JDI Journal of Diabetes Investigation Open access
Official Journal of the Asian Association for the Study of Diabetes

ORIGINAL ARTICLE

Serum high-density lipoprotein cholesterol is a protective predictor of executive function in older patients with diabetes mellitus

Yue Sun[1], Jenny Lee[2,3], Ronald C Ma[1], Timothy Kwok[1]*

[1]Department of Medicine and Therapeutics, the Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, [2]Department of Medicine, Alice Ho Miu Ling Nethersole Hospital, and [3]Department of Medicine & Geriatrics, Tai Po Hospital, Taipo, Hong Kong

Keywords
Cognitive function, Diabetes mellitus, High-density lipoprotein cholesterol

***Correspondence**
Timothy Kwok
Tel.: +852-2632-3173
Fax: +852-2632-3173
E-mail address:
tkwok@cuhk.edu.hk

J Diabetes Investig 2019; 10: 139–146

doi: 10.1111/jdi.12865

ABSTRACT

Aims/Introduction: Older people with diabetes mellitus are at high risk for cognitive impairment or dementia. The clinical predictors for cognitive decline in older people with diabetes mellitus were elucidated.

Materials and Methods: This was a secondary analysis of a vitamin B_{12} intervention trial in older people with diabetes mellitus. A total of 271 non-demented individuals were followed up at 9-month intervals for 27 months. We explored the association between baseline clinical features with changes in cognitive measures (Clinical Dementia Rating scale, Neuropsychological Test Battery including executive function *z*-scores, psychomotor speed *z*-scores and memory *z*-scores).

Results: A total of 152 participants had normal cognition (Clinical Dementia Rating 0) and 119 had cognitive impairment (Clinical Dementia Rating 0.5) at baseline. After 27 months, 41 participants had cognitive decline, 36 of whom were cognitively normal at baseline. Multiple logistic regression showed no significant clinical predictor of global cognitive decline. Higher high-density lipoprotein cholesterol (HDL-C) was associated with better executive performance at month 27 ($\beta = 0.359$, $P < 0.001$). Multilevel modeling showed that the highest tertile of HDL-C was associated with better executive function *z*-scores than the lowest tertile of HDL-C at all time-points.

Conclusions: Among older people with diabetes mellitus, higher serum HDL-C was associated with better executive function.

INTRODUCTION

Older people with diabetes mellitus, have an approximately 1.5- to twofold-increased risk of cognitive impairment and dementia[1]. Given the high prevalence of diabetes mellitus in older people, the identification of potentially modifiable risk factors of cognitive decline in this high-risk group is important. The mechanisms underlying progressive cognitive deficits are likely to be multifactorial, as diabetes mellitus is associated with cardiovascular disease, white matter brain changes and Alzheimer's disease[2].

Furthermore, hypoglycemia is associated with an increased risk of cognitive decline and dementia in patients with diabetes mellitus. In a cross-sectional study of >1,000 patients, a self-reported history of severe hypoglycemia was significantly associated with worse later-life cognitive function independent of initial cognitive function[3]. Another prospective study of >16,000 older adults with diabetes mellitus also suggested that the accumulation of severe hypoglycemic events over the preceding 20 years was significantly associated with a greater risk of dementia[4]. The effect of repeated hypoglycemia episodes on the development of cognitive decline is due to neuronal loss as a result of an impaired fuel supply[5].

Dyslipidemia has been shown to have a strong additive influence on the cognitive performance of patients with Alzheimer's disease[6]. Diabetes mellitus is related with microvascular complications, including nephropathy. Kidney dysfunction has been found to be associated with more rapid decline in performance in domains of attention and processing speed[7]. Diabetes mellitus is also associated with clinical stroke, white matter disease and asymptomatic cerebral infarctions, which could affect cognitive functions in older people with diabetes mellitus[8].

Received 6 March 2018; revised 25 April 2018; accepted 15 May 2018

Therefore, we explored clinical factors associated with global cognitive deficit and specific cognitive domains at the 27-month follow up among older people with diabetes mellitus.

METHODS

The sample was drawn from existing data of a randomized trial of vitamin B_{12} supplementation, who were administered the cognitive functional tests at baseline and at 9-month intervals until month 27[9]. This trial showed no significant effect of vitamin B_{12} supplementation on cognitive decline. Hence, we carried out the secondary analysis to identify risk factors associated with cognitive function in this intervention trial and adjusted for treatment assignment.

