SUPPLEMENTAL MATERIAL

Long-term levels of LDL-C and cognitive function: The CARDIA Study

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Supplemental Table 1. Baseline (Year 0) characteristics of participants included and excluded from the current study.

	Included in current study (n=3,328)	Did Not Attend Year 25 Exam (n=1,617)	Attended Year 25 and with < 3 LDL-C measures (n=31)	Attended Year 25 and had missing cognitive measures (n=139)	p-value
Age, mean (SD)	25.1 (3.6)	24.3 (3.7)	25.5 (3.8)	25 (3.7)	< 0.001
Female, n(%)	1,875 (56.3)	806 (49.8)	21 (67.7)	85 (61.2)	< 0.001
Black, n(%)	1,527 (45.9)	997 (61.7)	18 (58.1)	95 (68.3)	< 0.001
Education > 12 year, n(%)	2,198 (66.0)	800 (49.5)	12 (38.7)	73 (52.5)	< 0.001
Current Smoking, n(%)	863 (25.9)	618 (38.2)	10 (32.3)	55 (39.6)	< 0.001
Alcohol use, n(%)					
Heavy	405 (12.2)	208 (12.9)	3 (9.7)	15 (10.8)	0.64
Moderate	1,648 (49.5)	761 (47.1)	17 (54.8)	63 (45.3)	
Never	1,275 (38.3)	645 (39.9)	11 (35.5)	60 (43.2)	
Total physical activity, mean (SD) in exercise units	422.3 (297.5)	423.1 (307.8)	325.2 (296.7)	355.1 (288.5)	0.02
BMI, mean (SD)	26.7 (1.5)	26.7 (1.5)	27.4 (1.7)	26.9 (1.5)	0.02
Total cholesterol, mean (SD)	177.2 (33.0)	175.3 (34.4)	191.3 (44.1)	179.2 (29.9)	0.02
HDL-C, mean (SD)	53.2 (12.8)	53 (14)	52.1 (13.9)	55.1 (13.2)	0.36
Triglycerides, mean (SD)	71.6 (44.8)	75 (53.6)	105.5 (117.6)	72.6 (43.9)	< 0.001
History of illicit drug use, n(%)	2,353 (70.7)	1,089 (67.3)	20 (64.5)	102 (73.4)	0.16
Diabetes, n(%)	29 (0.9)	27 (1.7)	1 (3.2)	2 (1.4)	0.0549
SBP, mean (SD)	109.9 (10.7)	111.4 (11.3)	108.6 (10.8)	112 (10.7)	< 0.001
DBP, mean (SD)	68.4 (9.4)	69 (10.1)	68.5 (8.9)	68.8 (9.9)	0.18
Antihypertensive medication use, n(%)	68 (2.0)	42 (2.6)	2 (6.5)	3 (2.2)	0.26

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; SD, standard deviation; SBP, systolic blood pressure

Supplemental Table 2. Missing data for model covariates

Covariate	Missing data, n(%)
Age	0 (0)
Gender	0 (0)
Race	0 (0)
Education	0 (0)
Current Smoking	41 (1.2)
Alcohol use	6 (0.2)
Total physical activity	1 (0.03)
BMI	3 (0.09)
Elevated depressive symptoms	24 (0.7)
History of illicit drug use	0 (0)
Diabetes	28 (0.8)
History of CHD*	0 (0)
History of stroke/TIA*	0 (0)
eGFR	12 (0.4)
SBP	4 (0.1)
DBP	5 (0.1)
Antihypertensive medication use	11 (0.3)
Statin Use	0 (0)
Other Lipid Lowering Medication	0 (0)
Antidepressant medication use	19 (0.6)
PCSK9 LOF variant (Y20)[†]	404 (12.1)

Apolipoprotein E phenotypes‡	409 (12.3)

Abbreviations: BMI, body mass index; CARDIA, Coronary Artery Risk Development in Young Adults; CHD, coronary heart disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; LDL-C, low-density lipoprotein-cholesterol; LOF, loss of function; PCSK9, proprotein convertase subtilisin/kexin type 9; SBP, systolic blood pressure; TIA, transient ischemic attack

