Background

Diet rich in dietary fiber is beneficial for the treatment of type 2 diabetes mellitus [1], as dietary fiber ameliorates postprandial hyperglycemia by delaying digestion and absorption of carbohydrates and enhances satiety, which leads to a reduction in body weight [2]. In insulin-resistant subjects, dietary fiber may enhance peripheral insulin sensitivity possibly via short-chain fatty acids produced by fermentation of fiber in the intestines [3-5]. The hypoglycemic actions of dietary fiber in type 2 diabetic patients have been investigated by conducting interventions with high fiber diets or supplements [2]. In addition, an epidemiologic study [6] recently reported that HbA1c was significantly lower in type 2 diabetic patients with high fiber intake than in those with low fiber intake among 934 Chinese subjects who ate foods containing larger amounts of fiber than the Western diet [7].

As for cardiovascular disease (CVD) risk factors in type 2 diabetic patients, the effects of dietary fiber were not fully explored. Soluble fiber forms gels in the gastrointestinal tract, and may decrease the absorption of glucose and cholesterol from the intestinal lumen [8]. High fiber diet improved diabetic dyslipidemia in some studies [9], and a low fiber intake was associated with metabolic syndrome in Brazilian type 2 diabetic patients [10]. Although the consumption of whole grains rich in insoluble fiber was reported not to be associated with improvements in glycemic control [9,11], it suppressed low-grade systemic inflammation [12] and was inversely associated with all-cause and CVD-specific mortality among diabetic females in the Nurses' Health Study [13]. Recently, it was reported that increased dietary fiber, especially soluble fiber intake was associated with reduced all-cause and CVD-specific mortality in type 1 diabetic patients [14]. However, a recent review reported that adding fiber supplements in moderate amounts (4–19 g) to daily diet leads to little improvement in glycemic or CVD risk markers, although the effects of dietary fiber were investigated mostly in subjects consuming Western diet [9]. Dietary fiber is consumed differently in ethnic foods around the world, and the protective effects of dietary fiber on the development of diabetes differed by ethnic group according to consumed foods [15]. Japanese foods consist of dietary fiber primarily in the form of vegetables including seaweed, and contain smaller amounts of fiber than Western diet, of which the main source of fiber is whole grains [7,16]. It has been reported that increased intake of dietary fiber is associated with reduced mortality from CVD in the Japanese general population [17,18], although the effects of dietary fiber intake have not been investigated in diabetic patients. In the present study, we investigated the associations of dietary fiber intake with glycemic control and CVD risk factors, i.e., metabolic syndrome, LDL cholesterol, low-grade inflammation and chronic kidney disease (CKD) in Japanese type 2 diabetic patients. This cross-sectional study suggested the beneficial effects of dietary fiber on glycemia and a wide range of CVD risk factors including CKD.

Methods

Subjects

The Fukuoka Diabetes Registry is a multicenter prospective study designed to investigate the effects of modern treatment on the prognosis of diabetic patients attending teaching hospitals certified by the Japan Diabetes Society or certified diabetes clinics in Fukuoka Prefecture, Japan (UMIN Clinical Trial Registry 000002627) [19]. A total of 5,131 diabetic patients 20 years of age or older were registered between April 2008 and October 2010. After excluding 261 subjects with type 1 diabetes mellitus, 468 subjects who had already eaten breakfast and three subjects who reported consuming less than 500 kcal in a dietary survey, the remaining 4,399 subjects (2,493 males, 1,906 females) were enrolled in this cross-sectional study. The exclusion criteria were: 1) patients with drug-induced diabetes and those receiving steroid treatment, 2) patients under renal replacement therapy and 3) patients with serious diseases other than diabetes, such as advanced malignancy, decompensated liver cirrhosis, etc. and 4) patients unable to visit diabetologists regularly. This study was conducted with the approval of the Kyushu University Institutional Review Board, and written informed consent was obtained from all participants.

Dietary assessment

The dietary survey was conducted using a brief self-administered diet history questionnaire (BDHQ) to assess the subjects' dietary intake during the preceding month. The BDHQ includes 58 foods and beverage items. The subjects indicated their mean frequency of consumption in terms of the specified serving size by checking one of seven frequency categories ranging from "almost never" to "two or more times a day" [20]. The dietary intake estimates for total energy and several nutrients, including dietary fiber, were calculated using an ad hoc algorithm developed for the BDHQ based on the Standard Tables of Food Composition in Japan [21]. Validation of ranking energy-adjusted fiber intake has been previously studied in an adult Japanese population [22]. The correlation coefficient of dietary fiber intake between semi-weighed dietary records for 16 days and BDHQ was 0.66 in females (n = 92) and 0.70 in males (n = 92), respectively.

Clinical evaluation

Participants completed a self-administered questionnaire concerning the duration of diabetes mellitus, alcohol intake, smoking habits and physical activity. Body mass index (BMI) was calculated from each subject's height and weight,

and obesity was defined as BMI of ≥25 kg/m^2 according to Japan Society for the Study of Obesity [23]. Waist circumference at the umbilical level was measured by a trained staff member with the subject in the standing position, and blood pressure was measured with the subject in the sitting position. The subjects' medical records were reviewed for oral hypoglycemic agent and insulin use. Leisure time physical activity information was obtained using a self-reported questionnaire, and metabolic equivalent (met) hours per week was calculated using Ainsworth's methods [24].

Laboratory measurements

Blood was collected via venipuncture. Spot urine samples were obtained, and the assessments were performed at one central laboratory. HbA1c was determined using high-performance liquid chromatography (Tosoh Corp., Tokyo, Japan), plasma glucose by glucose oxidase method, serum C-peptide by chemiluminescent immunoassay (Kyowa Medex, Tokyo, Japan), serum adiponectin and high sensitivity C-reactive protein (HS-CRP) by latex immunonephelometry (Mitsubishi Chemical Medience, Tokyo, Japan; Siemens Healthcare Diagnostics, Tokyo, Japan), urinary albumin by immunonephelometry (Medical and Biological Laboratories, Nagoya, Japan) and serum total cholesterol, LDL cholesterol, HDL cholesterol, triglyceride, creatinine and urine creatinine by enzymatic methods. Estimated glomerular filtration rate (eGFR) was calculated using the equation proposed by the Japanese Society of Nephrology [25]. β cell function and insulin sensitivity were estimated based on fasting glucose and C-peptide concentrations using the HOMA Calculator, version 2.2.2 [http://www.dtu.ox.ac.uk, accessed June 2012], and expressed as the homeostasis model assessment β cell function (HOMA2-%B) and the homeostasis model assessment insulin sensitivity (HOMA2-%S), respectively. A total of 587 participants with unacceptable levels of plasma glucose (<3 mmol/l or >25 mmol/l) or C-peptide (<0.2 nmol/l or >3.5 nmol/l) were excluded [26]. Albuminuria was defined as urinary albumin excretion ≥30 mg/gCr, and CKD was defined as albuminuria and/or eGFR <60 ml/min/1.73 m^2 [27]. Metabolic syndrome was defined according to the definition of "Harmonizing the Metabolic Syndrome" [28], i.e., the presence of at least two of the following four components: central obesity for Asians (waist circumference ≥90 cm in males and ≥80 cm in females), elevated triglycerides (≥1.69 mmol/l and/or the use of triglyceride-lowering drugs), reduced HDL cholesterol (<1.03 mmo/l in males and <1.29 mmol/l in females) and elevated blood pressure (systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥85 mmHg and/or the use of antihypertensive drugs). The presence of depressive symptoms was assessed using the Center for Epidemiologic Studies Depression Scale [29], and subjects who scored more than 16 out of 60 points were defined as having depressive symptoms.

Statistical analysis

The correlations with dietary fiber intake were assessed by Pearson's correlation for continuous variables and a logistic regression analysis for categorical variables. The regression coefficients and 95% CIs' were calculated using a multiple regression analysis after multivariate adjustment for potential confounding factors, including age, sex, duration of diabetes, current smoking habits, current drinking habits, total energy intake, fat intake, saturated fatty acid intake, protein intake (only for urinary albumin excretion and eGFR), leisure time physical activity and use of oral hypoglycemic agents or insulin. Due to their skewed distributions, triglyceride, adiponectin and urinary albumin excretion values were log transformed, and the results were expressed as geometric means with 95% CIs. The multivariate-adjusted ORs and 95% CIs for metabolic syndrome and chronic kidney disease were calculated using a multiple logistic regression model. All statistical analyses were performed using the SAS software package version 9.3 (SAS Institute Inc., Cary, NC). Values of $P < 0.05$ were considered to be statistically significant in all of the analyses.

Results

Table 1 shows the clinical characteristics of the studied participants and correlations with dietary fiber intake. Regarding the source of dietary fiber, vegetables were most frequently eaten, followed by cereals, legumes and beans and fruits, as reported previously in the general population in Japan [16]. Age, fat and protein intakes and leisure time physical activity were positively associated with dietary fiber intake. The proportions of males, current smokers, current drinkers, saturated fatty acid intake and the proportion of participants with depressive symptoms were negatively associated with dietary fiber intake. However, the duration of diabetes and treatment for diabetes were not associated with dietary fiber intake.