A total of 271 participants with type 2 diabetes mellitus aged >70 years were recruited in Hong Kong from August 2011 to September 2013. Details of sampling procedures and collection methods of the original sample have been described previously[9]. In brief, all the participants with borderline low vitamin B_{12} (150–300 pmol/L) were screened in the research clinic at the Prince of Wales Hospital and seven family medicine/general outpatient clinics in the New Territories East cluster in Hong Kong. Exclusion criteria included: (i) individuals with a clinical diagnosis of dementia, peripheral neuropathy, anemia, disabling stroke, renal failure or clinical depression; (ii) individuals taking vitamin B_{12} supplementation or centrally-acting medications; and (iii) individuals without a family member who could reliably inform on cognitive functioning. At entry, all study participants attended the research clinic for extensive physical and cognitive function assessment, and every 9 months they came back to attend these examinations until 27 months. A total of 234 participants (86.4%) completed the follow up.

After having obtained written consent from participants, all of the participants had the following measurements:

1. Blood samples were taken after an overnight fast. The blood was analyzed for glycosylated hemoglobin, creatinine and low-density lipoprotein cholesterol, total cholesterol, high-density lipoprotein cholesterol (HDL-C), non-HDL-C and triglycerides. Apolipoprotein E genotyping was also analyzed from ethylenediaminetetraacetic acid blood samples.
2. All basic information of participants was collected at baseline by questionnaires that included: demographic information, education years, smoking status, medical diagnoses and medication. Additionally, a history of hypoglycemia was assessed by self-report (frequency in recent 1 month), and duration of diabetes mellitus was recorded.
3. Neuropsychological tests. (i) Chinese Mini-Mental State Examination – the version has been validated suitably for individuals in Hong Kong and the total score is 30. (ii) Clinical Dementia Rating scale (CDR) – a numeric scale used to rate the severity of symptoms of dementia and reflecting a clinical impression of global cognitive and functional impairment. It is a well-structured interview-based test. Besides an interview with a patient, a caregiver who has regular personal contact with the patient also completes the CDR rating ranges from 0 (normal) to 3 (severe dementia). A CDR score of 0 indicates normal cognition, 0.5 indicates 'questionable dementia' or mild cognitive impairment and a score of ≥1 might indicate 'clinical dementia.' All the participants were divided into two groups based on their CDR global scores at baseline, and participants with CDR global scores of 0 were defined as the cognitively normal group, whereas the participants with CDR global scores of ≥0.5 were the mild cognitive impairment group. Cognitive decline was defined as any increase in CDR global score at 27-month follow up. (iii) Neuropsychological Test Battery (NTB) – the cognitive test battery was chosen for specific assessments[10]. The tests included: Controlled Oral Word Association Test and the Category Fluency Test (to name animals, vegetables and fruits in 1 min each), International Shopping List Test, 'Detection' (a test of simple reaction time) and 'Identification' (a choice reaction time test) and Continuous Paired Associates Learning. The selected assessments were carried out face-to-face by well-trained research assistant using a touch-screen portable computer. From these tests, composite cognitive function scores were formed to represent three cognitive domains (executive function, psychomotor speed and memory), raw scores from the cognitive tests were converted to *z*-scores; (value – mean at baseline)/standard deviation at baseline was used to compute the *z*-scores, with higher *z*-scores indicating better performance. (iv) Geriatric Depression Scale – it contains 15 items with a score of ≥8 indicating depression. The version has been validated in the Hong Kong population.

Statistical analysis

The primary outcome was change in CDR global score, and the secondary outcomes were NTB domain *z*-scores. Continuous variables were presented as the mean (standard deviation) and prevalence (percentage), as appropriate, then compared by using independent samples *t*-test or the χ^2-test. Binomial logistic regression was carried out to examine predictors for CDR changes. All clinically plausible variables with $P < 0.20$ in the respective bivariate analyses were considered for the models. As the current study was based on a previous vitamin B_{12} supplementation randomized placebo trial, the effect of treatment assignment would be taken into consideration in all models.

The partial correlation coefficient was used to identify the biomarkers related to *z*-scores of domain performance in NTB at month 27 with correction for age and sex. Significant correlations ($P < 0.05$) were reported. Then, the linear regression model was carried out to investigate the association between significant factors and *z*-score in the NTB domain after adjustment for age, sex, education level, treatment assignment and corresponding baseline *z*-score. All the analysis were carried out with SPSS software (IBM SPSS Statistics version 24.0; IBM Corporation, Armonk, NY, USA).

RESULTS

Table 1 summarizes the baseline characteristics of the participants. A total of 271 older people aged 69–85 years were included. Majority of participants (77.49%) had diabetes mellitus for >10 years. More than half of the participants (56%) had a CDR score of 0 at baseline. The cognitive impaired group had received less education and had a higher proportion of women, stroke patients and smokers than the normal cognition group.

A total of 41 (15%) participants had an increase in the CDR global score at month 27. Among these participants, five had cognitive impairment at baseline. In contrast, among non-decliners, 16 participants' CDR global score decreased (improved) at month 27. Table 2 compares clinical characteristics among decliners and non-decliners. Variables associated with an increase in CDR global score in the univariate analysis were being male, and having higher serum creatinine and a higher Mini-Mental State Examination score. Use of statins, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, insulin, metformin, duration of diabetes mellitus and hypoglycemia frequency were not significantly different between the two groups.

