The Relationship Between Diabetic Retinopathy and Cognitive Impairment

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OBJECTIVE—Recent studies have shown an increased risk for cognitive impairment and dementia in patients with diabetes. An association between diabetic retinopathy (DR) and retinal microvasculature disease and cognitive impairment has been reported as potential evidence for a microvascular component to the cognitive impairment. It was hypothesized that severity of DR would be associated with cognitive impairment in individuals with type 2 diabetes.

RESEARCH DESIGN AND METHODS—Three hundred eighty patients with type 2 diabetes were recruited from a population-based eye screening program and grouped by severity of DR as follows: no/mild DR (n = 252) and proliferative diabetic retinopathy (PDR) (n = 128). Each participant underwent psychosocial assessment; depression screening; ophthalmic and physical examination, including blood assays; and cognitive assessment with the Addenbrooke's Cognitive Examination-Revised (ACE-R), Mini-Mental State Examination (MMSE), and the Mini-Cog. General linear modeling was used to examine severity of DR and cognitive impairment, adjusting for confounders.

RESULTS—Severity of DR demonstrated an inverse relationship with cognitive impairment (fully adjusted R^2 = 0.415, $P < 0.001$). Ethnicity contributed most to the variance observed (16%) followed by education (7.3%) and retinopathy status (6.8%). The no/mild DR group had lower cognitive impairment scores on ACE-R (adjusted mean ± SE 77.0 ± 1.9) compared with the PDR group (82.5 ± 2.2, $P < 0.001$). The MMSE cutoff scores showed that 12% of the no/mild DR group (n = 31) had positive screening results for dementia or significant cognitive impairment compared with 5% in the PDR group (n = 6).

CONCLUSIONS—Patients with minimal DR demonstrated more cognitive impairment than those with advanced DR. Therefore, the increased prevalence of cognitive impairment in diabetes may be associated with factors other than evident retinal microvascular disease.

The prevalence of both type 2 diabetes and dementia has increased significantly over the past 2 decades. These parallel increases may be explained by a common metabolic pathology because type 2 diabetes is an independent risk factor for the development of Alzheimer disease (1,2). Diabetes has also been associated with cognitive impairment, which is defined as the degree of cognitive dysfunction that exists between normal aging and dementia. Cognitive impairment, even when mild, is a predictor for the development of dementia and Alzheimer disease (3). Therefore, identifying the disease processes that link diabetes and cognitive impairment could be important for identifying patients at risk for dementia and for the development of preventive interventions in the diabetes population.

One current area of inquiry is the relationship between the severity of microvascular changes in the retina and cognitive impairment (4,5). Several groups have explored the association of diabetic retinopathy (DR) with cognitive impairment, showing conflicting results. Roberts et al. (6) found that if DR was present, the risk of mild cognitive impairment was more than doubled (odds ratio 2.36). A systematic review of six studies reported an increased risk (odds ratio 2.0) of cognitive impairment in patients with DR and type 1 and type 2 diabetes (7). Another recent systematic review of studies in type 2 diabetes alone also reported an association between cognitive impairment and DR, although only in older male patients or patients with established macrovascular disease (8). This review highlighted that case assignment in the reviewed studies was poor, with only a small number of patients having severe DR (n = 47). In the absence of studies comparing levels of DR, it is not possible to distinguish whether DR is just an associated risk factor for cognitive impairment or whether progression of DR is associated with increased cognitive decline. The later scenario would suggest a common pathology. A further limitation of previous studies is that they did not fully adjust for cardiovascular disease, which has been associated with increased cognitive impairment (9). In one study, the sample comprised patients who had a coronary artery bypass (10).

Therefore, the present study was designed to test whether severity of DR is associated with higher levels of cognitive impairment in patients with type 2 diabetes. It included a far greater number of patients with more severe DR than previously studied so that it would be possible to observe differences in cognitive performance between patients with milder and patients with more severe DR.

RESEARCH DESIGN AND METHODS

—The South East London Diabetic Retinopathy Study (SEL-DRS) is a cross-sectional study of patients with diabetes receiving retinal screening and eye care and residing in three boroughs of South East London. The SEL-DRS considers the association between DR and a range of other metabolic risk factors. In the U.K., all patients with diabetes are registered by general practices as part of the national remuneration program for primary care. This registration process

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includes admission to the regional DR screening program. In South East London, this program is called the Diabetes Eye Complication Service (DECS). Therefore, the majority (80%) of local patients are registered with a program (DECS, unpublished data). Individuals with screen-positive disease are referred to specified hospital eye services for further management, so it is possible to collate the retinopathy data on all patients with diabetes subject to use of these services. For the current study, we recruited patients with a documented diagnosis of type 2 diabetes from the DECS program.

Inclusion criteria for the study were recorded diagnosis of type 2 diabetes for ≥5 years, age >30 years, and presence of either no/mild DR or confirmed proliferative diabetic retinopathy (PDR). Patients were excluded from the study if they had severe mental illness, terminal illness, or stroke determined from their medical notes; had started insulin within 1 year of diagnosis; had any other form of diabetes; had nonassessable fundus photographs; were unable to converse in English; and had severe visual impairment with a bilateral best corrected visual acuity (BCVA) of logarithm of the minimum angle of resolution (logMAR) of 1.0 at 1 m or counting fingers, hand movements, and perception or no perception of light. Ethical approval for the study was granted by the King's College Hospital Ethics Committee. Each participant gave full informed consent.