*History of CHD and History of Stroke/TIA determined by adjudicated events prior to Year 25 examination

†Obtained at year 20 follow-up (2005-2006)

‡Obtained at year 7 follow-up (1992-1993)

Supplemental Table 3. Mean LDL-C and percentage of statin use and other lipid lowering medication use by time-averaged category of LDL-C

	Average LDL-C levels over follow-up, mg/dL			
	< 100 (n=519)	100–129 (n=1,094)	130-159 (n=961)	≥ 160 (n=754)
LDL-C, mean (SD)				
Year 0	77.7 (20)	98.1 (20.8)	115.4 (21.1)	141.9 (27.5)
Year 2	80.6 (21.7)	99.8 (22.1)	119.6 (21.3)	147 (29.5)
Year 5	75.6 (18.7)	95.8 (19.4)	114.6 (21.3)	142.1 (28.4)
Year 7	75.6 (18.7)	94.2 (19.1)	114.9 (21.7)	141.7 (25.5)
Year 10	76.8 (18.1)	96.1 (20.2)	116.3 (20.7)	142.4 (29.1)
Year 15	77.8 (18.2)	100.7 (20.7)	120 (22.6)	144.7 (28.1)
Year 20	76.6 (19.8)	100.3 (21.1)	117.2 (24.2)	138.3 (32.2)
Year 25	80.8 (20.3)	104.0 (22.3)	118.2 (27.3)	136.4 (36.2)
Statin use, %				
Year 0	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Year 2	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Year 5	0 (0%)	0 (0%)	0 (0%)	3 (0.4%)
Year 7	0 (0%)	0 (0%)	1 (0.1%)	0 (0%)
Year 10	0 (0%)	1 (0.1%)	2 (0.2%)	1 (0.1%)
Year 15	0 (0%)	6 (0.5%)	16 (1.7%)	31 (4.1%)
Year 20	2 (0.4%)	25 (2.3%)	66 (6.9%)	106 (14.1%)
Year 25	13 (2.5%)	63 (5.8%)	146 (15.2%)	219 (29.0%)
Other Lipid Lowering Medication Use, %				
Year 0	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Year 2	0 (0%)	1 (0.1%)	1 (0.1%)	1 (0.1%)
Year 5	0 (0%)	1 (0.1%)	0 (0%)	2 (0.3%)
Year 7	0 (0%)	0 (0%)	1 (0.1%)	1 (0.1%)
Year 10	0 (0%)	0 (0%)	3 (0.3%)	4 (0.5%)
Year 15	0 (0%)	1 (0.1%)	2 (0.2%)	4 (0.5%)

Year 20	2 (0.4%)	12 (1.1%)	18 (1.9%)	25 (3.3%)
Year 25	3 (0.6%)	16 (1.5%)	30 (3.1%)	26 (3.4%)

Abbreviations: LDL-C, low-density lipoprotein-cholesterol; SD, standard deviation

Supplemental Table 4. Multivariable adjusted standardized differences (95% confidence intervals) in cognitive function scores* across time-averaged LDL-C categories, by cognitive test and ApoE phenotype

Cognitive Test	ApoE Phenotype	Average LDL-C levels over follow-up, mg/dL				p-trend	p-interaction[†]
		< 100	100 – 129	130-159	≥ 160		
		Mean Difference (95% confidence interval)					
DSST	E2	Ref	-0.07 (-0.29, 0.15)	0.05 (-0.22, 0.32)	-0.14 (-0.53, 0.25)	0.81	0.57
	E3	Ref	-0.06 (-0.21, 0.09)	0.00 (-0.16, 0.16)	-0.09 (-0.27, 0.09)	0.57	
	E4	Ref	0.21 (-0.01, 0.44)	0.28 (0.03, 0.52)	0.33 (0.06, 0.59)	0.03	
RAVLT	E2	Ref	-0.10 (-0.33, 0.14)	-0.23 (-0.52, 0.06)	-0.15 (-0.56, 0.27)	0.20	0.09
	E3	Ref	-0.02 (-0.18, 0.13)	0.08 (-0.09, 0.25)	-0.12 (-0.30, 0.07)	0.40	

