or switching. The tests have been validated and described within the VLS and other studies (see Bielak, Mansueti, Strauss, & Dixon, 2006; de Frias et al., 2006; MacDonald, Hultsch, & Dixon, 2003). For this study, we grouped the tasks

according to our previous research and observed correlational relationships within the present data. Two tests reflected the inhibition aspect: (a) The *Hayling Sentence Completion Test* measured initiation speed (Section A) and response suppression (Section B) in finding suitable words to complete a series of sentences as rapidly as possible (Burgess & Shallice, 1997), and (b) the *Stroop Test* (Taylor, Kornblum, Lauber, Minoshima, & Koeppel, 1997) required participants to ignore the automatic response of reading a printed word (attending to verbal content) and instead name the color of ink in which it was printed. Three tests measured the “shifting” component: (a) the *Brixton Spatial Anticipation Test*, in which participants deduced simple and changing patterns, measuring their ability to abstract logical rules (Andrés & Van der Linden, 2000), (b) the *Color Trails Test* (Part 2; CTT-2; D’Elia, Satz, Uchiyama, & White, 1996), which is similar to the Trail Making Test but minimizes the influence of language; and (c) the *Digit Symbol Substitution Test* (DSS; Wechsler, 1991), which measured switching and perceptual speed. Raw scores from the Stroop and CTT-2 were reverse coded (so that a high score represented better performance). We developed three separate markers for this domain. First, the two measures of inhibition (i.e., Hayling, Stroop) were used as separate indicators. Second, the Brixton was used as a separate indicator of shifting and rule attainment. Third, the CTT-2 and DSS scores were combined to create a speeded shifting-related composite variable (DSS+CTT-2) using the summed average score.

Data analyses

From the battery of 15 tests, we evaluated group and longitudinal wave effects for five composite and four individual variables. Candidate composite variables were identified by theory and empirical evidence (correlations). Composite variables were created by summing and averaging across constituent tests: semantic memory (fact recall, vocabulary), RT (SRT, CRT4), fluency (opposites, figures of speech, similarities), semantic speed (lexical decision, sentence verification), and speed-intensive executive functions (CTT-2, DSS). All cognitive variables were converted to standardized *z*-score units. Overall, four sets of analyses were conducted, including: (a) preliminary attrition analyses, (b) reliability (retest correlations) analyses, (c) correlations between cognitive measures for the diabetes and control groups, and (d) a set of four 2 (group: controls, diabetes) $\times$ 2 (wave: W1, W2) repeated measures multivariate analyses of covariance (MANCOVAs), covarying for systolic blood pressure. The MANCOVAs were performed on each of four cognitive domains: (a) declarative memory (word recall measure, semantic memory composite), (b) verbal fluency composite, (c) neurocognitive speed (RT composite, semantic speed composite), and (d) executive function (DSS + CTT-2 composite, Stroop, Hayling, Brixton). For all the analyses reported, alpha levels of $p < .05$ were specified to indicate statistical significance. All statistical analyses were performed using SPSS version 16.0 statistical software.

RESULTS

Preliminary attrition analyses

Attrition analyses comprised a series of one-way ANOVAs to check for group differences between drop-out participants and those who completed both waves of testing. Attrition effects were checked both for the overall sample and for each group separately. Raw scores from all valid neuropsychological measures were evaluated as separate indicators. The 300 participants who completed and met inclusion criteria at both waves were compared to 135 participants who dropped out prior to W2. Drop-out participants did not differ significantly from continuers in gender or on measures of self-reported health, but were significantly older, $F(1, 433) = 8.73$, $p < .01$, partial $\eta^2 = .02$ (continuers: $M = 66.70$ years, $SD = 7.96$; drop-outs: $M = 69.42$ years, $SD = 8.78$) and had lower levels of education than continuing participants, $F(1, 433) = 15.34$, $p < .001$, partial $\eta^2 = .03$ (continuers: $M = 15.71$ years, $SD = 2.94$; drop-outs: $M = 14.53$ years, $SD = 2.88$). Drop-outs also had significantly ($p < .05$) worse performance on all but two

(measuring executive function: Hayling and Stroop) cognitive neuropsychological indicators, had higher overall systolic blood pressure, and differed significantly on global cognition. Notably, when examined separately by diabetes and control groups, the significant drop-out effects were observed almost exclusively for the control participants. Overall, diabetes continuers and drop-outs performed similarly at W1 on virtually all tasks (one exception: lexical decision). Thus, we note the fact that overall observed drop-out effects were selective to control participants.

Reliability analyses

Measurement reliability was assessed by computing retest Pearson product-moment correlations across the 3-year interval. As can be seen in Table 3 (column 7), magnitudes of the reliability correlations were moderate to high (except for Brixton for the diabetes group) and similar (except Stroop and Brixton) for the healthy control (range: .37 to .91) and the diabetes (range: -.04 to .91) groups. The results indicate relatively stable individual differences over a 3-year period.