Measures

Data were collected during a standardized clinical assessment and notes review undertaken by a researcher. This involved administering a set of standardized measures and the collection of biometric data. Sociodemographic data collected were age, sex, socioeconomic status (indices of multiple deprivation), marital status, self-assigned ethnicity, educational attainment, country of birth, medication usage, alcohol intake, smoking status, and history of cardiovascular and cerebrovascular disease not recorded in the medical notes. Clinical data were weight, height, waist circumference, blood pressure, HbA_{1c}, cholesterol level, full blood profile, and renal screen.

Cognition was assessed with the Addenbrooke's Cognitive Examination-Revised (ACE-R) (11), which incorporates the Mini-Mental State Examination (MMSE) (12) and the Mini-Cog (13). The ACE-R assesses five domains of cognition, namely, attention and orientation, memory, verbal fluency, language, and visuospatial ability. The ACE-R generates a composite score for cognition by the summation of the domains, with a maximum score of 100. It has a clinical cutoff score for cognitive impairment of ≤82. The MMSE is used as the gold standard for cognition deficit screening (12). The Mini-Cog has been shown to detect the early signs of cognitive impairment with an administration time of 3–5 min (13).

DR grade was assigned from retinal eye photographs by a trained researcher and an ophthalmologist in accordance with the Early Treatment of Diabetic Retinopathy Study grading criteria (no/mild retinopathy ≤ level 35 and PDR ≥ level 61). After mydriasis, two 45° field photographs were taken per eye (1 × fovea centered, 1 × disc centered) captured by a Topcon TRC NW6s (Topcon Corporation, Tokyo, Japan) high-resolution digital retinal camera (3,872 × 2,592 pixels). The participant's retinopathy status was determined by the retinopathy severity of the worst affected eye. Participants also had an ophthalmic examination (slit lamp biomicroscopy and ophthalmoscopy) and an optical coherence tomography scan.

Depression was assessed with the Patient Health Questionnaire-9 (PHQ-9) (14). Assessment for severe emotional problems in diabetes was assessed by the Problem Areas in Diabetes (PAID) scale (17). Vision-related quality of life was assessed with the National Eye Institute Visual Function Questionnaire (NEI VFQ-25) (18).

Statistical analysis

General linear modeling (ANCOVA and multivariate ANCOVA) was used to compare participants' cognition scores according to severity of retinopathy. All models were adjusted for age, sex, ethnicity, educational level, BCVA, duration of diabetes, socioeconomic status, nephropathy status, BMI, diastolic blood pressure, HbA_{1c}, triglyceride level, total cholesterol level, alcohol consumption, severe emotional distress, and depressive symptomatology. Selection of adjustment variables was based on univariate analysis and variables previously noted in the literature to be associated with cognition and DR. Interactions among all independent variables were assessed. Statistical significance was determined at ≤5% probability. The contribution of the variable to the model has been shown by the effect size η_p^2. SPSS version 17 for Windows was used in all analyses (19). The study was powered at >80% to estimate an effect size ≥0.15 (Cohen) for the primary fully adjusted model.

RESULTS

Participants versus nonparticipants

Of 581 eligible persons approached, 380 agreed to participate (65.4%). Nonparticipants were older (mean age 68 ± 11.0 vs. 65 ± 11.0 years) and had poorer visual acuity (mean logMAR 0.18 ± 0.3 vs. 0.12 ±0.2) than participants ($P < 0.001$ and $P = 0.004$, respectively). There were no differences between participants and nonparticipants in terms of sex, ethnicity, duration of diabetes, BMI, or glycemic control (HbA_{1c}).

Sample characteristics

The characteristics of the study participants are presented in Table 1, of which the first data column gives the data for the whole group. Of note, 50% of the study population was black. When the group was divided by retinopathy status, significant differences between the no/mild DR and the PDR groups were noted for educational attainment, visual acuity, HbA_{1c}, treatment regimens for diabetes, and diabetes complication rates. Participants with PDR had comparatively lower vision, higher HbA_{1c}, higher prevalence of diabetes-related distress, and lower vision-related quality of life. The PDR group also was more likely to be receiving insulin treatment and had a higher prevalence of other micro- and macrovascular diabetes complications. A higher proportion of patients in the no/mild DR was educated only to primary school level.

Cognitive function and retinopathy status

The bivariate analyses undertaken to identify confounding variables are presented in Table 2. In these unadjusted data, the mean ACE-R score for the no/mild DR group was significantly lower than that of the PDR group (79.7 ± 12.1 vs. 83.8 ± 10.7, $P = 0.001$). This difference was evident in all the cognitive impairment domains, with the exception of verbal fluency. The MMSE and the Mini-Cog scores also showed higher levels of cognitive impairment in the no/mild DR group than in the PDR group. The MMSE cutoff scores showed that 12% ($n = 31$) of the no/mild DR group had

