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RESEARCH ARTICLE

The association of cholesterol levels with memory and memory change over a 14-year period in a US national cohort

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Abstract

INTRODUCTION: The impact of cholesterol on late-life cognition remains controversial. We investigated the association of high-density lipoprotein cholesterol (HDL-C) and non–HDL-C with memory in a nationally representative cohort.

METHODS: Health and Retirement Study (HRS) participants (N = 13,258) aged 50+ (mean age: 67.2 years) followed from 2006 to 2020 provided cholesterol measures every 4 years and cognitive assessments biennially. Linear mixed models predicted memory scores using both baseline and time-updated cholesterol values.

RESULTS: Higher baseline HDL-C (mean: 53.9 mg/dL) predicted better memory scores (β: 0.05, 95% confidence interval [CI]: 0.03 to 0.08), but not memory change. Baseline non–HDL-C (mean: 143 mg/dL) predicted poorer memory scores (β: −0.01, 95% CI: −0.02 to 0.00), but not memory change. Time-updated HDL-C predicted better memory (β: 0.02, 95% CI: 0.00 to 0.04), but non–HDL-C showed no such associations.

DISCUSSION: While higher peripheral HDL-C is linked to better memory, the small effect sizes and absence of associations of HDL-C and non–HD-CL with memory change suggests that peripheral cholesterol has a small effect on the variation of memory scores.

KEYWORDS
cardiovascular risk factors, cognitive outcomes, high-density lipoprotein cholesterol, lipids, low-density lipoprotein cholesterol, modifiable risk factors, vascular risk factors

Highlights

- Higher HDL-C levels predict better memory scores but not memory change across 14 years of follow-up.
- Baseline higher LDL-C levels predict poorer memory scores across time, but not memory change.
- The small effects and absence of consistent association between cholesterol levels and memory change suggest that cholesterol plays a minor role in cognitive decline.

1 | BACKGROUND

Elevated low-density lipoprotein cholesterol (LDL-C) levels are a significant risk factor for cardiovascular disease (CVD).[1] Given the effects of CVD and CVD risk factors on cognitive decline and dementia incidence,[2] an association between lipid levels and cognitive outcomes is also expected. Intervening on cholesterol through medication or dietary adjustments could offer promising strategies for not only reducing the risk of CVD, but also mitigating cognitive decline and lowering the likelihood of dementia in at-risk populations.[3] Despite extensive research, the link between dyslipidemia, hyperlipidemia, and cognitive performance remains unclear due to inconsistent findings across studies.[4]

Recent studies across diverse populations show conflicting findings on the relationship between serum cholesterol levels and cognitive function. For instance, studies in elderly United States populations suggest that higher LDL-C levels correlate with faster cognitive decline,[5,6] whereas the CHARLS study suggests that non—high-density lipoprotein cholesterol difference between total cholesterol (TC) and high-density lipoprotein cholesterol (HDL-C) values may have a protective effect on cognition in younger women.[7] Conversely, research in Chinese populations at varying ages indicate that higher LDL-C levels are associated with accelerated cognitive decline.[8,9] Finnish middle-aged adults followed for nearly 2 decades showed no significant association between cholesterol levels (LDL-C, HDL-C) and cognitive scores.[10]

Studies in various cohorts also reveal mixed results regarding HDL-C serum levels. In Health and Retirement Study (HRS) cohorts with similar age averages, higher HDL-C levels correlate with better cognitive function.[11,12] However, a 16-year study in Sweden found that HDL did not predict cognitive change in men but was associated with better verbal ability in women across all ages.[13] In contrast, studies conducted in United States, Australian, Scottish, and Norwegian populations produced conflicting results, with a study indicating an increased risk of dementia with high HDL-C[14] and others finding no significant associations with cognitive outcomes.[15 to 17]

Meta-analyses across European, Swedish, American, Asian, and Australian populations reported no significant associations between HDL-C, LDL-C, and cognitive decline[18]

The inconsistency in prior studies may be attributed to variations in cholesterol measurement methods, timing of measurements relative to cognitive assessments, and the use of highly selected samples with diverse demographic profiles. Moreover, differences in lifestyle factors and prevalence of comorbid conditions between countries can significantly influence cognitive outcomes compared to the United States population. Therefore, to derive meaningful conclusions representative of the broader United States demographic, large-scale, long-term studies involving community-dwelling individuals are essential. Such studies would facilitate rigorous comparisons across different ages, cholesterol measurement timings, and comprehensive control of covariates, ensuring findings are both robust and broadly applicable.

In this study, we leverage the HRS to conduct a nationally representative longitudinal analysis spanning over a decade of follow-up. Our aim is to estimate the effects of cholesterol on memory and memory changes in adults aged 50 years and older. Leveraging up to three successive measures of cholesterol collected over a 14-year period, we compare memory estimates based on the first-available cholesterol measure with those based on time-updated cholesterol measures.

RESEARCH IN CONTEXT

1. **Systematic review**: The authors reviewed the current literature using PubMed. While the relationship between serum cholesterol and cognitive outcomes along with dementia risk has been heavily debated, prior studies show inconsistent results. Most of these discrepancies are due to differences in key study design characteristics and homogenous populations.
2. **Interpretation**: Our findings indicated that higher high-density lipoprotein cholesterol (HDL-C) levels at baseline and across time are indicative of improved memory scores, while higher non–HDL-C predicted poorer memory scores, but not memory change. While HDL-C is linked to better memory, the small effect sizes suggest that cholesterol plays a minor role in cognitive aging.
3. **Future directions**: Our paper adds to a growing body of literature suggesting cholesterol has a small effect on cognitive aging. Further research is required to investigate the mediating pathways between cholesterol and dementia.

