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Cholesteryl Ester Transfer Protein (*CETP*) genotype and cognitive function in persons aged 35 years or older

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Abstract

Common polymorphisms of the Cholestryl Ester Transfer Protein (*CETP*) gene may predict lower risk of cognitive decline. We investigated the association of cognitive function with *CETP* genotype in a population-based cohort of 4135 persons aged 35–82 years. Cognitive function was measured with the Ruff Figural Fluency Test (RFFT; worst score, 0 points; best score, 175 points) and *CETP* I405V and Taq1B genotypes were determined by polymerase chain reaction. RFFT score was not associated with I405V genotype in persons aged 35–64 years. Remarkably, beyond age 65, homozygous valine carriers had higher RFFT scores than heterozygous carriers and noncarriers: RFFT (SD), 52 (21), 49 (18), and 47 (17) points, respectively ($p = 0.005$). There also was a statistically significant interaction between I405V genotype and age. Beyond age 65, the difference between homozygous valine carriers and noncarriers increased by 0.11 point per year ($p = 0.005$). RFFT score was not associated with Taq1B genotype. In conclusion, *CETP* I405V valine homozygosity was associated with better cognitive function in persons aged 65 years or older.

Keywords: CETP; Cross-sectional analysis; Executive function; Genetic association study; Middle-aged; Systematic review

1. Introduction

It is well established that the risk of Alzheimer disease is dependent on *APOE* genotype (Bertram et al., 2007). However, there probably are several other genes that increase the susceptibility for Alzheimer disease, and recently, it was suggested that the risk of dementia and Alzheimer disease is also dependent on Cholesteryl Ester Transfer Protein (*CETP*) genotype (Sanders et al., 2010).

CETP facilitates the transfer of cholesteryl esters and triglycerides between different types of lipoproteins in plasma (Hamilton and Deckelbaum, 2007), and some variations in *CETP* are linked to higher levels of high density lipoprotein (HDL) cholesterol (Thompson et al., 2008). Accordingly, these variations in *CETP* may predict a lower incidence of cardiovascular disease (Prospective Studies Collaboration et al., 2007; Thompson et al., 2008). *CETP* may also play a role in dementia as it is increasingly recognized that cardiovascular disease and dementia share several common risk factors. Hypertension, diabetes mellitus, dyslipidemia, and obesity, for example, have all been linked to an increased risk of Alzheimer disease (Gustafson et al., 2003; Kivipelto et al., 2005; Luchsinger et al., 2005; Whitmer et al., 2005). Equally important, these cardiovascular risk factors have been associated with cognitive decline in persons without dementia (van den Berg et al., 2009). Thus, if variations in *CETP* predict HDL cholesterol and cardiovascular risk, *CETP* genotype

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could also be related to dementia and cognitive impairment in general.

The aim of this study was to investigate the association of common variations in *CETP* genotype with cognitive function in a large sample from the general population. Cognitive tests and *CETP* genotyping were performed in a population-based cohort of 4135 persons aged 35 to 82 years.

2. Methods

2.1. Study population

The study population comprised all participants of the third survey of the Prevention of Renal and Vascular ENd-stage Disease study (PREVEND) that is being conducted in the city of Groningen, the Netherlands (n = 5862). PREVEND was designed to investigate prospectively the natural course of (micro)albuminuria and its relation to renal and cardiovascular disease in the general population. Details of the study protocol have been published elsewhere (Lambers Heerspink et al., 2008; Mahmoodi et al., 2009).

The PREVEND study has been approved by the Medical Ethical Committee (METc) of the University Medical Center Groningen, Groningen, the Netherlands, and is conducted in accordance with the guidelines of the Declaration of Helsinki. All participants gave written informed consent.

2.2. Cognitive function

Cognitive function was measured with the Ruff Figural Fluency Test (RFFT) (Ruff, 1996; Ruff et al., 1987). The RFFT is a measure of nonverbal fluency. Fluency is generally seen as an executive function and is sensitive to early cognitive dysfunction (Twamley et al., 2006). The RFFT requires the participants to draw as many designs as possible within a set time limit while avoiding repetitions of designs (Ruff, 1996; Ruff et al., 1987). In contrast to many other neuropsychological tests, the RFFT is sensitive to changes in executive function in both young and older persons (Izaks et al., 2011; Ruff et al., 1987). The main outcome measure of the RFFT is the total number of unique designs, which varies from 0 points (worst score) to 175 points (best score). Each RFFT was analyzed by 2 independent examiners according to strict scoring rules (intraclass correlation coefficient, 1.00; 95% confidence interval [CI], 0.99–1.00) (Izaks et al., 2011; Ruff, 1996).