	E4	Ref	0.12 (-0.12, 0.35)	0.04 (-0.21, 0.30)	0.09 (-0.18, 0.37)	0.82	
Stroop Test	E2	Ref	0.11 (-0.14, 0.36)	0.13 (-0.17, 0.44)	0.05 (-0.39, 0.49)	0.54	0.63
	E3	Ref	-0.05 (-0.20, 0.09)	0.00 (-0.16, 0.16)	-0.01 (-0.19, 0.17)	0.72	
	E4	Ref	-0.06 (-0.31, 0.19)	-0.10 (-0.37, 0.17)	-0.04 (-0.34, 0.25)	0.89	

Abbreviations: ApoE, apolipoprotein E; CI, confidence interval; DSST, Digit Symbol Substitution Test; LDL, low-density lipoprotein-cholesterol; RAVLT, Rey Audio Visual Learning Test

Adjusts for age, race, sex, education, body mass index, diabetes, smoking status, alcohol use, physical activity, systolic and diastolic blood pressure and use of antihypertensive medications, estimated glomerular filtration rate, depressive symptoms, history of illicit drug use, history of coronary heart disease, and history of stroke/transient ischemic attack, statin use, other lipid lowering medication use and antidepressant medication use

*Lower standardized mean scores indicate worse performance on the DSST and RAVLT tests, but better performance on the Stroop Test.

†p-value for the interaction between ApoE phenotypes and LDL-C categories

Supplemental Table 5. Characteristics of participants included in the MRI subanalysis by category of time-averaged low-density lipoprotein-cholesterol.

	Time-averaged LDL-C levels over follow-up, mg/dL				
	< 100 (n=105)	100 – 129 (n=223)	130-159 (n=209)	≥ 160 (n=158)	p-trend[§]
Age, mean (SD)	47.5 (3.2)	49.4 (3.5)	51.1 (3)	52.5 (2.7)	< 0.001
Female, %	60 (57.1%)	122 (54.7%)	110 (52.6%)	71 (44.9%)	0.04
Black, %	51 (48.6%)	100 (44.8%)	66 (31.6%)	57 (36.1%)	0.004
Education > 12 years, %	71 (67.6%)	175 (78.5%)	168 (80.4%)	128 (81%)	0.02
Current Smoking, %	29 (27.6%)	34 (15.2%)	34 (16.3%)	16 (10.1%)	0.01
Alcohol use, %					
Heavy	21 (20%)	41 (18.4%)	30 (14.4%)	23 (14.6%)	0.51
Moderate	48 (45.7%)	94 (42.2%)	84 (40.2%)	71 (44.9%)	
Never	36 (34.3%)	88 (39.5%)	95 (45.5%)	64 (40.5%)	
Total physical activity, mean (SD) in exercise units	345.9 (268)	379.4 (279.1)	348.5 (275.1)	360.8 (274)	0.79
BMI, mean (SD)	26.6 (1.5)	26.7 (1.6)	26.5 (1.5)	26.6 (1.5)	0.46

BMI category, %					
<25	15 (14.3%)	28 (12.6%)	30 (14.4%)	23 (14.6%)	0.96
25-29.9	88 (83.8%)	193 (86.5%)	177 (84.7%)	134 (84.8%)	
>=30	2 (1.9%)	2 (0.9%)	2 (1%)	1 (0.6%)	
Total cholesterol	162.8 (23.4)	184.9 (25.9)	199.2 (28.2)	215.3 (40.3)	< 0.001
HDL cholesterol	61.4 (19.1)	59.1 (16.4)	56.5 (16.2)	54.3 (15.1)	< 0.001
Triglycerides	101.5 (89.1)	108.7 (86.6)	113.5 (70.6)	142.8 (159.7)	< 0.001
CES-D $\geq$ 16, %	14 (13.3%)	33 (14.8%)	25 (12%)	23 (14.6%)	0.95
History of illicit drug use, %	77 (73.3%)	170 (76.2%)	151 (72.2%)	120 (75.9%)	0.93
Diabetes, %	12 (11.4%)	21 (9.4%)	18 (8.6%)	19 (12%)	0.84
History of CHD*, %	0 (0%)	0 (0%)	3 (1.4%)	0 (0%)	0.49
History of stroke/TIA*, %	0 (0%)	0 (0%)	1 (0.5%)	2 (1.3%)	0.06
eGFR $\leq$ 60 ml/min/1.73m^2, %	1 (1%)	4 (1.8%)	3 (1.4%)	3 (1.9%)	0.68
SBP, mean (SD)	116 (14.7)	118.2 (15)	119.4 (15.9)	119.2 (13.3)	0.08
DBP, mean (SD)	72 (11.8)	73.9 (11.3)	74.4 (10.5)	74.2 (10.4)	0.12
Antihypertensive medication use, %	23 (21.9%)	36 (16.1%)	48 (23%)	45 (28.5%)	0.03