Table 1—*Study participant characteristics by retinopathy severity*

Variable	All participants (n = 380)	No/mild retinopathy (n = 252)	PDR (n = 128)	P value
Sociodemographic				
Age (y)	64.8 ± 10.8	65.4 ± 10.9	63.6 ± 10.4	0.121
Male sex	214 (56.2)	145 (57.5)	68 (53.1)	0.413
Ethnicity				
Asian	43 (11.3)	29 (11.5)	14 (11.0)	0.745
Black	191 (50.4)	130 (51.6)	61 (48.0)	
Caucasian	145 (38.3)	93 (36.9)	52 (40.9)	
Highest level of education				
Primary	73 (19.3)	58 (23.0)	15 (11.8)	0.029*
Secondary	218 (57.5)	135 (53.6)	83 (65.4)	
University	88 (23.2)	59 (23.4)	29 (22.8)	
Socioeconomic status				
Most deprived	142 (37.3)	92 (36.8)	45 (37.8)	0.977
Deprived	166 (43.6)	110 (43.9)	52 (43.7)	
Least deprived	71 (18.6)	49 (19.4)	22 (18.5)	
Diabetes				
Duration of diabetes (y)	17.7 ± 8.4	17.1 ± 7.8	18.8 ± 9.5	0.056
HbA_{1c} (%)	8.3 ± 1.9	8.1 ± 1.9	8.7 ± 2.0	0.012*
HbA_{1c} (mmol/mol)	67.0 ± 3.0	65.0 ± 3.0	72.0 ± 2.0	
Diabetes treatment				
Diet	26 (6.8)	19 (7.5)	7 (5.5)	<0.001*
Oral hypoglycemics	161 (42.4)	127 (50.4)	34 (26.6)	
Insulin (with or without oral hypoglycemics)	193 (50.8)	106 (42.1)	87 (68.0)	
Diabetes complications				
Leg ulceration	43 (11.3)	17 (6.8)	26 (20.3)	<0.001*
Limb amputation	13 (3.4)	5 (2.0)	8 (6.3)	0.031*
Neuropathy	52 (13.6)	11 (7.1)	26 (21.7)	<0.001*
Nephropathy (based on eGFR)				
CKD 1–2	212 (69.5)	149 (74.1)	63 (60.6)	0.051
CKD 3	62 (20.3)	35 (17.4)	27 (26.0)	
CKD 4–5	31 (10.2)	17 (8.5)	14 (13.5)	
Metabolic				
BMI (kg/m^2)	30.8 ± 6.3	30.3 ± 5.7	31.7 ± 7.1	0.058
Systolic BP (mmHg)	141.0 ± 16.2	140.4 ± 16.7	142.3 ± 15.2	0.292
Hypertension	272 (71.6)	176 (69.8)	96 (75.0)	0.292
HDL (mmol/L)	1.2 ± 0.4	1.2 ± 0.4	1.2 ± 0.3	0.460
Total cholesterol (mmol/L)	4.2 ± 1.1	4.1 ± 1.0	4.2 ± 1.2	0.466
ACR urine	8.6 ± 19.1	5.2 ± 6.4	16.4 ± 32.1	<0.001*
Alcohol consumption				
0 units/wk	190 (50.0)	117 (46.4)	73 (57.0)	0.317
<21 units/wk	147 (38.7)	102 (40.5)	45 (35.2)	
>21 units/wk	9 (2.4)	33 (13.1)	10 (7.8)	
Smoking				
Never	190 (49.9)	67 (43.2)	67 (55.8)	0.099
Current	43 (11.3)	23 (14.8)	9 (7.5)	
Former	148 (38.8)	65 (41.9)	44 (36.7)	
Cardiovascular				
Myocardial infarction	28 (7.4)	14 (5.6)	14 (11.0)	0.055
CABG/angioplasty	36 (9.5)	18 (7.1)	18 (14.5)	0.028*
Ophthalmics				
BCVA (logMAR)	0.12 ± 0.18	0.09 ± 0.15	0.18 ± 0.21	<0.001*
Psychosocial				
PAID action score				

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positive screening results for dementia or significant cognitive impairment compared with 5% (n = 6) in the PDR group.

Regression models

The final fully adjusted model presented in Table 3 explained 41.5% of the variance in the dependent variable (R^2 = 0.415). Cognition scores were significantly lower in the no/mild DR group (mean 77.0 [95% CI 73.2–80.8]) compared with the PDR group (82.5 [78.1–86.9], $P < 0.001$, η_p^2 = 0.068). The significant effects identified within the final model were as follows: ethnicity ($P < 0.001$, η_p^2 = 0.16), education (P = 0.001, η_p^2 = 0.073), and BCVA (P = 0.001, η_p^2 = 0.047). The model shows that ethnicity (16%) contributed most to the variance observed followed by education (7.3%) and retinopathy status (6.8%). Participants from ethnic minorities had lower mean cognition scores than Caucasian participants (black 75.4 [95% CI 71.5–79.2], $P < 0.001$, η_p^2 = 0.16; Asian 79.7 [74.3–85.2], P = 0.05, η_p^2 = 0.016; Caucasian 84.1 [80.1–88.1], reference population).

The five ACE-R domains of cognition were also regressed separately (multivariate ANCOVA) to assess their independent contribution to the overall effect (Table 3). Retinopathy status was a significant contributor to four of the domains of cognition, as follows: attention/orientation (P = 0.003, η_p^2 = 0.02), memory (P = 0.001, η_p^2 = 0.03), language (P = 0.04, η_p^2 = 0.01), and visuospatial ability (P = 0.002, η_p^2 = 0.03). Retinopathy status was not associated with verbal fluency (P = 0.413).

