ORIGINAL RESEARCH

Cardiovascular and Lifestyle Risk Factors and Cognitive Function in Patients With Stable Coronary Heart Disease

Ralph A. H. Stewart, MD; Claes Held, MD; Sue Krug-Gourley, PhD; Dawn Waterworth, PhD; Amanda Stebbins, MS, MSc; Karen Chiswell, PhD; Emil Hagstrom, MD; Paul W. Armstrong, MD; Lars Wallentin, MD; Harvey White, DSc

Background—Vascular risk factors have been associated with differences in cognitive performance in epidemiological studies, but evidence in patients with coronary heart disease is more limited.

Methods and Results—The Montreal Cognitive Assessment score obtained 3.2±0.37 years after randomization to darapladib, a reversible inhibitor of lipoprotein phospholipase A_2 or placebo was evaluated for 10 634 patients with coronary heart disease from 38 countries in the STABILITY (Stabilization of Atherosclerotic Plaque by Initiation of Darapladib Therapy) trial. The Montreal Cognitive Assessment scores for darapladib and placebo groups were similar (mean±SD, 25.3±3.84 versus 25.4±3.73, respectively; P=0.27) and the adjusted odds ratio (OR) for mild cognitive impairment (Montreal Cognitive Assessment score <26) was 1.00 (95% CI, 0.93–1.09). Mild cognitive impairment was more likely with increasing age (OR, 1.33 [1.27–1.41], +5 years after 65). For other baseline clinical characteristics, the strongest independent predictors of cognitive impairment were education (≤8 years versus college/university, OR, 2.95 [2.60–3.35]; >8 years/trade school versus college/university, OR, 1.38 [1.25–1.52] and geographic grouping). Cardiovascular risk factors independently associated with cognitive impairment were history of stroke (OR, 1.43 [1.20–1.71]); <2.5 hours of moderate or vigorous intensity exercise/week (OR, 1.19 [1.04–1.37]); high-density lipoprotein cholesterol <1.16 mmol/L (OR, 1.19 [1.04–1.37]); diabetes mellitus requiring treatment (OR, yes versus no: 1.15 [1.05–1.26]); and history of hypertension (OR, 1.12 [1.02–1.23]).

Conclusions—In patients with stable coronary heart disease, cognitive performance was associated with modifiable cardiovascular risk factors, educational level, and global region, but was not influenced by darapladib.

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Key Words: cognitive impairment • coronary heart disease • Montreal Cognitive Assessment • risk factor

Dementia is a major cause of disability in aging populations.[1,2] The most common causes are Alzheimer disease and vascular diseases.[3] Dementia is usually preceded by milder cognitive impairment that may progress gradually. Cardiovascular risk factors during middle age have been associated with a higher risk of cognitive impairment in later life,[4–7] possibly by increasing the risk of vascular or mixed dementia. Patients with coronary heart disease (CHD) could be at greater risk for vascular dementia because of established atherosclerotic disease and a greater burden of vascular risk factors.[8] It is also possible that treatments that lower vascular risk could reduce the risk of cognitive impairment.

Lipoprotein-associated phospholipase A_2 (Lp-PLA_2), which increases production of proinflammatory and proapoptotic mediators, is one of several inflammatory biomarkers that

From the Green Lane Cardiovascular Service, Auckland City Hospital, Auckland, New Zealand (R.A.H.S., H.W.); University of Auckland, New Zealand (R.A.H.S., H.W.); Department of Medical Sciences, Cardiology, Uppsala University, Uppsala, Sweden (C.H., E.H., L.W.); Uppsala Clinical Research Center (UCR), Uppsala, Sweden (C.H., E.H., L.W.); Metabolic Pathways and Cardiovascular Medicine Delivery Unit, GlaxoSmithKline Research and Development, Collegeville, PA (S.K.-G.); Department of Genetics, GlaxoSmithKIlne Medicines Research Centre, Upper Merion, Philadelphia, PA (D.W.); Duke Clinical Research Institute, Durham, NC (A.S., K.C.); Canadian VIGOUR Centre, University of Alberta, Edmonton, Canada (P.W.A.).

Accompanying Tables S1 through S4 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.118.010641

Correspondence to: Ralph A. H. Stewart, MD, Green Lane Cardiovascular Service, Auckland City Hospital, Private Bag 92024, Auckland 1030, New Zealand. E-mail: rstewart@adhb.govt.nz

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Clinical Perspective

What Is New?

- History of stroke, low high-density lipoprotein cholesterol, low physical activity, diabetes mellitus, and history of hypertension were cardiovascular risk factors independently associated with Montreal Cognitive Assessment scores indicative of cognitive impairment in 10 634 patients with stable coronary heart disease from 38 countries.
- The strongest independent predictors of cognitive impairment were educational level, history of stroke, and region of residence.
- Inhibition of lipoprotein-associated phospholipase A_2 activity with darapladib was not associated with cognitive impairment.

What Are the Clinical Implications?

- In patients with stable coronary heart disease, potentially modifiable risk factors may influence cognitive performance.

have been associated with the risk of dementia or impaired cognitive function. Lp-PLA_2 activity has been reported to be higher in patients with Alzheimer disease compared with controls,[9] and to be associated with dementia in epidemiologic studies.[10–13] However, it is not known whether these associations are causal.

The current study was undertaken as part of the STABILITY (Stabilization of Atherosclerotic Plaque by Initiation of Darapladib Therapy) trial. In this large global trial of patients with stable CHD, darapladib decreased plasma Lp-PLA_2 activity by ≈65% but did not decrease major cardiovascular events.[14,15] The aims of this evaluation were first to determine whether darapladib treatment had any effect on cognitive function, and second to evaluate whether other potentially modifiable risk factors are associated with cognitive function in patients with stable CHD.

