

# 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

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Received: 3 June 2010 / Accepted: 28 July 2010 / Published online: 29 August 2010  
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## Abstract

**Aims/hypothesis** In patients with type 1 diabetes, there has been concern about the effects of recurrent hypoglycaemia and chronic hyperglycaemia on cognitive function. Because other biomedical factors may also increase the risk of cognitive decline, this study examined whether macrovascular risk factors (hypertension, smoking, hypercholesterolaemia, obesity), sub-clinical macrovascular disease (carotid intima–media thickening, coronary calcification) and microvascular complications (retinopathy, nephropathy)

were associated with decrements in cognitive function over an extended time period.

**Methods** Type 1 diabetes patients ( $n=1,144$ ) who had completed a comprehensive cognitive test battery at entry into the Diabetes Control and Complications Trial were reassessed at a mean of 18.5 (range: 15–23) years later. Univariate and multivariable models examined the relationship between cognitive change and the presence of micro- and macrovascular complications and risk factors.

**Results** Univariate modelling showed that smoking history was modestly associated with decrements in learning, memory, spatial information-processing and psychomotor efficiency; hypertension was associated with only psychomotor slowing. Multivariable modelling demonstrated that HbA<sub>1c</sub> level, and retinal and renal complications were each independently associated with decrements in psychomotor efficiency. In contrast, no macrovascular risk factors were significant after correcting for multiple comparisons. No interactions were found between these predictors and sex, severe hypoglycaemic events or presence of the *APOE*  $\epsilon 4$  allele.

**Conclusions/interpretation** In relatively healthy, middle-aged adults with type 1 diabetes who had been followed for an average of 18.5 years, long-term metabolic control and microvascular factors are independently associated with a decline in cognitive function specifically affecting measures of psychomotor efficiency.

**Trial registration** ClinicalTrials.gov NCT00360893

**Funding** This study is supported by NIH grant number 5R01 DK062218-02. The DCCT/EDIC project is supported by contracts with the Division of Diabetes, Endocrinology and Metabolic Diseases of the National Institute of Diabetes and Digestive and Kidney Diseases, the National Eye Institute, the National Institute of Neurological Disorders and Stroke, the General Clinical Research Centers Program, the Clinical and Translational Science Awards Program, the

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W. Dahms died before publication of this work.

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**Electronic supplementary material** The online version of this article (doi:10.1007/s00125-010-1883-9) contains supplementary material, which is available to authorised users.

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National Center for Research Resources and by Genentech through a Cooperative Research and Development Agreement with the National Institute of Diabetes and Digestive and Kidney Diseases.

**Keywords** Cognition · Macrovascular · Microvascular · Psychomotor efficiency · Renal · Retinopathy · Type 1 diabetes

### Abbreviations

EDIC Epidemiology of Diabetes Interventions and Complications  
 IMT Intima—media thickening  
 PDR Proliferative diabetic retinopathy

### Introduction

Cognitive dysfunction has been found in multiple studies comparing both adolescents and adults with type 1 diabetes with non-diabetic individuals. These effects are most apparent on measures of psychomotor efficiency, intelligence, sustained attention, speed of information processing, cognitive flexibility and visual perception [1]. The pathophysiological basis for these findings remains poorly understood. Although earlier reports attributed such deficits to the effects of recurrent, moderately severe hypoglycaemia, a growing body of research has failed to substantiate such linkages [1–4]. This was particularly apparent in our analyses of the long-term follow-up data from 1,144 participants in the Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) study [2]. In those analyses, we found no relationship between decline in cognitive functioning over an 18 year follow-up period and the occurrence of one or more episodes of hypoglycaemia-associated seizure or coma.

On the other hand, results from the same DCCT/EDIC study [2], as well as findings from several recent cross-sectional and longitudinal studies [1, 3, 5–7], identified associations between mild cognitive dysfunction and chronic hyperglycaemia, defined as a long history of poor metabolic control and elevated HbA<sub>1c</sub> values. Two well-known outcomes of chronic hyperglycaemia, diabetic retinopathy [3, 4, 6] and distal symmetric polyneuropathy [7, 8], have previously been associated with cognitive dysfunction in several small studies of adults with type 1 diabetes, leading to speculation that diabetic cognitive complications may be largely microvascular in origin [9].

Cognitive function can also be influenced by other biomedical factors that are commonly associated with diabetes. Macrovascular risk factors like cigarette smoking [10], elevated blood pressure and hypertension [11], hyper-

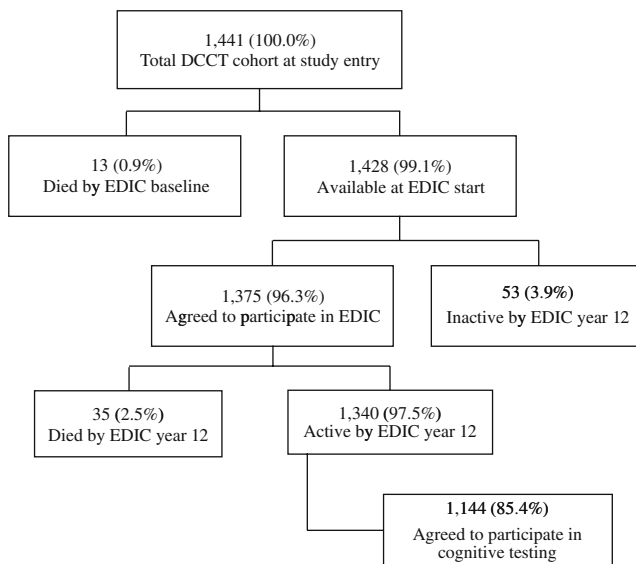
cholesterolaemia [12], and subclinical atherosclerosis have been reported to impair cognition in non-diabetic adults [13] and in older adults with type 2 diabetes [14, 15]. Despite those observations, no study has comprehensively assessed the degree to which macro- and microvascular complications individually and/or synergistically influence cognitive performance in large numbers of young and middle-aged adults with type 1 diabetes.