Statin Use, %	2 (1.9%)	9 (4%)	25 (12%)	46 (29.1%)	< 0.001
Other Lipid Lowering Medication, %	1 (1%)	3 (1.3%)	5 (2.4%)	5 (3.2%)	0.13
Antidepressant medication use, %	8 (7.6%)	17 (7.6%)	22 (10.5%)	22 (13.9%)	0.04
PCSK9 LOF variant carrier[†], %	8 (7.6%)	4 (1.8%)	5 (2.4%)	2 (1.3%)	0.01
Apolipoprotein E phenotypes[‡], %					
E2	35 (33.3%)	30 (13.5%)	21 (10%)	5 (3.2%)	< 0.001
E3	41 (39%)	115 (51.6%)	115 (55%)	88 (55.7%)	
E4	17 (16.2%)	56 (25.1%)	65 (31.1%)	53 (33.5%)	
Unknown	12 (11.4%)	22 (9.9%)	8 (3.8%)	12 (7.6%)	

Abbreviations: BMI, body mass index; CARDIA, Coronary Artery Risk Development in Young Adults; CES-D, Centers for Epidemiologic Studies Depression scale; CHD, coronary heart disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; LOF, loss of function; PCSK9, proprotein convertase subtilisin/kexin type 9; SD, standard deviation; SBP, systolic blood pressure; TIA, transient ischemic attack

Numbers in table are n(%) unless noted otherwise.

*History of CHD and History of Stroke/TIA determined by adjudicated events prior to Year 25 examination
†Obtained at year 20 follow-up (2005-2006)
‡Obtained at year 7 follow-up (1992-1993)
§Calculated using an interaction term between LDL-C category (ordinal) and each variable, separately

Supplemental Table 6. Characteristics of participants not included in the MRI subanalysis by category of time-averaged low-density lipoprotein-cholesterol.

	Time-averaged LDL-C levels over follow-up, mg/dL				
	< 100 (n=414)	100 – 129 (n=871)	130-159 (n=752)	≥ 160 (n=596)	p-trend[§]
Age, mean (SD)	46.8 (3.2)	49.1 (3.4)	51.1 (3.1)	52.7 (2.4)	< 0.001
Female, %	265 (64%)	537 (61.7%)	410 (54.5%)	300 (50.3%)	< 0.001
Black, %	251 (60.6%)	396 (45.5%)	324 (43.1%)	282 (47.3%)	< 0.001
Education > 12 years, %	306 (73.9%)	680 (78.1%)	598 (79.5%)	467 (78.4%)	0.11
Current Smoking, %	85 (20.5%)	149 (17.1%)	105 (14%)	91 (15.3%)	0.01
Alcohol use, %					
Heavy	61 (14.7%)	111 (12.7%)	105 (14%)	77 (12.9%)	0.76
Moderate	169 (40.8%)	353 (40.5%)	313 (41.6%)	230 (38.6%)	
Never	184 (44.4%)	404 (46.4%)	332 (44.1%)	288 (48.3%)	
Total physical activity, mean (SD) in exercise units	335.9 (287.6)	341 (267.4)	330.8 (282.3)	333.1 (270.8)	0.64
BMI, mean (SD)	26.8 (1.5)	26.7 (1.4)	26.8 (1.5)	26.6 (1.5)	0.06