2 | METHODS

2.1 | Study sample

The HRS cohort was launched in 1992 with a representative sample of community-dwelling United States residents born 1931 to 1941,[19] and it is sponsored by the National Institute on Aging (grant number NIA U01AG009740) and is conducted by the University of Michigan. In 1998, the cohort was expanded to be representative of all community-dwelling United States residents aged 50 years or older, with new enrollments occurring every 6 years to include newly aged-in birth cohorts. Spouses of age-eligible participants were also enrolled. Information is collected at the respondent and household level during biennial telephone or in-person interviews. HRS interviews proxy respondents (usually a spouse or other family member) for participants who die or are too impaired to participate.[20] In 2006, HRS randomly selected half of participants for enhanced face-to-face interviews which included dried-blood-spot (DBS) cholesterol collection repeated every 4 years (2006, 2010, and 2014). In 2008, the other half of HRS participants completed the face-to-face interviews and thereafter contributed DBS every 4 years (2008, 2012, and 2016).

For analyses using first-available cholesterol as the exposure, we included all enrollees aged 50 and older at their date of first DBS

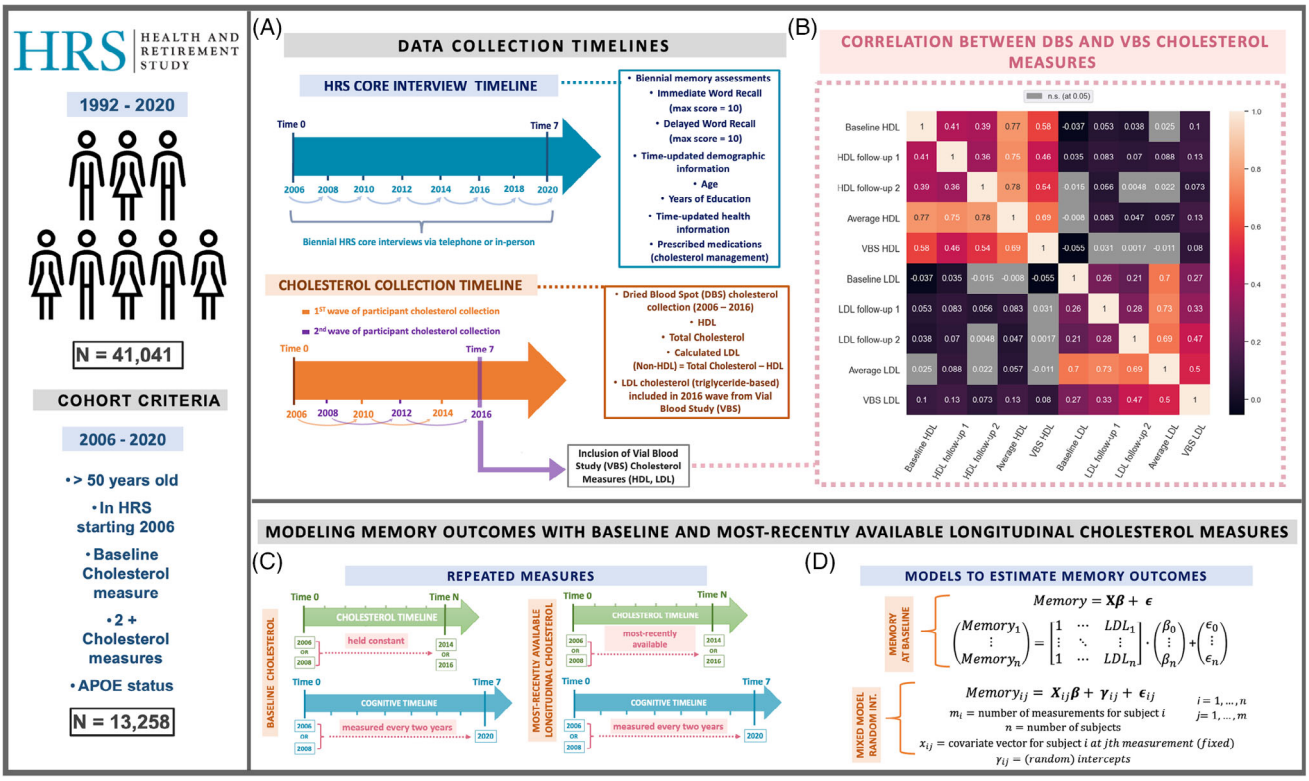

FIGURE 1 Health and retirement study specifications, cohort inclusion criteria, and study design. (A) Data Collection Timelines. Blue timeline depicts the HRS core interview assessments spanning from 2006 through 2020. (B) Correlation between DBS and VBS cholesterol measures taken at baseline (first visit), second, and third follow-up. Participants included in this correlation must have had a total of three cholesterol assessments spanning 2006 to 2020, including VBS measures. (C) Baseline and Longitudinal models for memory assessment given cholesterol value. (D) Linear model equations to estimate memory with cholesterol collections at baseline and across time. DBS, dried-blood-spot; HRS, Health and Retirement Study; VBS, Venous Blood Study.

collection (2006 or 2008, corresponding to HRS waves 8 or 9), who contributed to DNA collection (for apolipoprotein E-e4 [APOE-e4] status), with at least two memory assessments completed by the end of follow-up in 2020, for a final analytic sample of $N = 13,258$ included in analyses to estimate effects of baseline cholesterol on memory during follow-up. Analyses for estimating effects of most-recent prior cholesterol (i.e., time-updated cholesterol value measured in the same year as the memory assessment or in the most recently available prior year) on memory during follow-up were restricted to individuals for whom at least two cholesterol measurements were available through 2016 for a final sample of $N = 12,175$ individuals. Details on cholesterol measure timelines and inclusion criteria for each cohort are outlined in Figure 1 with cohort-selection workflow shown in Figure 2.

