ApoB, small-dense LDL-C, Lp(a), LpPLA₂ activity, and cognitive change

Yashashwi Pokharel, MD, MSCR, Farah Mouhanna, MS, Vijay Nambi, MD, PhD, Salim S. Virani, MD, PhD, Ron Hoogeveen, PhD, Alvaro Alonso, MD, PhD, Gerardo Heiss, MD, PhD, Josef Coresh, MD, PhD, Thomas Mosley, PhD, Rebecca F. Gottesman, MD, PhD, Christie M. Ballantyne, MD, and Melinda C. Power, ScD

Correspondence

Dr. Pokharel
pokharely@umkc.edu

Neurology® 2019;92:e2580-e2593. doi:10.1212/WNL.0000000000007574

Abstract

Objective

To examine the association of specific lipoproteins/inflammatory enzyme with cognitive change.

Methods

We examined the association of apolipoprotein B (ApoB), small-dense low-density lipoprotein cholesterol (sdLDL-C), lipoprotein (a) (Lp[a]), and lipoprotein-associated phospholipase A₂ (LpPLA₂) activity with 15-year change in Delayed Word Recall Test, Digit Symbol Substitution Test (DSST), Word Fluency Test (WFT), and overall summary score in 9,350 participants in the Atherosclerosis Risk in Communities study. We assessed interaction by race, sex, education, APOE ε4 status, and statin use. We also addressed questions of informative missingness, the role of stroke, and the influence of fasting status.

Results

The mean (SD) age was 63.4 (5.7) years; 56.4% were women and 17.4% were black. We observed faster cognitive decline on DSST and global z scores with every 10-mg/dL higher sdLDL-C level (Δ DSST z score, -0.010 ; 95% confidence interval [CI] -0.017 , -0.002 and Δ global z score, -0.011 ; -0.021 , -0.001) and the highest vs the lowest ApoB quintiles (Δ DSST z score, -0.092 ; -0.0164 , -0.019 and Δ global z score, -0.101 ; -0.200 , -0.002). Association for the ApoB quintiles with Δ global z score (-0.10) was comparable with that of having 1 APOE ε4 allele (-0.11). Higher Lp(a) was associated with slower decline in DSST, WFT, and global z scores. LpPLA₂ activity was not associated with cognitive change. Results were similar in sensitivity analyses. The associations of sdLDL-C or Lp(a) on cognitive change were more pronounced in statin users.

Conclusions

Optimal control of atherogenic lipoproteins such as ApoB and sdLDL-C in midlife for cardiovascular health may also benefit late-life cognitive health.

From Saint Luke's Mid-America Heart Institute (Y.P.), University of Missouri–Kansas City; Department of Epidemiology and Biostatistics (F.M., M.C.P.), George Washington University Milken Institute School of Public Health, Washington, DC; Department of Epidemiology (F.M., A.A.), Rollins School of Public Health, Emory University, Atlanta, GA; Section of Cardiology (V.N., S.S.V.), Michael E. DeBakey Veterans Affairs Medical Center; Section of Cardiology (V.N., S.S.V., R.H., C.M.B.), Baylor College of Medicine; Center for Cardiovascular Disease Prevention (V.N., S.S.V., R.H., C.M.B.), Houston Methodist DeBakey Heart and Vascular Center, TX; Department of Epidemiology (G.H.), Gillings School of Global Public Health, University of North Carolina, Chapel Hill; Department of Epidemiology (J.C., R.F.G.), Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD; Department of Medicine (T.M.), University of Mississippi Medical Center, Jackson; Department of Neurology (R.F.G.), Johns Hopkins University, Baltimore, MD.

Go to [Neurology.org/N](https://www.neurology.org/N) for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Glossary

ApoB = apolipoprotein B; **ARIC** = Atherosclerosis Risk in Communities; **CI** = confidence interval; **DSST** = Digit-Symbol Substitution Test; **DWRT** = Delayed Word Recall Test; **LDL-C** = low-density lipoprotein cholesterol; **Lp(a)** = lipoprotein (a); **LpPLA₂** = lipoprotein-associated phospholipase A₂; **sdLDL-C** = small dense low-density lipoprotein cholesterol; **WFT** = Word Fluency Test.

Evidence of cognitive decline is a requirement for dementia diagnosis,¹ and it is well-established that cognitive decline accelerates in the years prior to a dementia diagnosis.² Thus, this period, where cognitive change is occurring but cognition is not impaired, may represent a potential therapeutic window for interventions.³ Stroke,⁴ subclinical atherosclerosis,⁵ and traditional cardiovascular risk factors,^{6–9} including elevated total cholesterol and low-density lipoprotein cholesterol (LDL-C),^{6,10–13} are all associated with increased risk for cognitive decline, attesting to the importance of vascular health for late-life cognitive health. However, the mechanisms underlying the link between cardiovascular health and late-life cognition, as well as ideal treatment of vascular risk factors for the preservation of cognition, remain unclear.

Consideration of biomarkers linked to atherosclerosis and cardiovascular health may yield additional insight. Apolipoprotein B (ApoB) reflects total atherogenic lipoprotein particles including and beyond explained by LDL-C.¹⁴ Lipoprotein (a) (Lp[a]) has been implicated by Mendelian randomization studies to be in the causal pathway for atherosclerotic cardiovascular disease.¹⁵ Small dense LDL-C (sdLDL-C) is a measure of the cholesterol content in small dense low-density lipoproteins that likely have enhanced atherogenic potential.^{16,17} Lipoprotein-associated phospholipase A₂ (LpPLA₂) is an enzyme transported by lipoproteins and secreted by inflammatory cells in atherosclerotic plaques.¹⁸ These lipoproteins and enzymes may be involved in subclinical and overt brain injury leading to cognitive change through a variety of mechanisms, including enhancing atherosclerosis, thrombosis, inflammation, microvascular dysfunction, and hypoperfusion.^{14,19–22} However, the existing data on the association between these biomarkers and cognition show conflicting results and are constrained by smaller sample sizes and case-control or cross-sectional designs.^{23–31} Thus, the purpose of this study was to examine the associations of baseline levels of ApoB, sdLDL-C, Lp(a), and LpPLA₂ activity with 15-year change in cognitive function in the Atherosclerosis Risk in Communities (ARIC) study.

Methods

Study population

The ARIC study is an ongoing, prospective cohort study of adults ages 45–65 at baseline (1987–1989) recruited from 4 US communities: suburbs of Minneapolis, Minnesota; Jackson, Mississippi; Forsyth County, North Carolina; and Washington County, Maryland. ARIC visit 4 (1996–1998)

served as the baseline study visit for our analyses, as the lipoproteins/enzyme were quantified at this study visit. We excluded nonblack participants, nonwhite participants, nonwhite participants from the Minnesota or Maryland sites because of small numbers, persons who did not provide permission to use genetic data, and those who died before ARIC visit 4. The ARIC study has been approved by institutional review boards at all participating institutions. Study participants provided written informed consents.

Exposure assessment

Lipid measurements were performed on a plasma sample that was stored at -70°C with ethylenediaminetetraacetic acid as the anticoagulant; 98% of participants were fasting >8 hours at blood draw. Plasma ApoB levels were measured by immunonephelometric assay.²⁰ A homogeneous assay method was used for the direct measurement of sdLDL-C in plasma (sdLDL-EX Seiken; Denka Seiken, Tokyo, Japan) on a Hitachi 917 automated chemistry analyzer.²⁰ Lp(a) was measured using a commercially available automated isoform insensitive immunoturbidimetric assay (Denka Seiken).³² Plasma LpPLA₂ activity was measured at -70°C using an automated Colorimetric Activity Method assay (diaDexus, South San Francisco, CA) using a Beckman Coulter (Sharon Hill, PA) (Olympus) AU400e AutoAnalyzer. We excluded 2 individuals with implausible values of ApoB and LpPLA₂ activity. We modeled lipoprotein/enzyme levels using both linear terms and quintiles.