As shown in Table 2, BMI, waist circumference, fasting plasma glucose (FPG), HbA1c, fasting serum C-peptide, HS-CRP, triglyceride, systolic blood pressure and urinary albumin excretion were significantly and negatively associated with dietary fiber intake after adjusting for age, sex, duration of diabetes, current smoking habits, current drinking habits, total energy intake, fat intake, saturated fatty acid intake, protein intake (only for urinary albumin excretion), leisure time physical activity and use of oral hypoglycemic agents or insulin. The insulin sensitivity index HOMA2%-S, HDL cholesterol and eGFR were significantly and positively associated with dietary fiber intake after multivariate adjustments including protein intake (only for eGFR). The insulin secretion index HOMA2%-B, adiponectin, total cholesterol, LDL cholesterol and diastolic blood

Table 1 Characteristics of the studied participants and correlations with dietary fiber intake

	Mean or percentage	Correlation coefficient or odds ratio	p
Number	4,399		
Dietary fiber intake (g/1,000 kcal)	7.60 ± 0.03	-	
Fiber from vegetables (%)	47.1 ± 0.2	0.42*	<0.0001
Fiber from cereals (%)	22.5 ± 0.2	−0.60*	<0.0001
Fiber from legumes and beans (%)	11.8 ± 0.1	0.11*	<0.0001
Fiber from fruits (%)	9.5 ± 0.1	0.15*	<0.0001
Age (years)	65.4 ± 0.2	0.18*	<0.0001
Sex (male, %)	56.7	0.76 [0.74-0.78]#	<0.0001
Duration of diabetes (years)	15.5 ± 0.2	0.00*	ns
Current smoker (%)	18.3	0.79 [0.76-0.82]#	<0.0001
Current drinker (%)	38.8	0.77 [0.74-0.79]#	<0.0001
Total energy intake (kcal)	1689 ± 7	−0.12*	<0.0001
Fat intake (g/day)	52.4 ± 0.3	0.09*	<0.0001
Saturated fatty acid intake (g/day)	12.3 ± 0.1	−0.08*	<0.0001
Protein intake (g/day)	67.3 ± 0.4	0.04*	0.006
Leisure-time physical activity (met • hr/week)	11.8 ± 0.2	0.12*	<0.0001
Depressive symptoms (%)	8.9	0.95 [0.90-0.99]#	0.035
Oral hypoglycemic agents (%)	64.1	0.99 [0.96-1.01]#	ns
Insulin therapy (%)	27.1	0.98 [0.95-1.01]#	ns

Mean ± SE. *correlation coefficient, #odds ratio with 95% CI.

Table 2 Multiple regression analysis of dietary fiber intake with clinical and laboratory variables

Variables	Mean	Regression coefficient	p for trend
Body mass index (kg/m^2)	23.8 ± 0.06	−0.18 [−0.24,-0.11]	<0.0001
Waist circumference (cm)	85.9 ± 0.2	−0.56 [−0.73,-0.39]	<0.0001
Fasting plasma glucose (mmol/l)	7.73 ± 0.03	−0.049 [−0.084,-0.014]	0.007
HbA1c (%)	7.42 ± 0.02	−0.022 [−0.038,-0.005]	0.009
HbA1c (mmol/mol)	57.6 ± 0.2	−0.24 [−0.42,-0.06]	0.009
Fasting serum C-peptide (nmol/l)	0.402 ± 0.003	−0.009 [−0.013,-0.006]	<0.0001
HOMA2%-B	45.7 ± 0.4	−0.26 [−0.68, 0.17]	ns
HOMA2%-S	106.0 ± 0.6	1.95 [1.27, 2.62]	<0.0001
Adiponectin (μg/ml)*	9.1 [8.9-9.2]	0.006 [−0.003, 0.016]	ns
HS-CRP (mg/l)*	0.50 [0.48-0.52]	−0.067 [−0.090,-0.043]	<0.0001
Total cholesterol (mmol/l)	4.99 ± 0.01	0.009 [−0.005, 0.023]	ns
LDL cholesterol (mmol/l)	2.87 ± 0.01	0.010 [−0.002, 0.022]	ns
HDL cholesterol (mmol/l)	1.47 ± 0.01	0.008 [0.001, 0.014]	0.017
Triglyceride (mmol/l)*	1.22 [1.20-1.24]	−0.013 [−0.022,-0.005]	0.003
Systolic blood pressure (mmHg)	130.7 ± 0.3	−0.35 [−0.64,-0.06]	0.017
Diastolic blood pressure (mmHg)	74.7 ± 0.2	−0.05 [−0.22, 0.13]	ns
Urinary albumin excretion (mg/g)	28.2 [26.8-29.7]	−0.092 [−0.121,-0.063]	<0.0001
eGFR (ml/min/1.73 m^2)	75.0 ± 0.3	0.34 [0.01, 0.67]	0.042

Mean ± SE. *Geometric means with 95% CI in brackets. HOMA2-%B, homeostasis model assessment β-cell function; HOMA2-%S, homeostasis model assessment insulin sensitivity; HS-CRP, high sensitivity-C reactive protein; eGFR, estimated glomerular filtration rate. The multivariate adjustment included age, sex, duration of diabetes, current smoking habits, current drinking habits, total energy intake, fat intake, saturated fatty acid intake, protein intake (only for urinary albumin excretion and eGFR), leisure time physical activity and use of oral hypoglycemic agents or insulin.

pressure were not significantly associated with dietary fiber intake.

The results of multiple logistic analysis between metabolic syndrome and dietary fiber intake are shown in Table 3. The prevalence of obesity, abdominal obesity, hypertension, hypertriglyceridemia, low HDL cholesterol and metabolic syndrome in the study participants was 31.2%, 47.0%, 73.9%, 29.2%, 18.2% and 54.5%, respectively. Abdominal obesity and hypertension were negatively associated with dietary fiber intake after multivariate adjustments, and further adjustment with obesity did not change the trends. Hypertriglyceridemia and low HDL cholesterol were not associated with dietary fiber intake. Consequently, metabolic syndrome was negatively associated with dietary fiber intake after multivariate adjustment with additional adjustment for obesity.

The results of multiple logistic analysis between chronic kidney disease and dietary fiber intake are shown in Table 4. The prevalence of albuminuria, low eGFR and chronic kidney disease in the study participants was 38.4%, 21.5% and 46.9%, respectively. Albuminuria, low eGFR and CKD were negatively associated with dietary fiber intake after multivariate adjustments. These trends were not significantly affected by additional adjustment for obesity, hypertension or metabolic syndrome.

Discussion

The present study demonstrated that dietary fiber intake was associated with better glycemic control and more favorable CVD risk factors including abdominal obesity, hypertension and metabolic syndrome, along with enhanced insulin sensitivity and reduced HS-CRP after adjusting for confounding factors. Furthermore, the proportion of participants with CKD negatively associated with dietary fiber intake, even after adjusting for obesity, hypertension or metabolic syndrome. To the best of our knowledge, there are few epidemiological studies showing associations of dietary fiber intake with glycemia and CVD risk factors in Asia, where the epidemic of type 2 diabetes is rapidly becoming a serious medical and socioeconomic issue.

A recent systematic review of the literature reported that adding fiber supplements in moderate amounts (4–19 g) to daily diet achieved little improvement in glycemic control or CVD risk factors [9]. On the other hand, another meta-analysis [2] of intervention trials using high fiber diet (mean increase in fiber 18.3 g/d) in type 2 diabetic patients revealed that FPG and HbA1c were modestly lowered by 0.83 mmol/l and 0.26%, respectively, compared with a placebo. In the present study, both FPG and HbA1c negatively associated with dietary fiber intake (Table 2). In addition, the insulin sensitivity index HOMA2%-S and HS-CRP were associated with dietary fiber intake and the association remained statistically significant after the additional adjustment for BMI (regression coefficient 1.34 [0.71, 1.97], -0.048 [−0.070,-0.025], respectively). Although the effects of dietary fiber on insulin sensitivity have not been studied in type 2 diabetic patients, dietary fiber enhances insulin sensitivity in hepatic and peripheral tissues in insulin-resistant obese subjects [3-5].

It was recently reported that the consumption of high fiber diet for four weeks enhanced insulin secretion in nondiabetic overweight subjects [30]. Dietary fiber may activate incretin secretion due to short-chain fatty acid production induced by the fermentation of dietary fiber [31], although, in one study, it took one year for high fiber diet to enhance glucagon-like peptide-1 secretion in healthy subjects [32]. In the present study, the insulin secretion index HOMA2%-B was not associated with dietary fiber intake, suggesting that it is unlikely that insulin

Table 3 Multiple logistic analysis between metabolic syndrome and dietary fiber intake

		Odds ratio	p for trend
Elevated waist circumference	Model	0.90 [0.87-0.94]	<0.0001
	Model + obesity	0.93 [0.89-0.97]	0.002
Elevated blood pressure	Model	0.93 [0.89-0.97]	0.0002
	Model + obesity	0.94 [0.91-0.98]	0.006
Elevated triglyceride	Model	0.97 [0.93-1.00]	ns
	Model + obesity	0.98 [0.95-1.02]	ns
Low HDL cholesterol	Model	0.97 [0.93-1.01]	ns
	Model + obesity	0.98 [0.93-1.02]	ns
Metabolic syndrome	Model	0.92 [0.89-0.96]	<0.0001
	Model + obesity	0.95 [0.91-0.99]	0.009

Obesity: BMI ≥25.0 kg/m2; Elevated waist circumference, waist circumference ≥90 cm in males and ≥80 cm in females; Elevated blood pressure, systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥85 mmHg and/or the use of antihypertensive drugs; Elevated triglyceride, fasting serum triglyceride ≥1.69 mmol/l and/or the use of triglyceride-lowering drugs; Low HDL cholesterol, fasting serum HDL cholesterol <1.03 mmol/l in males and <1.29 mmol/l in females. Metabolic syndrome was defined according to the definition of "Harmonizing the Metabolic Syndrome." Model, multivariate adjustments with age, sex, duration of diabetes, current smoking habits, current drinking habits, total energy intake, fat intake, saturated fatty acid intake, leisure time physical activity and use of oral hypoglycemic agents or insulin.