Methods

The STABILITY trial was a randomized, double-blind, placebo-controlled global cardiovascular outcomes trial. The primary aim was to determine whether darapladib, a specific inhibitor of Lp-PLA_2, reduced the risk of major adverse cardiovascular events (MACE), defined as cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke in patients with CHD. The study recruited patients between December 2008 and April 2010 and was continued until ≈1500 major adverse cardiovascular events had occurred. Assessment of cognitive function was included as an exploratory outcome in a protocol modification in February 2010.[14] The study was approved by the institutional review board at all contributing centers, and all participants provided written informed consent for the STABILITY trial and separately for the cognitive function study. Anonymized individual participant data and study documents can be requested.[16]

Study Population

Participants had stable CHD, defined as prior myocardial infarction, prior coronary revascularization, or multivessel CHD, and also had to meet at least 1 of the following cardiovascular risk enrichment criteria: age ≥60 years; diabetes mellitus requiring pharmacotherapy; high-density lipoprotein (HDL) cholesterol <1.03 mmol/L; current or previous smoker defined as ≥5 cigarettes per day on average; significant renal dysfunction, defined as estimated glomerular filtration rate ≥30 and <60 mL/min per 1.73 m^2 or urine albumin-to-creatinine ratio ≥30 mg albumin/g creatinine; or polyvascular disease, defined as CHD and cerebrovascular disease (carotid artery disease, defined as >50% stenosis or previous carotid surgery, or ischemic stroke >3 months) or CHD and peripheral arterial disease. Patients were excluded if there was evidence of dementia. A total of 15 828 subjects from 39 countries were randomized into the study. Use of guideline-recommended standard of care therapies was encouraged, with 98% taking statins and ≥95% taking aspirin. There was no significant difference in major adverse cardiovascular events for subjects randomized to darapladib compared with placebo after a median follow-up of 3.7 years. More detailed descriptions of the study design and population have been published previously.[14]

Baseline Clinical Assessment

In addition to the risk markers listed above, body weight, body mass index, history of hypertension, prior coronary artery bypass grafting and history of paroxysmal or persistent atrial fibrillation were noted. Diabetes mellitus was defined as a physician diagnosis requiring pharmacotherapy. Fasting plasma low-density lipoprotein and HDL cholesterol, glucose, and Lp-PLA_2 activity were measured in core laboratories. ApoE4ε allele status was determined in 9388 participants using the HumanOmniExpressExome-8 version 1 array by Expression Analysis Inc. (Durham, NC).

Participants were also invited to complete a lifestyle questionnaire. Physical activity was assessed by asking, "How many hours during a typical week do you spend doing the following activities for 10 minutes or more?" (1) Doing MILD physical activity (estimated to be 2 metabolic equivalents) such as easy walking, yoga, tai chi, mild housework? (2) Doing MODERATE (4 metabolic equivalents) physical activity such as fast walking, jogging, aerobics, gardening, bicycling, dancing, swimming, or housecleaning. (3) Doing VIGOROUS (8

metabolic equivalents) physical activity such as running, lifting heavy objects, playing strenuous sport, or doing strenuous work?[17] The risk factor of low physical activity was defined as taking <2.5 hours of moderate or greater intensity physical activity recommended in physical activity guidleines.[18] A Mediterranean diet score (MDS) was based on self-reported weekly and daily consumption of foods from a Mediterranean dietary pattern using a food frequency questionnaire.[19] A Mediterranean diet score ≥15 was associated with a reduced risk of major adverse cardiovascular events and lower mortality, and therefore defined as "healthy."[19] Years of formal education completed were categorized as "none or 1 to 8 years," "9 to 12 years," "trade," and "college or university." Depressive symptoms were evaluated by responses (always, often, sometimes, never) to 2 short questions on mood and interest in activities.

Countries were grouped in the following "geographic" regions: North America (United States and Canada), South America (Argentina, Brazil, Chile, and Peru), Western Europe (Belgium, Denmark, France, Germany, Italy, Netherlands, Norway, Spain, Sweden, and United Kingdom) and Australia and New Zealand, Eastern Europe (Bulgaria, Czech Republic, Estonia, Greece, Hungary, Poland, Romania, Russia, Slovakia, Ukraine), and Asia/other (China, Hong Kong, India, Japan, Korea, Pakistan, Philippines, Taiwan, Thailand, and South Africa).

Assessment of Cognitive Function

Cognitive function was assessed once using an appropriate language version of the Montreal Cognitive Assessment (MoCA),[20] which is a screening test developed to identify potential cases of mild cognitive impairment. The MoCA was separately validated for each available language version. It was administered at the last routine study visit, conducted 3 to 6 months before study close-out as specified by the STABILITY coordinating center. Patients were eligible for inclusion in the cognitive function study if they had taken the study medication for at least 1 year and provided written informed consent. They were excluded if there was no suitable validated language version of the MoCA, or if they were unable to complete the MoCA for physical reasons.

The MoCA is sensitive for detection of mild cognitive impairment and can be completed in about 10 minutes. Questions are designed to assess several cognitive domains: memory, visual-spatial ability, executive function, attention, concentration, language, and orientation to time and place. Points are allocated for correct responses to a total of ≤30 points. An additional point was also allocated for people with <8 years education if the total score was <30. The primary outcome was a MoCA score <26, chosen to indicate cognitive impairment based on published literature.[21] Based on the overall distribution of MoCA scores, a score <22 representing the lowest 10% to 15% of MoCA scores among these subjects, was chosen as a secondary outcome to identify participants with "moderate" or "severe" cognitive impairment. A MoCA score <16 was chosen to indicate severe cognitive impairment.

Statistical Analysis

To compare MoCA scores by randomized treatment group, the mean and SD for the overall and components of the MoCA are reported, and the proportion of subjects with a MoCA <26, MoCA <22, and MoCA <16, with statistical testing using the MantelHaenszel test.

Baseline characteristics were then reported for categories of cognitive function classification. Discrete factors were reported as frequencies and percentages. Continuous factors were reported as means and SDs. Mantel-Haenszel tests were generated for discrete factors, and the Spearman rank sum test for continuous measurements. Three statistical models were generated to assess the MoCA score. Two logistic models were fitted, one for any cognitive impairment (MoCA score <26 versus ≥26) and a second for moderate or severe cognitive impairment (MoCA score <22 versus ≥22). A linear regression model was fitted for the continuous MoCA score. Although the marginal distribution of the MoCA score is left skewed, this modeling approach was chosen so that covariate effects could be quantified in terms of changes in the mean MoCA score. With our large sample size, inference based on asymptotic normality of the parameter estimates is reasonable even when the underlying response variable does not have a normal distribution. Before modeling continuous risk factors, the distribution of measurements was assessed and modeling assumptions verified. For continuous and ordinal covariates, a linearity test was performed by testing whether a model including restricted cubic spline transformations of the covariate improved the fit of the model. For age, we found significant evidence of nonlinearity in the 2 logisitic models. The nonlinear relationship was approximated using a linear spline with a knot at 65 years, that is, by including 2 linear terms in the model. This allows for a different coefficient (eg, odds ratio [OR]) to be estimated for unit increments in age <65 years than increments >65 years.