2.3. Age and educational level

Age was defined as the age in full years on the date of performance on the RFFT. Educational level was divided into 4 groups according to the International Standard Classification of Education (ISCED) (United Nations Educational, Scientific and Cultural Organization, 2006): primary school, ISCED 0 to 1 (0–8 years of education); lower secondary education, ISCED 2 (9–12 years of education); higher secondary education, ISCED 3–4 (13–15 years of education); university, ISCED 5 (16 or more years of education).

2.4. Genotyping

Genotyping was performed at the University Medical Center Groningen, Groningen, the Netherlands. DNA was extracted from whole blood using the QIAamp mini kit (Qiagen, Hilden, Germany). The *CETP* I405V (rs5882) and Taq1B (rs708272) single-nucleotide polymorphisms were analyzed using TaqMan-MGB probes and primers, designed through the Assay-by-Design service of Applied Biosystems (Applied Biosystems, Applera Nederland, Nieuwerkerk aan de IJssel, the Netherlands) (Borggreve et al., 2005). Assays were carried out according to the manufacturer's recommendations on an ABI 7900HT apparatus (Applied Biosystems).

APOE genotype (rs429358 and rs7412) was also determined. This was done by allelic discrimination on a TaqMan 7500 Real Time PCR system, using the single-nucleotide polymorphism genotyping mixes C-3084793-20 and C-904973-10 and TaqMan Universal PCR Master Mix No AmpErase (Applied Biosystems). The method has been validated against a previously described restriction isotyping procedure (Blaauwwiekel et al., 1998; Reymer et al., 1995).

2.5. Other measurements

The main cardiovascular risk factors were measured because they may be associated with *CETP* genotype as well as with cognitive function. Diabetes mellitus was defined as either a fasting glucose equal to or greater than 7.0 mmol/L, or a nonfasting glucose equal to or greater than 11.1 mmol/L, or the use of glucose-lowering drugs (World Health Organization, 1999). Smoking was defined as current smoking or cessation of smoking less than 1 year before the study. Blood pressure was automatically measured in supine position during 10 minutes (Dinamap monitor, Johnson & Johnson Medical, Inc., Tampa, FL, USA), and reported as the mean of the last 2 recordings. Plasma glucose and total cholesterol were measured by dry chemistry (Eastman Kodak, Rochester, NY, USA). HDL cholesterol was measured with a homogeneous method (direct HDL, Aeroset TM System, Abbott Laboratories, Abbott Park, IL, USA). Non-HDL cholesterol was calculated as total cholesterol minus HDL cholesterol. Albuminuria was determined in 2 consecutive 24-hour urine samples by nephelometry (Dade Behring Diagnostic, Marburg, Germany). Elevated albuminuria was defined as an average urinary albumin excretion equal to or greater than 30 mg per 24 hours. Data on disease history were derived from a questionnaire at inclusion, and from the Dutch national registries of hospital discharge diagnoses and death certificates during follow-up. Data on drug use were obtained from the InterAction DataBase (www.iadb.nl) which comprises pharmacy-dispensing data of the pharmacists in the study region (Monster et al., 2002).

2.6. Statistical analysis

Differences in numerical variables were tested with the independent-samples *t* test or, if appropriate, 1-way analysis of variance (ANOVA). Differences in categorical variables were tested by χ^2 test or by Fisher exact test where appropriate.

The association between RFFT score, age, and *CETP* polymorphisms was analyzed by linear regression analysis. The regression model also included the variables gender, educational level, diabetes mellitus, smoking status, body mass index (BMI), systolic blood pressure, glucose, HDL cholesterol, non-HDL cholesterol, elevated albuminuria, history of coronary heart disease, history of cerebrovascular disease, use of blood pressure-lowering agents, use of lipid-lowering agents, and *APOE* ε4 carriership. For the association between RFFT score and *CETP* I405V genotype, the regression model also included the interaction terms Age ≥ 65 years × Ile/Val × Age and Age ≥ 65 years × Val/Val × Age. The interaction terms were added to the model after initial inspection of the raw data. In all regression models, the variables age, body mass index, systolic blood pressure, glucose, HDL cholesterol, and non-HDL cholesterol were entered as continuous variables. All other variables were entered as categorical variables.

To adjust for multiple comparison, differences between groups were considered statistically significant if $p < 0.005$ (adjusted for multiple comparisons). Regression coefficients were considered statistically significant if $p < 0.05$. Statistical analysis was done with SPSS 16.0 for Windows (SPSS, Inc., Chicago, IL, USA).

2.7. Additional analysis

As a consequence of its design, the total PREVEND cohort comprised a relatively high number of persons with elevated albuminuria. Because this may influence some data analyses, all analyses were repeated in a representative sample of the Groningen population. This so-called Groningen Random Sample included 2404 persons.

2.8. Systematic review

Finally, we performed a systematic review of the literature to compare our findings with other studies. The search strategy and selection of the studies are detailed in the supplementary file.