Multiple logistic regression models were used to detect predictors of cognitive decline, and all clinically plausible variables with $P < 0.2$ in the univariate analyses were included in the model; that is, age, creatinine, smoking status, insulin treatment and sex (shown in Table 2). Mini-Mental State Examination was not included in the model, as its strong correlation with cognitive decline without dementia and randomization was included in model. None of these factors were significantly associated with cognitive decline.

Partial correlation analysis showed that serum HDL-C level was associated with executive function at month 27 (correlation coefficient 0.248, $P < 0.001$). No clinical factors correlated significantly with psychomotor speed and memory (shown in Table S1). A linear regression model was used to investigate the association between HDL-C level and executive function at month 27 with correction for age, sex, education years, trial group assignment and baseline executive function. HDL-C was positively associated with executive function at month 27 ($\beta = 0.359$, $P < 0.001$, 95% confidence interval 0.236–0.483). With further correction for the use of statin, HDL-C was still significantly associated with executive function at month 27 ($\beta = 0.366$, $P = 0.004$, 95% confidence interval 0.116–0.616). On multilevel modeling of executive function at all time-points, the highest tertile of the HDL-C group had better executive function than the lowest tertile of the HDL-C group after adjustment for age, sex, education and trial group assignment (Table 3; Figure 1). Time did not have an interaction effect on the association of the HDL-C group with executive function ($P = 0.963$). The clinical characteristics of the participants in the tertiles of serum HDL-C are shown in Table 4. Serum total cholesterol levels and triglyceride were significantly higher, whereas non HDL-C levels were significantly decreased in the upper tertile of serum HDL-C. In addition, the upper tertile of serum HDL-C included a higher proportion of

Table 1 | Clinical characteristics of all trial participants at baseline

	Normal (n = 152)		MCI (n = 119)		P
	Mean	SD	Mean	SD	
Age (years)	74.91	3.88	75.55	4.23	0.196
Education (years)	6.98	4.62	4.13	3.81	<0.001
HbA1c (%)	7.1	0.9	7.2	0.9	0.485
Creatinine (μmol/L)	91.63	25.14	87.44	24.83	0.172
HDL (mmol/L)	1.30	0.33	1.28	0.31	0.507
LDL (mmol/L)	2.33	0.69	2.32	0.67	0.937
Total-C (mmol/L)	4.24	0.86	4.25	0.74	0.961
Non-HDL (mmol/L)	2.91	0.82	2.97	0.76	0.598
Triglyceride (g/L)	1.37	0.87	1.45	0.76	0.456
Hemoglobin (g/dL)	13.28	1.16	12.90	1.39	0.016
Urine albu:creat	14.92	34.92	15.23	26.88	0.949
MCV (fL)	90.33	7.16	89.41	7.55	0.316
MMSE (max 30)	27.14	2.28	22.89	3.51	<0.001
GDS (max 15)	2.91	2.15	3.99	2.38	<0.001
NTB†					
Executive function	0.28	0.83	–0.39	0.73	<0.001
Psychomotor speed	0.16	0.89	–0.10	0.83	0.023
Memory	0.23	0.79	–0.28	0.73	<0.001
	n	%	n	%	
Hypertension	129	84.9	104	87.4	0.552
Stroke	6	3.9	12	10.1	0.044
Smoker	8	6	10	10.5	0.090
APOE4‡	19	12.5	19	16.1	0.358
APOE3/3	99	65.1	79	66.9	0.671
Drug use					
Aspirin	32	21.1	35	29.4	0.113
Insulin	24	15.8	15	12.6	0.459
Metformin	125	82.2	102	85.7	0.441
Statin	76	50	70	58.8	0.148
ACEI/ARB	116	76.8	92	77.3	0.920
Female	46	30.2	67	56.3	<0.001
Supplement group	76	50	61	51.3	0.903
DM duration ≥10 years	114	75	96	80.7	0.151
Hypoglycemia	25	16.4	14	11.8	0.280
Hospital admission for hypoglycemia	3	2.0	6	5.0	0.159

†The z-scores as compared with the mean of all participants; higher scores indicating better performance. ‡One copy. ACEI, angiotensin-converting enzyme inhibitor; albu:creat, albumin (g) and creatinine (μmol/L) ratio; ApoE, apolipoprotein E; ARB, angiotensin receptor blocker; DM, diabetes mellitus; GDS, Geriatric Depression Scale; HbA1c, glycosylated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; max, maximum; MCI, mild cognitive impaired (Clinical Dementia Rating scale score 0.5); MCV, mean corpuscular volume; MMSE, Mini-Mental State Examination; Non-HDL, non-high-density lipoprotein; NTB, Neuropsychological Test Battery; SD, standard deviation; Total-C, total cholesterol.