The DCCT and the follow-up EDIC study provide an excellent means of examining those inter-relationships in a very large sample of carefully monitored adults with type 1 diabetes. Participants completed an extensive battery of cognitive tests, which was repeated over the course of the DCCT/EDIC study period. They underwent frequent and systematic biomedical evaluations to ascertain changes in metabolic control over time and were also assessed for occurrence of micro- and macrovascular risk factors and clinically significant complications.

These data, collected prospectively over a mean of 18.5 years, allowed us to test the hypothesis that the cognitive changes occurring in adults with type 1 diabetes are associated with four broad classes of biomedical variables: (1) macrovascular risk factors (hypertension, smoking, abnormal lipid levels, obesity); (2) development of microvascular complications (retinopathy, nephropathy); (3) evidence of sub-clinical macrovascular disease (carotid intima—media thickening [IMT], coronary calcification); and (4) time-weighted HbA<sub>1c</sub> levels. We examined the relative contribution of these biomedical variables and carried out additional analyses to determine whether effects of these factors on cognitive performance were influenced by sex, age, history of severe hypoglycaemia or presence of the *APOE*  $\epsilon$ 4 allele.

### Methods

**Participants** Between 1983 and 1989, 1,441 patients from 13 to 39 years of age were enrolled in the DCCT and followed until 1993 [16]. At the end of the DCCT, 1,375 (96%) of the 1,428 surviving participants volunteered to continue in the EDIC observational follow-up study. In 2004, 85% of the surviving eligible participants ( $n=1,144$ ) (Fig. 1) were evaluated using the same cognitive test battery as that used at baseline in the DCCT. This group constitutes the sample reported on here [2]. DCCT participants who did not participate in this follow-up study were comparable to the 1,144 participants in terms of baseline demographic, biomedical and cognitive measures. This research protocol was approved by each site's institutional research ethics committee; each participant gave written informed consent prior to the initiation of research activities.



**Fig. 1** Flow diagram of participants who took part in cognitive testing at EDIC year 12

**Cognitive assessment** Cognitive testing was conducted at each site by personnel trained and certified by the DCCT/EDIC Central Neurobehavioral Coding Unit [17]. The test protocol, which took 4 to 5 h to complete, included the following widely used, well-validated tests that were administered initially during the DCCT: six subtests (similarities, comprehension, digit span, digit symbol, block design and object assembly) from the Wechsler Adult Intelligence Scale [18]; four subtests (category test, tactual performance test, trail making test and finger tapping test) from the Halstead–Reitan Neuropsychological Battery [19]; the logical memory and visual reproductions subtests from the Wechsler Memory Scale [20]; the Digit Vigilance Test [21]; the Grooved Pegboard Test [22]; the Verbal Fluency (FAS) Test [23]; the Four-Word Short Term Memory Test [24]; the Symbol-Digit Learning Test [25]; and the Embedded Figures Test [25]. Tests were administered in a fixed sequence and capillary blood glucose levels were routinely monitored to verify absence of hypoglycaemia during testing [2].

During the DCCT, 24 test variables were chosen a priori to be of particular diagnostic value when applied to patients with type 1 diabetes. A standardised ( $z$ ) score was calculated for each variable, with the mean and standard deviation from the baseline assessment of the DCCT cohort used as reference. These procedures have been outlined elsewhere [17]. To reduce the number of comparisons, the 24 standardised scores were grouped into one of eight cognitive domains consistent with standard neuropsychological assessment strategies [26]. For each domain, the simple average of the standardised scores was used to represent the change from baseline.

**Biomedical evaluations** During EDIC, participants had an annual history update, physical examination, electrocardiogram and laboratory testing, using the same methods employed during the DCCT [16]. Participants self-reported the presence of sensory symptoms of peripheral neuropathy [27]; best-corrected visual acuity was measured at 4-year intervals during EDIC. The visual acuity examination closest to the cognitive re-evaluation was used in these analyses. Participants were asked quarterly in the DCCT and annually in EDIC to provide information about smoking and alcohol consumption.

HbA<sub>1c</sub> values were measured in a central laboratory by high-performance liquid chromatography [28], with tests done quarterly during DCCT and annually during EDIC. Time-weighted values across the entire duration of the DCCT/EDIC study were used in our analyses. They were calculated from DCCT inception by weighting each DCCT value by one quarter of a year and weighting each EDIC value by 1 year. Severe hypoglycaemia was defined as any event leading to seizure or coma [2, 29]. Fasting lipid profiles and 4 h urine collections for measurement of albumin excretion rate and creatinine clearance were obtained in alternate years during EDIC. Renal complications were defined as a centrally measured serum creatinine level of at least 177  $\mu\text{mol/l}$ , or treatment with dialysis or transplantation for chronic renal failure [27]. Hypertension was defined as systolic blood pressure  $\geq 140$  mmHg or diastolic blood pressure  $\geq 90$  mmHg or documented hypertension or the use of anti-hypertensive agents for the treatment of hypertension. Hypercholesterolaemia was defined as LDL-cholesterol  $\geq 3.4$  mmol/l or the use of lipid-lowering agents. Retinopathy was assessed by seven-field stereoscopic fundus photography according to the DCCT/EDIC protocol [30]. For these analyses, retinopathy was defined by the presence of proliferative diabetic retinopathy (PDR) and/or history of panretinal scatter-photocoagulation (laser) therapy.

The measurement of intima-media thickness was performed during years 1, 6 and 12 of EDIC; for these analyses, the year 12 examination results were used. A single longitudinal lateral view of the distal 10 mm of the right and left common carotid arteries was obtained using B-mode ultrasonography [31]. Coronary artery calcification was measured with computed tomography on one occasion during years 7 and 9 of EDIC and scans were read centrally [32]. Genotyping of the *APOE* haplotype, rs7412 ( $\epsilon 2/\epsilon 3$ ) and rs429358 ( $\epsilon 3/\epsilon 4$ ), and of the *ACE* intron 16 indel (rs4340) was performed as described previously [33].