Sensitivity analysis

Given the impact of ethnicity in the main model, we tested the observed relationship in a Caucasian nonmigrant subset of participants (n = 123, mean age 65.0 ± 11.7 vs. 64.0 ± 10.6 years for no/mild DR vs. PDR groups, respectively, P = 0.621) and found no difference between groups for mean ACE-R score (85.7 ± 10.50 [n = 77] vs. 87.7 ± 7.5 [n = 46], P = 0.274). However, when the ACE-R clinical cutoff score (≤82) was applied, there was a greater proportion of positive screening results for cognitive impairment in the Caucasian no/mild DR (32.5% [n = 25]) than the Caucasian PDR (17.4% [n = 8]) group (P = 0.051). For education, the difference in cognition between the no/mild DR and PDR groups was greater in those who completed only

Table 1—*Continued*

Variable	All participants (n = 380)	No/mild retinopathy (n = 252)	PDR (n = 128)	P value
≤39	364 (97.3)	244 (98.4)	120 (95.2)	0.077
≥40	10 (2.7)	4 (1.6)	6 (4.8)	
NEI VFQ-25 action score				
≤87.5	200 (53.6)	113 (46.1)	87 (68.5)	<0.001*
≥87.6	173 (46.4)	132 (53.9)	41 (31.5)	
Cognition				
ACE-R composite score (0–100)	81.1 ± 11.8	79.7 ± 12.1	83.8 ± 10.7	0.001*
ACE-R domain				
Attention/orientation (0–18)	17.2 ± 1.7	17.0 ± 1.9	17.5 ± 1.1	0.002*
Memory (0–26)	19.2 ± 4.5	18.7 ± 4.8	20.2 ± 3.9	0.002*
Fluency (0–14)	8.8 ± 3.1	8.6 ± 3.3	9.1 ± 2.7	0.208
Language (0–26)	22.1 ± 4.0	21.8 ± 4.1	22.7 ± 3.7	0.041*
Visuospatial (0–16)	13.8 ± 2.3	13.6 ± 2.4	14.3 ± 1.9	0.004*
MMSE raw score	27.87 ± 2.64	27.62 ± 2.75	28.36 ± 2.36	0.009*
MMSE categories				
Dementia (≤18)	2 (0.5)	1 (0.4)	1 (0.8)	0.035*
Cognitive impairment (19–24)	35 (9.2)	30 (11.9)	5 (3.9)	
Normal (≥25)	343 (90.3)	221 (87.7)	122 (95.3)	
Mini-Cog raw sore	3.86 ± 1.29	3.71 ± 1.31	4.15 ± 1.22	0.002*
Mini-Cog action score				
0–2 dementia	60 (15.7)	44 (17.5)	16 (12.5)	0.210
3–5 no dementia	320 (84.3)	208 (82.5)	112 (87.5)	

Data are mean ± SD or n (%). ACR, albumin-creatinine ratio; BP, blood pressure; CABG, coronary artery bypass graft; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate. *Significant at $P \leq 0.05$.

primary school education (68.9 ± 11.9 [n = 58] vs. 79.7 ± 8.5 [n = 15], P = 0.002). Analyses were also conducted for insulin use, migrant status, and macrovascular risk. Again, the direction of relationship observed in the primary analyses remained.

To make explicit any differences among the groups (i.e., no retinopathy, mild retinopathy, and proliferative retinopathy), a separate analysis was undertaken, adjusted for age, education, and diabetes duration. The data show that the no DR group had a mean ACE-R score of 82.7 ± 1.7 vs. 79.3 ± 0.8 in the mild DR group and 83.4 ± 0.9 in the PDR group (P = 0.004).

CONCLUSIONS—In this study, we have found an inverse relationship between retinopathy status and cognition scores in that participants with no/mild DR had lower overall cognition and were deficient in the attention/orientation, memory, language, and visuospatial ability domains compared with those with more severe DR. These data suggest that there may not be a common pathological process for cognitive impairment and DR and raises the question about why patients with more extensive DR might exhibit better cognition.

The UK Prospective Diabetes Study (20) and the Diabetes Control and Complications Trial (21) are both randomized controlled trials that examined prospectively the impact of intensive glycemic control on diabetes complications in type 2 and type 1 diabetes, respectively, and both showed a dose-dependent relationship between glycemic control and risk for developing DR. The demonstrated inversion of this relationship in terms of cognition suggests that the brain (or at least the parts of the brain that govern cognitive function) may respond differently to elevated glucose levels. It is possible that because the brain consumes a high proportion of available glucose, it may be less susceptible to glucose-related tissue damage. Indeed, it has been postulated that the brain may prefer higher glucose levels (22).

However, this argument is contrary to the effect of elevated glucose on other nervous tissues where there is a relationship between glucotoxicity and neuropathic damage. This relationship is evident in the present data, as there was significantly more neuropathy in the PDR group than in the no/mild DR group. There is also evidence from animal studies that high glucose concentrations increase metabolic stress and damage cerebral tissues, although the evidence of this in humans is equivocal (23).

Therefore, the contribution of glucotoxicity to cognitive impairment is unclear. In the present study, HbA_{1c} did not have a significant effect in the final model, and when we examined glycemic control as an independent variable for cognitive function, we found that participants with higher HbA_{1c} values performed better on cognitive testing than those with lower HbA_{1c} values. Therefore, more studies are required to establish the role of hyperglycemia in cognitive function.

The sensitivity analysis showed that participants with no retinopathy had less cognitive impairment than those with mild retinopathy. This observation is in keeping with previous studies in which the comparison has largely been between patients with no retinopathy and patients with mild retinopathy (10,24,25). Therefore, although we have shown that severity of DR is not related to cognitive impairment, having some retinopathy may indicate an impact on cognition. Again, the data do not provide an explanation for this effect, although other metabolic factors may be at play. There is a high association between retinopathy and hypertension, dyslipidemia, and macrovascular disease, factors that have been associated with cognitive impairment (9). Therefore, if we are to identify useful risk predictors for cognitive impairment in patients with type 2 diabetes, we need to look beyond severity of retinopathy. Although having some retinopathy confers an increased risk of cognitive impairment, this risk does not hold for those with more severe DR.