Correlational analyses

We first checked correlations between cognitive variables separately for both diabetes and control groups at each wave. The magnitudes of the between-test correlations within cognitive domain were moderate to high and in the expected direction for both groups at both waves for the composite variables (a) semantic memory ($D_{W1} r = .67$; $D_{W2} r = .73$; $C_{W1} r = .56$; $C_{W2} r = .57$), (b) fluency ($D_{W1} r = .57$; $D_{W2} r = .69$; $C_{W1} r = .37$; $C_{W2} r = .52$; mean correlations), (c) semantic speed ($D_{W1} r = .73$; $D_{W2} r = .75$; $C_{W1} r = .69$; $C_{W2} r = .59$), RT ($D_{W1} r = .57$; $D_{W2} r = .65$; $C_{W1} r = .48$; $C_{W2} r = .59$), and (d) DSS + CTT-2 ($D_{W1} r = .53$; $D_{W2} r = .70$; $C_{W1} r = .47$; $C_{W2} r = .59$). The magnitudes of correlations for the single executive functioning indicators, Stroop, Hayling, and Brixton, were lower but in the expected direction at both waves for the diabetes (W1 range: -.07 to .38; W2 range: .04 to .45) and control (W1 range: .03 to .08; W2 range: .06 to .17) groups, highlighting the importance of analyzing them as separate variables. Overall, we observed a high level of task congruence for most measures, particularly those clustered as composite variables.

In addition, correlations of performance with age were computed at each wave separately for diabetes and control participants. As shown in Table 3 (columns 8 and 9), we observed moderate correlations between task performance and age at W1 and W2. Similar magnitudes and direction (generally indicating lower performance with advancing age) were observed in the diabetes and control groups. Specifically, age correlated broadly with task performance in diabetes participants (W1 range: .12 to .48; W2 range: .07 to .48) and in control participants (W1 range: .02 to .48; W2 range: .12 to .54), with 65.0% of W1 and 85.0% of W2 correlations within the .3 to .5 range.

Group and wave analyses

Separate 2 (group: controls, diabetes) $\times$ 2 (wave: W1, W2) repeated measures MANCOVAs were conducted for each of the four cognitive domains (declarative memory, verbal fluency, neurocognitive speed, and executive function). The multivariate test showed no significant effects for declarative memory (episodic or semantic memory) or verbal fluency. An overall main effect of group was observed for both neurocognitive speed, $F(2, 289) = 5.38$, $p < .01$, partial $\eta^2 = .04$, and executive function $F(4, 288) = 6.24$, $p < .01$, partial $\eta^2 = .04$. For neurocognitive speed, there was a significant main effect of group for semantic speed, $F(1, 289) = 15.73$, $p < .01$, partial $\eta^2 = .04$, and RT, $F(1, 289) = 6.43$, $p < .05$, partial $\eta^2 = .02$. The controls (semantic speed: $M = 0.05$, $SE = 0.05$; RT: $M = 0.01$, $SE = 0.05$) performed faster (i.e., shorter latency) than the diabetes group (semantic speed: $M = 0.63$, $SE = 0.16$; RT: $M = 0.38$, $SE = 0.16$). For executive function, main effects of group were observed for the DSS + CTT-2

composite, $F(1, 278) = 7.09, p < .01$, partial $\eta^2 = .03$, as well as for the Hayling, $F(1, 278) = 3.93, p < .05$, partial $\eta^2 = .01$, and Stroop, $F(1, 278) = 13.79, p < .001$, partial $\eta^2 = .05$, tasks. In all cases, the control group performed significantly better than the diabetes groups (DSS + CTT-2: $M_C = 0.05, SE_C = 0.05; M_D = -0.42, SE_D = 0.17$; Hayling: $M_C = -0.04, SE_C = 0.05; M_D = -0.39, SE_D = 0.17$; Stroop task: $M_C = 0.12, SE_C = 0.05; M_D = -0.54, SE_D = 0.17$). For executive function, one main effect of wave was observed for the Stroop task, $F(1, 278) = 4.58, p < .05$, partial $\eta^2 = .02$, with an overall sample improvement in task performance ($M_{W1} = -0.27, SE_{W1} = 0.11; M_{W2} = -0.15, SE_{W2} = 0.10$). No significant main effects were observed for the Brixton task. No significant interaction effects were observed for any variables.

DISCUSSION

Current diabetes and aging literature emphasizes the related issues of (a) determining whether (and when) the observed cross-sectional patterns of cognitive dysfunction diverge or remain stable across longitudinal waves and (b) delineating the earliest and most robust aspects of diabetes-related cognitive deficits and decline. The present study examines cognitive performance on two waves over a 3-year interval using a broad neuropsychological battery in an aging sample of control and relatively mild diabetes participants. Because not all areas of cognition are equivalently or simultaneously affected by diabetes (e.g., Nilsson, 2006), we measured changes in cognitive performance using multiple indicators of several theoretically derived cognitive domains. Our main findings revealed domain-specific diabetes group deficits in complex neurocognitive speed (semantic speed) and correspondingly speed-intensive tasks of executive function. These results qualify and extend the findings of our previous cross-sectional study (Yeung et al., in press) and point to important new directions of research.

Before reviewing the main results, we summarize the importance of three sets of preliminary analyses. First, for this VLS sample we experienced a relatively moderate 3-year retention rate, with overall attrition effects in the typical direction (i.e., favoring continuers at W1). This attrition effect, however, did not apply to the diabetes group per se, thus raising the possibility that the longitudinal diabetes group adequately reflected the cognitive abilities of the initial baseline group. Previous 3-wave (6-year) attrition analyses in the VLS have shown that the initial attrition effects (W1 to W2) are not repeated at later waves and have only marginal effect on subsequent change patterns (Hultsch et al., 1998). Nevertheless, careful monitoring of attrition for future waves will be imperative. Second, we established strong 3-year retest reliability for our measurement battery. This applied to both groups and to our indicators of executive function, a domain for which such reliability is not always observed (de Frias et al., 2008; Ettenhofer, Hambrick, & Abeles, 2006). Third, the correlational analyses showed that the cognitive measures within domains were related in both groups in the expected and generally equivalent patterns. In addition, within-group age-related correlations were in the expected direction and were similar across groups. In sum, this set of analyses established the empirical soundness of the composite variables, which also provided both psychometric and statistical advantages to our subsequent main analyses. These preliminary analyses also established the fundamentals for examining several aspects of cognitive neuropsychological performance in a diabetes group on two longitudinal waves.