**Statistical analyses** Separate analysis of covariance models were used to assess the relationship between each of the eight cognitive domain scores and HbA<sub>1c</sub> values, macrovascular risk factors (hypertension, waist circumference,

hypercholesterolaemia, smoking history), macro- and microvascular complications, and alcohol use. Adjustments were made for sex, baseline age, duration of follow-up, education level, the number of interval cognitive tests taken, presence of painful neuropathy and visual acuity at EDIC year 12. Additionally, five multivariable models were evaluated using psychomotor efficiency as the dependent variable to assess the independent effects of multiple complications and risk factors. Statistical analyses were performed using SAS version 8.2 statistical analysis software (Cary, NC, USA). Univariate comparisons are indicated as being significant at  $p < 0.006$  after Bonferroni correction. For the final model, where all previously significant variables were entered, the Hochberg correction ( $p < 0.05$ ) was used to control for the false discovery rate [34].

## Results

**Demographic and clinical characteristics of sample** When restudied an average of 18.5 years after their DCCT baseline assessment, participants ranged in age from 29 to 62 years (mean 45.7, SD 6.8) and were in relatively good health despite an average duration of 25 years of diabetes (Table 1). As reported previously, participants treated with intensive or conventional therapy during the DCCT had indistinguishable HbA<sub>1c</sub> levels during follow-up in EDIC, with values declining from 9.0±1.6% (mean ± SD) at DCCT baseline to 7.7±1.2% in the former conventional treatment group and to 7.8±1.2% in the former intensive treatment group. There were no statistically significant ( $p < 0.01$ ) differences between the two treatment groups for any of the demographic characteristics at DCCT baseline and EDIC year 12.

**Association of micro- and macrovascular risk factors and complications with change in cognitive function** After adjusting for sex, baseline age, baseline education, presence of painful neuropathy and visual acuity at EDIC year 12, length of follow-up and the number of interval cognitive tests taken, modest associations were found between complications and cognitive performance (Tables 2 and 3). The most consistent associations appeared in the domains of psychomotor efficiency (renal complication, PDR) and motor speed (PDR). Macrovascular risk factors were also found to be associated with cognitive outcomes, including hypertension (with psychomotor efficiency) and smoking (with learning, immediate memory delayed recall, spatial information processing and psychomotor efficiency). HbA<sub>1c</sub> was also associated with psychomotor efficiency and motor speed.

**Multivariable modelling of cognitive decline** To evaluate the independent effects of multiple complication and risk

**Table 1** Demographic characteristics at DCCT baseline and EDIC year 12

Characteristic	DCCT Baseline (1983–1989)	EDIC Year 12 (2005)
<i>n</i>	1,144	1,144
Female sex, <i>n</i> (%)	536 (47)	536 (47)
Mean age (years)	27.0±6.9	45.7±6.8
College graduates, <i>n</i> (%)	323 (28)	418 (38)
Diabetes duration (years)	5.7±4.2	24.5±4.9
HbA <sub>1c</sub> <sup>a</sup>	9.0±1.6	7.8±1.2
Decreased visual acuity, <i>n</i> (%) <sup>b</sup>		44 (4)
Painful neuropathy, <i>n</i> (%)	100 (9)	348 (31)
Blood pressure		
Systolic (mmHg)	113.9±11.7	120.5±14.0
Diastolic (mmHg)	72.5±8.9	73.8±8.8
Hypertension, <i>n</i> (%) <sup>d</sup>	0	478 (44)
Lipids		
Cholesterol (mmol/l)	4.5±0.8	4.6±0.8
LDL-cholesterol (mmol/l)	2.8±0.7	2.8±0.7
Hypercholesterolaemia, <i>n</i> (%) <sup>e</sup>	0	602 (55)
Current cigarette smoker, <i>n</i> (%)	230 (20)	143 (13)

Data are means ± SD or *n* (%)

<sup>a</sup> DCCT baseline value is eligibility value

<sup>b</sup> Participants with 20/40 vision or worse; at DCCT baseline, all patients had visual acuity of 20/32 or better, whereas in EDIC a Snellen value of 20/40 or worse in at least one eye was recorded

<sup>c</sup> DCCT baseline definition was pain or numbness in hands only, taken from the Neurological History and Examination form; EDIC definition was pain or numbness in hands or feet, taken from the Annual Medical History and Examination form

<sup>d</sup> Defined as systolic BP ≥140, diastolic BP ≥90, using hypertension medications or documented hypertension

<sup>e</sup> Defined as LDL ≥3.4 mmol/l or using lipid-lowering agents

Data on medication usage were not collected during the DCCT

factor predictor variables, we selected psychomotor efficiency as the dependent variable because it has been identified in other studies as the cognitive domain most often affected in patients with diabetes [1, 3, 4, 35] and, as expected, showed the strongest associations with vascular complications and risk factors in this study (Table 4). The domain included five test scores: verbal fluency (total correct); digit symbol (total correct in 90 seconds); trail making Part B (total time); and grooved pegboard (completion time for dominant and non-dominant hands). Five multivariate models were evaluated: (1) base model using the demographic covariates evaluated in the separate analysis of covariance models; (2) addition of macrovascular risk factors and HbA<sub>1c</sub> to the base model; (3) addition of macrovascular disease to the base model; (4) addition of microvascular