Outcome assessment

Three cognitive tests were administered at ARIC visits 2, 4, and 5 (2011–2013). We consider cognitive scores from eligible participants at visits 4 (analysis baseline) and 5. The 3 cognitive tests—the Delayed Word Recall Test (DWRT),³³ the Digit-Symbol Substitution Test (DSST),³⁴ and the Word Fluency Test (WFT)³⁵—assess different cognitive domains. The DWRT is a test of verbal learning and memory, the DSST is a test of executive function, and the WFT is a test of semantic fluency. Scores from each test were approximately normally distributed, without evidence of severe floor or ceiling effects. For use in analysis, we considered normalized scores, transformed based on the mean and SD of scores from ARIC participants at visit 2, and a standardized summary measure computed by normalizing and averaging the sum of the 3 individual test *z* scores in a similar manner.

Covariates

We obtained sociodemographic information via participants' self-report at ARIC visit 1, including sex (male/female), race/

Figure 1 Sample development

center (black in Mississippi, black in North Carolina, white in North Carolina, white in Minnesota, white in Maryland), education (< high school, high school or equivalent, > high school), and health insurance status (yes/no). We characterized *APOE* $\epsilon 4$ allele status (0, 1, or 2 $\epsilon 4$ alleles). We obtained measures of diet and leisure time physical activity from ARIC visit 3. Participants were considered to be inactive if they had a sport activity score of <2³⁶ from the Baecke Questionnaire.³⁷ Measures of adherence to 2 dietary patterns, a “prudent” and “Western” pattern, were obtained from principal components analysis of food frequency questionnaire data.³⁸ Briefly, the prudent dietary pattern was rich in cruciferous and carotenoid vegetables, fruit, fish, and poultry, whereas the Western dietary pattern was rich in refined grains, processed meat, fried foods, and red meat.³⁸ All other covariates were defined using data from visit 4. We considered age, self-reported alcohol use and smoking status (current, former, or never), and body mass index. We defined diabetes as self-reported physician diagnosis of diabetes, fasting glucose ≥ 126 mg/dL, nonfasting glucose ≥ 200 mg/dL, or use of prescribed diabetes medications. We defined hypertension as sitting systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg, or use of antihypertensive medications. Stroke was defined as sudden or rapid onset of neurologic symptoms that lasted for 24 hours or led to death in the absence of another cause.²¹ Participants were classified as users or non-users of lipid-lowering medications through an inventory of medications at the study visit, with linkage to Medi-Span Therapeutic Classification codes. Lipid-lowering therapy included statins, ezetimibe, bile-acid binding resins, niacin,

fibrates, and prescription fish oil, in isolation or in combination. Standard lipids were measured in stored blood samples obtained at visit 4. Plasma total cholesterol, high-density lipoprotein cholesterol, and triglycerides were measured using enzymatic methods,^{39,40} while LDL-C was calculated using the Friedewald equation for those with triglycerides <400 mg/dL.⁴¹

Statistical methods

We modeled the association of the lipoproteins/enzyme with 15-year change in cognitive test scores using linear mixed models. We used time on study as the time scale and an independent covariance matrix for the 2 random effects: a random intercept and a random slope. Lipids were parameterized as both continuous and categorical variables. Continuous lipid values and covariates were centered prior to inclusion in the model. Our primary analytic cohort comprised those with necessary nonmissing covariate, exposure, and cognitive data at visit 4. We treated the exposures as both linear and quintile terms, and in addition as clinically relevant cutoffs.^{15,42–44} All analyses were adjusted for age, age-squared, education, sex, race/center, body mass index, smoking status, alcohol use, diabetes, hypertension, physical activity, adherence to a prudent dietary pattern and Western dietary pattern, use of lipid-lowering medications, health insurance status, and *APOE* $\epsilon 4$ allele status, by including terms for both the main effects and their interaction with time.

We conducted several sensitivity analyses. First, we in addition adjusted analyses of Lp(a) and LpPLA₂ activity for LDL-

C cholesterol. Second, we repeated our primary analyses excluding persons who had experienced stroke prior to visit 5 and limiting analysis in those who were fasting at the time of blood collection. Third, we implemented multiple imputation to address missing data, including both missing exposure/covariate data and missing data due to loss to follow-up, which could lead to selection bias, using methods previously developed for this purpose.^{6,45} First, we multiply imputed missing exposure and covariate data at visit 4 to understand the effect of these missing data. Second, we multiply imputed missing exposure and covariate data, as well as cognitive scores at visits 4 and 5 for those known to be alive at the time of each study visit and who did not complete cognitive testing. Finally, we multiply imputed missing exposure, covariate, and cognitive data as above and in addition imputed cognitive tests scores from 6 months prior to death for those who died between visits 4 and 5. For all multiple imputation models, we used a burn-in of 25 iterations, and report results based on combined estimates from 5 imputations. Finally, we used multiplicative interaction terms to determine whether our associations differed by race, sex, education, *APOE* ϵ 4 status, lipid-lowering medication use at visit 4, and statin use at visit 4 and report stratified analyses where *p* values suggested significant evidence of interaction. In exploratory analyses, we also considered effect modification by whether or not the participant developed dementia during follow-up, ascertained via in-person assessment at visit 5 for those who attended the study visit and retrospective surveillance for visit 5 non-participants. All analyses were completed with Stata, version 15 (StataCorp, College Station, TX).

Data availability

Researchers can obtain ARIC data from the NIH public data repository (BioLINCC, biolincc.nhlbi.nih.gov/studies/aric/) after signing an agreement.

Results

Baseline data

While 13,848 persons met our eligibility criteria and were included in our sensitivity analyses using multiple imputations, 9,350 persons had necessary nonmissing covariate, exposure, and visit 4 cognitive data for inclusion in our primary analyses (figure 1 and tables 1 and 2). Of those meeting data availability criteria for inclusion in our primary analyses, 27.7% had missing visit 5 cognitive score (but were alive) and 21.6% were deceased by visit 5. Table 1 shows characteristics of the sample that met our eligibility criteria and table 2 shows characteristics for those meeting data availability criteria for inclusion in primary analyses.

Among the participants in our primary analyses sample, the mean (SD) age was 63.4 (5.7) years at baseline (visit 4) and 76.2 (5.2) years at follow-up (visit 5); 56.4% were women, 17.4% were black (table 2). Approximately 3.5% (*n* = 658) had prevalent stroke at visit 5. Distributions of triglycerides

and Lp(a) were highly skewed; the median (Q1, Q3) was 124 (90, 175) mg/dL for triglycerides and 12.2 (4.9, 38) mg/dL for Lp(a).

We found little correlation between Lp(a) and any of the other analytes (LpPLA₂ activity, ρ = -0.05; sdLDL, ρ = -0.03; ApoB, ρ = 0.12); moderate correlation between LpPLA₂ activity and sdLDL (ρ = 0.34) and ApoB (ρ = 0.37); and a strong correlation between sdLDL and ApoB (ρ = 0.75). Results were similar when we considered Pearson rather than Spearman correlations.