We turn now to the main results. The first domain showing a significant deficit for the diabetes group was neurocognitive speed, with both indicators (reaction time and semantic speed) producing group differences averaged over the 3-year period. Importantly, these results replicate and extend our earlier findings with slightly larger groups at baseline (Yeung et al., in press). Specifically, we found that the earlier observed deficit for complex semantic speed was robust across the 3-year interval, highlighting the theoretical significance and clinical potential for such tasks to be reliable markers of relatively early diabetes-related deficits. In addition, the more basic reaction time tasks have now produced a significant group difference

(averaged across the two waves), underscoring the extent to which neurocognitive slowing may be a hallmark of the deficits associated with diabetes in older adults. To be sure, the absence of an interaction suggests the possibility that more longitudinal follow-up time is required to establish whether these differences are exacerbated (or remain stable) with disease duration. Although semantic speed is unique in this literature, one previous study observed diabetes-related deficits for reaction time (albeit in a more advanced disease population; Hewer et al., 2003). However, the group effect became nonsignificant after treatment to improve metabolic control, suggesting (a) a possible mechanism of the effect and (b) the intriguing possibility that the deficits may be reversible. Future research could examine these issues, as well as crucial sequencing questions (e.g., are more basic elements of processing speed preserved longer but still at risk for decline as severity increases?). Whereas age-related declines in speeded performance are common, accelerated slowing may be an early marker of cognitive impairment in dementia (Dixon et al., 2007), and cognitive decline (including dementia) is one long-term potential outcome of diabetes. Given that literature involving tasks of semantic speed is rare, and speeded tasks in general are inconsistently applied, replication studies (and further longitudinal waves) would be useful to clarify their potential as clinically useful markers (Arvanitakis et al., 2006a; Nilsson, Fastbom, & Wahlin, 2002).

Executive function was the second domain that produced significant differences between diabetes participants and healthy controls. Again, baseline cross-sectional group differences (Yeung et al. in press) remained after the 3-year interval for tasks involving speed and inhibition (Hayling) and those requiring speeded responses to rule attainment and switching (the DSS +CTT-2 composite). Newly significant overall group differences in favor of the controls and a 3-year decrease in sample performance (pooled across groups) were observed for the Stroop (inhibition) task. These results contribute to resolving inconsistent patterns of diabetes-related executive deficits in the literature (Messier, 2005). Specifically, the replication and continuation of diabetes-related deficits in speed-intensive executive function tasks underscore the possibility that indicators of this domain may be candidates for earlier markers of cognitive decline in diabetes patients. Extended and large-scale longitudinal research can test within- and across-domain sequencing hypotheses more directly. For example, a cascade pattern may occur wherein initial deficits may be observed in complex speed-related domains (e.g., executive functioning) but eventually, as disease and neurological aging progress (Manschot et al., 2006), simpler speed-related domains and then broader cognitive involvement may occur. Expanding this line of investigation using clinical samples and longer follow-up intervals will aid in consolidating, sequencing, and explaining the pattern of diabetes effects on executive functioning and the timing and extent to which other cognitive domains are affected. From this perspective, some inconsistencies in the literature may be attributable to basic methodological variations in sampling along the dimensions of measures, participants, and disease severity.

Regarding other cognitive domains, we found no diabetes-related effects on any measure of declarative (episodic or semantic) memory or the verbal fluency composite (which, in this study, is conceptually related to semantic memory). Again, these null findings are consistent with (and extend to 3 years) our initial baseline null results (Yeung et al., in press). Unlike the previous domains under discussion, however, these particular cognitive domains are more frequently studied and are associated with mixed patterns of results. One potential pattern, observed in other reports (Arvanitakis et al., 2004; Fontbonne et al., 2001; Knopman et al., 2001), was for null findings at baseline (e.g., episodic memory) but emerging diabetes-related differences at W2. That we did not observe this pattern may be due to differences in disease severity among the various studies or to differences in measures of episodic memory. Further waves of the present sample will address the former, and other research with a variety of episodic memory indicators (including nonverbal measures, not available in the VLS battery) will address the latter. To explore this issue further (see also Rolandsson, Backström, Eriksson, Hallmans, & Nilsson, 2008), we performed a separate, post hoc analysis of

covariance (ANCOVA) on each of the three measures within this domain. No group or wave effects were observed for any indicator of episodic or semantic memory. Finally, a potential contributor to mixed evidence in these domains is whether and which covariate is used in the analyses. In our cross-sectional study, we checked this issue by both including and not including systolic blood pressure as a covariate, observing the appearance and disappearance of a group effect for baseline episodic memory (Yeung et al., in press). Because of the hypertension–cognition relationship (P. K. Elias, D'Agostino, Elias, & Wolf, 1995), covarying for systolic blood pressure is recommended in this literature, but to our knowledge no consensus on other covariates has emerged. Clearly, however, the differential presence of other active health comorbidities in diabetes patients may be related to both concurrent and longitudinal results (Hassing et al., 2004b; Waldstein, 1995). In the present study, we considered potential health confounds at the outset during our initial selection of participants into the study and in the subsequent application of exclusionary criteria. Parenthetically, a similar perspective applies to our null results in semantic memory and verbal fluency, given the array of mixed findings in these domains (Hewer et al., 2003; Wahlin et al., 2002; Yeung et al., in press) and the lack of statistically significant effects observed at our baseline evaluation.