3. Results

3.1. Study population

A total of 4158 persons (71%) performed the RFFT. The RFFT scores of the other 1704 persons (29%) were missing: 1271 persons (22%) refused to perform the RFFT, and 434 persons (7%) had missing RFFT scores for other reasons. In addition, 20 persons (0.5%) who performed the RFFT were excluded because the data on educational level were missing. Three persons (0.1%) were excluded because they were younger than 35 years and their number was too small to form a separate age group. Thus, the total study population included 4135 persons (Table 1). Information on *CETP* I405V genotype was available for 3986 persons (96%), and on *CETP* Taq1B genotype for 4000 persons (97%).

Table 1
Characteristics of study population

Characteristic	Value
n (%)	4135 (100)
Gender, *n* (%)	
Female	1978 (48)
Male	2157 (52)
Ethnicity, *n* (%)	
Western European	3963 (96)
Other	172 (4)
Age, mean (SD), y	55 (12)
Age, *n* (%), y	
35–44	920 (22)
45–54	1277 (31)
55–64	1002 (24)
65–74	691 (17)
≥ 75	245 (6)
Educational level, *n* (%)	
Primary school	406 (10)
Lower secondary education	1225 (29)
Higher secondary education	1108 (27)
University	1396 (34)
CETP I405V genotype, *n* (%)	
All	3986 (96)
Ile/Ile	1876 (45)
Ile/Val	1699 (41)
Val/Val	411 (10)
CETP Taq1B genotype, *n* (%)	
All	4000 (97)
B1/B1	1347 (33)
B1/B2	1881 (45)
B2/B2	772 (19)
RFFT score, mean (SD)	69 (26)

Key: Ile, isoleucine; RFFT, Ruff Figural Fluency Test; Val, valine.

The persons who performed the RFFT were slightly younger than the persons with missing RFFT scores (mean age [SD], 55 [12] vs. 56 [12] years; $p < 0.001$), and included fewer women (48% vs. 53%; $p < 0.001$). The persons who performed the RFFT also had higher educational levels ($p < 0.001$; data not shown). There was no difference in the distribution of *CETP* genotypes.

3.2. CETP I405V and RFFT score

The distribution of the *CETP* I405V genotypes was in Hardy-Weinberg equilibrium ($p > 0.99$). There were no differences in age, gender, or educational level between persons with different *CETP* I405V genotypes. As expected, homozygous valine carriers had higher levels of HDL cholesterol than heterozygous valine carriers and non-carriers (Table 2). There were no statistically significant differences in other cardiovascular risk factors or *APOE* ε4 carriership.

Overall, there was no difference in mean RFFT score between the 3 *CETP* I405V genotypes (Table 2). However,

Table 2
RFFT score, demographic characteristics and main cardiovascular risk factors dependent on *CETP* genotype

	CETP I405V genotype				*CETP* Taq1B genotype			
	Ile/Ile	Ile/Val	Val/Val	*p*	B1/B1	B1/B2	B2/B2	*p*
n	1876	1699	411		1347	1881	772	
RFFT score, mean (SD)	69 (26)	69 (26)	68 (26)	0.71	69 (26)	69 (26)	68 (26)	0.63
Women, *n* (%)	903 (48)	811 (48)	204 (50)	0.77	636 (47)	902 (48)	381 (49)	0.64
Age, mean (SD), y	55 (12)	55 (12)	55 (12)	0.84	54 (12)	55 (12)	55 (11)	0.41
Educational level, *n* (%)								
Primary school	168 (9)	183 (11)	39 (10)		127 (9)[a]	184 (10)[a]	83 (11)[a]	
Lower secondary education	542 (29)	501 (29)	129 (31)	0.55	406 (30)	537 (29)	231 (30)	0.62
Higher secondary education	513 (27)	453 (27)	108 (26)		378 (28)	502 (27)	198 (26)	
University	653 (35)	562 (33)	135 (33)		436 (32)	658 (35)	260 (34)	
Cardiovascular risk factors								
Diabetes mellitus, *n* (%)	119 (6)	103 (6)	23 (6)	0.80	88 (7)	103 (6)	53 (7)	0.29
Current smoker, *n* (%)[b]	429 (23)	420 (25)	92 (23)	0.36	307 (23)	446 (24)	190 (25)	0.56
Body mass index, mean (SD)	27 (4)	27 (4)	27 (5)	0.82	27 (4)	27 (4)	27 (5)	0.55
Systolic blood pressure, mean (SD), mm Hg	126 (18)	126 (18)	125 (17)	0.52	126 (17)	126 (18)	126 (18)	0.77
Glucose, mean (SD), mmol/L	4.9 (1.0)	4.9 (1.0)	4.8 (0.9)	0.74	4.9 (1.0)	4.9 (0.9)	4.9 (0.9)	0.34
Total cholesterol, mean (SD), mmol/L[c]	5.35 (1.08)	5.37 (1.04)	5.46 (1.05)	0.16	5.34 (1.08)	5.39 (1.04)	5.37 (1.05)	0.35
HDL cholesterol, mean (SD), mmol/L[c]	1.39 (0.38)	1.42 (0.38)	1.47 (0.39)	< 0.001	1.37 (0.37)	1.41 (0.39)	1.47 (0.39)	< 0.001
Non-HDL cholesterol, mean (SD), mmol/L[c]	3.96 (1.05)	3.95 (1.01)	3.99 (1.02)	0.75	3.97 (1.06)	3.98 (1.00)	3.90 (1.03)	0.17
Elevated albuminuria, *n* (%)[b]	273 (15)	237 (14)	64 (16)	0.72	208 (16)	258 (14)	108 (14)	0.33
History, *n* (%)								
Coronary heart disease	65 (3.5)	82 (4.8)	13 (3.2)	0.08	52 (4.0)	76 (4.0)	31 (4.0)	0.99
Cerebrovascular disease	16 (0.9)	14 (0.8)	6 (1.5)	0.45	14 (1.0)	13 (1.7)	9 (1.2)	0.40
Current medication, *n* (%)[b]								
Blood pressure-lowering agents	427 (30)	369 (29)	98 (30)	0.66	290 (28)	427 (30)	187 (32)	0.37
Lipid-lowering agents	255 (18)	238 (19)	59 (18)	0.96	191 (19)	253 (18)	114 (19)	0.69
APOE ε4 carrier, *n* (%)[d]	546 (30)[e]	502 (30)[e]	116 (29)[e]	0.89	395 (30)[f]	550 (30)[f]	221 (30)[f]	0.98