Covariates were selected in 2 steps in the logistic regression analysis of cognitive impairment (MoCA <26). At the first step, the model included treatment, age, and sex and allowed for the forward selection of region of enrollment, years of education (0–8 years, either 9–12 years or trade school [combined because MoCA scores were similar], and college/university), and physical activity level. Factors were allowed into the model if the $P \leq 0.05$. At the second step, factors found to be significant in the first step were included, and markers of disease severity (prior myocardial infarction, prior coronary

revascularization, multivessel disease confirmed by angiography, polyvascular disease, and estimated glomerular filtration rate <60 mL/min per m^2), prior stroke, current smoking, history of hypertension, diabetes mellitus requiring pharmacotherapy, ApoE4ε allele positive, Mediterranean diet score ≥15, alcohol consumption of 6 or more drinks in a single session at least once per week, HDL cholesterol (mmol/L), low-density lipoprotein cholesterol (mmol/L), and body mass index (kg/m^2) were added by forward selection using a $P \leq 0.05$. The same set of covariates was used in the models for moderate/severe cognitive impairment (MoCA <22) and continuous MoCA score. For the logistic regression models, the OR, 95% CI, and *P* values are reported. All modeling assumptions were verified. Transformations were used for continuous measurements when the assumption of linearity was not met. For the generalized linear regression model, the beta coefficients (average difference in MoCA), 95% CI, and *P* values are reported. Statistical significance was assessed using 2-sided *P* values. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

Results

A total of 5532 of 7904 (70%) of STABILITY participants randomized to placebo and 5191 of 7924 (66%) randomized to darapladib completed the MoCA after a mean (SD) duration of treatment of 3.2±0.37 years. Reasons for not completing the MoCA are displayed by treatment group in Figure 1. There were small differences in some baseline clinical characteristics for subjects who did and did not complete the MoCA, presented in Table S1. Subjects who did not complete the MoCA were slightly older and more likely to be women; have diabetes mellitus; get less exercise; have polyvascular disease, history of stroke, or significant renal disease; have fewer than 8 years of education; or live in North America. However, baseline characteristics for subjects who completed the MoCA were well matched by treatment allocation.

MoCA results are presented by treatment allocation in Table 1. There was no difference in overall MoCA scores between subjects randomized to placebo or darapladib (mean±SD: 25.3±3.82 versus 25.3±3.71, respectively; $P=0.27$). For each cognitive domain, scores were similar between treatment groups. For mild cognitive impairment, the adjusted OR (95% CI) comparing darapladib to placebo was 1.00 (0.93–1.09) and for moderate/severe cognitive impairment, the adjusted OR (95% CI) was 1.07 (0.95–1.21).

Associations With Cognitive Impairment

The baseline characteristics for all participants who completed the MoCA are displayed for all subjects and by MoCA score group in Table 2. The ORs for the multivariate model of any cognitive impairment or moderate/severe cognitive impairment according to prespecified risk factors are shown in Table 3. After adjusting for all other covariates, there were increased odds of cognitive impairment associated with baseline age, geographic regions of the United States/Canada and South America (compared with Western Europe), education less than college/university, diabetes mellitus requiring pharmacotherapy, history of hypertension, low physical activity, low HDL cholesterol, history of stroke, and severe depressive symptoms. In the multivariate model, there was no evidence for an association between cognitive impairment ($P>0.05$) and current smoking, body mass index, diet score, multivessel CHD, polyvascular disease, significant renal dysfunction, ApoE4ε allele, low-density lipoprotein cholesterol, plasma levels of Lp-PLA_2 activity, prior coronary artery bypass grafting, or history of atrial fibrillation.

Increased ORs for moderate or severe cognitive impairment were observed for the same baseline characteristics as for MoCA <26 versus ≥26, and the strength of association appeared to be stronger for most but not all associations (Table 3).

Multivariate Models and Continuous MoCA Scores

In the multivariable model that included all covariates, education and geographic region were the strongest independent predictors of continuous MoCA scores. Compared with people with a college or university education, MoCA score was on average 2.52 (95% CI, 2.31–2.73) points lower for those with ≤8 years education, and 0.61 (95% CI, 0.45–0.77) points lower for those with >8 years or a trade school education after adjusting for all other covariates. Compared with people living in Western Europe, Australia, or New Zealand, MoCA scores were lower for North America by 0.63 (95% CI, 0.83–0.43) points, Eastern Europe by 0.78 (95% CI, 0.97–0.58) points, Asia/Pacific by 1.08 (95% CI, 1.28–0.87) points, and South America by 2.27 (95% CI, 2.55–2.00) points after adjusting for all other covariates. Age and sex were also independently associated with MoCA score.

In fully adjusted models, MoCA score was lower (−0.59; 95% CI, −0.30 to −0.88 points) for patients with a history of stroke. Lower MoCA scores (95% CI) were also observed for participants reporting <2.5 h/wk of moderate or vigorous exercise (−0.45; 95% CI, −0.31 to −0.59 points), diabetes mellitus on pharmacotherapy (−0.21; 95% CI, −0.07 to −0.36 points), and history of hypertension (−0.17; 95% CI, −0.01 to −0.32 points). There was no evidence for differences ($P>0.05$) in MoCA score by Mediterranean diet score, ApoE4ε, body mass index, current smoking, prior coronary artery bypass grafting, or markers of cardiovascular disease after adjusting for all other covariates.