In summary, we found (a) all group differences observed at baseline in our unique cognitive domains (i.e., semantic speed, speed-intensive tasks of executive function) to be preserved across the 3-year interval, (b) additional group performance differences in reaction time and one additional speed-related task of executive function (i.e., Stroop), (c) continuing null effects in nonspeeded cognitive domains for which previous results have been inconsistent, and (d) no differential change in the effect of diabetes on cognitive performance over the 3-year period. An informal inspection of group means reflected generally expected patterns of decline in performance with advancing age. The main results point to the importance of pursuing questions regarding trends in the temporal ordering of cognitive areas affected in diabetes and on the clinical importance of decline patterns within distinct domains. The potential value of multidimensional neuropsychological batteries and continued longitudinal assessments is noted.

Several strengths of our study can be noted. First, the longitudinal design provided an initial opportunity to explore actual short-term change and stability in neuropsychological performance for clinical participants with a progressive and cognitively relevant disease. Second, our comprehensive cognitive battery enabled us to replicate and extend a robust profile of diabetes-associated differences within specific domains, some of which have not been previously included in earlier cross-sectional or longitudinal studies. Third, the broad age range of participants from both genders supplements many studies in the literature that typically focus on relatively narrow adult age groups and either men (e.g., Robertson-Tchabo et al., 1986) or women (e.g., Gregg et al., 2000; Grodstein et al., 2001; Logroscino et al., 2004). A fourth strength was our implementation of recommended and stringent diagnosis and exclusion criteria to control for prominent potential moderators, mediators, and covariates, such as the use of systolic blood pressure as a covariate to account for known hypertensive effects in diabetes-related cognitive dysfunction (Allen et al., 2004; Hassing et al., 2004b; Waldstein, 1995).

Several limitations of the study merit comment. The first derives from the facts that the VLS (a) is a Canadian, volunteer-based, study with initially relatively healthy and generally intact sample of predominantly Caucasian men and women, all of whom have access to national health care, and (b) excludes at intake prospective participants with serious cognitive health impairments (e.g., dementia, cerebrovascular disease). Because the focus is on tracking emerging and incident cases of neurocognitive diseases, the early waves of a sample capture a relatively healthy range of older adults and may not be representative of the general population of older adults, nor in this case the broader and more severe ranges of older adults with type 2

diabetes. Therefore, our goals in generalization are limited to relatively healthy older adults and to relatively mild cases of diabetes. Both, however, are growing aspects of the western older adult population. Second, biological markers provide a firm diagnosis of diabetes, and these markers were not available in the VLS. Instead, we used a precise and strict combination of several items of self-report data, validated for each patient at both waves, supplemented by objective medication validation. We have followed this multi-indicator procedure before (Yeung et al., in press), and the validity of self-report diagnoses, particularly for chronic lifestyle-management diseases such as diabetes, has been established by other researchers (Arvanitakis, Wilson, Li, Aggarwal, & Bennett, 2006b; Kreigsmann, Penninx, van Eijk, Boeke, & Deeg, 1996; Nilsson, 2006). Nevertheless, there is a chance of undiagnosed or preclinical diabetes participants within the control group, and these potential future cases could not be excluded from the present sample (Rolandsson et al., 2008). However, studies suggest that the incidence of undiagnosed cases in older community-dwelling samples is relatively low (Pendleton et al., 2005), and our control group is relatively large ($n = 272$) and undiagnosed over a 3-year period. Overall, these considerations minimize the potential effects of possible preclinical cases on our average control group performance. Third, although well characterized, our diabetes group ($n = 28$) is small, but within a general range found in recent cognitive neuropsychological literature on diabetes (e.g., Aberle et al., 2008, $n = 38$; Wahlin et al., 2002, $n = 31$; Watari et al., 2006, $n = 40$). Fourth, longitudinal studies are vulnerable to survivor bias, as those individuals with lower levels of cognition at baseline are more likely to have dropped out or died (Allen et al., 2004), and retest effects could apply (Strachan et al., 1997). We confirmed these expected overall attrition effects, but noted that (a) they did not apply to the diabetes group and (b) we replicated previously observed cross-sectional results and extended them to the 3-year longitudinal assessment, including both group differences and similarities in cognitive performance. With a future addition of a third wave, statistical techniques for including all participants (drop-outs and continuers) and accounting for retest effects in the analyses will be available (e.g., Hultsch et al., 1998; McArdle, Fisher, & Kadlec, 2007). At present, mitigating this potential problem are our 3-year interval, reliable and valid measures, and our attention to multiple indicators. Fifth, the VLS does not directly assess disease duration or account for treatment modality. A post hoc analysis of diabetes duration with cognitive performance found generally nonsignificant correlations. So far, no convincing evidence suggests a link between treatment modality and cognitive effects (Areosa Sastre & Grimley Evans, 2003), but further research is needed to fully examine effects of disease duration and to determine the etiology of cognitive effects.