To ensure population-level representation in the United States, HRS provides sampling weights to account for differential selection probabilities by race/ethnicity and birth cohort and to correct for differential non-response. Our analyses applied participants' sampling weights recorded at the time of baseline cholesterol assessment.

2.2 | Exposures

Our primary analyses (first-available and time-updated models) used the DBS-derived lipid measurements.[21,22] Non-HDL (estimated-LDL) cholesterol was obtained by subtracting HDL-C values from TC in DBS measures. Participants provided special informed consent for the blood acquisition process. We evaluated first-available cholesterol for each respondent using the cholesterol measure from either 2006 or 2008 and separately estimated models using time-updated cholesterol as the predictor.

In 2016, HRS fielded a Venous Blood Study[21] (VBS; $N = 9,480$ meeting our cohort criteria) for the assessment of triglycerides and LDL-cholesterol measurements, which we used to assess the validity of the DBS based measures. VBS data allowed estimation of LDL-C levels using the Friedewald formula (LDL = TC-HDL-TG/5 [mg/dL]).[23] We leveraged the 2016 VBS measures to compare the time-updated (2006 to 2016) DBS measures of LDL-C and non-HDL via associative models and include a linear regression model to estimate memory scores cross-sectionally for the 2016 wave.

2.3 | Outcomes

A brief cognitive assessment was completed as part of the biennial-core interview at the start of every HRS wave, with up to eight cognitive assessments through the follow-up period.[22] We summed scores from immediate and delayed recall of a 10-word list as a measure of memory. The assessments consisted of the interviewer reading a list of 10

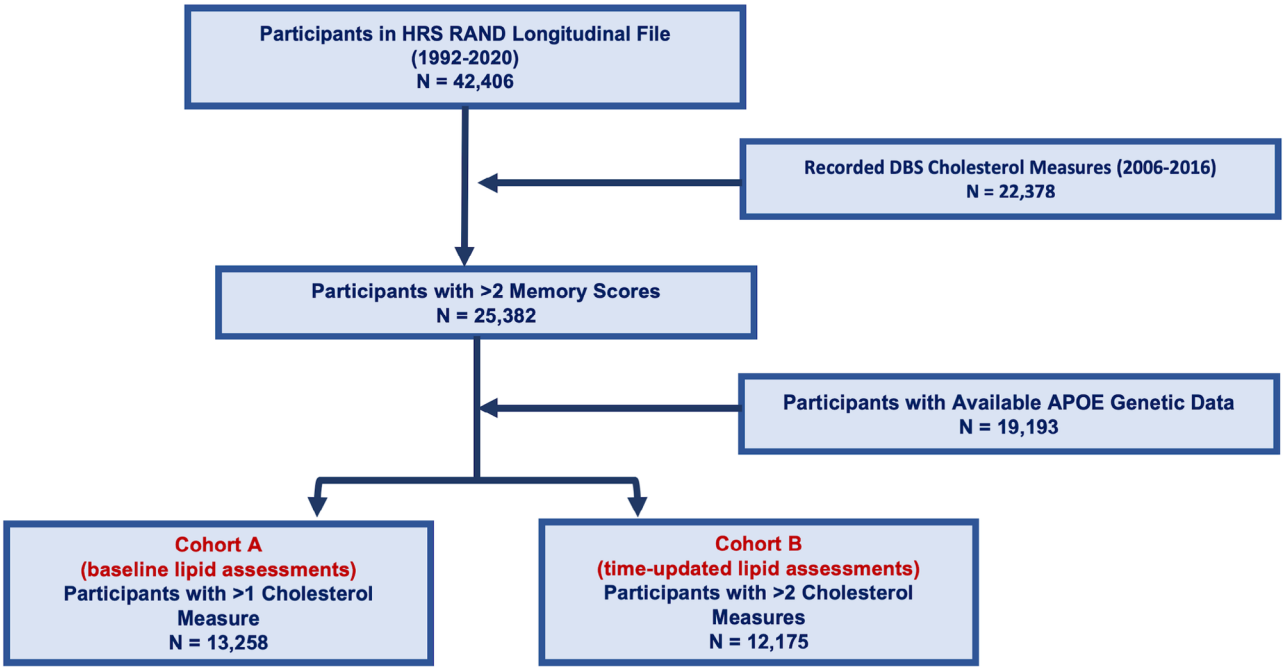

FIGURE 2 Cohort selection from HRS RAND longitudinal study. From top to bottom, this figure illustrates the filtering process leading to the final analytic datasets. DBS measures were added to the RAND HRS longitudinal file. Filtering to only include participants with at least 2 cognitive assessment scores leaves us with 25,382 participants. Once restricting to participants with available APOE Genetic Data and the number of available cholesterol assessments per participant, we obtain a total of 13,258 participants for our models leveraging first-available cholesterol measures, and 12,175 for the assessment of most-recent-prior cholesterol effects on memory. APOE, apolipoprotein E; DBS, dried-blood-spot; HRS, Health and Retirement Study.

words at a rate of approximately 2 s per word to each respondent, who was then asked to verbally recall as many words as possible. Approximately 5 min after the immediate word recall test, respondents were asked to recall the words again. For each task, the number of correctly recalled words was counted, for a range from 0 to 20 on total recall. All interviewers were trained to assess word-list recall in a standardized fashion. Interviewers read a list of 10 common nouns to the respondent. There were four candidate lists with non-overlapping words, rotated across successive interviews so participants received the same list to recall at 8-year intervals. The initial list was randomly assigned.[24]

2.4 | Covariates

We include age at baseline (at the time of first recorded cholesterol value), recorded time since baseline (when cognitive assessment was performed in the form of decades), number of years of education (0 to 17), sex, self-reported race/ethnicity (Hispanic-Other; Hispanic-White; Hispanic-Black; Non-Hispanic Black; Non-Hispanic Other; Non-Hispanic White), mode of interview (phone/face-to-face vs. Web-based only because prior evidence indicates no average difference between phone and face-to-face interview performance[25,26]), APOE-e4 allele status (dichotomized as 0 vs. 1 or 2) and self-report of current use of medications for cholesterol control. Prescription for cholesterol management medications and number of years of education were reported at baseline. In longitudinal models, cholesterol medication use was time updated.