The participants in this study had a mean duration of diabetes of ≥9 years, which was comparable between the no/mild DR and the PDR groups. This comparability allowed us to assess the association between DR and cognitive impairment independent of disease duration. Previous studies have either not reported duration or adjusted for it in their model; this may be an important reason

Table 2—*Bivariate analysis of sample characteristics with ACE-R composite and cognitive domains*

Variable	Composite	Attention/orientation	Memory	Fluency	Language	Visuospatial
Sociodemographic						
Age	−0.283 (<0.001)*	−0.127 (0.013)*	−0.259 (<0.001)*	−0.210 (<0.001)*	−0.173 (0.001)*	−0.273 (<0.001)*
Sex						
Male	81.1 ± 11.6	17.1 ± 1.8	19.1 ± 4.5	8.7 ± 3.1	22.2 ± 3.8	14.0 ± 2.3
Female	81.0 ± 12.0	17.3 ± 1.5	19.3 ± 4.7	8.8 ± 3.1	22.0 ± 4.2	13.6 ± 2.2
P value	0.988	0.4219	0.659	0.778	0.686	0.120
Ethnicity						
Asian	81.3 ± 9.1	17.2 ± 1.5	19.5 ± 4.1	8.6 ± 2.6	21.9 ± 3.2	14.0 ± 2.1
Black	77.3 ± 12.1	17.0 ± 1.8	18.1 ± 4.4	8.1 ± 3.1	20.8 ± 4.4	13.2 ± 2.4
Caucasian	85.9 ± 10.2	17.4 ± 1.5	20.5 ± 4.5	9.7 ± 3.0	23.9 ± 2.9	14.5 ± 1.9
P value	<0.001*	0.163	<0.001*	<0.001*	<0.001*	<0.001*
Highest level of education						
Primary	71.2 ± 12.1	16.4 ± 2.4	16.4 ± 5.0	6.6 ± 2.7	19.4 ± 4.3	12.3 ± 2.6
Secondary	82.2 ± 10.6	17.2 ± 1.5	19.5 ± 4.1	9.0 ± 2.9	22.6 ± 3.8	14.0 ± 2.1
University	86.3 ± 9.6	17.7 ± 1.0	20.8 ± 4.1	10.0 ± 3.1	23.2 ± 3.3	14.6 ± 1.7
P value	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*
Socioeconomic status						
Most deprived	79.0 ± 12.2	17.1 ± 1.8	18.9 ± 4.7	8.3 ± 3.0	21.4 ± 4.1	13.3 ± 2.4
Deprived	82.1 ± 11.4	17.3 ± 1.5	19.4 ± 4.3	8.9 ± 3.2	22.4 ± 3.9	14.1 ± 2.1
Least deprived	82.8 ± 11.7	17.2 ± 1.6	19.3 ± 4.9	9.4 ± 3.0	22.8 ± 3.7	14.1 ± 2.2
P value	0.030*	0.601	0.605	0.036*	0.031*	0.006*
Migrant						
No	86.6 ± 9.2	17.4 ± 1.4	20.8 ± 4.1	9.7 ± 3.0	24.1 ± 2.5	14.6 ± 1.8
Yes	78.0 ± 12.0	17.0 ± 1.8	18.3 ± 4.5	8.3 ± 3.0	21.1 ± 4.3	13.4 ± 2.4
P value	<0.001*	0.033*	<0.001*	<0.001*	<0.001*	<0.001*
Diabetes						
Duration of diabetes (y)	−0.084 (0.104)	−0.051 (0.321)	−0.041 (0.425)	−0.108 (0.036)*	−0.087 (0.094)	−0.016 (0.756)
HbA_{1c} (%)	0.007 (0.896)	0.001 (0.992)	0.026 (0.652)	−0.033 (0.556)	−0.038 (0.503)	0.101 (0.075)
Diabetes treatment						
Diet	75.6 ± 14.2	16.9 ± 1.6	17.4 ± 5.1	7.6 ± 3.1	20.4 ± 5.5	13.4 ± 2.7
Oral hypoglycemics	81.2 ± 11.6	17.2 ± 1.7	19.0 ± 4.5	9.0 ± 3.3	22.3 ± 3.8	13.8 ± 2.3
Insulin	81.7 ± 11.5	17.2 ± 1.6	19.6 ± 4.4	8.8 ± 3.1	22.2 ± 3.9	13.9 ± 2.2
P value	0.046*	0.634	0.061	0.102	0.063	0.613
Insulin use						
No	80.4 ± 12.1	17.1 ± 1.7	18.8 ± 4.6	8.8 ± 3.3	22.0 ± 4.1	13.7 ± 2.3
Yes	81.7 ± 11.5	17.2 ± 1.6	19.6 ± 4.4	8.8 ± 2.9	22.2 ± 3.9	13.9 ± 2.2
P value	0.319	0.557	0.107	0.996	0.570	0.597
Diabetes complications						
CABG/angioplasty						
No	80.7 ± 11.9	17.1 ± 1.7	19.1 ± 4.6	8.8 ± 3.1	22.0 ± 4.0	13.7 ± 2.3
Yes	83.8 ± 10.5	17.6 ± 1.0	19.8 ± 4.0	9.0 ± 2.7	23.1 ± 3.6	14.5 ± 1.8