For most biomarker–cognitive test score combinations, there was little evidence to support differences in baseline cognition per 10 mg/dL higher baseline biomarker levels. The 3 exceptions were as follows: (1) LpPLA₂ activity and global *z* score (difference at baseline per 10 mg/dL higher LpPLA₂ activity: -0.003; 95% confidence interval [CI] -0.006, 0; *p* value 0.048), (2) LpPLA₂ activity and WFT *z* score (difference at baseline per 10 mg/dL higher LpPLA₂ activity: -0.005; 95% CI -0.009, -0.002; *p* value 0.003), and (3) sdLDL-C and DSST *z* scores (difference at baseline per 10 mg/dL higher sdLDL-C: 0.009; 95% CI 0.002, 0.015; *p* value 0.01).

Primary analysis

Relative to persons in the lowest quintile of ApoB, those in the highest quintile exhibited greater cognitive decline in global *z* scores (-0.101; 95% CI -0.2, -0.002), which was largely driven by accelerated decline in DSST scores (-0.092; 95% CI -0.164, -0.019). However, there was little evidence for a linear trend (table 3). Although the associations between sdLDL-C and average cognitive change among those in higher quintiles compared to those in the lowest quintile were individually null, there was a significant linear trend when considering global *z* score (-0.011 per 10 mg/dL higher sdLDL-C; 95% CI -0.021, -0.001), which was mainly due to accelerated decline in DSST *z* score (-0.010 per 10 mg/dL higher sdLDL-C; 95% CI -0.017, -0.002). Individuals in the highest Lp(a) quintile compared with the lowest Lp(a) quintile had slower decline in global *z* score (0.079; 95% CI 0.002, 0.156), mostly driven by less decline in WFT *z* score (0.084; 95% CI 0.012, 0.157). Every 10 mg/dL higher Lp(a) level was associated with less decline in global *z* score of 0.007 standard units (95% CI 0, 0.014), mainly due to less decline in DSST *z* score (0.007; 95% CI 0.002, 0.012). There were no significant associations of LpPLA₂ activity with cognitive change. When comparing those with elevated levels to those with normal levels based on clinically relevant exposure cut-offs, we found faster decline in DSST *z* score with higher ApoB and sdLDL-C, less decline in DSST *z* score with higher Lp(a), and no significant association for LpPLA₂ activity (table 4).

Sensitivity analyses

When the models were further adjusted for LDL-C, associations were attenuated for Lp(a) and were similar for LpPLA₂

Table 1 Demographic and health characteristics at study baseline of eligible sample used in multiple imputation sensitivity analyses (n = 13,484)

Variables	Eligible sample, mean or n (%) ^a
Age, y	63.4
Male sex	5,919 (43.9)
Education, y	
<12	2,804 (20.8)
12 to <16	5,649 (41.9)
≥16	5,043 (37.4)
Race/center	
White, Minnesota	3,654 (27.1)
White, Maryland	3,492 (25.9)
White, North Carolina	3,155 (23.4)
Black, North Carolina	364 (2.7)
Black, Mississippi	2,818 (20.9)
APOE ε4 genotype status	
0 ε4 alleles	9,357 (69.4)
1 ε4 allele	3,775 (28.0)
2 ε4 alleles	350 (2.6)
Smoking status	
Current	2,184 (16.2)
Former	5,892 (43.7)
Never	5,407 (40.1)
Alcohol use	
Current	6,458 (47.9)
Former	4,072 (30.2)
Never	2,939 (21.8)
Hypertension	6,634 (49.2)
Diabetes	2,467 (18.3)
Physically active	10,126 (75.1)
Lipid-lowering medication user	2,022 (15.0)
Statin user	1,739 (12.9)
Preretirement health insurance present	12,364 (91.7)
Prudent diet score at visit 3 (unitless) ^b	−0.001
Western diet score at visit 3 (unitless) ^b	0.005
Body mass index, kg/m ²	28.8
Total cholesterol, mg/dL	200.6
Low-density lipoprotein cholesterol, mg/dL	122.4

Table 1 Demographic and health characteristics at study baseline of eligible sample used in multiple imputation sensitivity analyses (n = 13,484)
(continued)

Variables	Eligible sample, mean or n (%) ^a
High-density lipoprotein cholesterol, mg/dL	49.8
Triglycerides, mg/dL	144.9
Apolipoprotein B, mg/dL	99.4
Small dense low-density lipoprotein cholesterol, mg/dL	43.8
Lipoprotein (a), mg/dL	27.9
Lipoprotein-associated phospholipase A ₂ , nmol/min/mL	229.2

^a Based on multiply imputed datasets; thus, we do not provide SD.
^b Higher values indicate greater adherence to the dietary pattern.

activity (data not shown). For the most part, results of analyses using multiple imputation to address potential selection bias due to missing data were similar to primary analysis (table 5; other data not shown). However, we noted some differences, including the appearance of significant associations of sdLDL-C with excess decline in WFT *z* scores after imputing exposure, covariate, and cognitive data and significant associations of LpPLA₂ activity with slower decline in DWRT and WFT *z* scores after imputing exposure and covariate data for some individual quintile contrasts. Results were also broadly similar after excluding persons who had prevalent stroke at visit 5 or who were fasting at the time of blood collection (data not shown).

Effect modification

Results did not differ by race, education, sex, or APOE ε4 status. However, the adverse association relating higher sdLDL-C to faster cognitive decline was stronger in those using statins at visit 4 than in nonusers (interaction *p* values: 0.03, 0.05, 0.01, and 0.05 for DSST, DWRT, global, and WFT *z* scores, respectively; figure 2A). Conversely, the association of Lp(a) on slower cognitive change on global and DWRT *z* scores was more pronounced in statin users compared to nonusers (interaction *p* values: 0.03 and 0.01 for DWRT and global *z* scores, respectively; figure 2B). The pattern was similar, but with less often significant interaction, when considering effect modification by all lipid-lowering medications.

In our exploratory analyses, associations between a 10 mg/dL increase in sdLDL-C or ApoB and decline in DSST scores were stronger in those who ultimately developed dementia during follow-up (interaction *p* values 0.002 and 0.058 with sdLDL-C and ApoB, respectively). However, these did not translate into statistically significant effect modification of associations with the global *z* score. Interestingly, there was

Table 2 Demographic and health characteristics at study baseline of the primary analytic sample (n = 9,350)

Variables	Primary analysis sample (n = 9,350), mean (SD) or n (%)
Age, y	63.4 (5.7)
Male sex	4,072 (43.6)
Education, y	
<12	1,582 (16.9)
12 to <16	4,072 (43.6)
≥16	3,696 (39.5)
Race/center	
White, Minnesota	2,890 (30.9)
White, Maryland	2,548 (27.3)
White, North Carolina	2,288 (24.5)
Black, North Carolina	209 (2.4)
Black, Mississippi	1,415 (15.1)
APOE ε4 genotype status	
0 ε4 alleles	6,570 (70.3)
1 ε4 allele	2,544 (27.2)
2 ε4 alleles	236 (2.5)
Smoking status	
Current	1,290 (13.8)
Former	4,135 (44.2)
Never	3,925 (42.0)
Alcohol use	
Current	4,735 (50.6)
Former	2,762 (29.5)
Never	1,853 (19.8)
Hypertension	4,376 (46.8)
Diabetes	1,465 (15.7)
Physically active	7,173 (76.7)
Lipid-lowering medication user	1,350 (14.4)
Statin user	1,165 (12.5)
Preretirement health insurance present	8,778 (93.9)
Prudent diet score at visit 3 (unitless) ^a	−0.004 (0.94)
Western diet score at visit 3 (unitless) ^a	−0.043 (0.92)
Body mass index, kg/m ²	28.7 (5.5)
Total cholesterol, mg/dL	200.5 (36.3)