2.5 | Primary statistical analyses: Linear mixed models

All analyses were conducted using R version 4.3.1.

Covariate-adjusted linear mixed models with random intercepts for participants were estimated for longitudinal memory outcomes. We first specified mixed models to evaluate the overall average association between cholesterol measures and cognition throughout follow-up; in these models, we adjusted for time-since-baseline (in decades), but we did not evaluate the interaction of time-since-baseline with cholesterol measures. We next estimated separate models to evaluate the association between cholesterol measures and rate of cognitive change, we included time-since-baseline (in decades) and its interaction with cholesterol measures at baseline and across time. We evaluated restricted cubic splines (with knots at the 25th, 50th, and 75th percentiles) for cholesterol measures to assess non-linear associations of cholesterol with cognitive test scores.

All estimated associations of cholesterol exposures with cognitive outcomes were scaled to be interpreted as cognitive differences per 10 mg/dL increase in the cholesterol measure.

2.6 | Sensitivity analyses: APOE-e4 allele and age stratifications for memory and cholesterol prediction, and practice effects

Given prior evidence of heterogeneity in the association of cholesterol with cognition for older versus younger adults,[5 to 16] we conducted several sensitivity analyses. We repeated analyses stratified by sex and age (< 65 or ≥ 65 years old at the time of cholesterol measure).

Furthermore, because APOE-e4 allele status is a strong predictor of cognitive decline and is also associated with cholesterol levels, we evaluated how APOE-e4 status predicted cholesterol and change in cholesterol with age. To address this, we estimated four mixed models. We first estimated longitudinal cholesterol measures as the dependent variable and time-updated age as the predictor. Second, we estimated models predicting longitudinal cholesterol with age at baseline. For the last two models, we estimated models that predicted longitudinal cholesterol with time-updated age by APOE-e4 interactions, and baseline age by APOE-e4 interactions to assess whether APOE-e4 alleles predicted age-related difference in cholesterol levels.

We explored potential differences in the effects of cholesterol on cognition across age groups and APOE-e4 carrier status, aiming to evaluate groups at relatively lower versus higher risk of being affected by undiagnosed AD.[27 to 29] We evaluated whether the relationships between cholesterol values and cognitive function varied between middle-aged individuals (< 65 years, who are less likely to be experiencing AD-related cognitive decline) and those outside of this age range (≥ 65 years, for whom at least some AD-related cognitive decline would be common) with and without the APOE-e4 allele.

Lastly, to assess potential bias from practice effects in cognitive testing, as part of our sensitivity analyses, we re-estimated all our models using data only from participants enrolled in the HRS before the start of our study period in 2006. This restriction ensures that new HRS enrollees, who may score worse on cognitive tests at their initial assessment, do not influence our findings.

3 | RESULTS

HRS participants (59.5% female) had a mean age of 67.2 (SD: 10.3), average 12.6 years of education (SD: 3.17). At baseline, 56% of participants were 65 years or older. Further demographic information can be found in Table 1.

3.1 | Association of baseline and time-updated cholesterol with memory scores

Higher first-available (baseline) HDL-C was associated with slightly higher average memory score (β per 10 mg/dL: 0.05, 95% confidence interval [CI]: 0.03 to 0.08) (Table 2A). Estimates were very similar in every sex/age stratum. For example, for women under age 65, the coefficient was 0.05 (95% CI: 0.01 to 0.09), and for men 65 years or older, the coefficient was also 0.05 (95% CI: 0.01 to 0.10).

First-available non—HDL-C showed a small negative association with memory outcomes (β per 10 mg/dL: −0.01, 95% CI: −0.02 to −0.01). This association was small and not statistically significant when restricting to sex/age strata.

Splines for first-available HDL-C indicated a slightly non-linear relationship: the association between HDL-C and better memory was steepest at moderately low levels of HDL-C and flattened out above median HDL-C (Figure 3A). The association between first-available non–HDL-C and memory was nearly flat throughout the distribution of non–HDL-C (Figure 3B).

In models using the most-recent prior values of HDL-C, a 10 mg/dL unit higher measured HDL-C was associated with 0.02 higher memory score (95% CI: 0.00 to 0.04) (Table 2B). This association was similar in each sex/age stratum, though estimates were not statistically significant. The most-recent prior values of non–HDL-C were unrelated to memory levels (β = 0.01, 95% CI: 0.00 to 0.01), and the coefficient was in the opposite direction as baseline non-HDL. Across sex/age stratification groups, coefficients were small, although the association between higher non-HDL levels and better memory scores (β = 0.02, 95% CI: 0.00 to 0.03) was significant in women ≥ 65 years old.

3.2 | Association of baseline and time-updated cholesterol with memory change

First-available HDL-C did not modify rate of decline in memory (β for interaction of HDL-C and decade of follow-up: -0.02, 95% CI: −0.05 to 0.01) (Table 3A). Coefficients were similarly small and non-significant for all sex/age strata.