Continued on p. 6

Table 2—*Continued*

Variable	Composite	Attention/orientation	Memory	Fluency	Language	Visuospatial
P value	0.130	0.134	0.434	0.698	0.126	0.046*
Neuropathy						
No	81.2 ± 12.0	17.2 ± 1.7	19.2 ± 4.6	8.9 ± 3.1	22.1 ± 4.0	13.8 ± 2.3
Yes	80.4 ± 10.6	17.1 ± 1.7	19.0 ± 4.6	8.2 ± 2.9	22.3 ± 4.0	13.9 ± 2.0
P value	0.679	0.622	0.691	0.153	0.693	0.794
Nephropathy level						
CKD 1–2	81.8 ± 11.0	17.3 ± 1.6	19.4 ± 4.1	9.0 ± 3.1	22.3 ± 3.6	13.9 ± 2.2
CKD 3	80.6 ± 12.2	17.1 ± 1.6	18.8 ± 5.0	8.6 ± 3.0	22.0 ± 4.3	14.1 ± 1.9
CKD 4–5	74.4 ± 17.0	16.8 ± 2.1	17.4 ± 6.0	7.3 ± 3.5	20.5 ± 6.0	12.4 ± 3.0
P value	0.005*	0.283	0.061	0.021*	0.066	0.002*
Retinopathy status						
No/mild retinopathy	79.7 ± 12.1	17.0 ± 1.9	18.7 ± 4.8	8.6 ± 3.3	21.8 ± 4.1	13.6 ± 2.4
PDR	83.8 ± 10.7	17.5 ± 1.1	20.2 ± 3.9	9.1 ± 2.7	22.7 ± 3.7	14.3 ± 1.9
P value	0.001*	0.002*	0.002*	0.208	0.041*	0.004*
Microvascular disease						
No	82.2 ± 12.2	17.3 ± 1.8	19.7 ± 4.2	9.1 ± 3.1	22.3 ± 3.8	13.8 ± 2.3
Yes	79.4 ± 13.1	17.1 ± 1.7	18.6 ± 5.0	8.4 ± 3.1	21.7 ± 4.6	13.7 ± 2.3
P value	0.092	0.440	0.076	0.060	0.231	0.658
Macrovascular disease						
No	80.9 ± 11.6	17.2 ± 1.6	19.2 ± 4.6	8.8 ± 3.1	22.0 ± 4.0	13.7 ± 2.2
Yes	81.9 ± 12.7	17.2 ± 1.9	19.3 ± 4.5	8.8 ± 2.9	22.6 ± 4.1	14.1 ± 2.4
P value	0.547	0.920	0.848	0.925	0.280	0.287
Metabolic						
BMI	0.149 (0.007)*	0.070 (0.208)	0.100 (0.074)	0.099 (0.077)	0.141 (0.011)*	0.147 (0.008)*
Systolic BP	0.002 (0.964)	0.013 (0.810)	0.005 (0.923)	−0.008 (0.882)	0.006 (0.918)	−0.006 (0.912)
Diastolic BP	0.176 (0.001)*	0.062 (0.249)	0.207 (<0.001)*	0.130 (0.016)*	0.093 (0.086)	0.121 (0.024)*
Hypertension						
No	82.2 ± 11.2	17.1 ± 1.7	19.6 ± 4.0	9.0 ± 3.2	22.4 ± 4.1	14.2 ± 1.9
Yes	80.6 ± 12.0	17.2 ± 1.7	19.0 ± 4.7	8.7 ± 3.1	22.0 ± 4.0	13.6 ± 2.4
P value	0.228	0.650	0.272	0.428	0.466	0.039*
Total cholesterol	0.138 (0.018)*	0.152 (0.009)*	0.073 (0.211)	0.196 (0.001)*	0.057 (0.326)	0.100 (0.087)
Cholesterol (categorical)						
≤5 mmol/L normal	80.1 ± 12.3	17.1 ± 1.8	18.9 ± 4.6	8.6 ± 3.1	21.9 ± 4.2	13.7 ± 2.4
≥5.1 mmol/L elevated	85.3 ± 9.9	17.6 ± 0.8	20.1 ± 4.1	10.0 ± 3.0	23.1 ± 3.0	14.5 ± 1.8
P value	0.009*	0.039*	0.110	0.004*	0.079	0.039*
HDL	0.086 (0.166)	0.067 (0.280)	0.056 (0.365)	0.090 (0.146)	0.069 (0.264)	0.042 (0.502)
LDL	0.060 (0.333)	0.151 (0.014)*	0.047 (0.446)	0.106 (0.088)	−0.016 (0.791)	−0.008 (0.896)
ACR urine	0.049 (0.471)	0.032 (0.635)	0.086 (0.206)	0.047 (0.486)	−0.019 (0.785)	0.013 (0.854)
ACR urine (categorical)						
≤3.5 normal	81.1 ± 11.1	17.3 ± 1.6	18.7 ± 4.7	8.7 ± 3.1	22.4 ± 3.5	13.9 ± 2.2
≥3.6 elevated	80.6 ± 12.1	17.0 ± 2.0	19.4 ± 4.6	8.9 ± 3.0	21.6 ± 4.0	13.6 ± 2.4