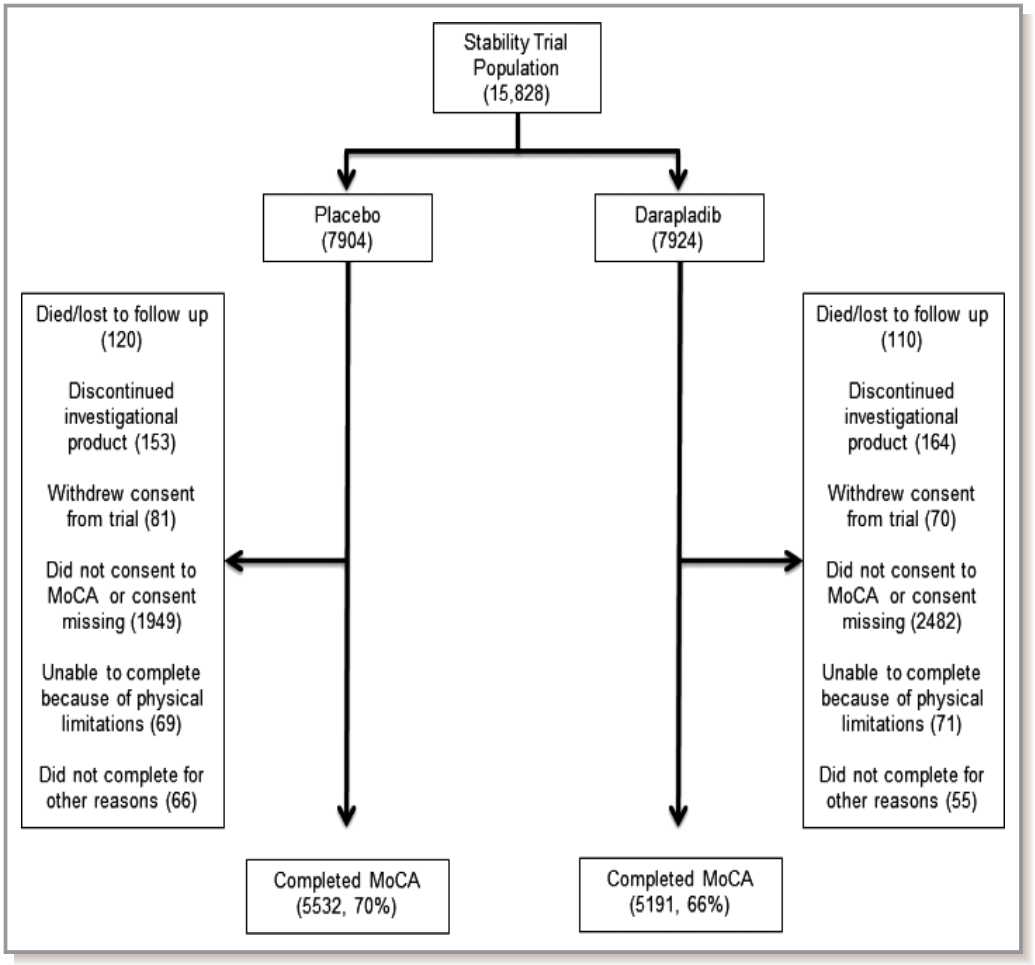

Figure 1. Study flow diagram. Flow diagram indicating STABILITY study participants who completed the MoCA after a median follow-up of 3.2±0.4 years, and reasons for noncompletion by treatment allocation. MoCA indicates Montreal Cognitive Assessment. Patients may have more than one reason for exclusion; STABILITY, Stabilization of Atherosclerotic Plaque by Initiation of Darapladib Therapy.

At baseline, 166 (1.6%) subjects reported feeling down "always," and these subjects were more likely to have a MoCA score <26 (OR, 1.94; 95% CI, 1.34–2.81) and a MoCA score <22 (OR, 2.66; 95% CI, 1.76–4.02). However, less persistent depressive symptoms and "loss of interest" in activities were not independently associated with MoCA score. Associations of other risk factors with MoCA score were similar before and after also adjusting for depressive symptoms (Table S2).

Interactions Between Age and Other Risk Factors

MoCA score decreased with older age throughout the distribution of scores. The decrease in median MoCA score (Figure 2) was parallel between strata based on physical activity less than versus ≥2.5 hours of moderate or vigorous physical activity (Figure 2A) or education (Figure 2B). There was no evidence for an interaction between MoCA score, age, and physical activity, education, diabetes mellitus requiring pharmacotherapy, hypertension, HDL cholesterol, history of stroke, or geographic region (P>0.05 for all).

Statistical tests for interaction between sex and MoCA were significant (P<0.0001) for geographic region and years of education but not age and other predictors of MoCA score in the multivariable model (P>0.05; Table S3). For subjects with <8 years' education, women had lower MoCA scores than men, while for participants with >12 years education, women were less likely to have lower MoCA scores than men. Adjusting for education and other covariates, MoCA scores were lower in women compared with men in Eastern Europe, South America, and Asia, but higher in North America, Western Europe, Australia, and New Zealand (Table S4).

Discussion

This study assessed effects of darapladib compared with placebo, as well as associations of potentially modifiable

Table 1. MoCA Results by Treatment Allocation to Darapladib or Placebo

	Possible Score on MoCA	Placebo	Darapladib
Number of subjects		5532	5191
		Mean±SD	Mean±SD
Components of MoCA			
Visuospatial/executive	6	4.0±1.19	4.0±1.18
Naming	3	2.9±0.41	2.9±0.42
Attention: digits	2	1.8±0.50	1.7±0.51
Attention: letters	1	0.9±0.29	0.9±0.29
Attention: subtraction	3	2.6±0.76	2.6±0.78
Language: repeat	2	1.6±0.60	1.6±0.62
Language: fluency	1	0.6±0.48	0.6±0.48
Abstraction	2	1.7±0.58	1.7±0.59
Delayed recall (no cue)	4	2.8±1.63	2.8±1.64
Orientation	6	5.9±0.49	5.9±0.49
Total score	30	25.4±3.73	25.3±3.84
MoCA <26, n (%)		2347 (42.4)	2231 (42.0)
MoCA <22, n (%)		751 (13.7)	751 (14.6)
MoCA <16, n (%)		106 (1.9)	123 (2.4)

Results are mean±standard deviation (SD) or n (%). One point is also added for people with <8 years education if total is <30. For all comparisons $P>0.10$. MoCA indicates Montreal Cognitive Assessment.

cardiovascular risk factors, with mild cognitive impairment, in a diverse global population of patients with stable CHD. Mild cognitive impairment is important because it is associated with an elevated risk of developing dementia.[22] The MoCA was chosen because it is a short, easily administered, validated test developed to screen patients for minor cognitive impairment, which is available in many languages.[20] A MoCA score <26 was the prespecified threshold for mild cognitive impairment,[20] but scores <26 have been reported as common in other ethnically diverse populations.[23] In this study, which included subjects with a mean age of 64 years, ≈40% of participants had a MoCA score <26. This prevalence of "mild cognitive impairment" was higher than the 4% to 19% reported in some general populations ≥65 years using other criteria.[8,24] It is probable MoCA scores below 26 reflect "usual" cognitive performance for some people, while for others there has been a change from a previously higher level. The lower MoCA score of <22, found in ≈14% of this study population, was included to provide information on associations with a lower level of cognitive function.

Each language version of the MoCA was validated before release. However, socioeconomic, cultural, and other differences between the validation studies and patients in the STABILITY trial, including differences in familiarity with this type of testing, may have been important. The odds of mild and moderate cognitive impairment differed between geographic regions. Because reasons for geographic differences are uncertain and may be multiple, using a single threshold may be misleading when assessing cognitive function in people from diverse cultures and backgrounds, unless effects of these potential covariates are considered.[23]

The strongest association was between cognitive function and level of education, which was consistent across the age range. Low education could also explain the lower MoCA scores in women compared with men in several geographic locations. These observations are consistent with the "brain reserve hypothesis" in which longer time in education allows a subject to compensate for neuropathological burden in later life.[22,25] However, while college- or university-level education was associated with a higher MoCA score, the decrease in MoCA score with increase in age was similar by education level.