First-available non-HDL was also unrelated to the average rate of decline in memory (β for interaction of non-HDL and decade follow-up: 0.00, 95% CI: −0.02 to 0.01). Among both younger and older women, first-available non–HDL-C was associated with slightly faster memory decline (β for interaction of non-HDL and decade follow-up: −0.03, 95% CI: −0.05 to −0.01 for both age groups). In contrast for men < 65 years of age, first-available non–HDL-C was associated with slower memory decline (β for interaction of non-HDL and decade follow-up: 0.04, 95% CI: 0.01 to 0.07). For older men, the association was negative but not statistically significant.

Using most-recent prior (time-updated) measure of HDL-C, higher levels of HDL were not significantly associated with slower memory decline (β = 0.05, 95% CI: 0.00 to 0.11). The association between time-updated HDL-C and memory change was modest and non-significant for each sex/age stratum except for women ≥65 years, for whom the coefficient was substantial and statistically significant (β = 0.10, 95% CI: 0.01 to 0.19).

Most-recently available longitudinal measures of non-HDL were not significantly associated with rate of memory change (β = 0.02, 95% CI: 0.00 to 0.04) (Table 3B) overall or in women <65 years, women ≥65 years, or men ≥65 years old. Among men <65 years old, longitudinal non-HDL was significantly associated with slower rate of cognitive decline (β = 0.09, 95% CI: 0.03 to 0.15).

TABLE 1 Health and retirement study statistics of participants at baseline.

Characteristics	Female (*N* = 7888) *n* (%) or mean (SD)	Male (*N* = 5370) *n* (%) or mean (SD)	Overall (*N* = 13,258) *n* (%) or mean (SD)
Baseline age			
Mean (SD)	67.0 (10.4)	67.4 (10.1)	67.2 (10.3)
Median [min, max]	66.0 [50.0, 100]	67.0 [50.0, 98.0]	67.0 [50.0, 100]
Race/ethnicity			
Hispanic	305 (3.9%)	212 (3.9%)	517 (3.9%)
Hispanic Black	22 (0.3%)	16 (0.3%)	38 (0.3%)
Hispanic White	582 (7.4%)	345 (6.4%)	927 (7.0%)
Non-Hispanic Black	1,460 (18.5%)	837 (15.6%)	2,297 (17.3%)
Non-Hispanic Other	180 (2.3%)	144 (2.7%)	324 (2.4%)
Non-Hispanic White	5,330 (67.6%)	3,807 (70.9%)	9,137 (68.9%)
Not specified	9 (0.1%)	9 (0.2%)	18 (0.1%)
APOE-e4 allele status			
Yes	2169 (27.5%)	1448 (27.0%)	3617 (27.3%)
No	5719 (72.5%)	3922 (73.0%)	9641 (72.7%)
Years of education			
Mean (SD)	12.4 (3.08)	12.8 (3.29)	12.6 (3.17)
Median [min, max]	12.0 [0, 17.0]	12.0 [0, 17.0]	12.0 [0, 17.0]
Baseline HDL			
Mean (SD)	57.5 (16.3)	48.7 (13.9)	53.9 (16.0)
Median [min, max]	55.7 [14.4, 130]	47.1 [12.1, 146]	51.6 [12.1, 146]
Baseline non-HDL*			
Mean (SD)	146 (39.7)	139 (37.2)	143 (38.8)
Median [min, max]	142 [10.1, 454]	136 [28.3, 361]	140 [10.1, 454]
Baseline delayed word Recall score			
Mean (SD)	4.44 (1.94)	3.97 (1.80)	4.25 (1.90)
Median [min, max]	5.0 [0, 10.0]	4.00 [0, 10.0]	4.00 [0.10.0]
Baseline immediate word recall score			
Mean (SD)	5.57 (1.57)	5.12 (1.54)	5.39 (1.57)
Median [min, max]	6.0 [0, 10.0]	5.00 [0, 10.0]	5.00 [0, 10.0]
Baseline total memory score			
Mean (SD)	10.0 (3.27)	9.09 (3.12)	9.64 (3.24)
Median [min, max]	10.0 [0, 20.0]	9.00 [0, 20.0]	10.0 [0, 20.0]
Age category			
65 years or older	4334 (54.9%)	3131 (58.3%)	7465 (56.3%)
Under 65 years	3554 (45.1%)	2239 (41.7%)	5793 (49.2%)
Cholesterol management Rx	3567 (45.2%)	3174 (59.1%)	6741 (50.8%)

Note: Non-HDL (calculated LDL) = Total Cholesterol - HDL Cholesterol.
Abbreviation: APOE-e4, apolipoprotein E-e4; HDL, high-density lipoprotein; LDL, low density lipoprotein; Rx, prescription.

3.3 | Association between VBS and DBS measures in HRS

To assess the validity of DBS cholesterol measures compared to VBS cholesterol measures in HRS, we estimated the associations between baseline, first, second, and average DBS cholesterol measures (Figure 1B) with VBS measures. We found small significant correlations of the baseline measures of HDL and non-HDL with first and second follow-up measures (with ranges HDL-C: [0.39 to 0.77] and LDL or non-HDL: [0.21 to 0.7]). Similarly, we found significant correlations when comparing each DBS-follow up measure to the obtained VBS measure in the 2016 study (with ranges for HDL-C: [0.46 to 0.69] and LDL or

TABLE 2 Association of cholesterol values at baseline and longitudinally with memory scores.*