Body mass index calculated as weight (kg)/height (m^2).

Key: HDL, high-density lipoprotein; Ile, isoleucine; RFFT, Ruff Figural Fluency Test; Val, valine.

[a] Sum of the percentages is not equal to 100 due to rounding.

[b] Different total number due to missing data. For the genotypes Ile/Ile, Ile/Val and Val/Val, data on smoking status were complete for 1867, 1689, and 407 persons, respectively; data on albuminuria were complete for 1860, 1680, and 410 persons, respectively; data on current medication were complete for 1410, 1285, and 325 persons, respectively. For the genotypes B1/B1, B1/B2 and B2/B2, data on smoking status were complete for 1343, 1871, and 763 persons, respectively; data on albuminuria were complete for 1330, 1867, and 767 persons, respectively; data on current medication were complete for 1052, 1427, and 592 persons, respectively.

[c] To convert from mmol/L to mg/dL, multiply mmol/L by 39.

[d] *APOE* genotypes, ε2/ε4, ε3/ε4, and ε4/ε4.

[e] Different total number due to missing data: $n_{total} = 3853$.

[f] Different total number due to missing data: $n_{total} = 3860$.

if the mean RFFT score was plotted against age group, it appeared that the association of *CETP* I405V genotype with RFFT score was dependent on age (Fig. 1). Up to the age of 64 years, there was no difference in RFFT score between persons with different *CETP* I405V genotypes but in persons aged 65 years or older, homozygous valine carriers had higher (better) RFFT scores than heterozygous valine carriers and the noncarriers. Accordingly, the unadjusted mean RFFT score (SD) in persons aged 65 or older was 52 (21) points for homozygous valine carriers, 49 (18) points for heterozygous valine carriers, and 47 (17) points for noncarriers ($p = 0.005$).

The difference between persons younger than 65 years and persons aged 65 years or older was confirmed in multiple linear regression analysis (Table 3). In the fully adjusted model, the RFFT score of the total number of homozygous valine carriers was 2.83 points lower than the RFFT score of noncarriers (95% CI, −5.77 to 0.11; $p = 0.06$). However, in persons aged 65 years or older ($n = 900$), there was a statistically significant interaction between valine homozygosity and age. Beyond age 65, homozygous valine carriers had higher RFFT scores than noncarriers and the difference in RFFT score increased by 0.11 point per year of age (95% CI, 0.03–0.19; $p = 0.005$), after adjusting for age, educational level, cardiovascular risk factors, and *APOE* ε4 carriership (Table 3). Using the full regression model, it was estimated that compared with the RFFT score of noncarriers, the RFFT score of homozygous valine carriers was 4.38 points higher at age 65, 5.49 points higher at age 75, and 6.60 points higher at age 85.