Table 2 | Comparisons of cognitive decliners and non-decliners according to Clinical Dementia Rating scale global score

	Decliners (*n* = 41)		Non-decliners (*n* = 202)		*P*
	Mean	SD	Mean	SD	
Age (years)	76.41	4.20	74.93	3.98	0.032
Education (years)	6.75	4.97	5.89	4.41	0.264
HbA1c, mmol/mol (%)	78 (7.1)	12 (1.1)	77 (7.1)	10 (0.9)	0.593
Creatinine (μmol/L)	97.39	24.06	87.74	24.95	0.024
Urine albu:creat	16.09	36.76	13.88	26.64	0.712
HDL (mmol/L)	1.28	0.32	1.30	0.32	0.624
LDL (mmol/L)	2.29	0.89	2.33	0.64	0.686
Total-C (mmol/L)	4.18	1.09	4.27	0.76	0.526
Non-HDL (mmol/L)	2.89	1.14	2.94	0.71	0.740
Triglyceride (g/L)	1.37	0.83	1.41	0.83	0.737
Hemoglobin (g/dL)	12.97	1.34	13.17	1.25	0.342
MCV (fL)	90.66	6.11	90.06	7.67	0.641
MMSE (max 30)	26.56	2.69	25.25	3.65	0.030
GDS (max 15)	3.00	1.73	3.41	2.41	0.301
NTB[†]					
Executive function	–0.001	0.88	0.004[§]	0.85	0.768
Psychomotor speed	–0.007[¶]	0.89	0.041[††]	0.88	0.311
Memory	0.029[‡‡]	0.82	0.002[§§]	0.79	0.809
Total	0.119	0.56	0.06	0.64	0.935
	n	%	*n*	%	
Hypertension	37	90.2	170	84.2	0.317
Stroke	3	7.31	13	6.44	0.836
Smoker	2	5.0	16	8.56	0.058
APOE4[‡]	6	14.63	28	13.93	0.906
APOE3/3	28	68.3	129	64.2	0.615
Drug use					
Aspirin	8	19.5	54	26.7	0.334
Insulin	1	2.43	25	12.4	0.177
Metformin	37	90.2	66	32.7	0.204
Statin	20	48.8	111	54.9	0.407
ACEI/ARB	23	56.1	122	60.39	0.609
Female	11	26.8	87	43.1	0.053
Supplement group	23	56.1	99	49	0.408
DM duration ≥10 years	33	80.5	156	77.2	0.560
Hypoglycemia	8	19.5	30	14.85	0.445
Hospital admission for hypoglycemia	1	2.4	8	4.0	0.641

[†]The *z*-scores as compared with the mean of all participants; higher scores indicating better performance. [‡]One copy. [§]*n* = 195 participants; [¶]*n* = 36 participants; [††]*n* = 181 participants; [‡‡]*n* = 39 participants; [§§]*n* = 192 participants. ACEI, angiotensin-converting enzyme inhibitor; albu:creat, albumin (g) and creatinine (μmol/L) ratio; ApoE, apolipoprotein E; ARB, angiotensin receptor blocker; DM, diabetes mellitus; GDS, Geriatric Depression Scale; HbA1c, glycosylated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; max, maximum; MCI, mild cognitive impaired (Clinical Dementia Rating scale score 0.5); MCV, mean corpuscular volume; MMSE, Mini-Mental State Examination; Non-HDL, non-high-density lipoprotein; NTB, Neuropsychological Test Battery; Total-C, total cholesterol.

women. There were no significant differences in other clinical characteristics.

DISCUSSION

The present study could not identify any clinical risk factor for global cognitive decline in older people with diabetes mellitus, except that lower serum HDL-C was significantly associated with worse executive function after adjustments for confounders.

During the 27-month observational period in this study, 15% of participants experienced cognitive decline. This contrasts with the 17% incidence in 1.6 years reported by Bruce *et al.*[11] This might be attributed to optimal diabetes control in this group of patients. Although the majority of participants had

Table 3 | Comparisons of executive function between HDL-C tertiles at follow up

	Baseline	9-month follow up	18-month follow up	27-month follow up
Lowest tertile	−0.01 (0.83)	−0.01 (0.89)	−0.09 (0.80)	0.04 (0.87)
Middle tertile	−0.11 (0.78)	−0.10 (0.87)	−0.01 (1.02)	−0.01 (0.82)
Highest tertile	0.16* (0.93)	0.18* (0.96)	0.18** (0.96)	0.33** (1.01)

Data presented as mean (standard deviation) of *z*-scores.
*,**Significantly different from the lowest tertile, $P < 0.05$ and $P < 0.01$, respectively.