Table 4 Multiple logistic analysis between chronic kidney disease and dietary fiber intake

		Odds ratio	p for trend
Albuminuria ≥30 mg/g	Model	0.92 [0.88-0.95]	<0.0001
	Model + obesity	0.93 [0.89-0.96]	<0.0001
	Model + elevated blood pressure	0.93 [0.89-0.96]	<0.0001
	Model + metabolic syndrome	0.93 [0.89-0.96]	<0.0001
eGFR < 60 ml/min/1.73 m^2	Model	0.94 [0.90-0.98]	0.006
	Model + obesity	0.95 [0.90-0.99]	0.015
	Model + elevated blood pressure	0.95 [0.91-0.99]	0.019
	Model + metabolic syndrome	0.95 [0.91-0.99]	0.027
Chronic kidney disease	Model	0.93 [0.90-0.96]	<0.0001
	Model + obesity	0.94 [0.90-0.97]	0.0005
	Model + elevated blood pressure	0.94 [0.91-0.97]	0.0009
	Model + metabolic syndrome	0.94 [0.91-0.98]	0.0011

Obesity: BMI ≥25.0 kg/m2; Elevated waist circumference, waist circumference ≥90 cm in males and ≥80 cm in females; Elevated blood pressure, systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥85 mmHg and/or the use of antihypertensive drugs; Elevated triglyceride, fasting serum triglyceride ≥1.69 mmol/l and/or the use of triglyceride-lowering drugs; Low HDL cholesterol, fasting serum HDL cholesterol <1.03 mmol/l in males and <1.29 mmol/l in females. Metabolic syndrome was defined according to the definition of "Harmonizing the Metabolic Syndrome." Model, multivariate adjustments with age, sex, duration of diabetes, current smoking habits, current drinking habits, total energy intake, fat intake, saturated fatty acid intake, protein intake, leisure time physical activity and use of oral hypoglycemic agents or insulin.

secretion induced by increased dietary fiber intake contributes to improving hyperglycemia.

In general, dietary fiber favorably affects CVD risk factors, including LDL cholesterol [33] and components of metabolic syndrome [34,35]. In type 2 diabetic patients, a recent review reported that high fiber diet failed to affect the lipid levels in four out of eight randomized controlled studies [9]. In the present study, total cholesterol and LDL cholesterol were not associated with dietary fiber intake. However, HDL cholesterol and triglyceride were significantly associated with dietary fiber intake. Dietary fiber exerts blood pressure-lowering effects [36,37], and recently, Jenkins et al. [38] reported that high fiber and low glycemic index diet with legumes reduced blood pressure compared with wheat fiber diet in type 2 diabetic patients. In the present study, systolic blood pressure and hypertension were negatively associated with dietary fiber intake. Enhanced insulin sensitivity may contribute to the blood pressure-lowering effects of dietary fiber. As a result, the prevalence of metabolic syndrome was significantly associated with dietary fiber intake. Reduced fiber intake, particularly at breakfast, was found to be associated with metabolic syndrome in Brazilian type 2 diabetic patients [10,39], although the authors did not report which component of metabolic syndrome was associated with low fiber intake. The present study demonstrated that dietary fiber intake was associated with reduced prevalence of abdominal obesity and hypertension of metabolic syndrome phenotypes independent of obesity. A reduction in abdominal obesity induced by increased dietary fiber intake has been reported in both intervention [40,41] and epidemiological studies [42]. However, the direct effects of dietary fiber on visceral adipose tissue remain to be elucidated.

CKD is an established CVD risk factor. The present study demonstrated the association between dietary fiber intake and lower prevalence of CKD (Table 4). Due to the cross-sectional nature of the study, preventing hyperkalemia in the advanced stage of CKD may limit the consumption of fresh fruits and green vegetables. Indeed, in this study, the proportion of participants with eGFR < 30 ml/min/1.73 m^2 was negatively associated with dietary fiber intake (odds ratio 0.83 [0.76-0.91]). However, excluding participants with eGFR < 30 ml/min/1.73 m^2 (n = 115) did not change the results (odds ratio 0.94 [0.91-0.97]). CVD risk factors, such as obesity, hypertension and metabolic syndrome, may contribute to the development and progression of CKD. However, adjusting for each CVD risk factor did not change the significant association between dietary fiber intake and CKD (Table 4). Although the mechanisms of action of dietary fiber in the kidneys are unknown, high dietary fiber intake is associated with a lower level of systemic micro-inflammation in both nondiabetic and diabetic patients [8,12], as shown in the present study (Table 2). The anti-inflammatory actions of dietary fiber may be related to reduced prevalence of CKD. Recently, a large follow-up study showed that increased dietary fiber intake was associated with reduced mortality in CKD patients [43]. In this context, dietary fiber appears to be promising non-pharmacological treatment for CKD.

The strength of the present study includes a relatively large sample size of type 2 diabetic patients consuming

foods different from Western diet [7]. A staple food in the Japanese diet is white rice, which has lower dietary fiber than whole grains. The amount of daily fiber intake in Japan declined from 20.5 g/d to 15 g/d after World War II [44] to a level that is lower than that observed in the US and UK [7]. The main source of dietary fiber of Japanese people is vegetables including seaweed, a typical Japanese food, followed by cereals, legumes and fruits [16]. The present study showed that the dietary fiber present in Japanese foods exerts beneficial effects on glycemia and CVD risk factors, thus suggesting that the usefulness of increased dietary fiber intake may extend beyond certain ethnic foods. Another strength of the study is that confounding factors included fat and saturated fatty acid intakes and physical activity, since high dietary fiber intake is often associated with healthy lifestyle, making it difficult to isolate fiber effects from general healthy lifestyle [14]. However, some limitations should be discussed. First, the use of a self-administered food frequency dietary assessment questionnaire BDHQ is subject to measurement error in dietary intake, and actual dietary habits may not be obtained. However, the ability to rank dietary fiber using the BDHQ has been reasonably verified [22]. Second, study participants who visit diabetologists regularly may be better educated about self-management of diabetes with respect to diet than the general population. However, the daily fiber intake of the study participants was similar to that of the general population in Japan (15 g/d). Third, since multiple outcomes were involved in the present study, multiple testing may induce false results. Finally, we cannot prove cause-and-effect relationships due to the cross-sectional design of our study, and there may be other confounding factors in addition to those evaluated in the present study.

Conclusion

We demonstrated that increased dietary fiber intake was associated with better glycemic control and more favorable CVD risk factors including hypertension, metabolic syndrome and CKD, along with improvements in insulin sensitivity and micro-inflammation, in Japanese type 2 diabetic patients after adjusting for confounding factors. Although the recommended amount of dietary fiber in the general population is >19 g/d for males and >17 g/d for females in Japan [45] and >38 g/d for males and >25 g/d for females in the US [46], diabetic patients should be encouraged to consume more dietary fiber in daily life according to the ethnic foods.

Abbreviations

BDHQ: Brief-type self-administered diet history questionnaire; BMI: Body mass index; CKD: Chronic kidney disease; CVD: Cardiovascular disease; eGFR: Estimated glomerular filtration rate; FPG: Fasting plasma glucose; HS-CRP: High sensitivity C-reactive protein; HOMA2-%B: Homeostasis model assessment β cell function; HOMA2-%S: Chomeostasis model assessment insulin sensitivity.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

HF and MI were responsible for the study concept and design. HF and MI conducted the analyses, and TO, SO, HI, YK, YI, TJ, YH, KU, SS, UN and TK helped with interpreting the data and contributed to the discussion. HF and MI drafted the manuscript. All authors participated in revising the manuscript critically and approved the final version.

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Author details

[1]Department of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu University, Maidashi 3-1-1, Higashi-ku, Fukuoka 812-8582, Japan. [2]Diabetes Centre, Hakujyuji Hospital, Fukuoka, Japan. [3]Department of Environmental Medicine, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan. [4]Department of Health Promotion, School of Health and Nutrition Science, Nakamura, Gakuen University, Fukuoka, Japan. [5]Department of Social and Preventive Epidemiology, School of Public Health, The University of Tokyo, Tokyo, Japan.