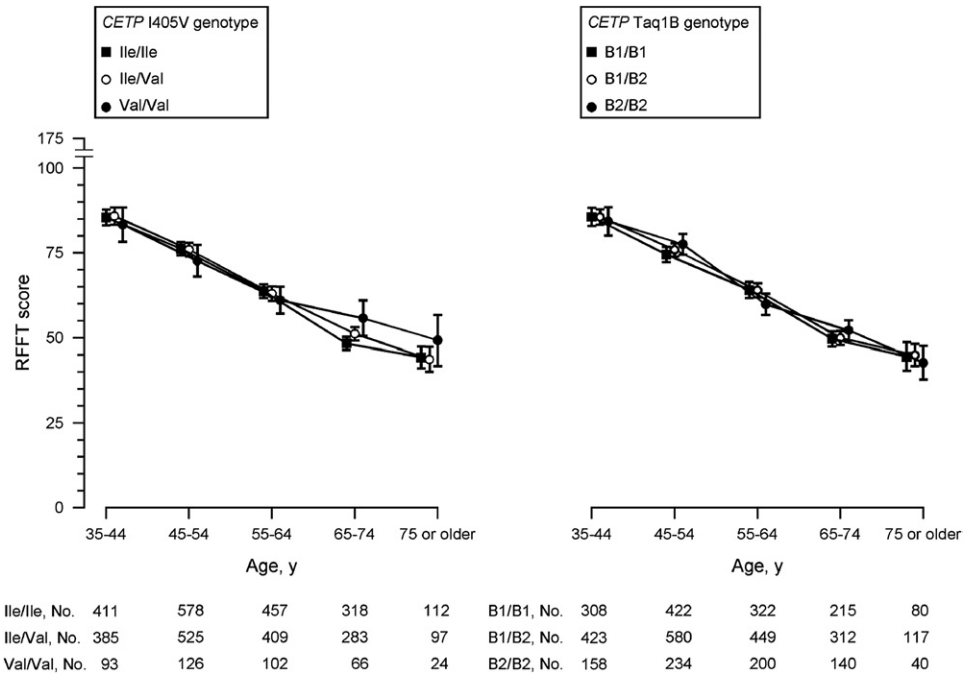

Fig. 1. Mean Ruff Figural Fluency Test (RFFT) score dependent on *CETP* genotype and age. For clarity, data are presented as mean and 95% confidence interval of ten-year age groups. Abbreviations: Ile, isoleucine; Val, valine.

3.3. CETP Taq1B and RFFT score

The distribution of the *CETP* Taq1B genotypes was also in Hardy-Weinberg equilibrium ($p > 0.99$). There was moderate linkage disequilibrium between the TaqIB and I405V polymorphisms (D' = 0.55). RFFT score was not dependent on *CETP* Taq1B genotype and in all age groups, homozygous B2 carriers had similar RFFT scores as heterozygous B2 carriers and noncarriers (Fig. 1). There were no differences in age, gender, or educational level between the *CETP* Taq1B genotypes but like homozygous I405V valine carriers, homozygous Taq1B B2 carriers had higher HDL cholesterol levels (Table 2). However, there were no differences in other cardiovascular risk factors or *APOE* ε4 carriership. *CETP* Taq1B genotype was not associated with

Table 3
Multiple linear regression analysis of RFFT score on *CETP* I405V genotype (n = 3986)

	Model 1[a]				Model 2[b]				Model 3[c]			
	B	SE (B)	β	p	B	SE (B)	β	p	B	SE (B)	β	p
Age, y	−0.96	0.04	−0.43	< 0.001	−0.93	0.04	−0.41	< 0.001	−0.91	0.05	−0.41	< 0.001
Gender												
Male	[d]				[d]				[d]			
Female	0.18	0.66	0.003	0.79	−0.62	0.76	−0.01	0.42	0.48	0.88	0.009	0.58
Genotype												
Ile/Ile	[d]				[d]				[d]			
Ile/Val	0.58	0.77	0.001	0.45	0.70	0.78	0.01	0.37	1.13	0.92	0.02	0.22
Val/Val	−1.77	1.26	−0.02	0.16	−1.86	1.28	−0.02	0.15	−2.83	1.47	−0.03	0.06
Age ≥ 65 y × Ile/Val × age	0.02	0.02	0.01	0.43	0.01	0.02	0.01	0.52	0.01	0.02	0.01	0.69
Age ≥ 65 y × Val/Val × age	0.11	0.04	0.04	0.003	0.10	0.04	0.04	0.005	0.11	0.04	0.05	0.005

Key: β, standardized coefficient; B, unstandardized coefficient; HDL, high-density lipoprotein; Ile, isoleucine; RFFT, Ruff Figural Fluency Test; Val, valine.

[a] Adjusted for educational level; adjusted R^2 and residual standard deviation, 0.37 and 21, respectively.

[b] Adjusted for the covariates in Model 1 plus diabetes mellitus, current smoking status, body mass index, systolic blood pressure, glucose, HDL cholesterol, non-HDL cholesterol, and elevated albuminuria; adjusted R^2 and residual standard deviation, 0.38 and 21, respectively.

[c] Adjusted for the covariates in Model 2 plus history of coronary heart disease, history of cerebrovascular disease, current use of blood pressure-lowering agents, current use of lipid-lowering agents, and *APOE* ε4 carriership; adjusted R^2 and residual standard deviation, 0.38 and 20, respectively.