**Table 2** Single predictor models for macrovascular and microvascular risk factors

Risk factor	n	Domains 1–8, adjusted mean change score <sup>a</sup>								
		Problem solving	Learning	Immediate memory	Delayed recall	Spatial information	Attention	Psychomotor efficiency	Motor speed	
Macrovascular										
Hypertension <sup>b</sup>										
No	619	0.06±0.05	0.05±0.07	-0.06±0.06	-0.14±0.06	0.18±0.06	0.04±0.06	-0.34±0.06	0.09±0.08	
Yes	478	0.09±0.05	-0.08±0.07	-0.09±0.06	-0.16±0.06	0.08±0.06	0.03±0.06	-0.48±0.06*	0.12±0.08	
Current smoker										
No	954	0.08±0.05	0.01±0.06	-0.04±0.06	-0.15±0.06	0.16±0.06	0.03±0.06	-0.38±0.05	0.13±0.08	
Yes	143	0.06±0.06	-0.17±0.09	-0.28±0.08*	-0.20±0.08	-0.05±0.08*	0.05±0.08	-0.59±0.08*	-0.02±0.11	
Ever smoker										
No	782	0.09±0.04	0.00±0.06	-0.04±0.06	-0.15±0.06	0.15±0.06	-0.04±0.06	-0.42±0.05	0.16±0.08	
Yes	362	0.05±0.05	-0.17±0.07*	-0.16±0.06	-0.25±0.07	0.04±0.07	-0.05±0.07	-0.51±0.06	0.10±0.09	
Smoking <sup>c</sup>										
I	119	0.06±0.09	-0.32±0.14	-0.17±0.13	-0.32±0.15	0.11±0.13	-0.27±0.14	-0.30±0.12	0.17±0.18	
II	160	0.04±0.08	-0.42±0.12	-0.25±0.11	-0.31±0.13	-0.07±0.11	-0.14±0.12	-0.37±0.10	0.09±0.16	
III	83	0.12±0.10	-0.27±0.15	-0.36±0.13	-0.33±0.16	-0.21±0.13	-0.17±0.14	-0.42±0.13	0.21±0.19	
Hypercholesterolaemia <sup>d</sup>										
No	496	0.09±0.05	-0.03±0.07	-0.07±0.06	-0.16±0.07	0.12±0.07	-0.00±0.07	-0.40±0.06	0.12±0.09	
Yes	602	0.07±0.05	-0.01±0.07	-0.07±0.06	-0.15±0.06	0.14±0.06	-0.06±0.06	-0.42±0.06	0.10±0.08	
Waist circumference <sup>e</sup>										
I	354	0.08±0.05	-0.05±0.08	-0.06±0.07	-0.21±0.07	0.13±0.07	-0.02±0.07	-0.35±0.07	0.02±0.09	
II	475	0.08±0.05	-0.01±0.07	-0.07±0.06	-0.13±0.06	0.13±0.06	0.06±0.06	-0.40±0.06	0.13±0.08	
III	247	0.04±0.06	0.01±0.08	-0.10±0.07	-0.14±0.07	0.14±0.07	0.05±0.07	-0.50±0.07	0.14±0.09	
Microvascular										
HbA <sub>1c</sub> <sup>f</sup>										
I	410	0.08±0.05	-0.04±0.07	-0.04±0.06	-0.17±0.06	0.13±0.06	0.01±0.06	-0.33±0.06	0.37±0.08	
II	478	0.07±0.05	-0.03±0.07	-0.10±0.06	-0.19±0.06	0.13±0.06	-0.06±0.06	-0.47±0.06	0.07±0.08	
III	248	0.07±0.05	-0.08±0.08	-0.10±0.07	-0.17±0.07	0.09±0.07	-0.08±0.07	-0.56±0.06*	-0.04±0.09*	
Others										
Never drinker	336	0.07±0.05	-0.01±0.07	-0.10±0.07	-0.14±0.07	0.11±0.07	-0.02±0.07	-0.37±0.06	0.11±0.09	
Ever drinker	808	0.07±0.04	-0.07±0.06	-0.07±0.06	-0.19±0.06	0.12±0.06	-0.05±0.06	-0.48±0.05	0.15±0.08	

Table 2 (continued)

Risk factor	n	Domains 1–8, adjusted mean change score <sup>a</sup>							
		Problem solving	Learning	Immediate memory	Delayed recall	Spatial information	Attention	Psychomotor efficiency	Motor speed
Alcohol intake <sup>g</sup>									
I	267	0.03±0.06	-0.08±0.08	-0.21±0.07	-0.21±0.08	0.05±0.08	-0.09±0.08	-0.49±0.07	0.07±0.10
II	355	0.06±0.06	-0.01±0.08	-0.08±0.07	-0.20±0.08	0.17±0.07	-0.14±0.07	-0.42±0.07	0.26±0.10
III	186	-0.03±0.06	-0.09±0.09	-0.04±0.08	-0.20±0.09	0.22±0.08	-0.10±0.08	-0.44±0.08	0.24±0.11

Data are least square means ± SD; those for hypertension, current smoker, hypercholesterolaemia and waist circumference were collected in EDIC year 12

<sup>a</sup> Mean changes adjusted for sex, baseline age, baseline education level, painful neuropathy at EDIC year 12, visual acuity, length of follow-up and the number of interval cognitive tests taken

<sup>b</sup> Defined as systolic BP ≥140 mmHg, diastolic BP ≥90 mmHg, using hypertension medications or documented hypertension

<sup>c</sup> In tertiles of average daily cigarettes/total follow-up): I <3.82, II 3.82–16.67, III >16.67 (only among the 362 ever smokers)

<sup>d</sup> Defined as LDL ≥3.4 mmol/l or using lipid-lowering agents

<sup>e</sup> In tertiles (cm): I <84.6, II 84.6–100.4, III >100.4

<sup>f</sup> In tertiles (time-weighted average over total follow-up): I <7.2, II 7.2–8.6, III >8.6

<sup>g</sup> In tertiles (average grams/week/total follow-up): I <10.59, II 10.59–57.68, III >57.68 (only among the 808 ever drinkers)