Table 2 Demographic and health characteristics at study baseline of the primary analytic sample (n = 9,350) (continued)

Variables	Primary analysis sample (n = 9,350), mean (SD) or n (%)
Low-density lipoprotein cholesterol, mg/dL	122.1 (33.1)
High-density lipoprotein cholesterol, mg/dL	50.0 (16.4)
Triglycerides, mg/dL	145.1 (85.2)
Apolipoprotein B, mg/dL	99.3 (23.4)
Small dense low-density lipoprotein cholesterol, mg/dL	43.9 (20.5)
Lipoprotein (a), mg/dL	25.4 (30.1)
Lipoprotein-associated phospholipase A ₂ , nmol/min/mL	229.9 (61.6)

^a Higher values indicate greater adherence to the dietary pattern.

also effect modification for the association between ApoB and WFT scores, with those who ultimately developed dementia exhibiting marked cognitive decline with ApoB (−0.047; 95% CI −0.091, −0.004) vs those who did not (−0.002; 95% CI −0.010, 0.006; *p* value for interaction: 0.04). Similarly, the associations observed between higher Lp(a) and slower cognitive decline on DSST, WFT, and global *z* scores was stronger in those who ultimately developed dementia during follow-up (figure 2C).

Discussion

Using a biracial, large, prospective cohort study, we showed that higher levels of ApoB as well as sdLDL-C were associated with greater cognitive decline, primarily in executive function, over 15 years. Analysis using quintile and linear terms to assess for nonlinear relationships indicated that the association between ApoB and cognitive change may be limited to those with high ApoB levels, whereas the association with sdLDL-C appears linear. Conversely, higher Lp(a) levels were associated with slower cognitive decline in semantic fluency. These associations were more pronounced in those with baseline use of statin therapy. Broadly, there was no association between LpPLA₂ activity and cognitive change. Results were similar across multiple sensitivity analyses. Associations were generally stronger in people who ultimately developed dementia during follow-up, supporting the hypothesis that our observed associations were driven by effects on dementia pathogenesis. To contextualize, the observed strength of association of the highest quintile of ApoB with 15-year change in global *z* score (i.e., −0.10) was almost comparable to 15-year change in global *z* score seen with the presence of 1 APOE ε4 allele (i.e., −0.11), a known risk factor for Alzheimer disease.

Table 3 Average adjusted difference in 15-year cognitive change across quintile categories and per 10 units higher lipoprotein levels, primary analysis sample (1996–2013)

Lipoproteins	Adjusted difference in 15-year cognitive change ^a							
	Global z score		DWRT z score		DSST z score		WFT z score	
	Estimate (95% CI)	p Value	Estimate (95% CI)	p Value	Estimate (95% CI)	p Value	Estimate (95% CI)	p Value
ApoB, mg/dL (n = 8,790)								
Per 10 mg/dL	−0.005 (−0.013, 0.004)	0.29	−0.003 (−0.018, 0.011)	0.65	−0.005 (−0.011, 0.002)	0.17	−0.002 (−0.011, 0.006)	0.55
<80	Ref		Ref		Ref		Ref	
80–100	−0.033 (−0.09, 0.023)	0.25	−0.08 (−0.174, 0.014)	0.09	0.033 (−0.009, 0.074)	0.12	−0.046 (−0.099, 0.006)	0.08
100–120	−0.034 (−0.092, 0.024)	0.25	−0.083 (−0.18, 0.015)	0.10	0.022 (−0.021, 0.064)	0.32	−0.027 (−0.081, 0.028)	0.34
120–140	−0.026 (−0.102, 0.049)	0.49	−0.027 (−0.152, 0.098)	0.67	−0.015 (−0.07, 0.039)	0.58	−0.04 (−0.11, 0.03)	0.27
140+	−0.101 (−0.2, −0.002)	0.046	−0.076 (−0.242, 0.09)	0.37	−0.092 (−0.164, −0.019)	0.01	−0.058 (−0.151, 0.035)	0.22
sdLDL-C, mg/dL (n = 9,304)								
Per 10 mg/dL	−0.011 (−0.021, −0.001)	0.04	−0.01 (−0.027, 0.007)	0.26	−0.01 (−0.017, −0.002)	0.01	−0.005 (−0.015, 0.005)	0.31
<28	Ref		Ref		Ref		Ref	
28–40	−0.028 (−0.084, 0.027)	0.32	−0.053 (−0.146, 0.039)	0.26	0.014 (−0.027, 0.055)	0.50	−0.038 (−0.09, 0.014)	0.16
40–55	0.011 (−0.046, 0.067)	0.72	−0.001 (−0.095, 0.094)	0.99	0.01 (−0.031, 0.051)	0.64	0.013 (−0.04, 0.067)	0.63
55–82	−0.051 (−0.112, 0.011)	0.10	−0.078 (−0.18, 0.023)	0.13	−0.029 (−0.073, 0.016)	0.21	−0.031 (−0.089, 0.027)	0.29
82+	−0.08 (−0.181, 0.02)	0.12	−0.068 (−0.235, 0.099)	0.42	−0.065 (−0.137, 0.008)	0.08	−0.008 (−0.103, 0.086)	0.86
Lp(a), mg/dL (n = 9,304)								
Per 10 mg/dL	0.007 (0, 0.014)	0.04	0.005 (−0.006, 0.017)	0.37	0.007 (0.002, 0.012)	0.01	0.006 (0, 0.013)	0.06
<5	Ref		Ref		Ref		Ref	
5–13	0.017 (−0.038, 0.071)	0.55	0.01 (−0.081, 0.1)	0.83	−0.012 (−0.051, 0.028)	0.57	0.017 (−0.034, 0.069)	0.50
13–40	0.015 (−0.043, 0.072)	0.61	0.033 (−0.063, 0.129)	0.50	−0.014 (−0.056, 0.028)	0.51	0.013 (−0.042, 0.067)	0.65
40–70	0.032 (−0.034, 0.097)	0.34	0.025 (−0.085, 0.134)	0.66	0.046 (−0.002, 0.093)	0.06	0.002 (−0.06, 0.063)	0.96
70+	0.079 (0.002, 0.156)	0.04	0.048 (−0.08, 0.176)	0.46	0.044 (−0.012, 0.1)	0.12	0.084 (0.012, 0.157)	0.02
LpPLA₂ activity, nmol/min/mL (n = 9,111)								
Per 10 nmol/min/mL	0.002 (−0.002, 0.007)	0.23	0.004 (−0.003, 0.01)	0.29	−0.002 (−0.005, 0.001)	0.22	0.003 (−0.001, 0.007)	0.10

Continued

Table 3 Average adjusted difference in 15-year cognitive change across quintile categories and per 10 units higher lipoprotein levels, primary analysis sample (1996–2013)
(continued)

Lipoproteins	Adjusted difference in 15-year cognitive change ^a					
	Global z score		DWRT z score		DSST z score	
	Estimate (95% CI)	p Value	Estimate (95% CI)	p Value	Estimate (95% CI)	p Value
	Ref	Ref	Ref	Ref	Ref	Ref
<190						
190–230	0.03 (–0.025, 0.084)	0.29	0.062 (–0.029, 0.153)	0.18	–0.003 (–0.043, 0.037)	0.87
230–270	0.006 (–0.056, 0.067)	0.85	–0.008 (–0.109, 0.094)	0.88	–0.01 (–0.055, 0.035)	0.65
270–330	0.024 (–0.046, 0.094)	0.50	0.012 (–0.104, 0.127)	0.84	–0.019 (–0.07, 0.033)	0.48
330+	0.036 (–0.071, 0.143)	0.51	0.088 (–0.087, 0.263)	0.32	–0.048 (–0.125, 0.03)	0.23

Abbreviations: ApoB = apolipoprotein B; CI = confidence interval; DSST = Digit-Symbol Substitution Test; DWRT = Delayed Word Recall Test; Lp(a) = lipoprotein (a); LpPLA₂ = lipoprotein-associated phospholipase A₂; sdLDL-C = small dense low-density lipoprotein cholesterol; WFT = Word Fluency Test.
^a Adjusted for baseline age, age squared, education, sex, race/center, body mass index, alcohol use, smoking status, diabetes, hypertension, physical activity, adherence to a Western dietary pattern, adherence to a prudent dietary pattern, cholesterol-lowering medication use, preretirement health insurance status, and APOE ε4 status.