Low physical activity, diabetes mellitus, hypertension, and stroke have each been associated with risk of dementia or cognitive impairment in previous epidemiological studies.[4–7]

The current study extends this evidence by demonstrating independent associations between cognitive impairment and these risk factors among patients with CHD. These results support the idea that interventions to reduce cardiovascular risk may have additional benefits of risk reduction for cognitive impairment.

Lp-PLA_2, which increases production of proinflammatory and proapoptotic mediators, is one of several inflammatory biomarkers that have been associated with the risk of dementia or impaired cognitive function.[26,27] Lp-PLA_2 activity has been reported to be higher in patients with Alzheimer disease compared with controls,[9] and to be associated with dementia in epidemiologic studies.[10–13] However, these associations may not be causal. In the current study, darapladib, which decreased plasma Lp-PLA_2 activity by ≈65%, was not associated with a difference in cognitive function. Compared with observational data, the randomized comparison of darapladib with placebo provides more reliable evidence regarding the potential role of Lp-PLA_2. However, this result does not exclude the importance of other pathways that could link cardiovascular risk factors to the risk of cognitive impairment.

Study Limitations

The primary aim of the STABILITY trial was to evaluate effects of darapladib on cardiovascular end points. A single MoCA assessment was included to evaluate a possible association between darapladib therapy and cognitive function, but with no attempt to ensure adequate power for this exploratory

Table 2. Baseline Characteristics of Study Population Overall and by MoCA Score After >1 Year of Randomized Treatment

Characteristics	All Patients (N=10 634)	Moderately Impaired Cognitive Function (N=1502)	Mildly Impaired Cognitive Function (N=3076)	Normal Cognitive Function (N=6056)	*P* Value
MoCA score after mean (SD) 3.2 (±0.37) years of treatment		<22	22 to 25	≥26	
Randomized treatment					0.31
Placebo	5485 (51.6%)	751 (50.0%)	1596 (51.9%)	3138 (51.8%)	
Darapladib	5149 (48.4%)	751 (50.0%)	1480 (48.1%)	2918 (48.2%)	
Baseline characteristics					
Age, y	64.0±9.0	67.8±8.6	64.8±8.7	62.6±9.0	<0.0001
Female sex	1908 (17.9%)	402 (26.8%)	548 (17.8%)	958 (15.8%)	<0.0001
Cardiovascular risk factors, n (%)					
Smoker status					<0.0001
Never smoked	3254 (30.6%)	570 (37.9%)	959 (31.2%)	1725 (28.5%)	
Former smoker	5484 (51.6%)	733 (48.8%)	1589 (51.7%)	3162 (52.2%)	
Current smoker	1895 (17.8%)	199 (13.2%)	527 (17.1%)	1169 (19.3%)	
LDL cholesterol, mmol/L	2.20±0.83	2.22±0.82	2.19±0.83	2.19±0.84	0.30
Lp-PLA_2 activity, μmol/min per liter	174±47	172±50	174±47	175±45	0.21
HDL cholesterol, mmol/L	1.21±0.32	1.22±0.31	1.21±0.32	1.21±0.32	0.13
Diabetes mellitus	3966 (37.3%)	608 (40.5%)	1186 (38.6%)	2172 (35.9%)	0.0002
Body mass index					0.0030
<25 kg/m^2	2138 (20.1%)	360 (24.0%)	608 (19.8%)	1170 (19.4%)	
25 to <30 kg/m^2	4567 (43.0%)	646 (43.1%)	1304 (42.5%)	2617 (43.3%)	
≥30 kg/m^2	3910 (36.8%)	493 (32.9%)	1158 (37.7%)	2259 (37.4%)	
Hypertension	7544 (70.9%)	1146 (76.3%)	2232 (72.6%)	4166 (68.8%)	<0.0001
Moderate or vigorous activity <2.5 h/wk	3786 (35.6%)	709 (47.2%)	1117 (36.3%)	1956 (32.3%)	<0.0001
Excessive alcohol use	606 (5.8%)	76 (5.2%)	183 (6.1%)	347 (5.8%)	0.65
Mediterranean diet score ≥15	1981 (18.9%)	245 (16.5%)	548 (18.0%)	1188 (19.8%)	0.0015
Cardiovascular and renal disease					
Prior myocardial infarction	6263 (58.9%)	887 (59.1%)	1777 (57.8%)	3599 (59.4%)	0.42
Prior coronary artery bypass graft	3505 (33.0%)	486 (32.4%)	1045 (34.0%)	1974 (32.6%)	0.72
Prior stroke	581 (5.5%)	106 (7.1%)	201 (6.5%)	274 (4.5%)	<0.0001
Multivessel CHD	1569 (14.8%)	257 (17.1%)	467 (15.2%)	845 (14.0%)	0.0016
Polyvascular disease	1480 (13.9%)	235 (15.6%)	459 (14.9%)	786 (13.0%)	0.0014
Significant renal disease	2998 (28.2%)	539 (35.9%)	953 (31.0%)	1506 (24.9%)	<0.0001
Atrial fibrillation	839 (7.9%)	132 (8.8%)	248 (8.1%)	459 (7.6%)	0.27
Genetic markers					
ApoE4ε					
1 allele	1967 (20.6%)	260 (19.5%)	563 (20.2%)	1144 (21.0%)	0.012
2 alleles	156 (1.6%)	24 (1.8%)	49 (1.8%)	83 (1.5%)	
Geographic region grouping					<0.0001
Western Europe Australia, New Zealand	2851 (26.8%)	305 (20.3%)	785 (25.5%)	1761 (29.1%)	
Asia, South Africa	1956 (18.4%)	346 (23.0%)	570 (18.5%)	1040 (17.2%)	

Continued

Table 2. Continued

Characteristics	All Patients (N=10 634)	Moderately Impaired Cognitive Function (N=1502)	Mildly Impaired Cognitive Function (N=3076)	Normal Cognitive Function (N=6056)	*P* Value
Eastern Europe	2614 (24.6%)	312 (20.8%)	771 (25.1%)	1531 (25.3%)	
South America	819 (7.7%)	273 (18.2%)	243 (7.9%)	303 (5.0%)	
North America	2394 (22.5%)	266 (17.7%)	707 (23.0%)	1421 (23.5%)	
Education					<0.0001
None	320 (3.1%)	132 (9.0%)	96 (3.2%)	92 (1.5%)	
1–8 y	1902 (18.2%)	542 (36.9%)	601 (19.8%)	759 (12.7%)	
9–12 y	3244 (31.0%)	396 (26.9%)	914 (30.2%)	1934 (32.4%)	
Trade school	1957 (18.7%)	198 (13.5%)	591 (19.5%)	1168 (19.6%)	
College/university	3047 (29.1%)	202 (13.7%)	827 (27.3%)	2018 (33.8%)	