Understanding the extent to which cognitive changes are characterized by stability or differential trajectories, as well as the cognitive areas selectively affected in type 2 diabetes, is of clinical and theoretical relevance. Our study contributes to the literature with a comprehensive neuropsychological battery and broad range of diabetic and nondiabetic older adults examined longitudinally. The results qualify and extend previous findings, noting that observed cross-sectional effects of diabetes on cognition are preserved and expand across time, particularly in speeded cognitive areas or demanding executive functions. Given the projected prevalence of diabetes, its close association with age, and its related comorbidities, examining trends in the cognitive profile of older adults with the disease will help determine both a pattern and timeline of cognitive effects exerted in type 2 diabetes.

Acknowledgments

The current research is supported by a grant (R37 AG008235) from the National Institutes of Health (National Institute on Aging) to Roger Dixon, who is also supported by the Canada Research Chairs program. Cindy de Frias, who is now at the Department of Psychology, Stockholm University, was supported by a postdoctoral award from the Canadian Institute of Health Research. Ashley Fischer is now at Simon Fraser University, Burnaby, Canada. The authors express gratitude to Jill Jenkins and Terry Perkins for technical support and to the staff and participants of the Victoria Longitudinal Study.

REFERENCES

- Aberle I, Kliegel M, Zimprich D. Cognitive development in young-old type-2 diabetes patients: A longitudinal analysis from the "Interdisciplinary Longitudinal Study of Aging.". *Current Psychology* 2008;27:6–15.
- Allen KV, Frier BM, Strachan MWJ. The relationship between type 2 diabetes and cognitive dysfunction: Longitudinal studies and their methodological limitations. *European Journal of Pharmacology* 2004;490:169–175. [PubMed: 15094083]
- Andrés P, Van der Linden M. Age-related differences in supervisory attentional system functions. *Journal of Gerontology: Psychological Sciences* 2000;55B:P373–P380.
- Areosa Sastre, A.; Grimley Evans, J. The Cochrane Library. Cochrane Review; Oxford, UK: 2003. Effect of the treatment of type II diabetes mellitus on the development of cognitive impairment and dementia [Update software].; p. 1-24.
- Arvanitakis Z, Wilson RS, Bennett DA. Diabetes mellitus, dementia, and cognitive function in older persons. *The Journal of Nutrition, Health, and Aging* 2006a;10:287–291.
- Arvanitakis Z, Wilson RS, Bienias JL, Evans DA, Bennett DA. Diabetes mellitus and risk of Alzheimer disease and decline in cognitive function. *Archives of Neurology* 2004;61:661–666. [PubMed: 15148141]
- Arvanitakis Z, Wilson RS, Li Y, Aggarwal NT, Bennett DA. Diabetes and function in different cognitive systems in older individuals without dementia. *Diabetes Care* 2006b;29:560–565. [PubMed: 16505506]
- Awad N, Gagnon M, Messier C. The relationship between impaired glucose tolerance, type 2 diabetes, and cognitive function. *Journal of Clinical and Experimental Neuropsychology* 2004;26:1044–1080. [PubMed: 15590460]
- Bielak AAM, Mansueti L, Strauss E, Dixon RA. Performance on the Hayling and Brixton tests in older adults: Norms and correlates. *Archives of Clinical Neuropsychology* 2006;21:141–149. [PubMed: 16242905]
- Burgess, PW.; Shallice, T. The Hayling and Brixton tests. Thames Valley Test Company; Thurston, UK: 1997.
- Coker L, Shumaker SA. Type 2 diabetes mellitus and cognition: An understudied issue in women's health. *Journal of Psychosomatic Research* 2003;54:129–139. [PubMed: 12573734]
- Cukierman T, Gerstein HC, Williamson JD. Cognitive decline and dementia in diabetes—systematic overview of prospective observational studies. *Diabetologia* 2005;48:2460–2469. [PubMed: 16283246]
- de Frias CM, Dixon RA, Strauss E. Structure of four executive functioning tests in healthy older adults. *Neuropsychology* 2006;20:206–214. [PubMed: 16594781]
- de Frias CM, Dixon RA, Strauss E. Characterizing executive functioning in older special populations: From cognitively elite to cognitively impaired. 2008 Manuscript submitted for publication.
- D'Elia, LF.; Satz, P.; Uchiyama, CL.; White, T. Color trails test professional manual. Psychological Assessment Resources; Odessa, FL: 1996.
- Dixon RA, de Frias CM. The Victoria Longitudinal Study: From characterizing cognitive aging to illustrating changes in memory compensation. *Aging, Neuropsychology, and Cognition* 2004;11:346–376.
- Dixon RA, Garrett DD, Lentz TL, MacDonald SWS, Strauss E, Hultsch DF. Neurocognitive markers of cognitive impairment: Exploring the roles of speed and inconsistency. *Neuropsychology* 2007;21:381–399. [PubMed: 17484601]
- Dixon RA, Wahlin Å, Maitland SB, Hultsch DF, Hertzog C, Bäckman L. Episodic memory change in late adulthood: Generalizability across samples and performance indices. *Memory & Cognition* 2004;32:768–778.
- Ekstrom, RB.; French, JEW.; Harman, HH.; Dermen, D. Manual for the kit of factor-referenced cognitive tests. Educational Testing Service; Princeton, NJ.: 1976.
- Elias MF, Elias PK, Sullivan LM, Wolf PA, D'Agostino RB. Obesity, diabetes, and cognitive deficit: The Framingham Heart Study. *Neurobiology of Aging* 2005;26S:S11–S16.