BMI category, %					
<25	51 (12.3%)	93 (10.7%)	85 (11.3%)	93 (15.6%)	0.07
25-29.9	358 (86.5%)	772 (88.6%)	656 (87.2%)	495 (83.1%)	
>=30	5 (1.2%)	5 (0.6%)	9 (1.2%)	8 (1.3%)	
Total cholesterol	162 (27.9)	184.1 (27.1)	197.3 (33.8)	217.4 (41.2)	< 0.001
HDL cholesterol	62.9 (22.1)	58.8 (18.4)	56.9 (16.5)	54.9 (16.2)	< 0.001
Triglycerides	92.3 (65.2)	110.3 (89.1)	116 (72.2)	129.6 (87)	< 0.001
CES-D ≥ 16, %	88 (21.3%)	155 (17.8%)	120 (16%)	101 (16.9%)	0.08
History of illicit drug use, %	273 (65.9%)	583 (66.9%)	555 (73.8%)	435 (73%)	< 0.001
Diabetes, %	38 (9.2%)	103 (11.8%)	96 (12.8%)	104 (17.4%)	< 0.001
History of CHD*, %	0 (0%)	9 (1%)	13 (1.7%)	26 (4.4%)	< 0.001
History of stroke/TIA*, %	2 (0.5%)	10 (1.1%)	5 (0.7%)	12 (2%)	0.06
eGFR ≤ 60 ml/min/1.73m^2, %	7 (1.7%)	9 (1%)	16 (2.1%)	12 (2%)	0.27
SBP, mean (SD)	117.8 (16.1)	118.9 (16.7)	120.4 (15.8)	121.5 (16.4)	< 0.001
DBP, mean (SD)	74.3 (11.3)	74.4 (11.9)	75.2 (10.7)	75.8 (10.7)	< 0.001
Antihypertensive medication use, %	93 (22.5%)	200 (23%)	229 (30.5%)	213 (35.7%)	< 0.001

Statin Use, %	11 (2.7%)	54 (6.2%)	121 (16.1%)	173 (29%)	< 0.001
Other Lipid Lowering Medication, %	2 (0.5%)	13 (1.5%)	25 (3.3%)	21 (3.5%)	< 0.001
Antidepressant medication use, %	48 (11.6%)	107 (12.3%)	99 (13.2%)	76 (12.8%)	0.49
PCSK9 LOF variant carrier†, %	24 (5.8%)	24 (2.8%)	16 (2.1%)	3 (0.5%)	< 0.001
Apolipoprotein E phenotypes‡, %					
E2	121 (29.2%)	126 (14.5%)	69 (9.2%)	33 (5.5%)	< 0.001
E3	159 (38.4%)	439 (50.4%)	371 (49.3%)	285 (47.8%)	
E4	73 (17.6%)	203 (23.3%)	204 (27.1%)	195 (32.7%)	
Unknown	61 (14.7%)	103 (11.8%)	108 (14.4%)	83 (13.9%)	

Abbreviations: BMI, body mass index; CARDIA, Coronary Artery Risk Development in Young Adults; CES-D, Centers for Epidemiologic Studies Depression scale; CHD, coronary heart disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; LOF, loss of function; PCSK9, proprotein convertase subtilisin/kexin type 9; SD, standard deviation; SBP, systolic blood pressure; TIA, transient ischemic attack

Numbers in table are n(%) unless noted otherwise.

*History of CHD and History of Stroke/TIA determined by adjudicated events prior to Year 25 examination
†Obtained at year 20 follow-up (2005-2006)
‡Obtained at year 7 follow-up (1992-1993)
§Calculated using an interaction term between LDL-C category (ordinal) and each variable, separately

Supplemental Table 7. Distribution of participants across time-averaged LDL-C categories using LDL-C calculated with Friedewald

and Martin-Hopkins equations.

Average LDL-C levels over follow-up, mg/dL (Friedewald equation)	Average LDL-C levels over follow-up, mg/dL (Martin-Hopkins equation)				
	< 100	100 – 129	130-159	≥ 160	Total
< 100	736	30	0	0	766
100 – 129	67	1265	63	0	1395
130-159	0	80	1129	24	1233
≥ 160	0	0	59	1180	1239
Total	803	1375	1251	1204	4633

Abbreviations: LDL-C, low-density lipoprotein-cholesterol

Supplemental Table 8. Mean and standardized mean cognitive function scores by Martin-Hopkins calculated, time-averaged LDL-C categories.