Results are number (%) or mean± SD. CHD indicates coronary heart disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein; Lp-PLA$_2$, lipoprotein-associated phospholipase A$_2$; MI, myocardial infarction; MoCA, Montreal Cognitive Assessment.

objective, and change in cognitive performance could not be assessed because a baseline MoCA was not included. Despite this, the 95% CIs suggest that a clinically important effect of darapladib on cognitive function is unlikely. The MoCA assessment was performed at a specified visit near study end. Although the length of treatment varied among patients depending on the timing of randomization, this was balanced by treatment group and is unlikely to bias assessment of the treatment effect.

Observed associations between cardiovascular risk factors and cognitive function are consistent with results from large epidemiologic cohorts,[4–7] but causality cannot be confirmed

Table 3. Independent Predictors of Cognitive Dysfunction

	Any Cognitive Dysfunction: MoCA <26 OR (95% CI)	*P* Value	Moderate or Severe Cognitive Dysfunction: MoCA <22 OR (95% CI)	*P* Value
Age ≤65 (+5 y)	1.17 (1.12, 1.22)	<0.0001	1.22 (1.14, 1.31)	<0.0001
Age >65 (+5 y)	1.33 (1.27, 1.41)	<0.0001	1.50 (1.41, 1.61)	<0.0001
Female vs male	1.09 (0.97, 1.21)	0.1508	1.29 (1.11, 1.49)	0.0008
Education level (vs college/university)				
≤8 y	2.95 (2.60, 3.35)	<0.0001	5.31 (4.40, 6.41)	<0.0001
>8 y/trade	1.38 (1.25, 1.52)	<0.0001	1.89 (1.60, 2.25)	0.0023
Geographic region (vs Western Europe/Australia/New Zealand)				
United States/Canada	1.34 (1.18, 1.51)	0.021	1.49 (1.23, 1.81)	0.0163
Asia	1.60 (1.41, 1.82)	0.069	2.06 (1.71, 2.48)	0.0054
Eastern Europe	1.45 (1.29, 1.64)	0.645	1.63 (1.35, 1.97)	0.2663
South America	2.27 (1.91, 2.70)	<0.0001	3.22 (2.61, 3.97)	<0.0001
Other risk factors				
Low physical activity	1.19 (1.04, 1.37)	0.0005	1.31 (1.16, 1.49)	<0.0001
Hypertension	1.12 (1.02, 1.23)	0.0215	1.19 (1.03, 1.38)	0.0159
Diabetes mellitus	1.15 (1.05, 1.26)	0.0027	1.15 (1.01, 1.31)	0.0335
HDL cholesterol ≤1.16 mmol/L	1.19 (1.04, 1.37)	0.0134	1.24 (1.01, 1.24)	0.0371
History of stroke	1.43 (1.20, 1.71)	<0.0001	1.27 (1.00, 1.62)	0.0494

The odds of mild (MoCA <26 vs MoCA ≥26) and moderate (MoCA <22 vs MoCA ≥22) cognitive dysfunction are presented as OR and 95% CI from multivariable models including all listed covariates as well as randomized treatment. Nonsignificant variables are not shown. An OR >1 indicates greater odds of cognitive dysfunction.
*<2.5 h/wk moderate or vigorous exercise. HDL indicates high-density lipoprotein; MoCA, Montreal Cognitive Assessment; OR, odds ratio.

from observational studies. Also, evaluations of predictors of cognitive function were post hoc. The study did not assess change in MoCA scores over time. The ability to identify some risk factors, such as ApoE4ε allele, would be reduced if most of the difference in MoCA scores were not related to Alzheimer disease. A history of paroxysmal or persistent atrial fibrillation was present at baseline in ≈8% of participants, so the study had low statistical power to evaluate a modest association with the risk of cognitive impairment or the impact of preventive treatments such as oral anticoagulants. The study did not include assessment of left ventricular function. In this study, 98% of subjects were taking statins. The lack of an association between low-density lipoprotein cholesterol, which is influenced by statin dose, and MoCA score is reassuring regarding possible concerns that statins may cause memory impairment.[28]

Depressive symptoms have been associated with risk of dementia in previous studies,[29] and a small proportion of the participants in this study who reported depressive symptoms "always" had lower MoCA scores. It is possible that depression is a marker of the presence of, rather than a risk factor for, cognitive impairment, and for this reason it was not included in the primary analysis. Other study results were similar in a secondary analysis that also included depressive symptoms as a covariate. Activities of daily living and social functioning were not assessed as part of this study.