Continued on p. 7

Table 2—*Continued*

Variable	Composite	Attention/orientation	Memory	Fluency	Language	Visuospatial
P value	0.751	0.330	0.280	0.717	0.112	0.340
Alcohol consumption						
0 units/wk	79.2 ± 12.4	17.0 ± 1.8	18.6 ± 4.7	8.4 ± 3.1	21.7 ± 4.2	13.5 ± 2.4
<21units/wk	83.5 ± 10.5	17.3 ± 1.4	20.0 ± 4.2	9.3 ± 3.0	22.7 ± 3.7	14.2 ± 2.0
P value	<0.001*	0.069	0.003*	0.008*	0.012*	0.002*
Smoking status						
Never	81.3 ± 11.2	17.3 ± 1.4	19.3 ± 4.3	8.8 ± 2.9	22.1 ± 3.9	13.9 ± 2.2
Current	80.7 ± 12.7	17.0 ± 1.9	19.0 ± 4.9	8.8 ± 3.4	22.2 ± 4.1	13.7 ± 2.3
Former	81.2 ± 11.7	16.9 ± 1.9	19.4 ± 4.1	9.0 ± 2.8	22.1 ± 4.2	13.9 ± 2.5
P value	0.880	0.130	0.749	0.863	0.917	0.781
Psychosocial						
PAID action score						
≤39 no problems (n = 364)	80.9 ± 11.8	17.2 ± 1.7	19.1 ± 4.6	8.7 ± 3.1	22.1 ± 4.0	13.8 ± 2.3
≥40 (n = 10)	81.9 ± 10.3	17.1 ± 1.4	20.7 ± 4.9	8.8 ± 1.7	21.5 ± 3.3	13.8 ± 2.3
P value	0.788	0.924	0.284	0.940	0.639	0.963
PHQ-9						
≤10 no problems (n = 351)	81.0 ± 11.7	17.2 ± 1.7	19.2 ± 4.5	8.7 ± 3.1	22.1 ± 4.0	13.8 ± 2.2
≥11 (n = 22)	78.2 ± 13.3	16.7 ± 1.5	18.2 ± 5.1	8.5 ± 2.8	21.3 ± 4.8	13.3 ± 2.7
P value	0.274	0.412	0.327	0.738	0.333	0.344
NEI VFQ-25						
≤87.5 reduced VRQOL	79.1 ± 12.9	17.1 ± 1.7	18.5 ± 4.7	8.5 ± 3.0	21.6 ± 4.4	13.5 ± 2.5
≥87.6 good VRQOL	82.9 ± 10.1	17.2 ± 1.6	19.9 ± 4.3	9.0 ± 3.1	22.7 ± 3.5	14.1 ± 1.9
P value	0.002*	0.319	0.004*	0.106	0.008*	0.011*

Data are mean ± SD. ACR, albumin-creatinine ratio; BP, blood pressure; CABG, coronary artery bypass graft; CKD, chronic kidney disease; PHQ-9, Patient Health Questionnaire-9; VRQOL, vision-related quality of life.
*Significant *P* value or Pearson correlation coefficient [*r* (*P* value)].

why the present study has findings that differ from previous studies (10,24–26). In Ding et al. (24), the median duration of diabetes was incremental among the retinopathy groups (5.5, 9.3, and 17.1 years for no retinopathy, mild retinopathy, and moderate-severe retinopathy, respectively), and the authors did not adjust for duration of diabetes in their model.

The inferior cognition we observed in the no/mild DR group compared with the PDR group was consistent for different age cohorts, although the level of cognitive impairment was greater in the older age cohorts, as expected. We found no differences in older male participants, which had been observed in Ding et al. (24).

Study limitations

There are a number of limitations to this study that need to be addressed. Most fundamentally, as with all cross-sectional studies, the observations cannot be causally related and represent associations between the variables studied. There are also some important factors in the sample that may have affected our observations. The multiethnic population of this study was unique, as the previous studies have been conducted in either monoethnic (25) or biethnic populations (26). One-half of the sample was of black African or Caribbean origin. This reflects the higher risk of diabetes in this ethnic group because only 20% of the population from which this sample was drawn self-report black ethnicity. Stewart and colleagues (27,28) reported lower scores on cognitive assessments in the U.K. black population. Other studies (29,30) conducted in the U.S. found that black participants had a 4.4 times increased risk of cognitive impairment and a 6.6 times increased risk of dementia. In the current study, black participants had lower general and domain-specific cognition scores. However, black ethnicity was evenly distributed between the no/mild DR and PDR groups, and the subgroup analysis of Caucasian participants found no association between cognitive impairment and level of DR, again with lower cognition in the no/mild DR group.

One important confounding factor within our model was education. The level of education was different between the no/mild DR and PDR groups, with more participants in the no/mild DR group having only primary school education. Although level of education was adjusted for in the model, it may have in some way biased the finding because the

Table 3—*Multivariable-adjusted mean (SE) for ACE-R and five domains of cognition by severity of retinopathy*

	No/mild retinopathy (n = 252)	PDR (n = 128)	P value for trend	Effect size‡
Age and sex adjusted				
ACE-R	79.9 (0.7)	83.4 (1.0)	0.004*	0.022
Attention and orientation	17.0 (0.1)	17.5 (0.1)	0.006*	0.020
Memory	18.7 (0.3)	20.0 (0.4)	0.008*	0.019
Fluency	8.6 (0.2)	9.0 (0.3)	0.295	0.003
Language	21.8 (0.3)	22.6 (0.4)	0.054	0.010
Visuospatial	13.5 (0.1)	14.2 (0.2)	0.008*	0.019
Fully adjusted§				
ACE-R	77.0 (1.9)	82.5 (2.2)	<0.001*	0.068
Attention and orientation	16.3 (0.2)	16.8 (0.2)	0.005*	0.022
Memory	18.1 (0.5)	19.6 (0.6)	0.001*	0.028
Fluency	7.8 (0.3)	8.2 (0.4)	0.335	0.003
Language	20.5 (0.4)	21.4 (0.5)	0.030*	0.013
Visuospatial	12.8 (0.2)	13.5 (0.3)	0.003*	0.024

‡The proportion of variance (effect size η_p^2) in the model explained by DR status in the model. *Significant at $P \leq 0.05$. §Also adjusted for ethnicity, educational level, BCVA, duration of diabetes, socioeconomic status, nephropathy status, BMI, diastolic blood pressure, HbA_{1c}, triglyceride level, total cholesterol level, alcohol consumption, severe emotional distress, and depressive symptomatology.

level of education is related to cognitive impairment screening results. In the sensitivity analysis for the primary school education group, the no/mild DR group had lower cognition scores than the PDR group. However, no significant differences were observed in the secondary school– and university-educated groups. These data suggest that education level may have contributed to the inverse relationship observed in the main model as a result of the difference noted in the primary school–educated group.