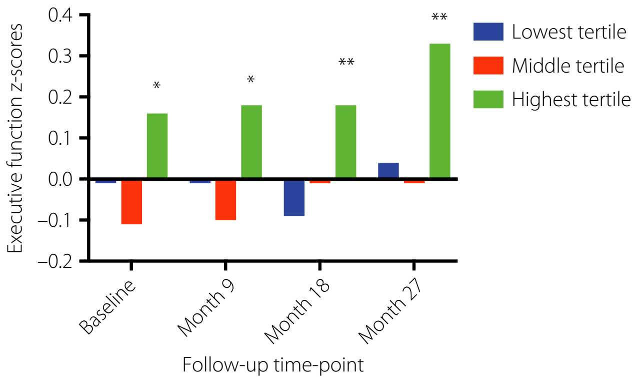

Figure 1 | Comparisons of executive function among high-density lipoprotein cholesterol tertiles at all time-points. *,**Significantly different from the lowest tertile, $P < 0.05$ and $P < 0.01$, respectively.

diabetes mellitus for >10 years, most of them were treated with statin, metformin and angiotensin receptor blockers, which have been reported to be neuroprotective in people with diabetes mellitus[11–13]. In addition, the prevalence of diabetic complications was relatively low. One observational study in Japan reported that the existence of diabetic nephropathy, higher systolic blood pressure and higher serum triglycerides (or lower HDL-C) were associated with cognitive decline after 6 years in participants with diabetes mellitus[14]. Another study found that a lower urinary albumin:creatinine ratio and use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers were protective for cognitive decline in older people with diabetes mellitus[11].

Serum creatinine was higher in the decliners, but the difference was not independent of confounders. Renal dysfunction, as indicated by reduced creatinine clearance or higher urinary albumin:creatinine ratio, has been shown to be associated with cognitive decline in older people[15]. This might be attributed to a higher prevalence of cerebral small vessel disease[16], which contributes to cognitive impairment[17]. The use of angiotensin-converting enzyme inhibitor/angiotensin receptor blocker and metformin did not show a significant effect on cognitive impairment, which might be due to the frequent use of these drugs among all the participants. In addition, hypoglycemia is also a possible contributor of cognitive impairment in older people with diabetes mellitus[18]. However, serious hypoglycemia was rarely reported in the present study.

None of the clinical features were associated with global cognitive decline, but we found a robust association between HDL-C and executive function. This suggests that serum HDL-C is specifically associated with executive function in older people with diabetes mellitus. A case–control study found a positive association between HDL-C levels and executive function in the diabetic statin users, but not in non-users[19]. A longitudinal study in France reported that lower HDL-C was associated with an increased risk of cognitive decline in executive function and psychomotor speed in older men[20]. In the present study, the association between HDL-C and executive function was independent of sex and statin use in older people with diabetes mellitus.

It has been well demonstrated that HDL-C undergoes significant qualitative changes in diabetes mellitus, in both structure and function[21]. When dealing with HDL-C and cognitive function, we should keep in mind that cholesterol exists in two independent pools, the central nervous system and peripheral circulation. HDL-C has multiple important functions in the brain. HDL-C dysfunction in the central nervous system can directly cause cognitive impairment[22]. Although it is generally thought that there is no net transfer of cholesterol from the periphery into the central nervous system because of the blood–brain barrier, plasma HDL can affect the blood–brain barrier through its effects on endothelial function[23]. In addition, some small particles of HDL-C; for example apolipoprotein A-1, can cross blood–brain barrier. Furthermore, the major protein component of plasma HDL-C, apolipoprotein A-I, has a role in Aβ clearance[24], and the anti-oxidant and anti-inflammatory properties of apolipoprotein A-I/HDL-C have been shown to play a significant role in neuroprotection[25]. Furthermore, the association between HDL-C levels and cognition could be attributed to the higher cardiovascular risk associated with lower HDL-C[26].

Executive function is a primary domain of cognition that involves a broad set of cognitive abilities, such as attention, working memory, organization and persistence, which are essential to complex, goal-directed activities[27]. Many studies have linked executive function with the pre-frontal cortex[28]. Furthermore, white matter hyperintensities, irrespective of location, are associated with reduced frontal lobe metabolism and executive dysfunction. Previous studies have found that executive deficits could adversely affect glycemic control, and poor glycemic control in turn impairs cognitive function in adults with diabetes mellitus[29]. Hence, the preservation of executive function is important for the prevention of diabetic complications and global cognitive function in the longer term.