Although the observed effect of these lipids on cognitive change in an average individual are estimated to be small, the population-attributable effect of the observed effects is relevant given unfavorable population distributions of these lipid parameters.⁴⁶ In the context of the increasing burden of dementia⁴⁷ and accumulating evidence for traditional and nontraditional cardiovascular risk factors in cognitive decline and dementia,^{6–13} our study provides support for the atherothrombotic hypothesis for cognitive decline and dementia.

Consistent with our findings, most prior studies of ApoB showed important adverse associations with cognitive decline or dementia.^{26,27} We found that sdLDL-C was also associated with increased cognitive decline. The association of sdLDL-C and cognitive decline was amplified in persons using statins. While we cannot rule out chance, this most likely reflects unmeasured confounding. People with higher sdLDL-C are more likely to be treated with statins (14.5% vs 11.5% in people with sdLDL-C ≥50 mg/dL vs those with <50 mg/dL in our study), as they have increased propensity to atherosclerosis and perhaps a longer lifetime exposure to higher cholesterol levels. This finding requires additional confirmation; it should not be used to justify ceasing or not starting statin use for cardiovascular benefits.

Prior studies of Lp(a) with cognitive performance and dementia have shown either null association²⁴ or increased risk,²³ but were limited in their design. We found that higher baseline Lp(a) was associated with slower cognitive decline, which was substantiated in multiple sensitivity analyses. This mirrors a prior prospective study showing a protective association of higher Lp(a) for incident dementia in middle-aged Finnish men.²⁵ We further observed that the association of Lp(a) and cognitive decline may be pronounced in those on statin or lipid-lowering therapy. This requires further understanding; while it could be a chance finding or unmeasured confounding, some plausible explanations include that people with elevated Lp(a) levels are more likely to be treated with a statin (18.5% vs 11.2% in people with Lp[a] ≥50 mg/dL vs <50 mg/dL in our study), and Lp(a) level can increase following the initiation of statin therapy.¹⁵

Our data do not support associations between LpPLA₂ activity and cognitive change. A prior case–control study of loss-of-function mutation of LpPLA₂ gene showed similar null results for Alzheimer dementia in a Japanese population.²⁸ Other studies have shown conflicting results.^{29–31} Although LpPLA₂ activity predicts cardiovascular risk,^{21,22} our data suggest that it is not associated with cognitive change.

Accelerated cognitive decline associated with ApoB and sdLDL-C could be related to their atherothrombotic properties, microvascular dysfunction, and hypoperfusion with subsequent ischemic clinical or subclinical cerebrovascular disease.^{14,19–22} Our results were similar after excluding prevalent stroke at follow-up. Excessive LDL-C is the major

Table 4 Average adjusted difference in 15-year cognitive change by clinically relevant cutoffs, primary analysis sample (1996–2013)

Lipoproteins	Adjusted difference in 15-year cognitive change ^a							
	Global z score		DWRT z score		DSST z score		WFT z score	
	Estimate (95% CI)	p Value	Estimate (95% CI)	p Value	Estimate (95% CI)	p Value	Estimate (95% CI)	p Value
ApoB, mg/dL								
<120	Ref		Ref		Ref		Ref	
≥120	−0.024 (−0.079, 0.03)	0.3824	0.02 (−0.071, 0.11)	0.6684	−0.061 (−0.1, −0.021)	0.0027	−0.017 (−0.068, 0.034)	0.5106
sdLDL-C, mg/dL								
<50	Ref		Ref		Ref		Ref	
≥50	−0.043 (−0.087, 0)	0.051	−0.05 (−0.122, 0.022)	0.1734	−0.036 (−0.067, −0.004)	0.0269	−0.025 (−0.066, 0.016)	0.2248
Lp(a), mg/dL								
≤50	Ref		Ref		Ref		Ref	
>50	0.037 (−0.014, 0.088)	0.1582	0.019 (−0.066, 0.104)	0.6657	0.043 (0.005, 0.08)	0.0246	0.039 (−0.009, 0.087)	0.1093
LpPLA₂ activity, nmol/min/mL								
<225	Ref		Ref		Ref		Ref	
≥225	0.017 (−0.03, 0.064)	0.4765	−0.002 (−0.079, 0.075)	0.9539	−0.007 (−0.042, 0.027)	0.6672	0.042 (−0.002, 0.085)	0.0596

Abbreviations: ApoB = apolipoprotein B; CI = confidence interval; DSST = Digit-Symbol Substitution Test; DWRT = Delayed Word Recall Test; Lp(a) = lipoprotein (a); LpPLA₂ = lipoprotein-associated phospholipase A₂; sdLDL-C = small dense low-density lipoprotein cholesterol; WFT = Word Fluency Test.
^a Adjusted for baseline age, age squared, education, sex, race/center, body mass index, alcohol use, smoking status, diabetes, hypertension, physical activity, adherence to a Western dietary pattern, adherence to a prudent dietary pattern, cholesterol-lowering medication use, preretirement health insurance status, and APOE ε4 status.

Table 5 Average adjusted difference in 15-year cognitive change across quintile categories and per 10 units higher lipoprotein levels, after imputing missing exposure, covariates, and cognitive scores data among alive persons (1996–2013)