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Normative Data for the Montreal Cognitive Assessment in a Japanese Community-Dwelling Older Population

Kenji Narazaki[a] Yu Nofuji[b] Takanori Honda[a] Eri Matsuo[b] Koji Yonemoto[c] Shuzo Kumagai[b]

[a]Graduate School of Human-Environment Studies and [b]Institute of Health Science, Kyushu University, and [c]Biostatistics Center, Kurume University, Fukuoka, Japan

Key Words
Cognitive decline · Cognitive screening · Dementia · Cross-sectional study · Community-based study · Elderly · Mild cognitive impairment

Abstract
Background: Although the Montreal Cognitive Assessment (MoCA) is acknowledged as a promising neuropsychological tool, its normative data for older populations have not been established yet. The purpose of this study was to provide normative data for the MoCA in Japanese community-dwelling older people. ***Methods:*** In a Japanese town, 1,977 participants aged 65 years or older (mean age 73.6 years; male 41.3%) completed MoCA tests. After descriptive and regression analyses, normative data were developed for MoCA scores in the population. ***Results:*** The mean MoCA score observed (21.8 points) was lower than that for normal controls (27.4 points) in the original validation study of the MoCA. Additionally, 82.6% of MoCA scores fell below the standard cutoff of 26 points for detecting mild cognitive impairment (MCI). The regression analysis showed that higher age and fewer years of formal education were associated with lower MoCA scores ($p < 0.001$). Normative data for MoCA scores were presented with respect to age and education. ***Conclusion:*** This study provided normative data for the MoCA in a Japanese community-dwelling older population. This research also suggests that conventional use of the MoCA as a screening tool for MCI might be problematic in cultures different from that in which the cutoff was developed.

Introduction

Mild cognitive impairment (MCI) represents an intermediate clinical state between normal cognitive aging and Alzheimer's disease or other types of dementia [1]. Although it is not always the case, MCI has been reported to often develop into either Alzheimer's disease or other forms of dementia and, therefore, recognized as a high-risk state for dementia development [2]. In recent discussions, community-based screening of MCI is considered one of the crucial steps to enable wide-reaching interventions for preventing or slowing the onset of dementia [3].

Montreal Cognitive Assessment (MoCA) is a brief neuropsychological tool designed for screening MCI in community health care [4] and is acknowledged as a promising instrument worldwide [5–7]. Given the need for ethnic-specific versions of neuropsychological tests [8, 9], 38 versions of the MoCA are currently developed in 31 languages (www.mocatest.org). MoCA has also

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E-Mail karger@karger.ch
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Dr. Shuzo Kumagai
Institute of Health Science, Kyushu University
6-1 Kasugakoen, Kasuga
Fukuoka 816-8580 (Japan)
Tel. +81 92 583 7853, E-Mail shuzo@ihs.kyushu-u.ac.jp

been reported to have higher sensitivity to a subtle cognitive decline than conventional tools such as the Mini-Mental State Examination [4, 10, 11]. To date, two cohort studies reported normative MoCA data in population-based samples including a multiethnic US population [12] and a Portuguese population [13]. Both studies, however, were conducted with subjects of a wide age range, and thus, the sample sizes were scarce for the older age groups.

Because older people are the primary subjects of MCI screening and subsequent interventions, their scoring characteristics on the MoCA should be examined and demonstrated with a larger sample size. This is an urgent matter, especially for a Japanese society undergoing the world's fastest aging with the highest life expectancy. Therefore, the aim of the present study was to provide normative MoCA data specific to community-dwelling older people in a Japanese town.

Materials and Methods

Participants

The present study involved analysis of data from the baseline phase of the Sasaguri Genkimon Study (SGS) conducted from May to August 2011. The SGS is an ongoing community-based prospective cohort study in a Japanese local town, Sasaguri, aiming to explore modifiable lifestyle factors causing older people to require nursing care. Subjects of the baseline study (SGS-1) were all residents of the town who were aged 65 years or older and not certified as individuals requiring nursing care by the town in January 2011 (n = 4,979). Sixty-six subjects were excluded due to being dead or moving out by the onset of the study. A set of study information sheets and a questionnaire were mailed to all remaining subjects (n = 4,913), and 2,629 individuals, hereafter referred to as the participants of the SGS-1, responded to the mail by (1) visiting a community center to submit the questionnaire and undergo multiple physical and cognitive tests in one of 31 group-testing sessions of the SGS-1, (2) contacting study coordinators to set up an appointment for an individual home-testing session or (3) visiting the city office to submit the questionnaire (recruitment rate: 53.5%). Of these, 2,129 individuals took part in the MoCA tests. After the testing, we excluded 32 individuals who were unable to complete the MoCA properly, 12 individuals with missing information about their years of formal education, and 108 individuals with self-reported medical histories of stroke, depression, Parkinson's disease and dementia. Accordingly, data from 1,977 participants (75.2% of the total participants of the SGS-1) were involved in the present study.

Standard Protocol Approvals, Registrations and Patient Consents

All the participants provided written informed consent to participate in the present study. The study protocol and the informed consent form were approved by the Institutional Review Board of the Institute of Health Science, Kyushu University.

Measurements

We used the Japanese version of the MoCA for all measurements. The details of the Japanese version are described elsewhere [5]. Briefly, it was developed and validated by investigators, including the inventor of the original MoCA (Dr. Nasreddine). As in the original one [4], the Japanese version of the MoCA was designed as a 30-point screening instrument administered in about 10 min and consists of the following 12 cognitive tasks: a five-item delayed recall task (5 points), a clock-drawing task (3 points), a cube-copying task (1 point), a trail-making task (1 point), a phonemic fluency task (1 point), a two-item verbal abstraction task (2 points), a target-tapping task (1 point), a serial subtraction task (3 points), a two-item digits-reading task (2 points), a three-item naming task (3 points), a two-item sentence-repeating task (2 points) and a six-item temporal and locational orientation task (6 points). In the standard procedure of the original as well as the Japanese versions, 1 point is added to the total score of the cognitive tasks if an individual has 12 years or fewer of formal education, and a final total score falling below 26 points is judged to have probable MCI.

Procedures

All MoCA tests were administered to the participants by trained personnel as part of the group-testing and home-testing sessions of the SGS-1. After the testing, MoCA scores were independently evaluated by two authors (K.N. and T.H.) and double-checked between the two before being finally determined. The interevaluator reliability, shown as a percentage of agreement in the MoCA scores, was 93.3% in the initial evaluation. To demonstrate normative data in participants with a wide range of years of formal education, the preferred 1-point correction for education was not adopted.

Statistical Analyses

All statistical analyses were conducted using SAS version 9.2 (SAS Institute Inc., Cary, N.C., USA). The Wilcoxon rank-sum test and the χ^2 test were conducted to compare age and sex, respectively, between the participants of the present study and the rest of the subjects (n = 2,936). The Wilcoxon rank-sum test was also performed to assess the difference in years of formal education between the participants of the present study and the rest of the participants of the SGS-1 answering educational history in the questionnaire (n = 608). Descriptive statistics were calculated for MoCA scores and for scores of respective cognitive tasks. A multiple regression analysis was performed with the MoCA score as a dependent variable and age, sex and years of formal education as independent variables. Additionally, to visualize changes in MoCA scores, simple regression analyses were conducted between the MoCA score and age in three education levels ($\leq$9, 10–12, and $\geq$13 years of formal education). Subsequently, normative data for MoCA scores in the community-dwelling older population were developed with respect to age and education. Overlapping age categories of 65–75, 70–80, 75–85, and $\geq$80 years, accompanied by the aforementioned three education levels, were adopted in the normative data based on the rationale previously described for practical use of the normative data in community health care [12, 14]. A significance level was set at two-sided $\alpha = 0.05$.

