SUPPLEMENTAL MATERIAL

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

Matthew T Mefforda, Ligong Chena, Cora E. Lewisa, Paul Muntnera, Stephen Sidneyb, Lenore J. Launerc, Keri L. Mondad, Andrea Ruzzae, Helina Kassahune, Robert S. Rosensonf, April P. Carsona

aUniversity of Alabama at Birmingham, Birmingham, AL

bKaiser Permanente Division of Research, Oakland, CA

cIntramural Research Program, National Institute on Aging, Bethesda, MD

d Center for Observational Research, Amgen Inc., Thousand Oaks, CA

e Global Clinical Development, Cardiovascular and Metabolic Therapeutic Area, Amgen Inc., Thousand Oaks, CA

f Icahn School of Medicine at Mount Sinai, New York, NY

Address correspondence and reprint requests to:

April P. Carson, Department of Epidemiology, University of Alabama at Birmingham, 1665 University Boulevard, Birmingham, AL 35233, Phone / Fax: (205) 934-6107 / (205) 934-8665, E-mail: [apcarson@uab.edu](mailto:apcarson@uab.edu)

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

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | Average LDL-C levels over follow-up, mg/dL | | | |  |  |
|  |  | < 100 | 100 – 129 | 130-159 | ≥ 160 |  |  |
| Cognitive Test | ApoE Phenotype | Mean Difference (95% confidence interval) | | | | p-trend | p-interaction† |
| 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 ≥ 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 ≤ 60 ml/min/1.73m2, % | 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/1.73m2, % | 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.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  |  | Average LDL-C levels over follow-up, mg/dL | | | |  |
|  | N | < 100 | 100 – 129 | 130-159 | ≥ 160 | p-trend |
|  |  | **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  (-0.16, 0.04) | -0.11  (-0.22, 0.00) | -0.19  (-0.31, -0.06) | 0.002 |
|  | | | | | |  |
| 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.