- Elias PK, D'Agostino RB, Elias MF, Wolf PA. Blood pressure, hypertension, and age as risk factors for poor cognitive performance. *Experimental Aging Research* 1995;21:393–417. [PubMed: 8595804]
- Ettenhofer ML, Hambrick DZ, Abeles N. Reliability and stability of executive functioning in older adults. *Neuropsychology* 2006;20:607–613. [PubMed: 16938023]
- Folstein MF, Folstein SE, McHugh PR. Mini-mental state. A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research* 1975;12:189–198. [PubMed: 1202204]
- Fontbonne A, Berr C, Ducimetiere P, Alperovitch A. Changes in cognitive abilities over a 4-year period are unfavorably affected in elderly diabetic subjects. *Diabetes Care* 2001;24:366–370. [PubMed: 11213894]
- Gispén WH, Biessels G-J. Cognition and synaptic plasticity in diabetes mellitus. *Trends in Neurosciences* 2000;23:542–549. [PubMed: 11074263]
- Gregg EW, Yaffe K, Cauley JA, Rolka DB, Blackwell TL, Venkat Narayan KM, et al. Is diabetes associated with cognitive impairment and cognitive decline among older women? *Archives of Internal Medicine* 2000;160:174–180. [PubMed: 10647755]
- Grodstein F, Chen J, Wilson RS, Manson JE. Type 2 diabetes and cognitive function in community-dwelling elderly women. *Diabetes Care* 2001;24:1060–1065. [PubMed: 11375371]
- Hassing LB, Grant MD, Hofer SM, Pedersen NL, Nilsson SE, Berg S, et al. Type 2 diabetes mellitus contributes to cognitive decline in old age: A longitudinal population-based study. *Journal of the International Neuropsychological Society* 2004a;10:599–607. [PubMed: 15327738]
- Hassing LB, Hofer SM, Nilsson SE, Berg S, Pederson NL, McClearn G, et al. Comorbid type 2 diabetes mellitus and hypertension exacerbates cognitive decline: Evidence from a longitudinal study. *Age and Ageing* 2004b;33:355–361. [PubMed: 15136287]
- Hassing LB, Johansson B, Pedersen NL, Nilsson SE, Berg S, McClearn G. Type 2 diabetes mellitus and cognitive performance in a population-based sample of the oldest old: Impact of comorbid dementia. *Aging, Neuropsychology, and Cognition* 2003;10:99–107.
- Hertzog C, Dixon RA, Hultsch DF, MacDonald SWS. Latent change models of adult cognition: Are changes in processing speed and working memory associated with changes in episodic memory? *Psychology and Aging* 2003;18:755–770. [PubMed: 14692862]
- Hewer W, Mussell M, Rist F, Kulzer B, Bergis K. Short-term effects of improved glycemic control on cognitive function in patients with type 2 diabetes. *Gerontology* 2003;49:86–92. [PubMed: 12574669]
- Hultsch, DF.; Hertzog, C.; Dixon, RA.; Small, BJ. *Memory change in the aged*. Cambridge University Press; New York: 1998.
- Knopman D, Boland LL, Mosley T, Howard G, Liao D, Szklo M, et al. Cardiovascular risk factors and cognitive decline in middle-aged adults. *Neurology* 2001;56:42–48. [PubMed: 11148234]
- Kreisman DMW, Penninx BWJH, van Eijk JTM, Boeke AJP, Deeg DJH. Self-reports and general practitioner information on the presence of chronic disease in community dwelling elderly: A study on the accuracy of patients' self-reports and on determinants of inaccuracy. *Journal of Clinical Epidemiology* 1996;49:1407–1417. [PubMed: 8970491]
- Logroscino G, Kang JH, Grodstein F. Prospective study of type 2 diabetes and cognitive decline in women aged 70–81 years. *British Medical Journal* 2004;328:584.
- MacDonald SWS, Hultsch DF, Dixon RA. Age-related slowing of digit symbol substitution revisited: What do longitudinal trends reflect? *Journal of Gerontology: Psychological Sciences* 2003;58:187–194.
- Manschot SM, Brands AMA, van der Grond J, Kessels RPC, 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]
- McArdle JJ, Fisher GG, Kadlec KM. Latent variable analyses of age trends of cognition in the Health and Retirement Study, 1992–2004. *Psychology and Aging* 2007;22:525–545. [PubMed: 17874952]
- Messier C. Impact of impaired glucose tolerance and type 2 diabetes on cognitive aging. *Neurobiology of Aging* 2005;26S:S26–S30.