Serum HDL-C can be increased by lifestyle modification. A meta-analysis of 25 studies reported a mean net change in serum HDL-C level of 2.53 mg/dL (95% confidence interval 1.36–3.70) with exercise averaging 3.7 sessions per week and 40.5 min per session[30]. Furthermore, several trials showed that

Table 4 | Clinical characteristics of the participants in the tertiles of serum high-density lipoprotein cholesterol

	Lowest tertile		Middle tertile		Upper tertile		P
	Mean	SD	Mean	SD	Mean	SD	
Age (years)	75.40	4.19	75.67	4.01	74.83	4.00	0.445
Education (years)	6.77	4.22	5.53	4.98	5.29	4.07	0.067
HbA1c (%)	7.21	1.04	7.04	0.79	7.00	0.94	0.313
Creatinine (μmol/L)	97.09	24.69	84.94	23.96	85.65	26.90	0.213
LDL (mmol/L)	2.37	0.72	2.32	0.60	2.27	0.72	0.648
Total-C (mmol/L)	4.09	0.82	4.23	0.77	4.46	0.80	0.013*
Non-HDL (mmol/L)	3.10	0.82	2.97	0.63	2.70	0.85	0.010*
Triglyceride (g/L)	1.61	0.81	1.42	1.01	1.11	0.46	<0.001*
Hemoglobin (g/dL)	13.47	1.30	12.82	1.25	13.09	1.21	0.312
Urine albu:creat	16.82	32.52	20.65	41.30	8.30	17.62	0.165
MCV (fL)	90.32	6.35	89.08	8.26	90.59	7.35	0.396
MMSE (max 30)	25.99	3.02	24.95	3.78	24.82	3.82	0.059
GDS (max 15)	3.82	2.25	3.23	2.24	3.19	2.32	0.426
Hypertension	82	87.23	70	89.74	56	78.87	0.143
Stroke	8	8.51	5	6.41	2	2.82	0.321
Smoker	10	10.64	3	3.85	5	7.04	0.131
APOE4†	19	20.21	7	8.97	7	9.86	0.059
APOE3/3	64	68.09	54	69.23	41	57.75	0.458
Drug use							
Aspirin	25	26.60	21	26.92	15	21.13	0.655
Insulin	10	10.64	9	11.54	7	9.86	0.946
Metformin	75	79.79	69	88.46	60	84.51	0.301
Statin	49	52.13	45	57.69	40	56.34	0.744
ACEI/ARB	57	60.64	50	64.10	39	54.93	0.505
Female	18	19.15	36	46.15	41	57.75	<0.001*
Supplement group	48	51.06	37	47.44	36	50.70	0.879

*Comparison between the highest and lowest tertiles, $P < 0.05$. †One copy. ACEI, angiotensin-converting enzyme inhibitor; albu:creat, albumin (g) and creatinine (μmol/L) ratio; ApoE, apolipoprotein E; ARB, angiotensin receptor blocker; DM, diabetes mellitus; GDS, Geriatric Depression Scale; HbA1c, glycosylated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; max, maximum; MCI, mild cognitive impaired (Clinical Dementia Rating scale score 0.5); MCV, mean corpuscular volume; MMSE, Mini-Mental State Examination; Non-HDL, non-high-density lipoprotein; NTB, Neuropsychological Test Battery; SD, standard deviation; Total-C, total cholesterol.

exercise training programs improved the qualitative aspects of HDL-C[31–33]. Polyunsaturated and monounsaturated fats, such as olive oil and coconut oil, mainly affect HDL_2-C or HDL_3-C concentration[34], whereas very high polyunsaturated:saturated fat ratios and extremely high intakes of linoleic acid could significantly change serum HDL-C levels[35,36]. In addition, studies of very low carbohydrate diets together with weight loss have shown a mean increase of 11% in serum HDL-C level compared with low-fat diets[37]. Overall, the dietary influence on serum HDL-C level is therefore limited.

Nicotinic acid, statins, cholesteryl ester transfer protein inhibitors and fibrates are four classes of agents targeted at increasing HDL-C levels[38]. Nicotinic acid and fibrates can reduce low-density lipoprotein cholesterol by 5–25% and triglyceride by 20–50% simultaneously[39,40]. Cholesteryl ester transfer protein inhibitors can inhibit transferring of cholesterol esters from HDL-C to larger lipoproteins, which could significantly increase HDL-C levels and reduce low-density lipoprotein cholesterol levels[41].

Serum HDL-C is a crude marker of HDL-C function. Further studies on the influence of specific measures of HDL-C function; for example, cholesterol efflux capacity of HDL-C on cognitive function in older people with diabetes mellitus, are warranted.

The strengths of the present study included detailed neurocognitive assessments that tapped a range of cognitive domains at multiple time-points, and the comprehensiveness of clinical factors. There were limitations. First, causality cannot be inferred, as it was an observational study. Second, the patients in the present study were the participants of a clinical trial. They might have been more health conscious than older people with diabetes mellitus in the general population. Third, we did not have data on diet and physical activity, which might confound the results.

In summary, no significant clinical factor for cognitive decline in older people with diabetes mellitus was found in the present study. Higher serum HDL-C levels were associated with better performance in executive function. Elucidation of the underlying mechanisms of this association might lead to effective prevention strategies to prevent cognitive decline in older people with diabetes mellitus.