[d] Reference category.

Table 4
Multiple linear regression analysis of RFFT score on *CETP* Taq1B genotype ($n = 4000$)

	Model 1[a]				Model 2[b]				Model 3[c]			
	B	SE (B)	β	*p*	B	SE (B)	β	*p*	B	SE (B)	β	*p*
Age, y	−0.92	0.03	−0.41	< 0.001	−0.89	0.04	−0.40	< 0.001	−0.87	0.04	−0.39	< 0.001
Gender												
Male	[d]				[d]				[d]			
Female	0.29	0.66	0.006	0.66	−0.50	0.76	−0.01	0.51	0.44	0.89	0.009	0.62
Genotype												
B1/B1	[d]				[d]				[d]			
B1/B2	0.01	0.74	0.001	0.99	−0.22	0.76	−0.004	0.77	−0.13	0.87	−0.002	0.88
B2/B2	−0.23	0.94	−0.003	0.82	−0.26	0.96	−0.004	0.78	−0.36	1.10	−0.005	0.75

Key: β, standardized coefficient; B, unstandardized coefficient; HDL, high-density lipoprotein; Ile, isoleucine; SE (B), standard error of B; RFFT, Ruff Figural Fluency Test; Val, valine.

[a] Adjusted for educational level; adjusted R^2 and residual standard deviation, 0.37 and 21, respectively.

[b] Adjusted for the covariates in Model 1 plus diabetes mellitus, current smoking status, body mass index, systolic blood pressure, glucose, HDL cholesterol, non-HDL cholesterol, and elevated albuminuria; adjusted R^2 and residual standard deviation, 0.37 and 21, respectively.

[c] Adjusted for the covariates in Model 2 plus history of coronary heart disease, history of cerebrovascular disease, current use of blood pressure-lowering agents, current use of lipid-lowering agents, and *APOE* ε4 carriership; adjusted R^2 and residual standard deviation, 0.38 and 20, respectively.

[d] Reference category.

RFFT score in multiple linear regression analysis after adjusting for various demographic characteristics, cardiovascular risk factors, and *APOE* ε4 carriership (Table 4).

3.4. Additional analysis

Essentially similar results were found if the analyses were limited to the persons recruited from the Groningen Random Sample that is representative of the Groningen general population. Unadjusted, the mean RFFT score (SD) in persons aged 65 or older was 56 (24) points for homozygous valine carriers, 51 (18) points for heterozygous valine carriers, and 47 (16) points for noncarriers ($p = 0.02$). In multiple linear regression analysis (fully adjusted model), the RFFT score of the total number of homozygous valine carriers was 6.72 points lower than the RFFT score of noncarriers (95% CI, −11.29 to −2.14; $p = 0.004$). However, beyond age 65, homozygous valine carriers had higher RFFT scores than noncarriers and the difference in RFFT score increased by 0.18 point per year of age (95% CI, 0.06–0.30; $p = 0.002$). Compared with noncarriers, the predicted RFFT score of homozygous valine carriers was 4.86 points higher at age 65, 6.64 points higher at age 75, and 8.42 points higher at age 85 (fully adjusted model).

3.5. Systematic review

Thirteen studies were included in the systematic review. Of these, 5 studies comprised data on *CETP* genotype and cognitive function (Table 5), and 11 comprised data on *CETP* genotype and dementia (Table 6). Most studies were case-control studies but 3 studies were prospective cohort studies (Reynolds et al., 2011; Sanders et al., 2010; Yu et al., 2012). However, 1 prospective cohort study was relatively small with short follow-up (Sanders et al., 2010), and 1 prospective cohort study was limited to a highly selected study population (Yu et al., 2012). The mean age of the participants was high. Thus, the level of evidence of the studies was low and their generalizability limited.

Most studies yielded negative results. A few studies found an association for the *CETP* I405V polymorphism but the results of these studies were contradictory. Overall, the findings on an association of *CETP* genotype with cognitive function or the risk of dementia were equivocal.

4. Discussion

In this study, homozygous *CETP* I405V valine carriers aged 65 years or older had better cognitive function than heterozygous valine carriers and noncarriers. The difference between homozygous valine carriers and heterozygous carriers and noncarriers was small but increased with increasing age. Surprisingly, there was no association of *CETP* I405V genotype with cognitive function in younger age groups. By contrast, it appeared that *CETP* Taq1B genotype was not associated with cognitive function in any age group.