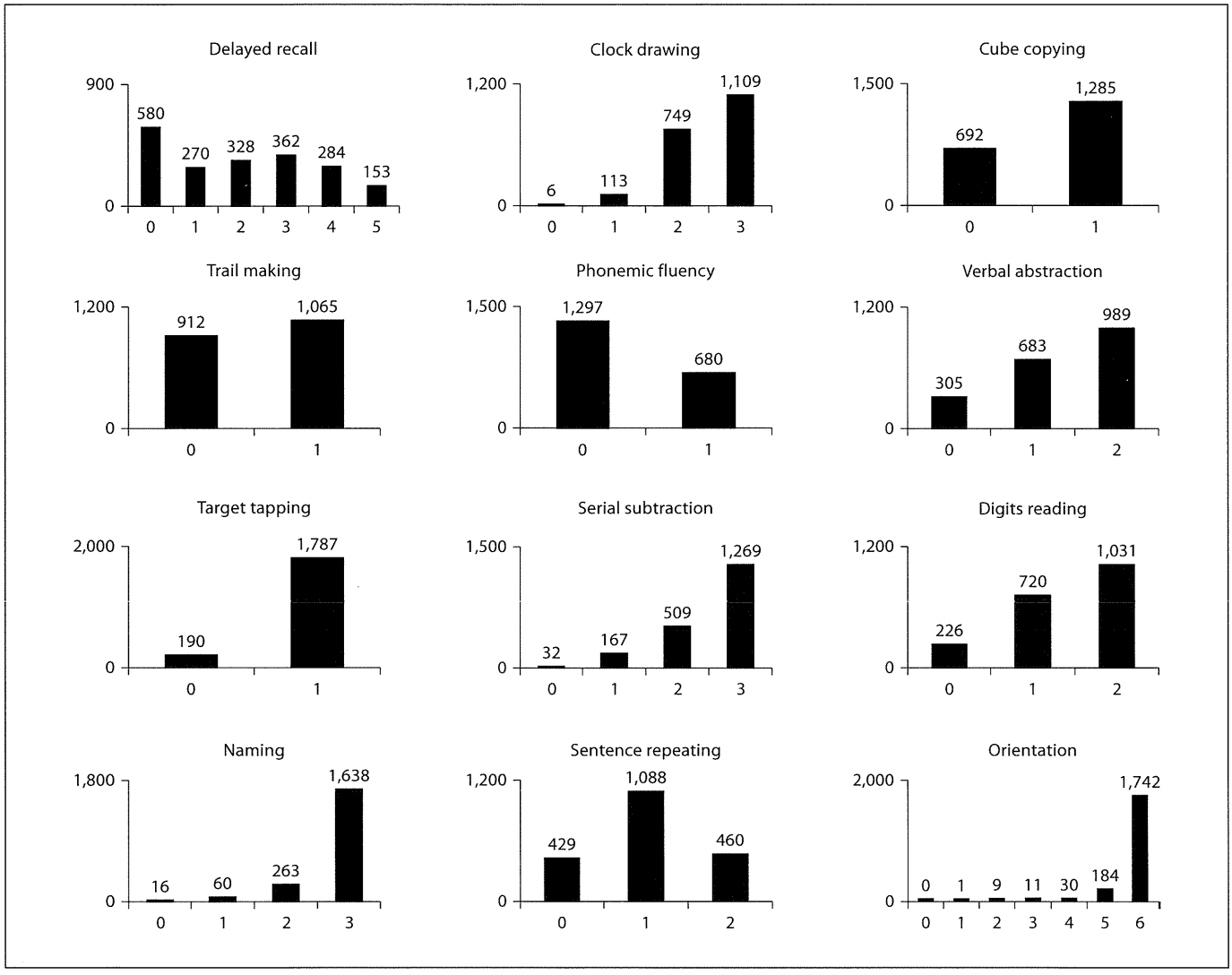

Fig. 1. Histograms of scores for respective cognitive tasks in MoCA. Each panel shows a histogram for one of the 16 cognitive tasks in the MoCA. Horizontal and longitudinal axes of each panel indicate points scored and frequency count for each point, respectively.

Results

The participants of the present study differed from the rest of the subjects in terms of sex (percentage of males, 41.3 vs. 45.3%; p = 0.008), but not in terms of age (median, 72 years for both groups; interquartile range, 68–78 years for both groups; p = 0.860). Also, the number of years of formal education was not different between the participants of the present study and the rest of the participants of the SGS-1 answering educational history in the questionnaire (median, 12 years for both groups; interquartile range, 9–12 years for both groups; p = 0.216). The mean age of the participants was 73.6 years (standard deviation, SD, 6.2; median, 72; range, 65–96) and the number of years of formal education was 11.0 years (SD, 2.5; median, 12; range, 2–23); 41.3% of the participants were male (n = 817). The mean MoCA score was 21.8 points (SD, 3.9; median, 22; range, 5–30), with 82.6% of scores falling below the preferred cutoff of 26 points for probable MCI. Histograms with scores of the respective cognitive tasks are summarized in figure 1.

In the multiple regression analysis, significant associations with the MoCA score were found for age (regression coefficient, –0.21; 95% confidence interval, CI, –0.23

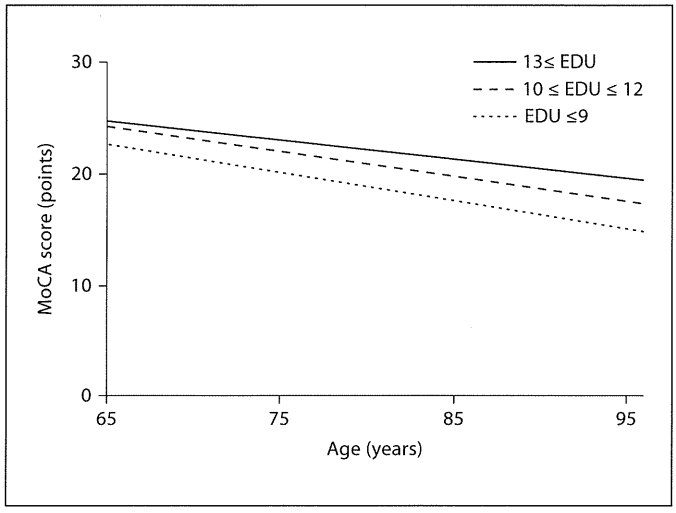

Fig. 2. Regression lines between age and MoCA scores in three education levels. EDU denotes years of formal education. Intercepts (at 65 years) and slopes for respective regression lines are as follows: 24.73 and −0.17 in 13 ≤ EDU; 24.30 and −0.22 in 10 ≤ EDU ≤ 12; 22.66 and −0.25 in EDU ≤9.

Table 1. Normative data for MoCA scores

	Education level			Total by age
	≤9 years	10–12 years	≥13 years	
Age category				
65–75 years	371	659	248	1,278
	21.4 ± 3.7	23.3 ± 3.1	24.0 ± 3.0	22.9 ± 3.4
	22 (9–29)	23 (14–30)	24 (13–30)	23 (9–30)
70–80 years	406	471	157	1,034
	20.2 ± 3.8	22.1 ± 3.4	23.2 ± 3.0	21.6 ± 3.7
	20 (6–29)	22 (12–30)	23 (13–29)	22 (6–30)
75–85 years	327	320	83	730
	19.2 ± 4.0	21.3 ± 3.4	22.6 ± 3.1	20.5 ± 3.9
	19 (5–28)	21 (12–29)	23 (16–29)	21 (5–29)
≥80 years	161	170	35	366
	18.0 ± 4.4	20.5 ± 3.5	22.1 ± 4.0	19.6 ± 4.2
	19 (5–28)	21 (8–29)	23 (12–29)	20 (5–29)
Total by education	692	964	321	1,977
	20.1 ± 4.1	22.5 ± 3.4	23.6 ± 3.2	21.8 ± 3.9
	20 (5–29)	23 (8–30)	24 (12–30)	22 (5–30)

Data are expressed as number, mean ± SD and median (with range in parentheses).

to −0.18; $p < 0.001$) and education (regression coefficient, 0.42; 95% CI, 0.36–0.49; $p < 0.001$) but not for sex (regression coefficient, 0.21; 95% CI, −0.10 to 0.52; $p = 0.186$). Figure 2 demonstrates the results of the simple regression analyses showing significant associations between the MoCA score and age in all three education levels ($p < 0.001$). Specifically, higher age was associated with lower MoCA scores in all the education levels. Finally, normative data for MoCA, specific to the community-dwelling older people, were determined with respect to the four age categories and three education levels (table 1).

Discussion

Population-based screening for MCI is recognized as a key step in establishing sound wide-reaching intervention programs for preventing or delaying older people from developing dementia [3]. Although the MoCA has great promise as a screening tool for MCI, knowledge regarding its scoring characteristics in population-based older samples has still been limited. To our knowledge, the present study was the first to demonstrate normative MoCA data specific to community-dwelling older people not only in Japanese society but worldwide. Reflecting the world's highest population aging rate in Japan, the normative data were formed with a relatively high proportion of old-old and oldest-old samples (table 1), which should be informative for other societies besides Japan. The present study also examined the associations of socio-demographic factors, including age, sex and years of formal education with MoCA scores in the older population.

In an attempt to develop normative data reflecting cognitively normal samples, we excluded individuals from the present analyses if they self-reported medical history of diseases contributing to or reflecting the development of clinical cognitive decline [2, 10, 15, 16]. There exists an argument that normative values should be representative and, therefore, should be developed from samples including both cognitively normal and abnormal individuals [17]. However, we made the exclusion based on the promise that the sensitivity of screening or detecting cognitively impaired individuals can be enhanced by comparing a patient's score to that of a reference group free of any clinical cognitive decline [18]. The exclusion of individuals requiring nursing care in the subject selection process may also be conducive to enhancing the sensitivity.

The mean MoCA score of 21.8 points observed in the present study was lower than that for the normal controls

(n = 90; mean, 27.4 points; SD, 2.2) and was indeed close to that for the patients with MCI (n = 94; mean, 22.1 points; SD, 3.1) in the original normative study performed by the development group of the MoCA [4]. These trends were unchanged even after the preferred 1-point correction of MoCA scores for formal education (mean, 22.7 points; SD, 3.8). Furthermore, more than three quarters of the scores (82.6% without the correction or 75.1% with the correction) fell below the preferred cutoff of 26 points for detecting MCI while the reported prevalence of MCI in older populations ranges from 15 to below 30% [19–23]. This percentage is still high even considering the potential inclusion of patients with undiagnosed dementia. Because multiple population-based studies have also observed MoCA scores comparable to the present one [12, 13, 24], this discrepancy may not be attributed to some administrative issues in the present study but to a low external validity of the cutoff score due to the limited number of samples and/or possible selection bias for the non-population-based samples in the original study [4]. Other possible causes of the discrepancy are some cultural and linguistic artifacts occurring in the translation process of the original MoCA into the Japanese version [8, 18]. Although the cross-cultural and cross-linguistic adaptations appear to be taken into account during the development process of the Japanese version [5], the validity of the adaptations was examined with a limited number of clinical-based subjects and, therefore, the possibility of cultural and linguistic artifacts in population-based use cannot be ruled out.