\*  $p < 0.006$  for Bonferroni correction

**Table 3** Single predictor models for macrovascular and microvascular complications

Complication	n	Domains 1–8, adjusted mean change score <sup>a</sup>							
		Problem solving	Learning	Immediate memory	Delayed recall	Spatial information	Attention	Psychomotor efficiency	Motor speed
<b>Macrovascular</b>									
Common carotid IMT <sup>b</sup>									
I	328	0.04±0.06	0.02±0.08	0.03±0.07	-0.13±0.07	0.26±0.07	-0.01±0.07	-0.36±0.07	0.20±0.09
II	443	0.10±0.05	-0.03±0.08	-0.04±0.07	-0.15±0.07	0.24±0.07	-0.06±0.07	-0.35±0.06	0.08±0.09
III	232	-0.03±0.06	-0.01±0.09	-0.08±0.08	-0.11±0.08	0.13±0.08	0.03±0.08	-0.46±0.08	0.07±0.10
Coronary Ca deposit <sup>c</sup>									
No	730	0.08±0.05	-0.02±0.06	-0.04±0.06	-0.17±0.06	0.16±0.06	-0.08±0.06	-0.41±0.06	0.16±0.08
Yes	315	0.10±0.035	-0.02±0.07	-0.14±0.07	-0.16±0.07	0.07±0.07	-0.09±0.07	-0.49±0.07	0.17±0.09
<b>Microvascular</b>									
PDR <sup>d</sup>									
No	876	0.06±0.05	-0.09±0.07	-0.08±0.06	-0.17±0.06	0.14±0.06	-0.10±0.06	-0.34±0.06	0.20±0.08
Yes	177	0.09±0.05	-0.01±0.08	-0.07±0.07	-0.16±0.07	0.06±0.07	0.02±0.07	-0.66±0.07*	-0.08±0.09*
Renal complications									
No	1,012	0.08±0.04	-0.07±0.06	-0.09±0.06	-0.17±0.06	0.15±0.06	-0.05±0.06	-0.38±0.05	0.17±0.08
Yes	106	0.08±0.07	0.01±0.09	-0.05±0.09	-0.11±0.09	0.03±0.09	0.11±0.09	-0.73±0.08*	-0.08±0.11

Data are least square means ± SD; data for IMT measurements, lipid and renal complications were collected in EDIC year 12, computed tomography data between EDIC years 7–9 and retinopathy data in EDIC year 10

<sup>a</sup> Mean changes adjusted for sex, baseline age, baseline education level, painful neuropathy reported in EDIC year 12, visual acuity, length of follow-up and the number of interval cognitive tests taken

<sup>b</sup> In tertiles: I <0.62, II 0.62–0.75, III >0.75

<sup>c</sup> Greater than zero (0)

<sup>d</sup> PDR (proliferative diabetic retinopathy) and/or panretinal laser therapy

\* $p < 0.006$  for Bonferroni correction

complications to the base model; and (5) evaluation of all previously significant variables in a single model.

Based on the fifth (final) model described above (Table 4), five variables predicted decline in psychomotor efficiency over the 18.5 year follow-up period: two demographic variables (age, education), two microvascular complications (renal complication, PDR) and HbA<sub>1c</sub>. One additional variable (common carotid IMT) was significant at  $p < 0.01$ , but was marginally beyond the established level of Hochberg-corrected statistical significance (Hochberg-corrected  $p = 0.08$ ). Taken together, these variables explained 23% of the variance in change in psychomotor speed. Somewhat surprisingly, other well-known candidate variables (e.g. hypertension, hypercholesterolaemia, smoking) were unrelated to cognitive outcomes in these multivariable models. We also found no interactions between any of the predictors and sex, age (older vs younger), number of severe hypoglycaemic events or presence of the *APOE*  $\epsilon 4$  allele (data not shown). The correlation matrix between all possible covariates was examined to assess for potential multicollinearity. Interactions were fit in the final model for correlations exceeding 0.40 and none were found to be statistically significant.

## Discussion

This study indicates that over an 18 year period, the development of clinically significant microvascular complications is associated with modest declines in cognitive functioning in relatively healthy young and middle-aged adults with type 1 diabetes. Multivariable modelling demonstrated that the level of glycaemic control, indexed by HbA<sub>1c</sub> level, the occurrence of serious diabetic retinopathy (defined as presence of PDR and/or history of panretinal laser therapy) and renal complications were each independently associated with declining performance in measures of psychomotor efficiency. These relationships persisted even after controlling for demographic characteristics (age, education) and health factors (symptomatic peripheral neuropathy, reduced visual acuity) known to influence cognitive performance. In contrast, test scores were unrelated to recurrent episodes of severe hypoglycaemia, presence of the *APOE*  $\epsilon 4$  allele or diabetes-related comorbid conditions like hypertension or hypercholesterolaemia. Because participants were treated for hypertension and lipid disorders during the entire DCCT and EDIC follow-up period, the

**Table 4** Multivariable models for domain seven (psychomotor efficiency)

Variable	Base model		+ Macro <sup>a</sup> risk factors		+ Risk factors + macro <sup>a</sup> disease		+ Micro <sup>a</sup> disease		+ Final model	
	Estimate	SE	Estimate	SE	Estimate	SE	Estimate	SE	Estimate	SE
Intercept	0.96	0.32	1.88	0.44	1.50	0.47	0.71	0.41	0.79	0.51
Age (years)	-0.04	0.004	-0.04	0.004	-0.03	0.004	-0.04	0.004	-0.03	0.005
Female sex	0.14	0.04	0.06	0.05	0.08	0.05	0.13	0.05	0.07	0.06
Education (years)	0.06	0.01	0.05	0.01	0.05	0.01	0.05	0.01	0.05	0.01
Painful neuropathy	-0.22	0.05	-0.14	0.05	-0.12	0.05	-0.14	0.05	-0.10	0.06
Decreased visual acuity <sup>b</sup>	-0.36	0.10	-0.34	0.11	-0.22	0.12	-0.29	0.13	-0.19	0.13
Length of follow-up	-0.08	0.02	-0.07	0.02	-0.05	0.02	-0.08	0.02	-0.05	0.03
Cognitive tests taken	0.15	0.05	0.13	0.05	0.11	0.05	0.15	0.05	0.12	0.06
HbA <sub>1c</sub> (%)			-0.09	0.02	-0.08	0.02	-0.07	0.02	-0.07	0.02
Hypertension			-0.14	0.05	-0.11	0.05			-0.05	0.05
Ever smoker			0.05	0.05						
Hypercholesterolaemia			0.04	0.05						
Waist circumference			-0.01	0.002	-0.004	0.002			-0.004	0.002
Ever drinker			-0.12	0.05	-0.15	0.05			-0.13	0.06
Common carotid					-0.47	0.18			-0.50	0.19
Coronary calcium >0					-0.11	0.06			-0.08	0.06
PDR or worse							-0.24	0.07	-0.25	0.07
Renal complication							-0.50	0.13	-0.50	0.14
Domain 7 mean	-0.25		-0.25		-0.23		-0.25		-0.24	
Model R <sup>2</sup>	0.17		0.21		0.20		0.21		0.23	