Parameter	All participants β	Females < 65 β	Females ≥ 65 β	Males < 65 β	Males ≥ 65 β
A. Association of baseline cholesterol with all memory scores					
Participants	13,258	3554	4334	2239	3131
Outcomes	65,580	19,645	20,555	11,437	13,943
HDL	**0.05* (0.03 to 0.08)**	**0.05* (0.01 to 0.09)**	**0.05* (0.00–0.09)**	0.04 (−0.02 to 0.10)	**0.05* (0.01 to 0.10)**
Non-HDL	**−0.01* (−0.02 to 0.00)**	0.00 (−0.02 to 0.01)	−0.01 (−0.03 to 0.01)	−0.02 (−0.04 to 0.00)	−0.02 (−0.03 to 0.00)
APOE-e4 (ref = 1)	**−0.42* (−0.50 to −0.35)**	−0.11 (−0.29 to 0.07)	**−0.98* (−1.14 to −0.80)**	0.05 (−0.20 to 0.30)	**−0.51* (−0.65 to −0.36)**
B. Association of longitudinal cholesterol with all memory scores					
Participants	12,175	3007	4363	1860	2945
Outcomes	23,317	5214	8990	3139	6013
HDL	**0.02* (0.00 to 0.04)**	0.02 (−0.02 to 0.06)	0.02 (−0.02 to 0.05)	0.04 (−0.01 to 0.10)	0.02 (−0.03 to 0.07)
Non-HDL	0.01 (0.00 to 0.01)	0.00 (−0.02 to 0.02)	**0.02* (0.00 to 0.03)**	−0.02 (−0.04 to 0.01)	0.01 (−0.03 to 0.07)
APOE-e4 (ref = 1)	**−0.32* (−0.42 to −0.21)**	−0.13 (−0.34 to 0.08)	**−0.60* (−0.77 to −0.43)**	0.07 (−0.21 to 0.35)	**−0.25* (−0.44 to −0.06)**

Note: Each column depicts a new model following the described population stratification. Outcomes refer to the total number of cognitive assessments available for each stratified population. (A) Depicts beta-coefficients for the association of cholesterol measured at baseline (first available) with memory scores; (B) Depicts beta-coefficients for most-recently available longitudinal cholesterol with memory scores. All memory scores span from 2006-2020 in HRS participants. Sub tables are stratified by age and sex. All models are adjusted for age, sex, education, use of cholesterol prescription medications, APOE-e4 status (0 vs. 1-2 alleles, ref. category: 1-2 alleles), and race/ethnicity. * and bold numbers indicate statistical significance (p-value <0.05).
Abbreviation: APOE-e4, apolipoprotein E-e4; HDL, high-density lipoprotein.

non-HDL: [0.27 to 0.5]). The linear regression model conducted to estimate memory scores using the cross-sectional VBS measures collected in 2016 yielded consistent findings, showing predominantly negligible coefficients associated with cholesterol values in relation to memory scores (Table S1).

3.4 | Sensitivity analyses: APOE-e4 and cholesterol

Baseline age was not associated with HDL-C among individuals with no APOE-e4 alleles (Table S2) and there was no evidence that APOE-e4 status modified the rate of change in HDL-C (Table S3). Baseline age was associated with lower non–HDL-C among both non–APOE-e4 carriers (β: −0.50, 95% CI: −0.58 to −0.43) and APOE-e4 carriers (β: −0.48, 95% CI: −0.61 to −0.34) (Table S2) but no significant interaction between age and APOE-e4 status (Table S3).

Time-updated age was not associated with HDL-C among individuals with or without APOE-e4 alleles (Table S2). There was also no evidence that APOE-e4 status modified rate of change in HDL-C (Table S3). Although time-updated age was associated with lower non–HDL-C among both non–APOE-e4 carriers (β: −0.57, 95% CI: −0.64 to −0.51) and APOE-e4 carriers (β: −0.57, 95% CI: −0.64 to −0.51) (Table S2), there was no significant interaction between time-updated age and APOE-e4 status (Table S3).

3.5 | Sensitivity analyses: Cholesterol and memory associations stratified by age and APOE-e4 status

We evaluated whether the associations between cholesterol and memory outcomes differed between age groups (<65 years and ≥ 65 years) and APOE-e4 allele status. Across the four strata defined by age and APOE-e4 carrier status, neither time-updated HDL nor non-HDL were associated with memory scores (Table S4).

3.6 | Sensitivity analyses: Addressing practice effects in HRS

Upon re-running all models to account for potential practice effects, we observed no significant changes in memory scores among all participants in HRS enrolled before 2006, whether estimating scores based on baseline cholesterol or measurements collected over time. Unlike the primary analyses, HDL measured at baseline was no longer found to have a statistically significant impact on memory scores among older females. When restricting to people enrolled prior to 2006, we observed a statistically significant positive association of baseline HDL with average memory in younger males ($\beta = 0.10$, 95% CI: 0.02 to 0.19), contrasting with a negative association of baseline non-HDL measurements with average memory ($\beta = -0.03$, 95% CI: −0.06 to −0.00) (Tables S5,S6).