As observed in previous population-based studies with subjects in a wide age range [12, 13], the present results show significant associations of age and education with the MoCA scores in older samples. Specifically, MoCA scores were lower in participants with higher age and/or fewer years of formal education. In contrast, no association was found between sex and the MoCA score. The effects of age and education have been well documented for neuropsychological tests in population-based studies and have been taken into account with age- and education-specific norms when the obtained scores have been evaluated [17, 18]. Because both age and education are now recognized as risk factors of cognitive decline [25, 26] rather than just biasing factors of the tests, it can be misleading and problematic to count the effects by adjusting an obtained score for these variables and evaluate the adjusted score using a single cutoff [17, 27]. In the light of this discussion, the current MoCA procedure, comprising a 1-point adjustment for 12 or fewer years of formal education and a subsequent evaluation with a single cutoff of 25/26, may not be the best for screening MCI in population-based samples.

Taken together, it is considered reasonable to assume that the current MoCA procedure is somewhat premature for MCI screening in community-dwelling older people. However, because we didn't employ a clinical diagnosis of MCI in the research design, the present study is unable to further propose any alternative criteria for population-based MCI screening. Instead, at this stage, the normative data demonstrated in the present study can allow clinicians and researchers to detect individuals with abnormal cognitive decline from the community-dwelling older samples while taking into account the influence of age and education. For example, if a 75-year-old patient with 9 years of formal education scored 12 points on the MoCA test, his or her personal physician can appreciate that the score was lower than the mean minus 2 × SD [i.e. 20.2 – (2 × 3.8) = 12.6] for the age- and education-matched normal group and can suspect the patient's clinical cognitive decline. Similarly, the normative data may be useful for professionals when monitoring subtle cognitive change within a patient in longitudinal observations. It should be noted here that the definition of normal or abnormal needs to be carefully made in practical use, depending on the context and circumstances in which the MoCA test is administered.

Our report has some limitations which are worth noting here. First, the sample of the present study was affected to some extent by the nonresponse, withdrawal and exclusion of originally designated subjects. Specifically, the participants of the present study differed from the rest of the subjects in terms of sex distribution. However, we believe the influence of this discrepancy on the present results was not considerable because the regression analysis showed no association between sex and the MoCA score. Second, because the present study was performed in a single Japanese town, generalizability of the results is somewhat limited. Nevertheless, the present normative data can be considered applicable to other places in Japan because ethnicity and educational system are almost homogeneous across Japan. Finally, in the normative data, some strata were formed with relatively small numbers of samples and, thus, are probably less reliable in terms of age-education relationships.

Associations of MoCA scores with other socio-demographic factors, such as ethnicity, culture, language, financial security and family configuration, remain to be explored by future investigations in order to generalize the findings of this research. Obtaining these types of re-

search findings might be essential before establishing the cutoff for population-based MCI screening. In parallel with exploring the future use of the MoCA as a population-based MCI screening tool, we are going to follow the present participants in prospective observations of the SGS to determine the ability of the test to predict the future onset of dementia in the community-dwelling older population.

Conclusion

In summary, the present research reported normative data for MoCA scores derived from a relatively large-scale community-dwelling older population in Japan and proposed practical applications of the normative data in community health care. This research also suggests that conventional use of the MoCA as a screening tool for MCI might be problematic in cultures different from that in which the cutoff was developed.

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Disclosure Statement

The authors declare that there are no conflicts of interest.

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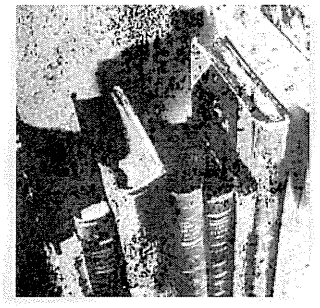
Brief report

Effect of plasma lipids and APOE genotype on cognitive decline

Fumihiko Yasuno, MD, PhD; Takashi Asada, MD, PhD



A central tenet of brain aging is that "what is good for the heart is good for the brain." We examined the combined effect of plasma lipids and APOE genotype on cognitive function in elderly individuals. Plasma concentrations of high-density lipoprotein (HDL), low-density lipoprotein, triglyceride, total cholesterol, and apolipoprotein E (apoE) were evaluated in 622 community-dwelling individuals aged 65 years and older. We investigated the associations between plasma lipids and cognitive function in APOE4 carrier (E4+) and APOE4 noncarrier (E4-) groups using 3-year longitudinal data. At baseline and 3 years later, cognitive scores were correlated with plasma apoE levels in both E4- and E4+, and HDL level in E4-. Our findings suggest that an interaction between apoE and HDL is facilitated by APOE4, and is possibly linked with an enhancement of neuroplasticity and with resultant protective effects on cognitive function in later life. Preservation of higher plasma apoE and HDL from early life is proposed as a possible strategy for maintaining cognitive function in later life, especially for APOE4-positive individuals.

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Keywords: *cognitive decline; APOE genotype; apolipoprotein E; high-density lipoprotein; low-density lipoprotein; triglyceride; total cholesterol*

Introduction

The presence of an apolipoprotein E4 allele (APOE4) increases the risk of, and reduces the age at onset of, Alzheimer's disease (AD) in a dose-dependent manner.[1-3] Additionally, APOE4 carriers have been reported to have higher rates of cognitive decline than noncarriers before the diagnosis of mild cognitive impairment.[4]

Apolipoprotein E (apoE) plays a significant role in cholesterol delivery to neurons and AD pathogenesis associated with amyloid beta (A β).[5-7] The plasma level of apoE has been shown to depend upon the APOE genotype.[8,9] In elderly individuals without dementia, the interactive effect of apoE and other plasma lipids on cognitive function has also been reported to vary, depending upon the APOE genotype.[8,9]

A complex synergism of APOE4 and cerebrovascular pathology in cognitive function of the elderly has been reported. The detrimental effect of APOE4 may be exacerbated by synergistic preventable risk factors such as plasma apoE/lipids. With stratification by APOE allele status, we examined the effect of plasma apoE/lipids on

Author affiliations: Department of Neuropsychiatry, Institute of Clinical Medicine, University of Tsukuba, Japan (Fumihiko Yasuno, Takashi Asada); Department of Neuropsychiatry, Nara Medical University, Nara, Japan (Fumihiko Yasuno)

Address for correspondence: Takashi Asada, MD, PhD, Department of Neuropsychiatry, University of Tsukuba, 1-1-1 Tennoudai, Tsukuba, Ibaraki 305-8575, Japan
(e-mail: tasada@md.tsukuba.ac.jp)

longitudinal change in the cognitive function of community-dwelling elderly using the data from a 3-year follow-up study.

Three-year follow-up examinations of the effect of plasma apoE/lipids on cognitive function in the elderly

Participants were recruited in the present study from the "Tone Project" in Tone town, Ibaraki, Japan.[10] A total of 1395 volunteers participated in the first baseline study between December 2001 and April 2002. Three years later, 622 of them who had no history of stroke during follow-up were able to be evaluated again between December 2004 and April 2005, and we used the results from those subjects tested twice. At the initial examination, all of the eligible subjects provided written informed consent for their participation in the study. This study was approved by the ethics committee of Tsukuba University.

All participants underwent the same cognitive assessment at the baseline and 3-year examinations using a set of four tests to measure the following cognitive domains: attention, memory, language, and reasoning. We evaluated attention by using the Japanese version of a Set-dependent activity,[11] memory ability using the Category Cued Recall test,[12] and language ability with a category fluency test.[13] Abstract reasoning ability was evaluated with the Similarities subtest of the Wechsler Adult Intelligence Scale-Revised (WAIS-R).[14] The assessment procedures have been described elsewhere.[8,9] A composite cognitive score was computed from the four scores using the first component of the scores of principal component analysis.

Blood samples were collected from the subjects at fasting visits at the initial examination. Plasma levels of low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides (TG), and total cholesterol (TC) were measured using standard enzymatic methods on routine automated chemistry systems. Plasma apoE levels were determined by turbidimetric immunoassay. Genomic DNA was used for APOE typing. Subjects were divided into two APOE groups by E4 status with E4-(n=509) (genotypes ε2/ε3 [n=52], ε3/ε3 [n=457]) and E4+ (n=113) (genotypes [ε2/ε4 n=6], ε3/ε4 [n=99] and ε4/ε4 [n=8]) to test for the influence of genotype on the association between lipids and cognitive function.

The subjects in each category were divided into three strata according to the plasma concentrations of lipids. To examine the influence of plasma lipids on cognitive function, composite cognitive scores of the three strata of plasma concentrations were compared in E4- and E4+ groups separately by ANCOVA, with age, sex, years of education, Geriatric Depression Scale score, cigarette smoking, and medical history of diseases as covariates.