ACKNOWLEDGMENTS

This study was supported by a General Research Grant from the Hong Kong Research Grant Council (CUHK468110). All authors have reviewed and approved the manuscript.

DISCLOSURE

The authors declare no conflict of interest.

REFERENCES

1. Chen L, Magliano DJ, Zimmet PZ. The worldwide epidemiology of type 2 diabetes mellitus–present and future perspectives. *Nat Rev Endocrinol* 2011; 8: 228–236.
2. Strachan MW, Reynolds RM, Marioni RE, *et al.* Cognitive function, dementia and type 2 diabetes mellitus in the elderly. *Nat Rev Endocrinol* 2011; 7: 108–114.
3. Aung PP, Strachan MW, Frier BM, *et al.* Severe hypoglycaemia and late-life cognitive ability in older people with Type 2 diabetes: the Edinburgh Type 2 Diabetes Study. *Diabet Med* 2012; 29: 328–336.
4. Whitmer RA, Karter AJ, Yaffe K, *et al.* Hypoglycemic episodes and risk of dementia in older patients with type 2 diabetes mellitus. *JAMA* 2009; 301: 1565–1572.
5. McNay EC, Cotero VE. Mini-review: impact of recurrent hypoglycemia on cognitive and brain function. *Physiol Behav* 2010; 100: 234–238.
6. Blom K, Vaartjes I, Peters SA, *et al.* The influence of vascular risk factors on cognitive decline in patients with Alzheimer's disease. *Maturitas* 2014; 79: 96–99.
7. Lee S, Shimada H, Park H, *et al.* The association between kidney function and cognitive decline in community-dwelling, elderly Japanese people. *J Am Med Dir Assoc* 2015; 16: 349.e1–349.e5.
8. Ryan JP, Fine DF, Rosano C, *et al.* Type 2 diabetes and cognitive impairment: contributions from neuroimaging. *J Geriatr Psychiatry Neurol* 2014; 27: 47–55.
9. Kwok T, Lee J, Ma RC, *et al.* A randomized placebo controlled trial of vitamin B12 supplementation to prevent cognitive decline in older diabetic people with borderline low serum vitamin B12. *Clin Nutr* 2017; 36: 1509–1515.
10. Harrison J, Minassian SL, Jenkins L, *et al.* A neuropsychological test battery for use in Alzheimer disease clinical trials. *Arch Neurol* 2007; 64: 1323–1329.
11. Bruce DG, Davis WA, Casey GP, *et al.* Predictors of cognitive decline in older individuals with diabetes. *Diabetes Care* 2008; 31: 2103–2107.
12. Manschot SM, Biessels GJ, de Valk H, *et al.* Metabolic and vascular determinants of impaired cognitive performance and abnormalities on brain magnetic resonance imaging in patients with type 2 diabetes. *Diabetologia* 2007; 50: 2388–2397.
13. Guo M, Mi J, Jiang QM, *et al.* Metformin may produce antidepressant effects through improvement of cognitive function among depressed patients with diabetes mellitus. *Clin Exp Pharmacol Physiol* 2014; 41: 650–656.
14. Umegaki H, Iimuro S, Shinozaki T, *et al.* Risk factors associated with cognitive decline in the elderly with type 2 diabetes: baseline data analysis of the Japanese Elderly Diabetes Intervention Trial. *Geriatr Gerontol Int* 2012; 12 (Suppl 1): 103–109.
15. Kurella Tamura M, Wadley V, Yaffe K, *et al.* Kidney function and cognitive impairment in US adults: the Reasons for Geographic and Racial Differences in Stroke (REGARDS) Study. *Am J Kidney Dis* 2008; 52: 227–234.
16. Makin SD, Cook FA, Dennis MS, *et al.* Cerebral small vessel disease and renal function: systematic review and meta-analysis. *Cerebrovasc Dis* 2015; 39: 39–52.
17. Yao H, Araki Y, Takashima Y, *et al.* Chronic kidney disease and subclinical brain infarction increase the risk of vascular cognitive impairment: the Sefuri study. *J Stroke Cerebrovasc Dis* 2017; 26: 420–424.
18. Feinkohl I, Aung PP, Keller M, *et al.* Severe hypoglycemia and cognitive decline in older people with type 2 diabetes: the Edinburgh type 2 diabetes study. *Diabetes Care* 2014; 37: 507–515.
19. Goh DA, Dong Y, Lee WY, *et al.* A pilot study to examine the correlation between cognition and blood biomarkers in a Singapore Chinese male cohort with type 2 diabetes mellitus. *PLoS One* 2014; 9: e96874.
20. Ancelin ML, Ripoche E, Dupuy AM, *et al.* Gender-specific associations between lipids and cognitive decline in the elderly. *Eur Neuropsychopharmacol* 2014; 24: 1056–1066.
21. Farbstein D, Levy AP. HDL dysfunction in diabetes: causes and possible treatments. *Expert Rev Cardiovasc Ther* 2012; 10: 353–361.
22. Gonzalez-Escamilla G, Atienza M, Garcia-Solis D, *et al.* Cerebral and blood correlates of reduced functional connectivity in mild cognitive impairment. *Brain Struct Funct* 2016; 221: 631–645.
23. Balazs Z, Panzenboeck U, Hammer A, *et al.* Uptake and transport of high-density lipoprotein (HDL) and HDL-associated alpha-tocopherol by an in vitro blood-brain barrier model. *J Neurochem* 2004; 89: 939–950.
24. Koldamova RP, Lefterov IM, Lefterova MI, *et al.* Apolipoprotein A-I directly interacts with amyloid precursor protein and inhibits A beta aggregation and toxicity. *Biochemistry* 2001; 40: 3553–3560.
25. Kay AD, Day SP, Kerr M, *et al.* Remodeling of cerebrospinal fluid lipoprotein particles after human traumatic brain injury. *J Neurotrauma* 2003; 20: 717–723.
26. Khera AV, Cuchel M, de la Llera-Moya M, *et al.* Cholesterol efflux capacity, high-density lipoprotein function, and atherosclerosis. *N Engl J Med* 2011; 364: 127–135.