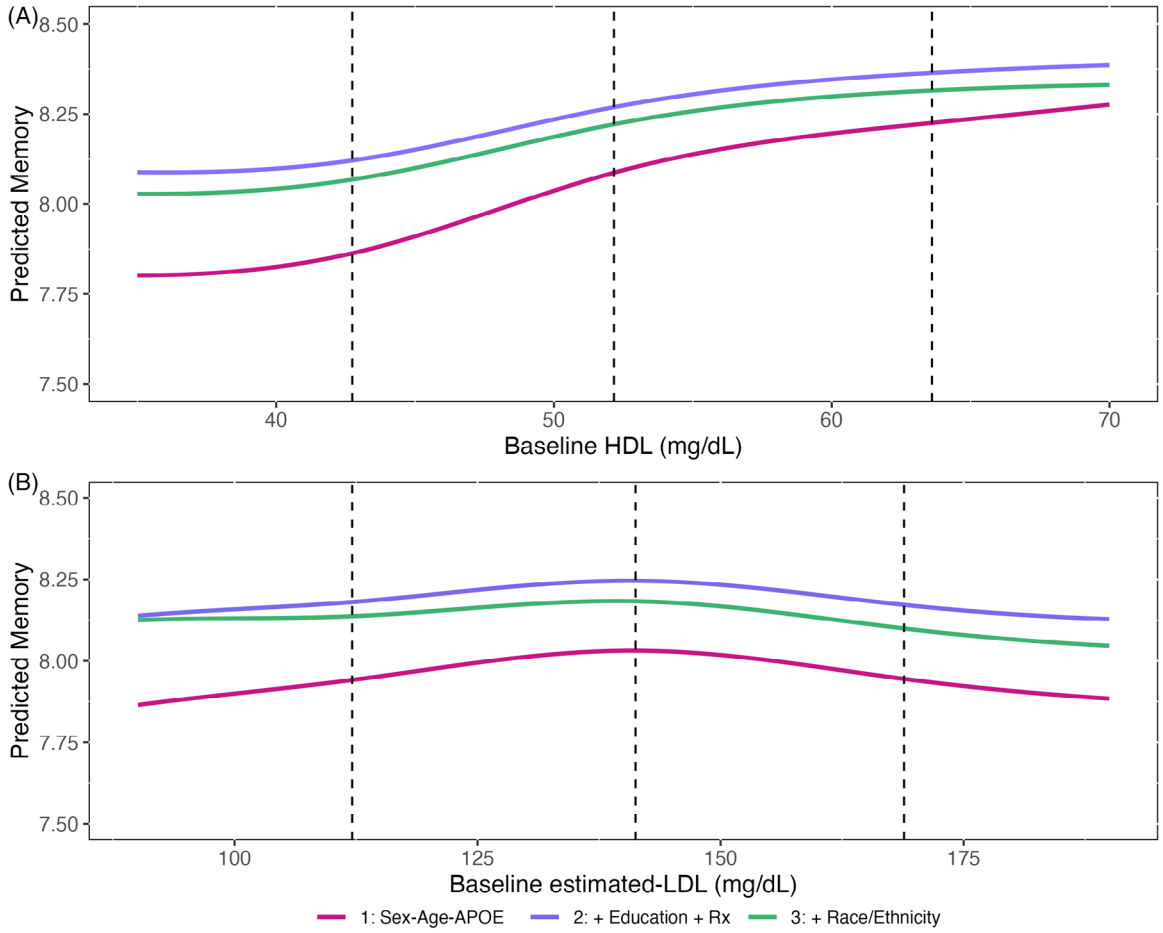

FIGURE 3 Predicted memory scores across all follow-up waves given baseline HDL (A) and non-HDL (B) cholesterol values. Model 1 is adjusted for sex, age at the time of cholesterol measurement and APOE-e4 allele status (in magenta). Model 2 additionally includes adjustment for years of education and prescription for cholesterol medications (in purple). Model 3 additionally includes control for self-reported race and ethnicity (in green). Cholesterol values at the 25th, 50th, and 75th percentiles are depicted in vertical dashed lines. APOE-e4, apolipoprotein E-e4; HDL, high-density lipoprotein

4 | DISCUSSION

We found statistically significant but small associations of higher HDL-C (first-available and most-recent prior) with better memory scores in a nationally representative sample of United States adults ages 50+ (N = 13,258). Non–HDL-C showed small and inconsistent associations with average memory. Neither first-available HDL nor first-available non-HDL were consistently associated with rate of memory change, although there was some evidence that first available non-HDL was associated with faster memory decline in women but slower memory decline in men under age 65. Most-recent previously measured HDL was also associated with slower memory decline men <65.

Our research aligns with existing studies, indicating a modest positive association between elevated HDL-C levels and enhanced memory function. Previous evidence suggests that this association holds true for adults aged 45 and above, regardless of sex or the timing of cholesterol measurements compared to memory assessments.[7,30,31] Although prior studies found that non–HDL-C levels were associated with slower cognitive decline, these studies were predominately focused on homogenous populations.[7–10,13,15–17,32–34] In our diverse cohort, we observed a very small adverse relationship between non–HDL-C levels and memory scores, which was not consistent across subgroups or timing of cholesterol measures.

The associations between elevated HDL-C levels and improved memory scores suggest that sustaining HDL-C levels throughout adulthood may modestly support cognitive performance. For context, the estimated effect of a year of education on average memory was nearly two times as large as the effect of a 10 mg/dL difference in HDL-C on memory change over a decade; the estimated effect of APOE-e4 allele status on average memory was 16 times larger than the HDL-C coefficient. Our spline models suggested slight non-linearities, with HDL-C being more important at low levels, but these differences were generally modest.

Our findings are consistent with prior results suggesting that non–HDL-C is harmful for women's cognition but not men's cognition; however, given the inconsistency of this pattern based on the timing of measurement of non-HDL and average memory versus

TABLE 3 Association of cholesterol values at baseline and longitudinally with memory change.*

Parameter	All participants β	Females < 65 β	Females ≥ 65 β	Males < 65 β	Males ≥ 65 β
A. Association of baseline cholesterol with memory change					
Participants	13,258	3554	4334	2239	3131
Outcomes	65,580	19,645	20,555	11,437	13,943
HDL	−0.02 (−0.05 to 0.01)	−0.02 (−0.07 to 0.04)	−0.02 (−0.07 to 0.04)	0.00 (−0.08 to 0.08)	−0.04 (−0.13 to −0.04)
Non-HDL	0.00 (−0.02 to 0.01)	**−0.03* (−0.05 to −0.01)**	**−0.03* (−0.05 to −0.01)**	**0.04* (0.01 to 0.07)**	−0.02 (−0.05 to 0.01)
APOE-e4 (ref = 1)	**−0.42* (−0.50 to −0.35)**	−0.11 (−0.29 to 0.07)	**−0.98* (−1.14 to −0.80)**	0.05 (−0.20 to 0.30)	**−0.51* (−0.65 to −0.36)**
B. Association of longitudinal cholesterol with memory change					
Participants	12,175	3007	4363	1860	2945
Outcomes	23,317	5214	8990	3139	6013
HDL	0.05 (0.00 to 0.11)	0.08 (−0.03 to 0.19)	**0.10* (0.01 to 0.19)**	0.06 (−0.10 to 0.22)	−0.01 (−0.14 to 0.12)
Non-HDL	0.02 (0.00 to 0.04)	−0.01 (-0.06 to 0.05)	−0.02 (-0.06 to 0.02)	**0.09* (0.03 to 0.15)**	0.03 (−0.03 to 0.08)
APOE-e4 (ref = 1)	**−0.32* (−0.42 to −0.21)**	−0.13 (−0.34 to 0.08)	**−0.60* (−0.77 to −0.43)**	0.07 (−0.21 to 0.35)	**−0.25* (−0.44 to −0.06)**