Cognitive scores were associated with plasma apoE level in both E4- and E4+, and the HDL level in E4-

The demographic data for the E4- and E4+ groups in the analysis of the effect of lipids/apoE on cognitive function are shown in *Table I*. There were no group differences in demographic characteristics, except for the cognitive score. Our finding of a higher cognitive score at 2002 and 2005 in the E4- group is consistent with previous studies.[15]

Figures 1 and *2* show the median plasma concentrations of lipids for the three strata according to the tertiles of plasma levels of lipids/apoE, and the mean cognitive scores of the E4- and E4+ groups at 2002 and 2005 according to the three strata of plasma concentrations of lipids/apoE.

ANCOVA analysis evaluating the influence of lipids level on cognitive function showed a significant influence of the HDL level on composite cognitive scores at both 2002 and 2005 in the E4- group ($F_{2, 498}$=9.3, P<0.001 for 2002, $F_{2, 498}$=9.3, P<0.001 for 2005). Subjects with higher HDL concentrations had higher cognitive scores. The effect size of the influence of the plasma HDL level on cognitive score was more than 0.01(η^2=0.04 for 2002, η^2=0.04 for 2005). No such significant association was observed in the E4+ group *(Figure 2)*.

A significant main effect of the apoE level was found by ANCOVA on composite cognitive scores at 2002 and 2005 in both of the E4- and E4+ group ($F_{2, 498}$ =11.3, P<0.001 for 2002, $F_{2, 498}$=7.3, P=0.001 for 2005 in the E4-, and $F_{2, 102}$=7.0, P=0.001 for 2002, $F_{2, 102}$=4.0, P=0.02 for 2005 in the E4+). Subjects with higher plasma apoE concentration had higher cognitive scores in both groups. The effect size of the association of the plasma apoE level on these cognitive scores was more than 0.01(η^2=0.04 for 2002, η^2=0.03 for 2005 in the E4-,and η^2=0.12 for 2002, η^2=0.07 for 2005 in the E4+).

Brief report

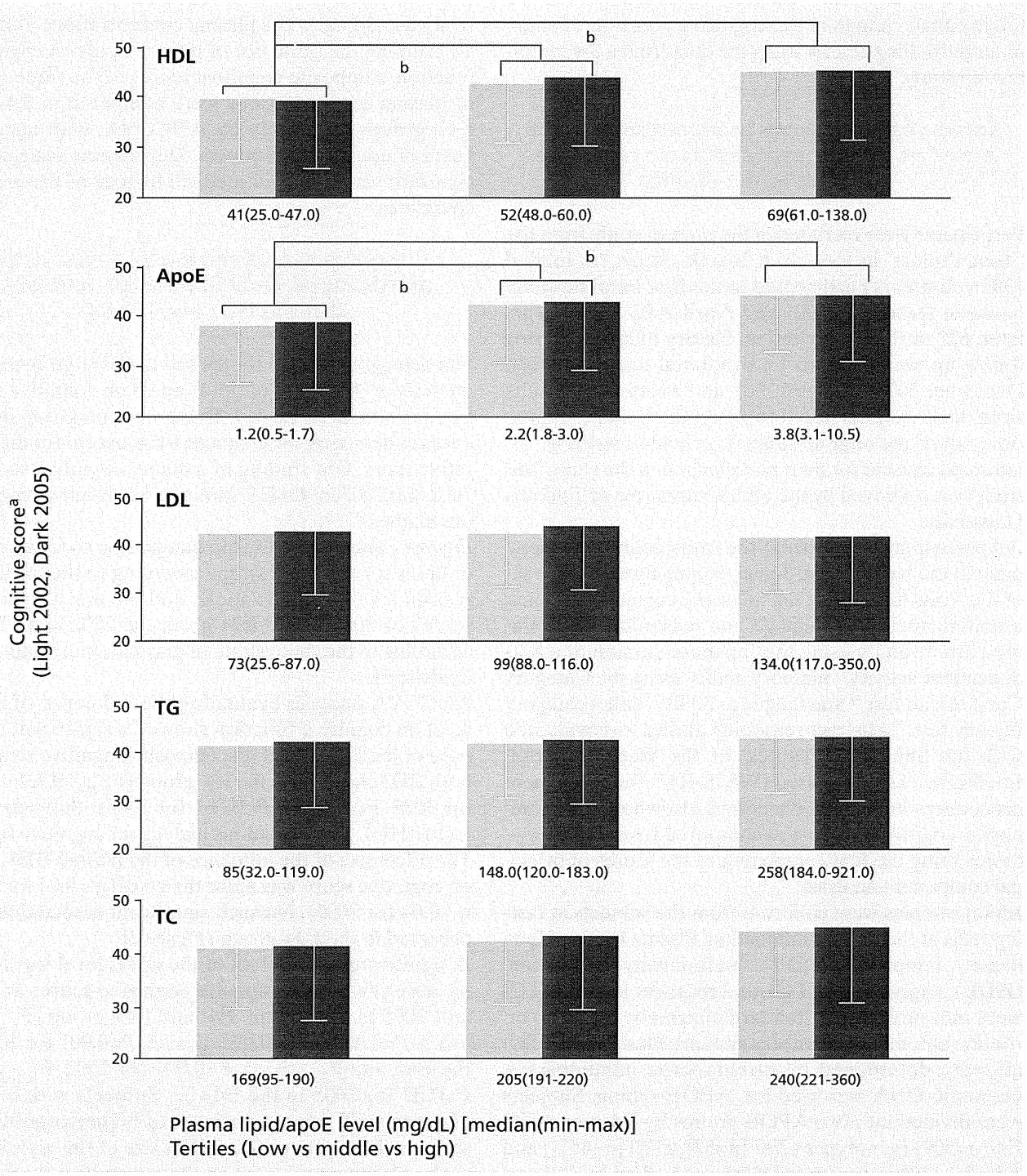

Figure 1. Mean cognitive test score of each tertile groups of lipid levels in the ApoE4- group. [a], data are mean after adjustment for age, sex, years of education, Geriatric Depression Scale score, cigarette smoking, and medical history of cardiovascular disease, diabetes mellitus, and hypertension; [b], indicates significance at $P<.05$ after Bonferroni adjustment for multiple comparisons. HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglycerides; TC, total cholesterol; apoE, apolipoprotein E

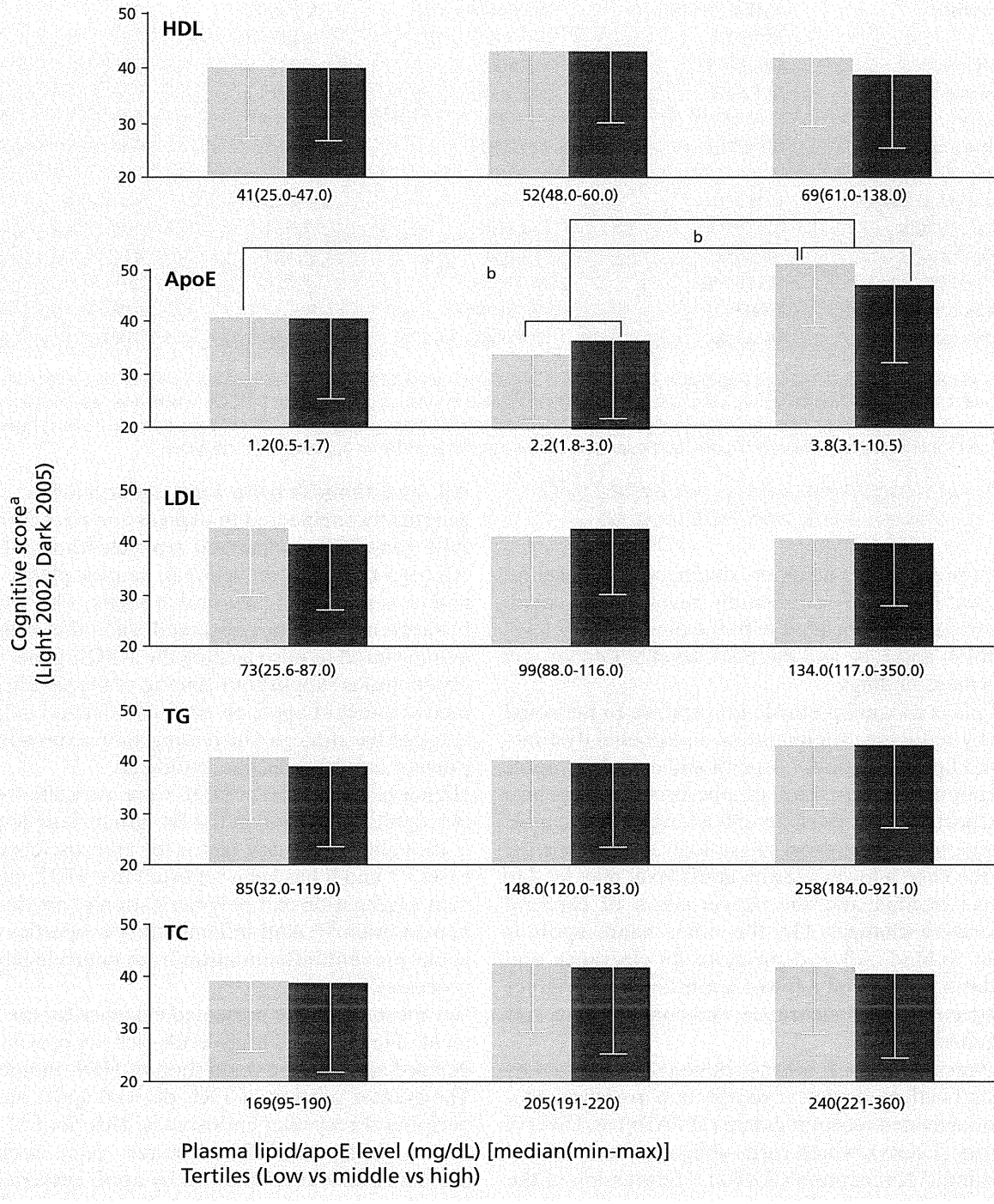

Figure 2. Mean cognitive test score of each tertile groups of lipid levels in ApoE4+ group. [a], data are mean after adjustment for age, sex, years of education; Geriatric Depression Scale score, cigarette smoking, and medical history of cardiovascular disease, diabetes mellitus, and hypertension; [b], indicates significance at $P<.05$ after Bonferroni adjustment for multiple comparisons.HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglycerides; TC, total cholesterol; apoE, apolipoprotein E