Data are analysis of covariance model variables (estimates) ± SE; base model included in all other models

<sup>a</sup> Macrovascular or microvascular

<sup>b</sup> Comparison of those with better than 20/40 vs 20/40 or worse

\**p* < 0.05 after making Hochberg correction for multiple comparisons  
PDR, proliferative diabetic retinopathy



cognitive effects of such variables may have been lessened by the interventions. Previously we had reported that level of depression measured using the SCL-90 was associated with cognitive function [2], but found that it did not interact with biomedical predictors in that set of analyses.

Several earlier, smaller studies reported associations between retinopathy and psychomotor efficiency in adults with [4, 6] and without diabetes [36]. Our study is the first to show that the presence of another common microvascular complication, significant kidney dysfunction, also independently predicts cognitive decline in adults with type 1 diabetes. The relationship between cognitive decline and clinically significant microvascular complications suggests that a ‘microvascular’ pathway may contribute to cerebral dysfunction by reducing the efficient delivery of substrate to neurons as a consequence of microangiopathy [5]. Studies of non-diabetic adults [36] have shown that the presence of retinal microvascular abnormalities is associated with the same pattern of psychomotor slowing as seen in our cohort and is also associated with evidence of cerebral atrophy detected by magnetic resonance imaging [37] and subclinical cerebral infarcts [38]. Given the close anatomical and physiological relationships between retinal and cerebral vascular networks [39], it now appears that retinal microvascular disease may be a marker of damage to cerebral microcirculation [40, 41]. Our work also suggests that diabetic renal disease is a marker of brain dysfunction. The underlying mechanism remains poorly understood, but may reflect the magnitude of microvascular complications in multiple organ systems.

In addition to detecting relationships between microvascular complications and cognitive outcomes, our study also found an independent association between change in cognition and time-weighted HbA<sub>1c</sub> values. This apparent ‘non-vascular’ relationship may reflect the deleterious effects of high brain glucose levels on neuronal integrity. Recent research using proton magnetic resonance spectroscopy has detected elevated levels of brain glucose and glutamate (an excitatory neurotransmitter that can cause neuronal damage in high concentrations) within prefrontal regions in a large sample of young adults with childhood onset of type 1 diabetes compared with non-diabetic control participants [42]. Among patients with type 1 diabetes, higher HbA<sub>1c</sub> values were associated with elevated prefrontal glutamate concentration. Elevated glutamate was, in turn, negatively correlated with performance in measures of psychomotor speed. Duration of poorer metabolic control is also inversely correlated with levels of *N*-acetylaspartate and choline-containing compounds in white matter and in deep grey matter [43]. These and other [44] brain magnetic resonance spectroscopy findings suggest that axonal injury, demyelination and increased membrane proliferation secondary to gliosis have occurred and may be a consequence of glucose

neurotoxicity [45]. This non-vascular pathway could explain, at least in part, the recent observation that adults with a long history of type 1 diabetes manifest psychomotor slowing associated with microstructural damage to white matter fibre tracts in the corpus callosum and corona radiata [46].

The magnitude of cognitive decline reported in this study is modest, but comparable in size and scope to that reported in other studies of adults with type 1 diabetes [1]. It now appears that tests of mental and motor slowing, particularly those requiring ‘psychomotor integration’ or eye–hand coordination, are especially sensitive to the effects of chronic hyperglycaemia and are associated with severity of retinal microangiopathy [4, 6]. The neuro-imaging literature suggests that optimal performance of these types of cognitive tasks requires the integrity of multiple small and distinct anatomical substrates in the left and right hemispheres, compared with other types of cognitive tasks, which may activate more limited neuro-anatomic areas [47]. Thus, if chronic hyperglycaemia leads to significant hypoperfusion in multiple brain regions and also disrupts the integrity of associative axonal networks, one might expect to see greater decline in psychomotor speed than with changes in other cognitive domains. This prediction is consistent with our data, as well as with the cognitive literature on type 1 diabetes [1].

In many ways it is not surprising that, as a group, our participants showed minimal cognitive dysfunction. All are relatively healthy young and middle-aged adults who developed diabetes in adolescence or early adulthood (mean age at diagnosis 21 years) and whose diabetes has been carefully managed and monitored. To date, two other studies have measured cognitive function in patients with type 1 diabetes over an extended period of time [6, 44]. Only one of those studies explicitly examined the relationship between changes in cognitive function and the development of vascular complications [6]. In that study, the authors reported stronger relationships between cognitive change and vascular complications in their relatively small ( $n=103$ ) study sample, but their participants differed from the DCCT/EDIC cohort in several potentially important ways, including longer duration of diabetes and poorer metabolic control.