	N	< 100	100 – 129	130-159	≥ 160	p-trend
		Average LDL-C levels over follow-up, mg/dL				
		Mean (SD)*				
DSST	3321	71.7 (16.9)	70.7 (16.6)	70.3 (15.5)	67.9 (14.9)	<0.001
RAVLT	3322	9.1 (2.0)	9.1 (1.9)	9.0 (1.9)	8.7 (1.9)	<0.001
Stroop Test	3320	22.4 (11.7)	22.3 (10.7)	22.5 (9.8)	23.9 (12.1)	0.01
		Standardized Mean* (SD)				
DSST	3321	0.10 (1.05)	0.03 (1.04)	0.01 (1.00)	-0.14 (0.93)	<0.001
RAVLT	3322	0.06 (1.04)	0.06 (1.00)	0.01 (1.00)	-0.13 (0.99)	<0.001
Stroop Test	3320	-0.03 (1.06)	-0.04 (0.97)	-0.02 (0.90)	0.10 (1.11)	0.01

Abbreviations: DSST, Digit Symbol Substitution Test; LDL-C, low-density lipoprotein-cholesterol; RAVLT, Rey Auditory Verbal Learning Test; SD, standard deviation
*Lower mean and standardized mean scores indicate worse performance on the DSST and RAVLT tests, but better performance on the Stroop Test.

Supplemental Table 9. Mean differences in standardized cognitive function scores* (95% confidence intervals) associated with Martin-Hopkins calculated, time-averaged LDL-C categories.

		Average LDL-C levels over follow-up, mg/dL				
		< 100	100 – 129	130-159	≥ 160	
		Estimate (95% confidence interval)				p-trend
DSST	Model 1	Ref	-0.08 (-0.18, 0.02)	-0.06 (-0.17, 0.04)	-0.10 (-0.22, 0.02)	0.23
	Model 2	Ref	-0.07 (-0.17, 0.02)	-0.04 (-0.14, 0.06)	-0.06 (-0.18, 0.05)	0.57
	Model 3	Ref	-0.07 (-0.17, 0.02)	-0.04 (-0.15, 0.06)	-0.07 (-0.19, 0.05)	0.48
RAVLT	Model 1	Ref	-0.07 (-0.17, 0.03)	-0.11 (-0.22, 0.00)	-0.19 (-0.32, -0.07)	0.001
	Model 2	Ref	-0.06 (-0.16, 0.04)	-0.10 (-0.21, 0.01)	-0.17 (-0.29, -0.05)	0.004
	Model 3	Ref	-0.06	-0.11	-0.19	0.002

			(-0.16, 0.04)	(-0.22, 0.00)	(-0.31, -0.06)	
Stroop Test	Model 1	Ref	0.04 (-0.06, 0.14)	0.09 (-0.02, 0.21)	0.11 (-0.01, 0.24)	0.046
	Model 2	Ref	0.03 (-0.07, 0.13)	0.07 (-0.04, 0.18)	0.09 (-0.04, 0.21)	0.12
	Model 3	Ref	0.03 (-0.07, 0.13)	0.07 (-0.04, 0.18)	0.08 (-0.05, 0.20)	0.17

Abbreviations: DSST, Digit Symbol Substitution Test; LDL, low-density lipoprotein-cholesterol; RAVLT, Rey Auditory Verbal Learning Test
Model 1 adjusts for age, race, sex, and education
Model 2 adjusts for Model 1 covariates plus BMI, diabetes, smoking status, alcohol use, physical activity, systolic and diastolic blood pressure and use of antihypertensive medications, eGFR, depressive symptoms, history of illicit drug use, history of CHD, and history of stroke/TIA
Model 3 adjusts for Model 2 covariates plus statin use, other lipid lowering medication use and antidepressant medication use
*Lower standardized mean scores indicate worse performance on the DSST and RAVLT tests, but better performance on the Stroop Test.