Characteristic	ApoE4- (n =509)	ApoE4+ (n = 113)	t, χ^2 or F [a-c]	P [a-c]
Age, y[a]	73.0 ± 5.4	72.7 ± 4.8	t_{620}=0.5	0.6
Male, No (%)[b]	226 (44%)	43 (38%)	χ^2_1=1.5	0.2
Years of education, y[a]	10.1 ± 2.6	10.3 ± 2.9	t_{620}=0.3	0.5
GDS score[a]	2.6 ± 2.5	2.1 ± 2.2	t_{620}=1.8	0.1
Cigarette smoking, No (%)[b]	188 (37%)	37 (33%)	χ^2_1=0.7	0.4
History of disease, No (%)				
Cardiovascular disease[b]	15 (2.9%)	2 (1.7%)	χ^2_1=0.5	0.5
Diabetes mellitus[b]	20 (3.9%)	7 (6.1%)	χ^2_1=1.1	0.3
Hyperlipidemia[b]	19 (3.7%)	7 (6.1%)	χ^2_1=1.4	0.2
Hypertension[b]	195 (38.3%)	44 (38.9%)	χ^2_1=0.02	0.9
Cognitive score in 2002[c]	42.8±11.7	40.3±11.8	$F_{1,611}$=4.1	0.04
Cognitive score in 2005[c]	43.1±13.8	39.0±13.8	$F_{1,611}$=8.3	0.004

Table I. Demographic characteristics in the analysis of the effect of lipids/lipoproteins. [a] *P* value was calculated by unpaired two-tailed t test. [b] *P* value was calculated by Pearson χ^2 two-tailed test. [c] *P* value was calculated by analysis of covariance (ANCOVA) with age, sex, and years of education, Global Depression Scale (GDS) score, cigarette smoking, and medical history of cardiovascular disease, diabetes mellitus, hyperlipidemia, and hypertension as covariates. ApoE4, apolipoprotein E4. Data are mean±sd after adjustment for covariates.

Why are cognitive scores associated with plasma apoE and HDL levels?

Each of the analyses using the data from the baseline and 3-year follow-up examinations revealed that cognitive scores were associated with the plasma apoE level in both E4- and E4+, and the HDL level in E4-. We will discuss these findings.

ApoE plays a significant role in response to neuronal injury by reducing inflammation, endothelial dysfunction, and lipid oxidation.[16] An antioxidant role of apoE in promoting the regression of atherosclerosis has also been reported.[17] It is possible that a lower plasma apoE level impairs these normal physiological functions.[18] If this is the case, a lower plasma apoE level may lead to cognitive decline and the exacerbation of cerebral degenerative changes. On the other hand, apoE is thought to bind Aβ and promote its clearance and degradation, such that a lower apoE level may reduce the efficiency of Aβ clearance, and contribute to AD pathogenesis.[19]

The expression of apoE is transcriptionally regulated by the ligand-activated nuclear receptors, peroxisome proliferator-activated receptor gamma (PPARγ) and liver X receptors (LXRs), which form obligate heterodimers with retinoid X receptors (RXRs).[20] Expression of the ApoE gene is increased by agonist of these receptors. Recently, Cramer et al tested whether the RXR agonist bexarotene, which activates both the PPAR-RXR and LXR-RXR receptors, would rapidly alter the amount of Aβ, and diminish behavioral abnormalities , in mice genetically engineered to express a mutant form of the APP gene.[21] They observed rapid clearance of soluble Aβ from the brain, reduction in neuritic plaque burden, and reversal of behavioral deficits. The effects of bexarotene were not observed when the drug was administered to mice lacking the APOE gene.[21,22] These observations support our finding of the significant protective effect of apoE on cognitive decline in later life, and that the strategies increasing apoE expression might prevent cognitive decline in old age.

Higher plasma levels of HDL were associated with better cognitive function in the E4- group. Low-level HDL is thought to be a risk factor for atherosclerotic diseases,[23,24] and it has been reported that HDL might prevent aggregation and polymerization of amyloid in the human brain.[25,26] Anti-inflammatory properties of HDL could prevent inflammation from neurodegenerative processes.[27]

Recent studies have presented evidence for the involvement of internalized triglyceride-rich lipoprotein (TRL)-derived apoE in the regulation of HDL metabolism.[28] The greater portion of TRL-derived apoE remains in peripheral recycling endosomes. This pool of apoE is then mobilized by HDL to be rec ycled back to the plasma membrane, followed by apoE resecretion and the subsequent formation of apoE-containing HDL. This recycling of apoE may prevent cognitive decline. We found no significant association between HDL and cognitive function in the E4+ group . A recent study has

shown that HDL-induced rec ycling of TRL-derived apoE4 is relatively inefficient.[29] Thus, in the E4+ group, the inefficiency might reduce the recycling of apoE and decrease the protective effect of HDL on cognitive decline.

Conclusion

Our findings showed positive effect of plasma apoE and HDL on better cognitive function of elderly. They suggest a possible interaction between apoE and HDL may be linked to a protective effect on cognitive decline and that the interaction is affected by APOE4 allele in later life. It is known that neuropathological cascades leading to cognitive impairment and AD start to develop before the manifestation of cognitive impairment. Therefore, ensuring higher plasma apoE and HDL from an earlier stage of life may be useful for the maintenance of cognitive function in later life, and especially for APOE4 carriers. ❑

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Efecto de los lípidos plasmáticos y el genotipo APOE en la declinación cognitiva

Un postulado central del envejecimiento cerebral es que "lo que es bueno para el corazón es bueno para el cerebro". Se examinó el efecto combinado de los lípidos plasmáticos y del genotipo APOE sobre la función cognitiva de sujetos de edad avanzada. Se evaluaron las concentraciones plasmáticas de lipoproteína de alta densidad (HDL), lipoproteína de baja densidad, triglicéridos, colesterol total y apoliproteína E (apoE) en 622 individuos de 65 años y más que viven en la comunidad. Se investigaron las asociaciones entre lípidos plasmáticos y función cognitiva en grupos portadores de APOE4 (E4+) y no portadores de APOE4 (E4-) empleando información a lo largo de tres años. Al momento inicial y 3 años después las puntuaciones cognitivas se correlacionaron con los niveles plasmáticos de apoE tanto en el grupo E4- como en el E4+ y el nivel de HDL en el grupo E4-. Los resultados sugieren que una interacción entre apoE y HDL está facilitada por APOE4 y posiblemente relacionada con un aumento de neuroplasticidad y los consiguientes efectos protectores en la función cognitiva en la vejez. Una posible estrategia para el mantenimiento de la función cognitiva en la edad avanzada es la conservación de niveles plasmáticos más altos de apoE y HDL desde la juventud, especialmente en los sujetos APOE4-positivos.

Effet des lipides plasmatiques et du génotype APOE sur le déclin cognitif

Le principe central du vieillissement cérébral est que « ce qui est bon pour le cœur est bon pour le cerveau ». Nous avons donc examiné l'effet combiné des lipides plasmatiques et du génotype APOE sur la fonction cognitive chez les personnes âgées. Les concentrations plasmatiques des HDL (high-density lipoprotein), des LDL (low-density lipoprotein), des triglycérides, du cholestérol total et de l'apo E (apolipoprotéine E) ont été évaluées chez 622 résidents en institution âgés de 65 ans et plus. Nous avons analysé les associations entre les lipides plasmatiques et la fonction cognitive dans les groupes porteurs de l'APOE4 (E4+) et non porteurs de l'APOE4 (E4-) en utilisant des données longitudinales sur 3 ans. Initialement et 3 ans plus tard, les scores cognitifs étaient corrélés aux concentrations plasmatiques en apoE chez les E4- et les E4+ et les concentrations en HDL chez les E4- . Nos résultats suggèrent qu'une interaction entre apoE et HDL est facilitée par les APOE4 et probablement liée à une amélioration de la neuroplasticité et à des effets protecteurs sur la fonction cognitive dans la vie future. La préservation de concentrations de HDL et d'apoE plasmatiques plus élevées dès le plus jeune âge est proposée comme stratégie éventuelle pour maintenir la fonction cognitive ultérieure, en particulier pour les sujets qui sont APOE4-positifs.