The *CETP* I405V genotype is the most investigated *CETP* genotype if it comes to the association of *CETP* genotype with cognitive function. Several studies reported on the association of the I405V valine genotype with the risk of Alzheimer disease or age-related cognitive decline (Arias-Vásquez et al., 2007; Barzilai et al., 2006; Chen et al., 2008; Qureischie et al., 2008; Reynolds et al., 2011; Rodríguez et al., 2006; Yu et al., 2012). Up until now, however, their findings have been divergent. Although, I405V valine carriers and noncarriers had a similar risk of Alzheimer disease in most studies, 1 study showed that homozygous valine carriers had an increased risk of Alzheimer disease (Arias-Vásquez et al., 2007). Because most studies had a cross-sectional design and included a relatively small number of persons, the equivocal findings may be due to methodological differences. Our findings suggested that homozygous *CETP* I405V valine carriers had

Table 5
Systematic review of studies on the association of *CETP* genotype with cognitive function[a]

Outcome/Reference	*CETP* polymorphism	Design	Mean age, y	Male, %	Cases, *n*	Controls, *n*	Cohort, *n*	Follow-up, y	Association with genotype
Global cognition									
Barzilai et al. (2006)	I405V	Case-control	99	24, 26[b]	90	68	[c]	[c]	Val/Val better performance[d]
Johnson et al. (2007)	I405V	Case-control	79	42	35	488	[c]	[c]	—
Yu et al. (2012)	I405V	Cohort	78	30	[c]	[c]	1384	8	Val/Val worse performance[e]
Declarative memory									
Johnson et al. (2007)	I405V	Cross-sectional	79	42	[c]	[c]	525	[c]	—
Sanders et al. (2010)	I405V	Cohort	78[f]	49	[c]	[c]	523	3	Val/Val better performance
Reynolds et al. (2011)	I405V	Cohort	74[f]	42	[c]	[c]	1540	8	—
	C-629A								—
Yu et al. (2012)	I405V	Cohort	78	30	[c]	[c]	1384	8	—
Working memory									
Sanders et al. (2010)	I405V	Cohort	78[f]	49	[c]	[c]	523	3	—
Reynolds et al. (2011)	I405V	Cohort	74[f]	42	[c]	[c]	1540	8	—
	C-629A								—
Yu et al. (2012)	I405V	Cohort	78	30	[c]	[c]	1384	8	Val/Val worse performance[e]
Processing speed									
Sanders et al. (2010)	I405V	Cohort	78[f]	49	[c]	[c]	523	3	—
Reynolds et al. (2011)	I405V	Cohort	74[f]	42	[c]	[c]	1540	8	—
	C-629A								—
Yu et al. (2012)	I405V	Cohort	78	30	[c]	[c]	1384	8	—
Executive function									
Johnson et al. (2007)	I405V	Cross-sectional	79	42	[c]	[c]	525	[c]	—

Key: Val, valine.
[a] A detailed description of the search strategy and selection of the studies is given in the supplementary file. Most studies investigated various *CETP* polymorphisms and used several cognitive domains as outcome measure. For brevity, data are reported only for the most common polymorphisms and outcomes.
[b] Reported separately for cases and controls.
[c] Not applicable.
[d] Ashkenazi Jews.
[e] Catholic nuns and priests.
[f] Median age.

slower decline of cognitive function than heterozygous carriers and noncarriers after the age of 65 years. This concurred with the findings of a recently published, prospective study on *CETP* genotype and cognitive function (Sanders et al., 2010). In this study, it was found that homozygous valine carriers had lower risk of both Alzheimer disease and memory decline. However, another prospective population-based study that was published even more recently, did not find an association of *CETP* genotype with cognitive function (Reynolds et al., 2011). In contrast to this report, our study included young as well as older persons and used the RFFT as outcome measure. As performance on the RFFT starts to decline at a relatively young age (Izaks et al., 2011), it is likely that the RFFT is more sensitive to cognitive decline in an early phase than other tests.

The mechanism by which *CETP* I405V valine genotype is associated with better cognitive function remains to be elucidated. As the I405V valine genotype is associated with higher HDL cholesterol levels, it is often assumed that it is associated with lower cardiovascular risk (Thompson et al., 2008), and thereby with lower risk of cognitive decline. Indeed, several studies have found that high levels of HDL cholesterol are protective against Alzheimer disease and cognitive decline (Raffaitin et al., 2011; Reitz et al., 2010; Singh-Manoux et al., 2008; van Exel et al., 2002). An HDL-dependent mechanism could also explain why the association of I405V valine with cognitive function was only found in persons aged 65 years or older as generally, cardiovascular sequelae become most apparent at advanced age (Lloyd-Jones et al., 2009). However, older homozygous

Table 6
Systematic review of studies on the association of *CETP* genotype with dementia risk[a]