- National Institute of Health. National diabetes statistics fact sheet: General information and national estimates on diabetes in the United States (NIH Publication No. 06–3892). U.S. Department of Health and Human Services; Bethesda, MD: 2005.
- Nelson TO, Narens L. Norms of 300 general-information questions: Accuracy of recall, latency of recall, and feeling-of-knowing ratings. *Journal of Verbal Learning and Verbal Behavior* 1980;19:338–368.
- Nilsson, E. Diabetes and cognitive functioning: The role of age and comorbidity. 2006. Unpublished doctoral dissertation, Karolinska Institutet, Stockholm, Sweden
- Nilsson E, Fastbom J, Wahlin Å. Cognitive functioning in a population-based sample of very old non-demented and non-depressed persons: The impact of diabetes. *Archives of Gerontology and Geriatrics* 2002;35:95–105. [PubMed: 14764348]
- Okereke OI, Kang JH, Cook NR, Gaziano JM, Manson JE, Buring JE, et al. Type 2 diabetes mellitus and cognitive decline in two large cohorts of community-dwelling older adults. *Journal of the American Geriatrics Society* 2008;56:1028–1036. [PubMed: 18384580]
- Ott A, Stolk RP, Hofman A, van Harskamp F, Grobbee DE, Breteler MMB. Association of diabetes mellitus and dementia: The Rotterdam Study. *Diabetologia* 1996;39:1392–1397. [PubMed: 8933010]
- Pendleton N, Clague JE, Cobain M, Thethi K, Jones M, Horan MA, et al. Relationship between self-reported prevalence of diabetes mellitus using the Cornell Medical Index (CMI) and prevalence determined by glycosylated haemoglobin (HbA_{1c}) in an elderly community-dwelling population. *Archives of Gerontology and Geriatrics* 2005;41:289–296. [PubMed: 15992945]
- Public Health Agency of Canada. National Diabetes Fact Sheet Canada. Public Health Agency of Canada; Ottawa, Ontario, Canada: 2007.
- Reunanen A, Kangas T, Martikainen J, Klaukka T. Nationwide survey of comorbidity, use, and costs of all medications in Finnish diabetic individuals. *Diabetes Care* 2000;23:1265–1271. [PubMed: 10977017]
- Robertson-Tchabo EA, Arenberg D, Tobin JD, Plotz JB. A longitudinal study of cognitive performance in noninsulin dependent (type II) diabetic men. *Experimental Gerontology* 1986;21:459–467. [PubMed: 3493169]
- Rolandsson O, Backeström A, Eriksson S, Hallmans G, Nilsson L-G. Increased glucose levels are associated with episodic memory in nondiabetic women. *Diabetes* 2008;57:440–443. [PubMed: 17977953]
- Ryan CM, Geckle M. Why is learning and memory dysfunction in Type 2 diabetes limited to older adults? *Diabetes/Metabolism Research and Reviews* 2000;16:308–315. [PubMed: 11025555]
- Stegmayr B, Asplund K. Diabetes as a risk factor for stroke. A population perspective. *Diabetologia* 1995;38:1061–1068. [PubMed: 8591820]
- Stewart R, Liolitsa D. Type 2 diabetes mellitus, cognitive impairment and dementia. *Diabetic Medicine* 1999;16:93–112. [PubMed: 10229302]
- Strachan MWJ, Deary IJ, Ewing FME, Frier BM. Is type II diabetes associated with an increased risk of cognitive dysfunction? *Diabetes Care* 1997;3:438–445. [PubMed: 9051402]
- Taylor SF, Kornblum S, Lauber EJ, Minoshima S, Koeppe RA. Isolation of specific interference processing in the Stroop task: PET activation studies. *NeuroImage* 1997;6:81–92. [PubMed: 9299382]
- Vanhanen M, Kuusisto J, Koivisto K, Mykkanen L, Helkala E-L, Hanninen T, et al. Type-2 diabetes and cognitive function in a non-demented population. *Acta Neurologica Scandinavica* 1999;100:97–101. [PubMed: 10442450]
- Wahlin Å, Nilsson E, Fastbom J. Cognitive performance in very old diabetic persons: The impact of semantic structure, preclinical dementia, and impending death. *Neuropsychology* 2002;16:208–216. [PubMed: 11949713]
- Waldstein SR. Hypertension and neuropsychological function: A lifespan perspective. *Experimental Aging Research* 1995;21:321–352. [PubMed: 8595801]
- Watari K, Letamendi A, Elderkin-Thompson V, Haroon E, Miller J, Darwin C, et al. Cognitive function in adults with type 2 diabetes and major depression. *Archives of Clinical Neuropsychology* 2006;21:787–796. [PubMed: 17030111]
- Wechsler, D. Manual for the Wechsler Adult Intelligence Scale–Revised. Psychological Corporation; New York: 1991.

- Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: Estimates for the year 2000 and projections for 2030. *Diabetes Care* 2004;27:1047–1053. [PubMed: 15111519]
- Xu WL, Qiu CX, Wahlin Å, Winblad B, Fratiglioni L. Diabetes mellitus and risk of dementia in the Kungsholmen project: A 6-year follow-up study. *Neurology* 2004;63:1181–1186. [PubMed: 15477535]
- Yeung SE, Fischer AL, Dixon RA. Exploring effects of Type 2 diabetes on cognitive functioning in older adults. *Neuropsychology*. (in press).