Another factor in the present sample was the exclusion of patients with a BCVA ≤6/60. These patients were excluded because they would not have been able to perform a number of the cognitive impairment measures. Their exclusion means that patients with the most extensive DR (high risk of visual impairment) were not included in the analysis and that these patients may have had an elevated risk of cognitive impairment. Previous studies either excluded patients with better vision compared with the present cutoff (excluded patients with BCVA ≤6/36 or who were unable to read large-print text) (31) or did not measure or adjust for visual acuity in their analyses (10,25,26). Therefore, although the present analysis excluded patients with severe visual impairment, the overall assessment and adjustment for vision within the study is more explicit than that in previous studies. Methods for measuring cognition independent of visual ability need to be considered in future studies.

The present study only had a limited number of patients with no retinopathy (n = 37), and these were combined with the mild DR group for the analysis. This decision was related to the fact that clinically, both groups exhibited absent or limited eye disease, and our interest was in whether those with more severe disease showed increased cognitive impairment. The low number of patients without any retinopathy was inevitable given that we wanted to recruit patients with similar diabetes duration to ensure parity of exposure. Cases of severe retinopathy are very uncommon in <5 years of diabetes duration, with most occurring after 10 years; conversely, up to 20% of patients will have some background retinopathy at diagnosis, and by 10 years, 60% will have some retinopathy, rising to 80% at 15 years (32). The differences between the subgroups have been explicit in the results.

It is also acknowledged that there may have been an issue of survival bias in the sample. A person with PDR is more likely to have increased morbidity and mortality compared with a person without PDR (33,34). It is possible that the observations are skewed because the less-well PDR patients with multiple comorbid conditions may not be attending clinics or may have died; therefore, they may have been underrepresented in recruitment. It is also acknowledged that patients with dementia would have been underrepresented in the study because they would be less likely to attend eye screening examinations or be able to participate in the study. Therefore, higher dementia in the PDR group may be underreported. These limitations are common to the previous studies discussed.

Other potential areas of selection bias were the exclusion of patients with severe mental illness, dementia, and stroke and the slightly higher proportion of nonsmokers in the PDR group. In terms of exclusions, 20 patients with a severe mental illness were excluded from the PDR group (the majority had a psychotic disorder), 20 with dementia in the PDR group and 12 in the no/mild DR group were excluded, and 25 with a history of stroke in the PDR group and 9 in the no/mild DR group were excluded. As with the issue of potential survival bias, exclusion of patients with dementia and stroke could have led to an underestimate of the true level of cognitive impairment in the PDR group. If the rate of progression to dementia and related risk factors such as stroke is faster in patients with PDR, excluding them could have diluted the observable level of impairment and may have contributed to the inverse association we observed, although it should also be noted that the inverse association was evident in the younger age cohorts. In terms of smoking, the slightly higher proportion of nonsmokers in the PDR group may have also been a biasing factor. However, further sensitivity analysis showed that for both nonsmokers and ex-smokers, the inverse association between the PDR and the no/mild DR groups was consistent with the main study finding.

A further limitation of this study may have been the use of the ACE-R in a multiethnic sample. Although the ACE-R was developed in the U.K., it was developed in a largely Caucasian sample. There may have been some cultural bias in the responses. For example, some of the pictorial images used in one test have a Eurocentric context. This bias may have been reflected in the lower cognition observed in the black participants. However, the overall impact of this bias does not challenge the main findings because the finding was also observed in the MMSE and the Mini-Cog tools, which have limited scope for cultural bias.

Although mood and emotional distress in diabetes were adjusted for, the analysis would have been strengthened by including a measure of premorbid intelligence

(e.g., the National Adult Reading Test). Such a measure would have allowed a more comparable estimation of cognition scores between groups with different educational levels by enabling some adjustment for variations in test performance related to education rather than to underlying cognitive impairment.

In conclusion, in patients with type 2 diabetes, we observed that severe DR is associated with less cognitive impairment compared with no/mild DR. This relationship was found to be constant after adjusting for a wide range of confounding factors. The implication of this study is that we need to explore further the relationship between DR and cognitive impairment. Ideally, this research would be prospective in nature, following patients without significant retinopathy at diagnosis to establish whether there is a cumulative association between the progression of DR and cognitive impairment; either inverse or positive. Such inquiries will be important both in identifying groups of patients who may be at higher risk of cognitive impairment and in understanding the underpinning mechanisms for cognitive impairment in diabetes.

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R.R.C.-N. contributed to the literature search, study design, data collection, data analysis, data interpretation and wrote the manuscript. S.S. contributed to the study design, data analysis, and data interpretation and edited the manuscript. S.A. contributed to the discussion and reviewed and edited the manuscript. A.F. contributed to the study design, data analysis, and data interpretation and edited the manuscript. R.R.C.-N. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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