Outcome/Reference	*CETP* polymorphism	Design	Mean age, y	Men, %	Cases, *n*	Controls, *n*	Cohort, *n*	Incident cases, *n*	Association with genotype
Alzheimer disease									
Fidani et al. (2004)	Taq1B	Case-control	78, 84[b]	27, 28[b]	102	97	[c]	[c]	—
Zhu et al. (2005)	Taq1B	Case-control	73, 88[b]	35, 46[b]	163	154	[c]	[c]	—
Rodríguez et al. (2006)	I405V	Case-control	75, 80[b]	29, 32[b]	286	315	[c]	[c]	—
	Taq1B								—
	C-629A								A/A lower risk[d]
Arias-Vásquez et al. (2007)	I405V	Case-control	69	40	544	5644	[c]	[c]	Val/Val higher risk
Chen et al. (2008)	I405V	Case-control	76, 78[b]	39, 50[b]	107	115	[c]	[c]	—
	Taq1B								—
Qureischie et al. (2008)	I405V	Case-control	72	32, 47[b]	351	388	[c]	[c]	—
	C-629A								—
Sanders et al. (2010)	I405V	Cohort	78[c]	49	[d]	[d]	523	40	Val/Val lower risk
Murphy et al. (2012)	I405V	Case-control	75, 76[b]	54	318	188	[c]	[c]	Val allele higher risk[e,f]
	C-629A								—
Reynolds et al. (2011)	I405V	Cohort	78[g]	42	[c]	[c]	2389	122	—
	C-629A								—
Yu et al. (2012)	I405V	Cohort	78	30	[c]	[c]	1384	336	Val/Val higher risk[h]
Vascular dementia									
Qureischie et al. (2009)	I405V	Case-control	71, 74[b]	43, 47[b]	164	443	[c]	[c]	—
	C-629A								A/A higher risk[e]

Cholesteryl Ester Transfer Protein (*CETP*) genotype and cognitive function in persons aged 35 years or older.
Key: Ile, isoleucine; Val, valine.
[a] A detailed description of the search strategy and selection of the studies is given in the supplementary file. For brevity, data on the *CETP* polymorphisms D442G (1 study), L269Q (1 study), and -1946 VNTR (1 study) were omitted.
[b] Reported separately for cases and controls.
[c] Not applicable.
[d] In *APOE* ε4 carriers.
[e] In *APOE* ε4 noncarriers.
[f] Ile/Val compared to Ile/Ile.
[g] Median age.
[h] Catholic nuns and priests.

I405V valine carriers still had better cognitive function after adjusting for HDL cholesterol level and other cardiovascular risk factors. Besides, the *CETP* Taq1B B2/B2 genotype, which relates to more pronounced differences in HDL cholesterol compared with the I405V variation (Thompson et al., 2008), was not predictive of cognitive function. Therefore, it seems unlikely that the association of *CETP* I405V genotype with cognitive function can be attributed in large part to its effect on HDL cholesterol.

The role of *CETP* in plasma has been well characterized but its role in the brain is largely unknown (Carter, 2007), and to some extent controversial. *CETP* activity could be detected in cerebrospinal fluid in 1 study (Albers et al., 1992), but this was not confirmed in a more recent report (Demeester et al., 2000). However, *CETP* may be expressed in astrocytes (Yamada et al., 1995). Until recently, astrocytes were generally believed to have a mainly supportive function for neurons in the central nervous system but new evidence suggests that astrocytes also play a role in signaling between brain cells and provide metabolic support for neurons (Halassa and Haydon, 2010). Thus, an alternative explanation for the association of *CETP* I405V genotype with cognitive function might be sought in the role of astrocytes in various brain regions.

There are some methodological aspects to our study that need to be acknowledged. First, our findings could not be validated in a replication cohort. This was largely due to the use of the RFFT as outcome measure. The RFFT is a sensitive cognitive test so that it was possible to measure differences in cognitive function in relatively young persons (Izaks et al., 2011), but it also is relatively new and yet not widely known. As a consequence, an independent sample

with similar data on genotype and cognitive function was not available. Second, the cross-sectional analysis may be considered as a limitation because in general, it is not an appropriate approach to investigate causal relationships. Third, it should be mentioned that we used only 1 test of cognitive function. Even so, the RFFT score is the outcome of many different cognitive abilities. Moreover, In contrast to many other tests, the RFFT does not seem to exhibit a strong floor or ceiling effect as it has a wide range of scores. Fourth, due to the design of the PREVEND study, the study sample included a relatively high proportion of persons with elevated albuminuria and hence, with increased cardiovascular risk. However, similar results were found when the analyses were repeated in a random sample from the general population. Also, the association of *CETP* I405V genotype with cognitive function appeared to be independent of cardiovascular risk factors in multivariate analysis.

In conclusion, in this study, homozygous carriers of the *CETP* I405V valine allele who were aged 65 years or older had better cognitive function than heterozygous carriers and noncarriers of comparable age. No differences were found in persons aged 35 to 64 years.

Disclosure statement

The authors have no actual or potential conflicts of interest.

The PREVEND study has been approved by the Medical Ethical Committee (METc) of the University Medical Center Groningen, Groningen, the Netherlands, and is conducted in accordance with the guidelines of the Declaration of Helsinki. Written informed consent was obtained from all participants.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.neurobiolaging.2012.02.022.

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