Very few cognitive studies have been conducted on older adults with type 1 diabetes [3], but extensive research on older adults with type 2 diabetes clearly demonstrates that in those over the age of 65, the presence of diabetes accelerates the rate of cognitive decline. Relative to their non-diabetic peers, individuals with type 2 diabetes showed 1.2- to 1.5-fold faster declines in cognitive function over time [48]. Such declines in cognitive performance may be worsened by the presence of diabetes-related comorbid conditions like hypertension [49] or macrovascular disease (e.g. carotid IMT) [50]. The current high level of cognitive

function within our study cohort may explain the small amount of variance accounted for by our glycaemic and microvascular predictors. Moreover, the absence of a statistically reliable relationship between cognitive change and early macrovascular complications may be a consequence of the relatively low prevalence of those complications in this carefully monitored study cohort [32]. However, as our patients with type 1 diabetes continue to age, they may show more pronounced evidence of cognitive decline as their exposure to chronic hyperglycaemia increases and their diabetic vascular complications worsen. Those diabetic patients who are successful in maintaining optimal metabolic control and in slowing or preventing the development of complications should also manifest relatively less cognitive decline over time.

**Acknowledgements** A complete list of participants in the DCCT/EDIC research group is included in Electronic supplementary material (ESM). We thank H. Chen for providing thoughtful comments on the statistical analyses described in this manuscript. We thank the following for providing free or discounted supplies and/or equipment: Lifescan, Roche, Aventis, Eli Lilly, OmniPod, Can-Am, B-D, Animas, Medtronic, Medtronic Minimed, Bayer (one donation in 2008) and Omron. This study is supported by NIH grant number 5R01DK062218-02. The DCCT/EDIC project is supported by contracts with the Division of Diabetes, Endocrinology and Metabolic Diseases of the National Institute of Diabetes and Digestive and Kidney Diseases, the National Eye Institute, the National Institute of Neurological Disorders and Stroke, the General Clinical Research Centers Program, the Clinical and Translational Science Awards Program, the National Center for Research Resources and by Genentech through a Cooperative Research and Development Agreement with the National Institute of Diabetes and Digestive and Kidney Diseases.

**Duality of interest** C. M. Ryan is a consultant to a clinical trial sponsored by GlaxoSmithkline. He has received an honorarium from NovoNordisk for his role as Associate Editor of the on-line journal, *Diabetic Hypoglycaemia*. He has also received an honorarium from Eli Lilly as a speaker in their 'Peaks and Valleys' program. A. M. Jacobson received travel expenses and an honorarium from Eli Lilly for a lecture on quality of life issues in diabetes. All other authors declare that there is no duality of interest associated with this manuscript.

## References

- Brands AMA, Biessels G-J, de Haan EHF, Kappelle LJ, Kessels RPC (2005) The effects of type 1 diabetes on cognitive performance: a meta-analysis. *Diab Care* 28:726–735
- Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group, Jacobson AM, Musen G et al (2007) Long-term effects of diabetes and its treatment on cognitive function. *N Engl J Med* 356:1842–1852
- Brands AMA, Kessels RPC, Biessels GJ et al (2006) Cognitive performance, psychological well-being, and brain magnetic resonance imaging in older patients with type 1 diabetes. *Diabetes* 55:1800–1806
- Ferguson SC, Blane A, Perros P et al (2003) Cognitive ability and brain structure in type 1 diabetes: relation to microangiopathy and preceding severe hypoglycemia. *Diabetes* 52:149–156
- Wessels AM, Scheltens P, Barkhof F, Heine RJ (2008) Hyperglycaemia as a determinant of cognitive decline in patients with type 1 diabetes. *Eur J Pharmacol* 585:88–96
- Ryan CM, Geckle MO, Orchard TJ (2003) Cognitive efficiency declines over time in adults with type 1 diabetes: effects of micro- and macrovascular complications. *Diabetologia* 46:940–948
- Brismar T, Maurex L, Cooray G et al (2007) Predictors of cognitive impairment in type 1 diabetes. *Psychoneuroendocrinology* 32:1041–1051
- Ryan CM, Williams TM, Orchard TJ, Finegold DN (1992) Psychomotor slowing is associated with distal symmetrical polyneuropathy in adults with diabetes mellitus. *Diabetes* 41:107–113
- Biessels GJ, Deary IJ, Ryan CM (2008) Cognition and diabetes: a lifespan perspective. *Lancet Neurol* 7:184–190
- Swan GE, Lessov-Schlaggar CN (2007) The effects of tobacco smoke and nicotine on cognition and the brain. *Neuropsychol Rev* 17:259–273
- Obisesan TO, Obisesan OA, Martins S et al (2008) High blood pressure, hypertension, and high pulse pressure are associated with poorer cognitive function in persons aged 60 and older: The Third National Health and Nutrition Examination. *J Am Geriatr Soc* 56:501–509
- Solomon A, Käreholt I, Ngandu T et al (2007) Serum cholesterol changes after midlife and late-life cognition: twenty-one year follow-up study. *Neurology* 68:751–756
- Muller M, Grobbee DE, Aleman A, Bots M, van der Schouw YT (2007) Cardiovascular disease and cognitive performance in middle-aged and elderly men. *Atherosclerosis* 190:140–149
- Romero JR, Beiser A, Seshadri S et al (2009) Carotid artery atherosclerosis, MRI indices of brain ischemia, aging, and cognitive impairment: The Framingham Study. *Stroke* 40:1590–1596
- Manschot SM, Biessels GJ, de Valk HW et al (2007) Metabolic and vascular determinants of impaired cognitive performance and abnormalities on brain magnetic resonance imaging in patients with type 2 diabetes. *Diabetologia* 50:2388–2397
- Diabetes Control and Complications Trial Research Group (1993) The effect of intensive treatment on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 329:977–986
- Diabetes Control and Complications Trial Research Group (1996) Effects of intensive diabetes therapy on neuropsychological function in adults in the Diabetes Control and Complications Trial. *Ann Intern Med* 124:379–388
- Wechsler D (1955) Manual for the Wechsler adult intelligence scale. Psychological Corporation, New York
- Reitan RM, Wolfson D (1993) The Halstead-Reitan neuropsychological test battery: theory and clinical interpretation. Neuropsychology Press, Tucson
- Wechsler D (1945) A standardized memory scale for clinical use. *J Psychol* 19:87–95
- Lewis RF (1990) Digit vigilance test. Psychological Assessment Resources, Lutz
- Ruff RM, Parker SB (1993) Gender- and age-specific changes in motor speed and eye-hand coordination in adults: normative values for the finger tapping and grooved pegboard tests. *Percept Mot Skills* 76:1219–1230
- Mitrushina MN, Boone KB, D'Elia LF (1999) Handbook of normative data for neuropsychological assessment. Oxford University Press, New York
- Morrow LA, Ryan CM (2002) Normative data for a working memory test: the four word short-term memory test. *Clin Neuropsychol* 16:373–380
- Ryan CM, Morrow LA, Bromet EJ, Parkinson DK (1987) Assessment of neuropsychological dysfunction in the workplace:

- normative data from the Pittsburgh Occupational Exposures Test Battery. *J Clin Exp Neuropsychol* 9:665–679
26. Lezak MD (1995) *Neuropsychological assessment*. Oxford University Press, New York
  27. Epidemiology of Diabetes Interventions and Complications (EDIC) (1999) Design, implementation, and preliminary results of a long-term follow-up of the Diabetes Control and Complications Trial cohort. *Diab Care* 22:99–111
  28. Steffes M, Cleary P, Goldstein D et al (2005) Hemoglobin A<sub>1c</sub> measurements over nearly two decades: sustaining comparable values throughout the Diabetes Control and Complications Trial and the Epidemiology of Diabetes Interventions and Complications Study. *Clin Chem* 51:753–758
  29. Diabetes Control and Complications Trial Research Group (1997) Hypoglycemia in the Diabetes Control and Complications Trial. *Diabetes* 46:271–286
  30. Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group (2000) Retinopathy and nephropathy in patients with type 1 diabetes four years after a trial of intensive therapy. *N Engl J Med* 342:381–389
  31. Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group (2003) Intensive diabetes therapy and carotid intima-media thickness in type 1 diabetes mellitus. *N Engl J Med* 348:2294–2303
  32. Cleary PA, Orchard TJ, Genuth S et al (2006) The effect of intensive glycemic treatment on coronary artery calcification in type 1 diabetic participants of the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study. *Diabetes* 55:3556–3565
  33. Murdoch SJ, Boright AP, Paterson AD et al (2007) LDL composition in E2/E2 subjects and LDL distribution by Apo E genotype in type 1 diabetes. *Atherosclerosis* 192:138–147
  34. Yoav B, Hochberg Y (1995) Controlling the false discovery rate: a practical and powerful approach to multiple testing. *J R Stat Soc B Stat Methodol* 57:125–133
  35. Ryan CM (2005) Diabetes, aging, and cognitive decline. *Neurobiol Aging* 26S:S21–S25
  36. Wong TY, Klein R, Sharrett AR et al (2002) Retinal microvascular abnormalities and cognitive impairment in middle-aged persons: the Atherosclerosis Risk in Communities Study. *Stroke* 33:1487–1492
  37. Wong TY, Mosley TH, Klein R et al (2003) Retinal microvascular changes and MRI signs of cerebral atrophy in healthy, middle-aged people. *Neurology* 61:806–811
  38. Cooper LS, Wong TY, Klein R et al (2006) Retinal microvascular abnormalities and MRI-defined subclinical cerebral infarction: the Atherosclerosis Risk in Communities Study. *Stroke* 37:82–86
  39. Patton N, Aslam T, MacGillivray T, Pattie A, Deary IJ, Dhillion B (2005) Retinal vascular image analysis as a potential screening tool for cerebrovascular disease: a rationale based on homology between cerebral and retinal microvasculatures. *J Anat* 206:319–348
  40. Wong TY, Klein R, Klein BEK, Tielsch JM, Hubbard L, Nieto FJ (2001) Retinal microvascular abnormalities and their relationship with hypertension, cardiovascular disease, and mortality. *Surv Ophthalmol* 46:59–80
  41. Qiu C, Cotch MF, Sigurdsson S et al (2008) Retinal and cerebral microvascular signs and diabetes: the Age, Gene/Environment Susceptibility-Reykjavik Study. *Diabetes* 57:1645–1650
  42. Lyoo IK, Yoon SJ, Musen G et al (2009) Altered prefrontal glutamate-glutamine- $\gamma$ -aminobutyric acid levels and relation to low cognitive performance and depressive symptoms in type 1 diabetes mellitus. *Arch Gen Psychiatry* 66:879–887
  43. Heikkilä O, Lundbom N, Timonen M, Groop P-H, Heikkinen S, Mäkimattila S (2009) Hyperglycaemia is associated with changes in the regional concentrations of glucose and myo-inositol within the brain. *Diabetologia* 52:534–540
  44. Northam EA, Rankins D, Lin A et al (2009) Central nervous system function in youth with type 1 diabetes 12 years after disease onset. *Diab Care* 32:445–450
  45. Tomlinson DR, Gardiner NJ (2008) Glucose neurotoxicity. *Nat Rev Neurosci* 9:36–45
  46. Kodl CT, Franc DT, Rao JP et al (2008) Diffusion tensor imaging identifies deficits in white matter microstructure in subjects with type 1 diabetes that correlate with reduced neurocognitive function. *Diabetes* 57:3083–3089
  47. Gläscher J, Tranel D, Paul LK et al (2009) Lesion mapping of cognitive abilities linked to intelligence. *Neuron* 61:681–691
  48. Cukierman T, Gerstein HC, Williamson JD (2005) Cognitive decline and dementia in diabetes—systematic overview of prospective observational studies. *Diabetologia* 48:2460–2469
  49. Hassing LB, Hofer SM, Nilsson SE et al (2004) Comorbid type 2 diabetes mellitus and hypertension exacerbates cognitive decline: evidence from a longitudinal study. *Age Ageing* 33:355–361
  50. Wendell CR, Zonderman AB, Metter EJ, Najjar SS, Waldstein SR (2009) Carotid intimal medial thickness predicts cognitive decline among adults without clinical vascular disease. *Stroke* 40:3180–3185