Lipoproteins	Adjusted difference in 15-year cognitive change ^a							
	Global z score, n = 13,484		DWRT z score, n = 13,484		DSST z score, n = 13,484		WFT z score, n = 13,484	
	Estimate (95% CI)	p Value	Estimate (95% CI)	p Value	Estimate (95% CI)	p Value	Estimate (95% CI)	p Value
ApoB, mg/dL								
Per 10 mg/dL	−0.008 (−0.016, 0.001)	0.08	−0.009 (−0.022, 0.004)	0.18	−0.005 (−0.011, 0.001)	0.11	−0.004 (−0.014, 0.006)	0.41
<80	Ref		Ref		Ref		Ref	
80–100	−0.035 (−0.082, 0.013)	0.15	−0.054 (−0.13, 0.022)	0.16	0.005 (−0.034, 0.043)	0.82	−0.03 (−0.073, 0.012)	0.16
100–120	−0.031 (−0.09, 0.029)	0.31	−0.049 (−0.141, 0.042)	0.29	−0.003 (−0.048, 0.041)	0.88	−0.021 (−0.076, 0.035)	0.46
120–140	−0.063 (−0.141, 0.015)	0.11	−0.066 (−0.174, 0.041)	0.22	−0.029 (−0.076, 0.018)	0.22	−0.051 (−0.149, 0.047)	0.31
140+	−0.104 (−0.184, −0.025)	0.01	−0.119 (−0.255, 0.016)	0.08	−0.075 (−0.141, −0.009)	0.03	−0.049 (−0.117, 0.02)	0.17
sdLDL-C, mg/dL								
Per 10 mg/dL	−0.01 (−0.021, 0.001)	0.07	−0.011 (−0.027, 0.004)	0.16	−0.006 (−0.014, 0.001)	0.11	−0.006 (−0.012, 0)	0.04
<28	Ref		Ref		Ref		Ref	
28–40	−0.028 (−0.074, 0.017)	0.23	−0.064 (−0.143, 0.015)	0.11	0.003 (−0.031, 0.038)	0.84	−0.009 (−0.057, 0.039)	0.71
40–55	−0.027 (−0.082, 0.028)	0.34	−0.062 (−0.146, 0.022)	0.15	−0.008 (−0.045, 0.028)	0.65	0.004 (−0.053, 0.06)	0.90
55–82	−0.076 (−0.147, −0.005)	0.04	−0.096 (−0.191, −0.001)	0.047	−0.048 (−0.098, 0.003)	0.07	−0.04 (−0.103, 0.023)	0.21
82+	−0.078 (−0.173, 0.018)	0.11	−0.108 (−0.266, 0.051)	0.18	−0.045 (−0.111, 0.021)	0.18	−0.032 (−0.112, 0.048)	0.44
Lp(a), mg/dL								
Per 10 mg/dL	0.004 (−0.003, 0.012)	0.29	0.003 (−0.013, 0.019)	0.70	0.003 (0, 0.006)	0.06	0.004 (−0.001, 0.009)	0.08
<5	Ref		Ref		Ref		Ref	
5–13	−0.004 (−0.057, 0.05)	0.90	−0.012 (−0.096, 0.072)	0.78	−0.006 (−0.044, 0.031)	0.74	0.008 (−0.036, 0.051)	0.73
13–40	0.015 (−0.043, 0.072)	0.61	0.007 (−0.089, 0.103)	0.89	0.006 (−0.031, 0.043)	0.75	0.024 (−0.028, 0.076)	0.37
40–70	0.016 (−0.049, 0.081)	0.64	0.004 (−0.097, 0.105)	0.93	0.027 (−0.022, 0.076)	0.28	0.018 (−0.044, 0.079)	0.57
70+	0.088 (0.003, 0.172)	0.04	0.083 (−0.093, 0.259)	0.36	0.049 (−0.004, 0.103)	0.07	0.078 (0.017, 0.138)	0.01
LpPLA₂ activity, nmol/min/mL								
Per 10 nmol/min/mL	0.003 (−0.002, 0.007)	0.28	0.005 (−0.002, 0.012)	0.17	−0.001 (−0.004, 0.002)	0.59	0.002 (−0.002, 0.007)	0.31

Continued

Table 5 Average adjusted difference in 15-year cognitive change across quintile categories and per 10 units higher lipoprotein levels, after imputing missing exposure, covariates, and cognitive scores data among alive persons (1996–2013) (continued)

Lipoproteins	Adjusted difference in 15-year cognitive change ^a					
	Global z score, n = 13,484		DWRT z score, n = 13,484		DSST z score, n = 13,484	
	Estimate (95% CI)	p Value	Estimate (95% CI)	p Value	Estimate (95% CI)	p Value
<190	Ref		Ref		Ref	
190–230	0.042 (–0.013, 0.096)	0.14	0.072 (–0.007, 0.151)	0.07	0.002 (–0.033, 0.037)	0.90
230–270	0.013 (–0.046, 0.071)	0.67	0.03 (–0.062, 0.122)	0.53	–0.004 (–0.042, 0.034)	0.85
270–330	0.045 (–0.028, 0.118)	0.23	0.056 (–0.059, 0.172)	0.34	0.001 (–0.049, 0.051)	0.98
330+	0.044 (–0.071, 0.159)	0.45	0.119 (–0.037, 0.276)	0.14	–0.019 (–0.092, 0.054)	0.61
					0.021 (–0.032, 0.073)	0.44
					0.005 (–0.059, 0.069)	0.88
					0.046 (–0.036, 0.129)	0.27
					0.011 (–0.1, 0.122)	0.84

Abbreviations: ApoB = apolipoprotein B; CI = confidence interval; DSST = Digit-Symbol Substitution Test; DWRT = Delayed Word Recall Test; Lp(a) = lipoprotein (a); LpPLA₂ = lipoprotein-associated phospholipase A₂; sdLDL-C = small dense low-density lipoprotein cholesterol; WFT = Word Fluency Test.

^a Adjusted for baseline age, age squared, education, sex, race/center, body mass index, alcohol use, smoking status, diabetes, hypertension, physical activity, adherence to a Western dietary pattern, adherence to a prudent dietary pattern, cholesterol-lowering medication use, preretirement health insurance status, and APOE ε4 status.

component of ApoB and sdLDL-C and high triglycerides and low high-density lipoprotein levels are common in people with elevated sdLDL-C.^{16,17,20} Such lipid abnormality is associated with both large^{12,20} and small vessel ischemic diseases,^{48,49} which may be the intermediary step for accelerated cognitive decline and subsequent dementia.

The findings of our study should be interpreted in the context of several strengths and limitations. Strengths include large sample size, high-quality measures of multiple nontraditional lipid fractions/enzyme levels, comprehensive data, and a long follow-up. Limitations include possible bias from informative missingness, although comparable results from analyses using multiple imputations suggest this is less likely. While the 3 cognitive tests examined are commonly used, they do not cover the full range of cognitive functions. Furthermore, these cognitive tests may not have similar sensitivity. Elevated ApoB and sdLDL-C were preferentially associated with accelerated decline in executive function, but whether this is because vascular damage tends to affect executive function or whether the DSST is a more sensitive measure of cognitive changes than the other cognitive tests considered is unclear. The mean age of our study population was 63 years at the time of biomarker measurement. Although cognitive change is a precursor of dementia,³ it is possible that some irreparable cognitive damage may have already occurred due to cumulative lifetime exposure to the lipids examined; questions about a role of exposures prior to midlife and possible lag effects could not be addressed by this study. Bias due to residual confounding cannot be ruled out, despite adjustment for numerous potential confounders. Additional work with alternate methods (e.g., Mendelian randomization studies) may be valuable to better characterize the validity and potential causal nature of the associations reported here. Further investigation using imaging markers of subclinical cerebrovascular disease is also warranted.

ApoB and sdLDL-C were associated with faster 15-year decline in executive function. Lp(a) was associated with less decline in executive function and processing speed, while LpPLA₂ activity did not appear to be associated with cognitive change. The estimated effects of sdLDL-C and Lp(a) on cognitive change were more pronounced in statin users. Future research should explore mechanisms for lower cognitive decline associated with Lp(a) levels and for effect modification by statin use. Controlling ApoB and sdLDL-C to reduce atherosclerotic cardiovascular disease may have additional benefit on cognitive health. This could further motivate patients and clinicians to better control atherogenic lipoproteins.

Acknowledgment

The authors thank the staff and participants of the ARIC study and Pamela Lutsey, PhD, for providing the dietary pattern scores.