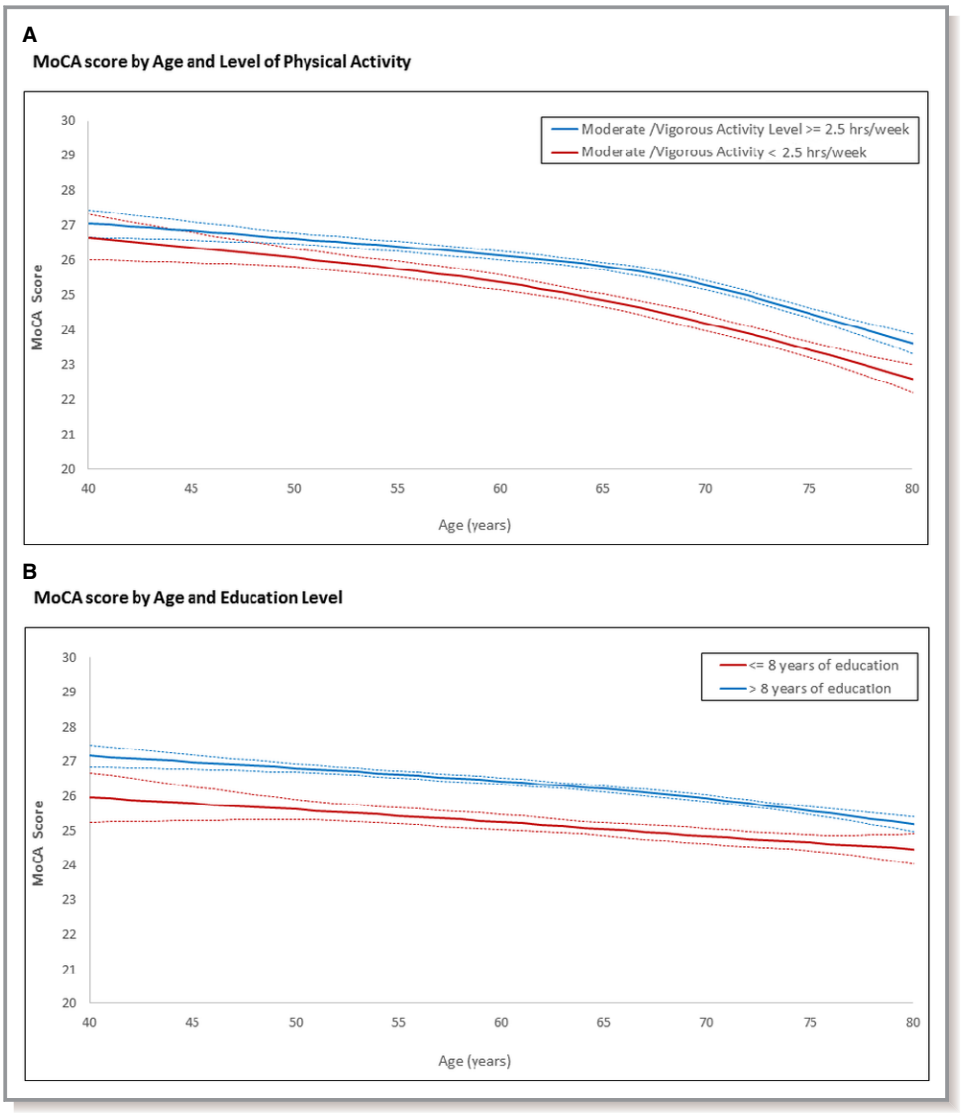

Figure 2. MoCA score by age stratified by (**A**) physical activity level, and (**B**) education. Average age-related change in MoCA score is plotted for subjects by presence or absence of (**A**) <2.5 h/wk of moderate or vigorous physical activity and (**B**) education level. MoCA indicates Montreal Cognitive Assessment.

Conclusions

In patients with stable CHD, inhibition of Lp-PLA_2 with darapladib did not influence cognitive function. However, low physical activity, diabetes mellitus, stroke, education, and geography were associated with differences in cognitive performance. Although causality was not confirmed, these observations are consistent with the hypothesis that long-term adherence to a healthy lifestyle and optimal management of cardiovascular risk factors may have favorable effects on cognitive function.

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Author Contributions

The study was conceived and designed in collaboration with GlaxoSmithKline by Drs Stewart, Krug-Gourley, Waterworth, Hagstrom, Held, Armstrong, Wallentin, and White. Statistical analysis was undertaken by Ms Stebbins and Dr Chiswell, who had full access to study data and take responsibility for the integrity of the data and the accuracy of the data analysis. The manuscript was drafted by Dr Stewart. All authors contributed to the critical review and final approval of the submitted manuscript.

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SUPPLEMENTAL MATERIAL

Table S1. Baseline Characteristics for STABILITY trial patients included and not included in the MoCA Assessment Cohort.

Characteristics	All patients (N=15828)	Not in MoCA (N=5105)	In MoCA (N=10723)	P value
Randomized Treatment				<.0001
Placebo	7904(49.9%)	2372(46.5%)	5532(51.6%)	
Darapladib	7924(50.1%)	2733(53.5%)	5191(48.4%)	
Baseline Characteristics				
Age (25th, 75th) (years)	65.0 (59.0, 71.0)	66.0 (59.0, 72.0)	64.0 (59.0, 70.0)	<0.0001
Female Sex	2967(18.7%)	1045(20.5%)	1922(17.9%)	0.0001
Cardiovascular risk factors, n (%)				
Smoker Status				0.3540
Never smoked	4887(30.9%)	1599(31.3%)	3288(30.7%)	
Former smoker	8081(51.1%)	2557(50.1%)	5524(51.5%)	
Current smoker	2858(18.1%)	948(18.6%)	1910(17.8%)	
LDL cholesterol ≥100 (mmol/L)	4105(26.0%)	1372(27.0%)	2733(25.5%)	0.0182
$LpPLA_2$ activity (µmol/min/L)				
HDL cholesterol < 40mg/dL (mmol/L)	5432(34.3%)	1767(34.6%)	3665(34.2%)	0.5789
Diabetes	6136(38.8%)	2131(41.7%)	4005(37.3%)	<.0001
Body mass index				0.0004
<25 kg/m^2	3304(20.9%)	1157(22.8%)	2147(20.1%)	
25-<30 kg/m^2	6752(42.8%)	2139(42.1%)	4613(43.1%)	
≥30 kg/m^2	5729(36.3%)	1786(35.1%)	3943(36.8%)	
Hypertension	11318(71.5%)	3720(72.9%)	7598(70.9%)	0.0087
Moderate or Vigorous activity ≥2.5 MET.hrs/ week	9442(61.2%)	2679(54.4%)	6763(64.4%)	<.0001
Activity level				<.0001
Not active	4002(26.0%)	1583(32.2%)	2419(23.0%)	
Some exercise	1973(12.8%)	659(13.4%)	1314(12.5%)	

Mod/Strenuous exercise	9442(61.2%)	2679(54.4%)	6763(64.4%)	
Excessive alcohol use	879(5.7%)	267(5.4%)	612(5.8%)	0.3282
Mediterranean diet score ≥15	2894(18.6%)	898(18.0%)	1996(18.8%)	0.2337
CV and renal disease				
Prior MI	9323(58.9%)	3000(58.8%)	6323(59.0%)	0.8103
Prior CABG	5236(33.1%)	1711(33.5%)	3525(32.9%)	0.4239
Prior stroke	975(6.2%)	391(7.7%)	584(5.4%)	<.0001
Multi-vessel CHD	2390(15.1%)	803(15.7%)	1587(14.8%)	0.1268
Poly-vascular disease	2372(15.0%)	879(17.2%)	1493(13.9%)	<.0001
Significant renal disease	4784(30.2%)	1761(34.5%)	3023(28.2%)	<.0001
Atrial fibrillation	1369(8.6%)	523(10.2%)	846(7.9%)	<.0001
Genetic Markers				
ApoE4ε				0.4091
1	2744(20.6%)	768(20.9%)	1976(20.5%)	
2	224(1.7%)	67(1.8%)	157(1.6%)	
Geographic Region Grouping				<.0001
Western Europe	3986(25.2%)	1184(23.2%)	2802(26.1%)	
Asia/Pacific	3089(19.5%)	1039(20.4%)	2050(19.1%)	
Eastern Europe	3531(22.3%)	896(17.6%)	2635(24.6%)	
South America	1199(7.6%)	367(7.2%)	832(7.8%)	
North America	4023(25.4%)	1619(31.7%)	2404(22.4%)	
Education				<.0001
None	567(3.7%)	241(4.9%)	326(3.1%)	
1-8 years	2998(19.3%)	1075(21.7%)	1923(18.2%)	
9-12 years	4751(30.6%)	1485(30.0%)	3266(30.9%)	
Trade school	2831(18.3%)	854(17.2%)	1977(18.7%)	
College/university	4365(28.1%)	1299(26.2%)	3066(29.0%)	

Table S2. Independent predictors of cognitive dysfunction after also adjusting for depressive symptoms at baseline.