27. Nguyen HT, Grzywacz JG, Arcury TA, *et al.* Linking glycemic control and executive function in rural older adults with diabetes mellitus. *J Am Geriatr Soc* 2010; 58: 1123–1127.
28. Nakamizo A, Kikkawa Y, Hiwatashi A, *et al.* Executive function and diffusion in frontal white matter of adults with moyamoya disease. *J Stroke Cerebrovasc Dis* 2014; 23: 457–461.
29. Thabit H, Kyaw Tun T, McDermott J, *et al.* Executive function and diabetes mellitus–a stone left unturned? *Curr Diabetes Rev* 2012; 8: 109–115.
30. Kodama S, Tanaka S, Saito K, *et al.* Effect of aerobic exercise training on serum levels of high-density lipoprotein cholesterol: a meta-analysis. *Arch Intern Med* 2007; 167: 999–1008.
31. Casella-Filho A, Chagas AC, Maranhão RC, *et al.* Effect of exercise training on plasma levels and functional properties of high-density lipoprotein cholesterol in the metabolic syndrome. *Am J Cardiol* 2011; 107: 1168–1172.
32. Roberts CK, Ng C, Hama S, *et al.* Effect of a short-term diet and exercise intervention on inflammatory/anti-inflammatory properties of HDL in overweight/obese men with cardiovascular risk factors. *J Appl Physiol (1985)* 2006; 101: 1727–1732.
33. Ribeiro IC, Iborra RT, Neves MQ, *et al.* HDL atheroprotection by aerobic exercise training in type 2 diabetes mellitus. *Med Sci Sports Exerc* 2008; 40: 779–786.
34. Dreon DM, Vranizan KM, Krauss RM, *et al.* The effects of polyunsaturated fat vs monounsaturated fat on plasma lipoproteins. *JAMA* 1990; 263: 2462–2466.
35. Mattson FH, Grundy SM. Comparison of effects of dietary saturated, monounsaturated, and polyunsaturated fatty acids on plasma lipids and lipoproteins in man. *J Lipid Res* 1985; 26: 194–202.
36. Shepherd J, Packard CJ, Patsch JR, *et al.* Effects of dietary polyunsaturated and saturated fat on the properties of high density lipoproteins and the metabolism of apolipoprotein A-I. *J Clin Invest* 1978; 61: 1582–1592.
37. Volek JS, Sharman MJ, Forsythe CE. Modification of lipoproteins by very low-carbohydrate diets. *J Nutr* 2005; 135: 1339–1342.
38. Keene D, Price C, Shun-Shin MJ, *et al.* Effect on cardiovascular risk of high density lipoprotein targeted drug treatments niacin, fibrates, and CETP inhibitors: meta-analysis of randomised controlled trials including 117411 patients. *BMJ* 2014; 349: g4379.
39. Expert Panel on Detection, Evaluation. Executive summary of the Third Report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). *JAMA* 2001; 285: 2486.
40. Jacobson TA, Ito MK, Maki KC, *et al.* National Lipid Association recommendations for patient-centered management of dyslipidemia: part 1 - executive summary. *J Clin Lipidol* 2014; 8: 473–488.
41. Rensen PCN, Havekes LM. Cholesteryl ester transfer protein inhibition: effect on reverse cholesterol transport? *Arterioscler Thromb Vasc Biol* 2006; 26: 681–684.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1 | Partial correlation analysis between baseline characteristics and Neuropsychological Test Battery domain *z*-scores