Study funding

The Atherosclerosis Risk in Communities study has been funded in whole or in part with Federal funds from

Figure 2 Effect modification

(A) Effect modification by visit 4 statin use for the association between small dense low-density lipoprotein cholesterol (sdLDL-C) and cognitive decline. Interaction *p* values are 0.03, 0.05, 0.01, and 0.05 for Digit-Symbol Substitution Test (DSST), Delayed Word Recall Test (DWRT), global, and Word Fluency Test (WFT) z scores, respectively. (B) Effect modification by visit 4 statin use for the association between lipoprotein (a) (Lp[a]) and cognitive decline. Interaction *p* values are 0.03 and 0.01 for DWRT and global z scores, respectively. (C) Effect modification of Lp(a) and cognitive decline by subsequent development of dementia. Interaction *p* values are 0.001, <0.001, and 0.051 for global z scores, DSST, and WFT, respectively. CI = confidence interval.

the National Heart, Lung, and Blood Institute, NIH, Department of Health and Human Services, under contract nos. HHSN268201700001I, HHSN268201700002I, HHSN268201700003I, HHSN268201700004I, and HHSN268201700005I. Neurocognitive data are collected

with the support of the National Heart, Lung, and Blood Institute U01 HL096812, HL096814, HL096899, HL096902, and HL096917, with previous brain MRI examinations funded by R01-HL70825. Dr. Pokharel was supported by the National Heart, Lung, and Blood Institute of the NIH under

award number T32HL110837 and the American Heart Association SWA Summer 2014 Postdoctoral Fellowship Award (15POST23080014). Dr. Power was supported by the National Institute of Aging R03AG055485 during the period of this work.

Disclosure

Y. Pokharel and F. Mouhanna report no disclosures relevant to the manuscript. V. Nambi: research grant: significant; Denka Seiken to provide reagents for small dense low-density lipoprotein cholesterol and lipoprotein (a) assays; other: modest; Biomarkers to Improve Prediction of Heart Failure Risk: patent no. 61721475; filed by Roche, Baylor College of Medicine, along with 4 investigators including Drs. Ballantyne, Hoozeveen, and Nambi. S. Virani reports no disclosures relevant to the manuscript. R. Hoozeveen: research grant: significant; Denka Seiken to provide reagents for small dense low-density lipoprotein cholesterol and lipoprotein (a) assays; other: modest; Biomarkers to Improve Prediction of Heart Failure Risk: patent no. 61721475; filed by Roche, Baylor College of Medicine, along with 4 investigators including C.H. Ballantyne, R. Hoozeveen, and V. Nambi; consultant to Denka Seiken. A. Alonso, G. Heiss, J. Coresh, and T. Mosley report no disclosures relevant to the manuscript. R. Gottesman: Associate Editor, *Neurology*[®], significant. C. Ballantyne: research grant: significant; Denka Seiken to provide reagents for small dense low-density lipoprotein cholesterol and lipoprotein (a) assays; other: modest; Biomarkers to Improve Prediction of Heart Failure Risk: patent no. 61721475; filed by Roche, Baylor College of Medicine, along with 4 investigators including C.H. Ballantyne, R. Hoozeveen, and V. Nambi; consultant to Denka Seiken. M. Power reports no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

Publication history

Received by *Neurology* September 29, 2018. Accepted in final form January 29, 2019.

Appendix Authors

Name	Location	Role	Contribution
Yashashwi Pokharel, MD	University of Missouri-Kansas City	Corresponding author	Designed and conceptualized study, interpreted the data, drafted the manuscript for intellectual content, has access to all the data and takes responsibility for the data, accuracy of the data analysis, and conduct of the research

Appendix (continued)

Name	Location	Role	Contribution
Farah Mouhanna, MS	George Washington University, Washington, DC	Author	Interpreted the data, revised the manuscript for intellectual content
Vijay Nambi, MD	Baylor College of Medicine, Houston, TX	Author	Designed and conceptualized study, interpreted the data, revised the manuscript for intellectual content
Salim S. Virani, MD	Baylor College of Medicine, Houston, TX	Author	Designed and conceptualized study, interpreted the data, revised the manuscript for intellectual content
Ron Hoozeveen, PhD	Baylor College of Medicine, Houston, TX	Author	Designed and conceptualized study, interpreted the data, revised the manuscript for intellectual content
Alvaro Alonso, MD	Emory University, Atlanta, GA	Author	Interpreted the data, revised the manuscript for intellectual content
Gerardo Heiss, MD	University of North Carolina, Chapel Hill	Author	Interpreted the data, revised the manuscript for intellectual content
Josef Coresh, MD	Johns Hopkins University, Baltimore, MD	Author	Interpreted the data, revised the manuscript for intellectual content
Thomas Mosley, PhD	University of Mississippi Medical Center, Jackson	Author	Interpreted the data, revised the manuscript for intellectual content
Rebecca F. Gottesman, MD	Johns Hopkins University, Baltimore, MD	Author	Designed and conceptualized study, interpreted the data, revised the manuscript for intellectual content
Christie M. Ballantyne, MD	Baylor College of Medicine, Houston, TX	Author	Designed and conceptualized study, interpreted the data, drafted the manuscript for intellectual content

Appendix (continued)

Name	Location	Role	Contribution
Melinda C. Power, ScD	George Washington University, Washington, DC	Author	Designed and conceptualized study, analyzed and interpreted the data, drafted the manuscript for intellectual content, had access to all the data and takes responsibility for the data, accuracy of the data analysis, and the conduct of the research