	MoCA <26 OR (95% CI)	P value	MoCA<22 OR (95% CI)	P value
Age ≤65 (+5 years)	1.19 (1.14,1.24)	<.0001	1.24 (1.16, 1.34)	<.0001
Age >65 (+5 years)	1.33 (1.26, 1.41)	<.0001	1.51 (1.41, 1.62)	<.0001
Female vs male	1.06 (0.94, 1.18)	0.3560	1.22 (1.04, 1.42)	0.0126
Education level (vs college/university)				
≤8 years	2.92 (2.57, 3.32)	<.0001	5.32 (4.40, 6.44)	<.0001
>8 years/trade	1.39 (1.26,1.54)	<.0001	1.90 (1.60, 2.27)	<.0001
Geographic region (vs W Europe/Australia/NZ)				
US/Canada	1.34 (1.18, 1.52)	<.0001	1.51 (1.24, 1.84)	<.0001
Asia	1.63 (1.43, 1.85)	<.0001	2.11 (1.75, 2.55)	<.0001
Eastern Europe	1.45 (1.28, 1.64)	<.0001	1.69 (1.39, 2.05)	<.0001
South America	2.21 (1.86, 2.63)	<.0001	3.16 (2.55, 3.91)	<.0001
Other risk factors				
Physical activity <2.5 hours/week	1.15 (1.05, 1.25)	0.003	1.29 (1.13, 1.46)	<.0001
Hypertension	1.12 (1.01, 1.23)	0.025	1.16 (1.00, 1.34)	0.0445
Diabetes	1.13 (1.03, 1.24)	0.007	1.12 (0.99, 1.28)	0.0824
HDL chol (1 unit decrease)	0.85 (0.73, 0.97)	0.019	0.81 (0.66, 1.00)	0.0446
History of Stroke	1.41 (1.17, 1.69)	0.0002	1.24 (0.97, 1.59)	0.0823
Feeling Down (vs Never/rarely)				
Always	1.94 (1.34, 2.81)	0.0004	2.66 (1.76, 4.02)	<.0001
Often	1.14 (0.96, 1.35)	0.1305	0.92 (0.72, 1.18)	0.4974
Sometimes	1.00 (0.91, 1.09)	0.9124	0.99 (0.86, 1.14)	0.8839
Lost Pleasure in Activities (vs Never/rarely)				
Always	1.20 (0.90, 1.61)	0.2157	1.06 (0.73, 1.53)	0.7647
Often	1.04 (0.88, 1.25)	0.6355	1.22 (0.95, 1.56)	0.1197
Sometimes	1.03 (0.93, 1.14)	0.5560	1.12 (0.96, 1.29)	0.1451

The odds of ≥ mild (MoCA<26 vs. MoCA≥26) and moderate (MoCA<22 vs. MoCA ≥22) cognitive dysfunction are presented as odds ratios (OR) and 95% confidence intervals (CI) from multivariable models including all listed co-variates as well as randomized treatment. An OR>1 indicates greater odds of cognitive dysfunction. Depressive symptoms were 'low mood' and loss of interest in hobbies and activities with possible responses 'always', 'often', 'sometimes' and 'never'. Only low mood 'always', reported in 1.6% of respondents was associated with MoCA score <26 and <22. Associations of other risk factors with MoCA were similar before and after also adjusting for depressive symptoms.

Table S3. Statistical tests for interaction between sex, other risk factors and MoCA score.

All analyses are adjusted for all other covariates. The strongest interaction was between sex, geographic region and MoCA scores, and between sex, education and MOCA <22. There was also an interaction between sex, age and MoCA <26, but not MoCA <22.

	MoCA score <22		MoCA score <26	
(Sex and Baseline Factors)	**Chi-Square**	**P-value**	**Chi-Square**	**P-value**
Sex* Age <=65	1.431	0.232	8.006	0.005
Sex * Age > 65	0.020	0.889	3.844	0.050
Sex * Geographic Region	17.201	0.002	27.141	<.001
Sex * Physical Activity	4.054	0.044	1.094	0.296
Sex * Education	16.683	<.001	8.896	0.012
Sex * Hypertension	0.664	0.415	0.661	0.416
Sex * Diabetes requiring treatment	0.010	0.922	2.189	0.139
Sex * HDL	0.578	0.447	0.006	0.940
Sex * History of Stroke	1.534	0.215	2.006	0.157

Table S4. Sex differences in MoCA scores by geographic region of enrolment and by level of education.

	MoCA score <26			MoCA score <22		
Characteristics	**Male (N=3628)**	**Female (N=950)**	**P value**	**Male (N=1100)**	**Female (N=402)**	**P value**
Region of Enrollment			<.0001			<.0001
W. Europe Australia, NZ	927(25.6%)	163(17.2%)		251(22.8%)	54(13.4%)	
North America	835(23.0%)	138(14.5%)		222(20.2%)	44(10.9%)	
S. Africa Asia Pacific	675(18.6%)	241(25.4%)		229(20.8%)	117(29.1%)	
Eastern Europe	817(22.5%)	266(28.0%)		217(19.7%)	95(23.6%)	
South America	374(10.3%)	142(14.9%)		181(16.5%)	92(22.9%)	
Years of Education			<.0001			<.0001
None/1-8 years	951(26.6%)	420(45.4%)		425(39.2%)	249(64.3%)	
9-12 years	1061(29.7%)	249(26.9%)		315(29.1%)	81(20.9%)	
Trade school	664(18.6%)	125(13.5%)		165(15.2%)	33(8.5%)	
College/university	898(25.1%)	131(14.2%)		178(16.4%)	24(6.2%)	

P values are for interaction.