Note: Each column depicts a new model following the described population stratification. Outcomes refer to the total number of cognitive assessments available for each stratified population. (A) Depicts beta-coefficients for the association of cholesterol measured at baseline (first-available) with memory change; (B) Depicts beta-coefficients for most-recently available longitudinal cholesterol with memory change. Coefficients are obtained from linear mixed models and represent the interaction of time-since baseline (in decades) with each cholesterol measure, stratified by age and sex. * and bold numbers indicate statistical significance (p-value <0.05).
Abbreviation: APOE-e4, apolipoprotein E-e4; HDL, high-density lipoprotein.

memory change, we interpret this pattern very cautiously and plausibly attributable to chance.

A major concern in research on cognitive aging is the possibility that early neurodegenerative processes influence risk factors among older adults, as has been demonstrated with body mass index.[35,36] As expected, baseline age was associated with lower non-HDL and the presence of APOE-e4 alleles were associated with higher non-HDL values. To assess whether participants might have reached an age at which incipient neurodegenerative disease influenced cholesterol levels, we assessed the association of APOE and age-related changes in cholesterol. APOE was not associated with faster age-related non-HDL changes, suggesting that changes in cholesterol due to incipient Alzheimer's disease did not notably contribute to our findings. Likewise, our findings when restricting to young individuals without APOE-e4 alleles (low risk of incipient Alzheimer's) were quite similar to results when restricting to older individuals with APOE-e4 alleles (high risk of incipient Alzheimer's).

Our study has several limitations. DBS assessments of cholesterol are subject to measurement error, as illustrated in the validation against VBS measurements. We also could not disentangle triglycerides from LDL or non-HDL-C, and triglycerides might be an important confounder of the association of non-HDL with cognitive outcomes, since non-HDL measures are calculated by subtracting HDL-C values from TC values. Absence of trygliceride values in the HRS study prevents us from properly calculated LDL-C values. Because DBS were collected only every other wave, even using most-recent prior cholesterol assessments left us with up to a 4-year lag between cholesterol measure and memory outcome. Importantly, our study only captured cognition from word list recall. Inclusion of a wider range of cognitive domains with higher-quality assessments might reveal stronger associations.

These limitations are offset by key strengths, including a large, nationally representative sample with up to 14 years of follow-up for memory assessments. The large sample allowed us to evaluate heterogeneity by sex and age of cholesterol assessment and compare associations with average memory versus rate of decline in memory. With longitudinal cholesterol measures, we were able to assess differences in patterns based on using first-available versus most-recent previously measured cholesterol level.

Contemporary clinical guidelines emphasize the importance of maintaining optimal levels of HDL-C and non–HDL-C in adults to mitigate the risk of CVD and dementia. Despite this, our analyses reveal only small associations between cholesterol values and memory scores. This finding is unexpected, given the well-established link between CVD and dementia risk. This may be reflective of the influence of multiple, offsetting pathways connecting cholesterol and dementia. We note that this study exclusively evaluates cognition through changes in memory scores over a 14-year period and future studies should aim to measure cognition using more comprehensive cognitive tests to provide a more well-rounded assessment. Additionally, it is crucial to investigate sex differences across the lifespan, including comparisons between middle-aged and elderly men and women. Furthermore, understanding the impact of early-life cholesterol on cognitive outcomes later in life, compared to the effects of cholesterol in mid-to-late life, warrants further investigation. The tantalizing but inconclusive heterogeneity by sex may also offer insights into

the reasons that such well-established predictors of CVD are not strongly related to longitudinal memory changes. The overall small or null associations suggest the importance of prioritizing other strategies for maintaining cognitive function and offsetting dementia risk through the focus of alternative major risk factors such as education and presence of APOE-e4 alleles.

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CONFLICT OF INTEREST STATEMENT

The authors report no relevant conflicts of interest or disclosures. Author disclosures are available in the Supporting Information.

CONSENT STATEMENT

Prior to each HRS interview, participants are provided with a written formal informed consent information document. At the start of each interview, all respondents are read a confidentiality statement, and give oral consent by agreeing to do the interview.

DIVERSITY, EQUITY, AND INCLUSION STATEMENT

Equitable representation of racial and ethnic groups is a priority in our approach to our research. The Health and Retirement Study prioritizes the inclusivity of individuals with a multi-racial background. so that their surveys are conducted in a multi-racial sample. The present data source includes 517(3.9%) individuals who identified as Hispanic, 38 (0.3%) individuals who identify as Hispanic Black, 927 (7.0%) individuals who identify as Hispanic White, 2297 (17.3%) individuals who identify as Non-Hispanic Black, 324 (2.4%) individuals who identified as Non-Hispanic Other, 9137 (68.9%) individuals who identify as Non-Hispanic White, and 8 (0.1%) individuals without a specified race/ethnicity.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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