TABLE 1

Demographic characteristics of diabetes and control groups by wave

Group	Wave 1		Wave 2	
	Mean	Range	Mean	Range
Age (years)				
Diabetes	68.45 (7.82)	55.41–80.91	72.80 (7.67)	60.51–85.14
Control	66.74 (7.97)	53.24–90.32	71.08 (7.85)	57.27–93.27
Gender (% female)				
Diabetes	64.3		64.3	
Control	69.1		69.1	
Education (years)				
Diabetes	15.21 (3.40)		14.96 (3.63)	
Control	15.79 (2.79)		15.79 (2.86)	
Systolic blood pressure				
Diabetes	134.99 (13.09)***		136.89 (18.91)***	
Control	123.93 (13.70)***		125.00 (15.62)***	
Subjective health (absolute rating)				
Diabetes	2.29 (0.85)***		2.50 (0.84)***	
Control	1.62 (0.66)***		1.72 (0.66)***	
Subjective health (relative rating)				
Diabetes	1.86 (0.76)**		2.07 (0.86)***	
Control	1.45 (0.65)**		1.52 (0.57)***	
BMI				
Diabetes	30.12 (4.14)***		28.91 (5.16)**	
Control	26.50 (3.86)***		26.25 (3.89)**	
MMSE				
Diabetes	28.86 (1.04)		28.79 (1.07)	
Control	28.98 (0.98)		28.81 (1.02)	
Tobacco use (%)				
Yes	3.6 (4.4)		0.0 (3.3)	
Previously	50.0 (48.2)		53.6 (52.6)	
Never	46.4 (47.4)		46.4 (44.1)	
Alcohol consumption (%)				
Yes	60.7 (91.2)		78.6 (92.6)	
Previously	21.4 (4.0)		21.4 (5.1)	
Never	17.9 (4.8)		0.0 (2.2)	

Note. Diabetes group: $n = 28$. Control group: $n = 272$. BMI = body mass index. MMSE = Mini-Mental State Examination. Standard deviations are represented in parentheses.

**
 $p < .01$.

***
 $p < .001$.

TABLE 2

Characteristics of diabetes sample by wave

	Wave 1	Wave 2
Disease duration (years)	8.31 (7.68) ^a	12.69 (7.65) ^b
Diabetes medication use (%)		
Insulin	10.71	21.43
Oral hypoglycemics	50.00	60.71
Diet/exercise	21.43	14.29
No treatment used	17.86	3.57
Diabetes severity (%)		
Mild	53.57	46.43
Moderate	42.86	50.00
Severe	3.57	3.57

Note. $n = 28$. Standard deviations are represented in parentheses.

^aRange: 0.25–34.27.

^bRange: 3.85–38.58.

TABLE 3

Descriptives and correlations in control and diabetes groups

Variable	M (SD)		F		r (age)	
	W1	W2	Group effect ^a	Group × Wave ^b	W1	W2
Word recall			2.44	0.64		
C	0.02 (0.98)	0.02 (0.98)			-.34***	-.41***
D	-0.30 (1.20)	-0.34 (1.18)			-.47*	-.43*
Semantic memory			3.48	0.18		
C	0.02 (0.88)	-0.02 (0.88)			-.02	-.12*
D	-0.25 (0.98)	-0.33 (1.02)			-.19	-.30
Verbal fluency			3.11	1.72		
C	0.01 (0.76)	0.06 (0.82)			-.19**	-.38***
D	-0.15 (0.89)	-0.25 (0.97)			-.30	-.37
Semantic speed			9.79**	0.52		
C	-0.05 (0.90)	0.19 (0.93)			.23***	.31***
D	0.60 (1.07)	0.70 (0.91)			.31	.36
Reaction time			4.83*	0.25		
C	-0.04 (0.83)	0.05 (0.87)			.44***	.18**
D	0.44 (1.12)	0.47 (1.08)			.18	.38*
Digit Symbol			3.23	0.08		
C	0.04 (0.97)	-0.12 (0.97)			-.42***	-.47***
D	-0.44 (1.21)	-0.59 (1.21)			-.48**	-.48***
Stroop			13.79*	0.01		
C	0.06 (0.95)	0.17 (0.74)			-.30***	-.33***
D	-0.58 (1.34)	-0.53 (1.95)			-.13	-.24
Hayling			3.93*	0.49		
C	0.03 (0.97)	-0.09 (0.99)			-.30***	-.33***
D	-0.27 (1.01)	-0.61 (1.11)			-.29	-.39*

Variable	M (SD)		F		r (age)	
	W1	W2	Group effect ^a	Group × Wave ^b	W1	W2
Color Trails						
C	0.06 (0.92)	0.17 (0.91)	11.88***	0.39	.59***	-.51***
D	-0.57 (1.40)	-0.61 (1.48)			.66***	-.28
Brixton						
C	0.05 (1.00)	0.23 (0.97)	3.27	0.02	-.25***	-.28***
D	-0.26 (0.97)	-0.12 (1.17)			-.04	-.06
DSS+CTT-2						
C	0.07 (0.81)	0.04 (0.83)	7.09**	1.58	.78***	-.55***
D	-0.39 (1.10)	-0.59 (1.27)			.84***	-.41*

Note Correlations: retest, and age-cognition. C = control; D = diabetes. W1 = Wave 1. W2 = Wave 2. DSS+CTT-2 = composite of Digit Symbol Substitution Test (DSS) score and Color Trails Test Part 2 (CTT-2) score. For all cognitive variables (except semantic speed and reaction time) a higher score indicates better performance. For the latter two variables, a higher score indicates slower (poorer) performance.

^a F test for group effect in repeated measures analyses of covariance (ANCOVAs) with systolic blood pressure as the covariate. For all group effects the controls performed better than the diabetes group.

^b F test for group by wave interaction in repeated measures ANCOVAs with systolic blood pressure as the covariate.

^c Test-retest correlations.

* $p < .05$.

** $p < .01$.

*** $p < .001$.