References

- American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 5th ed. Arlington, VA: American Psychiatric Publishing; 2013.
- Wilson RS, Leurgans SE, Boyle PA, Bennett DA. Cognitive decline in prodromal Alzheimer disease and mild cognitive impairment. *Arch Neurol* 2011;68:351–356.
- Sperling RA, Aisen PS, Beckett LA, et al. Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* 2011;7:280–292.
- Douiri A, Rudd AG, Wolfe CD. Prevalence of poststroke cognitive impairment: South London Stroke Register 1995–2010. *Stroke* 2013;44:138–145.
- Reis JP, Launer LJ, Terry JG, et al. Subclinical atherosclerotic calcification and cognitive functioning in middle-aged adults: the CARDIA study. *Atherosclerosis* 2013; 231:72–77.
- Power MC, Rawlings A, Sharrett AR, et al. Association of midlife lipids with 20-year cognitive change: a cohort study. *Alzheimers Dement* 2018;14:167–177.
- Rovio SP, Pakkala K, Nevalainen J, et al. Cardiovascular risk factors from childhood and midlife cognitive performance: the Young Finns Study. *J Am Coll Cardiol* 2017; 69:2279–2289.
- Rawlings AM, Sharrett AR, Schneider AL, et al. Diabetes in midlife and cognitive change over 20 years: a cohort study. *Ann Intern Med* 2014;161: 785–793.
- Gottesman RF, Schneider AL, Albert M, et al. Midlife hypertension and 20-year cognitive change: the Atherosclerosis Risk in Communities neurocognitive study. *JAMA Neurol* 2014;71:1218–1227.
- Solomon A, Kivipelto M, Wolozin B, Zhou J, Whitmer RA. Midlife serum cholesterol and increased risk of Alzheimer's and vascular dementia three decades later. *Dement Geriatr Cogn Disord* 2009;28:75–80.
- Mielke MM, Zandi PP, Shao H, et al. The 32-year relationship between cholesterol and dementia from midlife to late life. *Neurology* 2010;75:1888–1895.
- Benn M, Nordestgaard BG, Frikke-Schmidt R, Tybjaerg-Hansen A. Low LDL cholesterol, PCSK9 and HMGCR genetic variation, and risk of Alzheimer's disease and Parkinson's disease: Mendelian randomisation study. *BMJ* 2017; 357:j1648.
- Baumgart M, Snyder HM, Carrillo MC, Fazio S, Kim H, Johns H. Summary of the evidence on modifiable risk factors for cognitive decline and dementia: a population-based perspective. *Alzheimers Dement* 2015;11:718–726.
- Pokharel Y, Negi S, Virani SS. Clinical Lipidology: A Companion to Braunwald's Heart Disease. Chapter 8. Cholesterol: Concentration, Ratio, and Particle Number, 2nd ed. Philadelphia: Saunders; 2014.
- Tsimikas S. A test in context: lipoprotein(a): diagnosis, prognosis, controversies, and emerging therapies. *J Am Coll Cardiol* 2017;69:692–711.
- Chait A, Bazzaz RL, Tribble DL, Krauss RM. Susceptibility of small, dense, low-density lipoproteins to oxidative modification in subjects with the atherogenic lipoprotein phenotype, pattern B. *Am J Med* 1993;94:350–356.
- Galeano NF, Al-Haideri M, Keyserman F, Rumsey SC, Deckelbaum RJ. Small dense low density lipoprotein has increased affinity for LDL receptor-independent cell surface binding sites: a potential mechanism for increased atherogenicity. *J Lipid Res* 1998;39:1263–1273.
- Kolodgie FD, Burke AP, Skoriya KS, et al. Lipoprotein-associated phospholipase A2 protein expression in the natural progression of human coronary atherosclerosis. *Arterioscler Thromb Vasc Biol* 2006;26:2523–2529.
- Kamstrup PR, Tybjaerg-Hansen A, Steffensen R, Nordestgaard BG. Genetically elevated lipoprotein(a) and increased risk of myocardial infarction. *JAMA* 2009;301: 2331–2339.
- Hoogeveen RC, Gaubatz JW, Sun W, et al. Small dense low-density lipoprotein-cholesterol concentrations predict risk for coronary heart disease: the Atherosclerosis Risk in Communities (ARIC) study. *Arterioscler Thromb Vasc Biol* 2014;34: 1069–1077.
- Pokharel Y, Sun W, Polfus LM, et al. Lipoprotein associated phospholipase A2 activity, apolipoprotein C3 loss-of-function variants and cardiovascular disease: the Atherosclerosis Risk In Communities Study. *Atherosclerosis* 2015;241:641–648.
- Thompson A, Thompson A, Gao P, et al. Lipoprotein-associated phospholipase A(2) and risk of coronary disease, stroke, and mortality: collaborative analysis of 32 prospective studies. *Lancet* 2010;375:1536–1544.
- Ray L, Khemka VK, Behera P, et al. Serum homocysteine, dehydroepiandrosterone sulphate and lipoprotein (a) in Alzheimer's disease and vascular dementia. *Aging Dis* 2013;4:57–64.
- Sarti C, Pantoni L, Pracucci G, Di Carlo A, Vanni P, Inzitari D. Lipoprotein(a) and cognitive performances in an elderly white population: cross-sectional and follow-up data. *Stroke* 2001;32:1678–1683.
- Kunutsor SK, Khan H, Nyyssonen K, Laukkanen JA. Is lipoprotein (a) protective of dementia? *Eur J Epidemiol* 2016;31:1149–1152.
- Song F, Poljak A, Crawford J, et al. Plasma apolipoprotein levels are associated with cognitive status and decline in a community cohort of older individuals. *PLoS One* 2012;7:e34078.
- Reynolds CA, Gatz M, Prince JA, Berg S, Pedersen NL. Serum lipid levels and cognitive change in late life. *J Am Geriatr Soc* 2010;58:501–509.
- Koshy B, Miyashita A, St Jean P, et al. Genetic deficiency of plasma lipoprotein-associated phospholipase A2 (PLA2G7 V297F null mutation) and risk of Alzheimer's disease in Japan. *J Alzheimers Dis* 2010;21:775–780.
- Fitzpatrick AL, Irizarry MC, Cushman M, Jenny NS, Chi GC, Koro C. Lipoprotein-associated phospholipase A2 and risk of dementia in the Cardiovascular Health Study. *Atherosclerosis* 2014;235:384–391.
- van Himbergen TM, Beiser AS, Ai M, et al. Biomarkers for insulin resistance and inflammation and the risk for all-cause dementia and Alzheimer disease: results from the Framingham Heart Study. *Arch Neurol* 2012;69:594–600.
- van Oijen M, van der Meer IM, Hofman A, Witteman JC, Koudstaal PJ, Breteler MM. Lipoprotein-associated phospholipase A2 is associated with risk of dementia. *Ann Neurol* 2006;59:139–144.
- Agarwala A, Pokharel Y, Saeed A, et al. The association of lipoprotein(a) with incident heart failure hospitalization: Atherosclerosis Risk In Communities Study. *Atherosclerosis* 2017;262:131–137.
- Knopman DS, Ryberg S. A verbal memory test with high predictive accuracy for dementia of the Alzheimer type. *Arch Neurol* 1989;46:141–145.
- Wechsler D. Wechsler Adult Intelligence Scale—Revised (WAIS-R). San Antonio: The Psychological Corporation; 1981.
- Lezak M. Neuropsychological Assessment. New York: Oxford University Press; 1995: 335–384.
- Demerath EW, Lutsey PL, Monda KL, et al. Interaction of FTO and physical activity level on adiposity in African-American and European-American adults: the ARIC study. *Obesity* 2011;19:1866–1872.
- Baecke JA, Burema J, Frijters JE. A short questionnaire for the measurement of habitual physical activity in epidemiological studies. *Am J Clin Nutr* 1982;36: 936–942.
- Lutsey PL, Steffen LM, Stevens J. Dietary intake and the development of the metabolic syndrome: the Atherosclerosis Risk in Communities study. *Circulation* 2008; 117:754–761.
- Siedel J, Hägele EO, Ziegenhorn J, Wahlefeld AW. Reagent for the enzymatic determination of serum total cholesterol with improved lipolytic efficiency. *Clin Chem* 1983;29:1075–1080.
- Nägele U, Hägele EO, Sauer G, et al. Reagent for the enzymatic determination of serum total triglycerides with improved lipolytic efficiency. *J Clin Chem Clin Biochem* 1984;22:165–174.
- McNamara JR, Cohn JS, Wilson PW, Schaefer EJ. Calculated values for low-density lipoprotein cholesterol in the assessment of lipid abnormalities and coronary disease risk. *Clin Chem* 1990;36:36–42.
- Mayo Medical Laboratories. mayomedicalaboratories.com/test-catalog/Clinical+and+Interpretive/80308. Accessed November 22, 2017.
- Denka Seiken Receives FDA Clearance for Small Dense LDL-C Assay. aacc.org/publications/clin/articles/2017/november/denka-seiken-receives-fda-clearance-for-small-dense-ldlc-assay. Accessed November 22, 2017.
- US FDA Approves diaDexus' PLAC Test for Lp-PLA2 Activity. pharmabiz.com/NewsDetails.aspx?aid=85716&sid=2. Accessed November 22, 2017.
- Rawlings AM, Sang Y, Sharrett AR, et al. Multiple imputation of cognitive performance as a repeatedly measured outcome. *Eur J Epidemiol* 2017;32: 55–56.
- Toth PP, Potter D, Ming EE. Prevalence of lipid abnormalities in the United States: the National Health and Nutrition Examination Survey 2003–2006. *J Clin Lipidol* 2012;6:325–330.
- Hurd MD, Martorell P, Delavande A, Mullen KJ, Langa KM. Monetary costs of dementia in the United States. *N Engl J Med* 2013;368:1326–1334.
- Kraft P, Schuhmann MK, Garz C, et al. Hypercholesterolemia induced cerebral small vessel disease. *PLoS One* 2017;12:e0182822.
- Appleton JP, Scutt P, Sprigg N, Bath PM. Hypercholesterolaemia and vascular dementia. *Clin Sci* 2017;131:1561–1578.