Association Between HDL Cholesterol and Incident Cognitive Impairment in Black and White Adults in The Reasons For Geographic and Racial Differences in Stroke Study

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Abstract

BACKGROUND:

Low levels of high-density lipoprotein cholesterol (HDL-C) have been associated with incident cognitive impairment (ICI) in some, but not all studies.

METHODS:

We examine the association between HDL-C and ICI among 18,378 Reasons for Geographic and Racial Differences in Stroke (REGARDS) study participants without cognitive impairment or stroke at baseline in 2003 to 2007, and who did not have a stroke event during follow-up.

RESULTS:

Over a median follow-up of 9.6 years, 1,359 participants developed ICI. In fully adjusted models, the RR for ICI was 1.51 (95% CI 1.06, 2.15) in White women and 1.25 (95% CI 0.95, 1.65) in Black women. The association was not statistically significant after adjustment for triglycerides. There was no evidence of an association between HDL-C and ICI among White or Black men.

CONCLUSIONS:

Low HDL-C was associated with a higher risk of ICI in White and Black women in models not including triglycerides.

Introduction:

Low high-density lipoprotein cholesterol (HDL-C) has been associated with higher rates of incident cognitive impairment (ICI) in some, but not all, prior studies (1–5). The heterogeneity in the association between HDL-C and ICI in prior studies may result from residual confounding by lifestyle, cardiovascular risk factors, systemic inflammation, and history of stroke (5–8). This study aimed to determine the association between HDL-C and ICI among race and sex subgroups in a population-based longitudinal cohort of White and Black middle-aged and older adults (9). The association between HDL-C and ICI was determined before and after adjustment for lifestyle behaviors, menopausal status and hormonal replacement therapies (HRT) in women, C-reactive protein, hypertension and triglycerides.

Methods:

Details on the design and methods of the REGARDS study have been published.(9) The Reasons for Geographic and Racial Differences in Stroke (REGARDS) study enrolled 30,239 US Black and White adults

≥ 45 years of age between 2003 and 2007. Overall, 42% of enrolled participants were Black and 55% were women (9). The study was approved by the institutional review boards at all participating institutions, and all participants provided written informed consent.

Serum HDL-C was measured using blood collected at baseline by colorimetric reflectance spectrophotometry. For the current analysis, we included 26,977 study participants without CI, defined by a score ≥ 5 , at their first Six Item Screener (SIS) assessment. During follow-up, cognitive status was assessed using the SIS beginning in December 2003, and the three battery tests in the Consortium to Establish a Registry for Alzheimer's Disease (CERAD): Word List Learning, Word List Delayed Recall and Semantic Animal Fluency tests (10). CERAD and SIS tests were administered by telephone at 18–24 month and 12-month intervals, respectively. We excluded participants who did not complete ≥ 1 assessment for each of the 3 CERAD battery tests during follow-up ($n=6,119$), did not have valid data on HDL-C ($n=867$), or who had a history of stroke at baseline or a stroke event during follow-up ($n=1,613$). The final cohort included 18,378 participants. ICI was defined as a score ≥ 1.5 standard deviations (SD) below the age, sex, and education-based stratum-specific means on 2 or 3 of the CERAD battery tests at any single determination during follow up.

Statistical analysis

We described participant characteristics and used Poisson regression models with robust variance estimators to calculate the risk ratio (RR) for ICI associated with HDL-C levels in a series of progressively adjusted models. We adjusted for income and education, smoking, second-hand smoke, body mass index, physical activity, alcohol consumption, use of HRT, and menopausal status among women. We further adjusted for systolic blood pressure and diagnosis of hypertension, and C-reactive protein (CRP). We adjusted for triglycerides due to inverse association with HDL-C. All analyses were conducted among White women, Black women, White men, and Black men, separately.

Results:

The characteristics of study participants and the distribution of HDL-C stratified by sex and race are presented in Table 1. Overall, 5.2% of White women, 11.6% of Black women, 5.8% of White men and 9.2% of Black men developed ICI over a median follow up of 9.6 years. After adjustment for age and region of residence (Model 1), HDL-C <40 mg/dL versus ≥ 60 mg/dL was associated with an increased RR (95% Confidence Interval [CI]) for ICI among White women (1.60 [1.16, 2.21]) and Black women (1.35 [1.03, 1.76], Table 2). HDL-C remained associated with ICI after additional adjustment for income and education in White women (RR 1.66 [95% CI 1.20, 2.31]) and Black women (RR 1.34 [95% CI 1.03, 1.75]). After further adjustment for body mass index, lifestyle factors (smoking, second-hand smoke, body mass index, physical activity, alcohol consumption), menopausal status, and hormone replacement therapy, the RR for ICI was 1.51 (95% CI 1.06, 2.15) in White women and 1.25 (95% CI 0.95, 1.65) in Black women. The association between a low HDL-C and ICI was attenuated after additional adjustment for triglycerides

(White women: RR 1.31 [95% CI 0.89, 1.94], Black women: RR 1.12 [95% CI 0.84, 1.51]). There was no evidence of associations between HDL-C and ICI in Black or White men.

Table 1
Characteristics of REGARDS study participants stratified by sex and race.

	Women		Men	
	White (n=6,222)	Black (n=4,259)	White (n=5,588)	Black (n=2,309)
Characteristics				
Age, years, mean (SD)	63.6 (9.1)	62.7 (8.6)	64.5 (8.7)	63.0 (8.6)
Age, years				
45-54	941 (15.1%)	675 (15.8%)	596 (10.7%)	349 (15.1%)
55-64	2530 (40.7%)	1882 (44.2%)	2303 (41.2%)	1005 (43.5%)
65-74	1889 (30.4%)	1274 (29.9%)	1914 (34.3%)	715 (31.0%)
≥75	862 (13.9%)	428 (10.0%)	775 (13.9%)	240 (10.4%)
Education level, n (%)				
No high school graduate	381 (6.1%)	641 (15.1%)	252 (4.5%)	276 (12.0%)
High school graduate	1673 (26.9%)	1146 (26.9%)	1074 (19.2%)	611 (26.5%)
Some college education	1767 (28.4%)	1200 (28.2%)	1330 (23.8%)	668 (28.9%)
College graduate or higher	2400 (38.6%)	1269 (29.8%)	2931 (52.5%)	754 (32.7%)
Annual household Income, n (%)				
<\$20,000	806 (13.0%)	1094 (25.7%)	295 (5.3%)	297 (12.9%)
\$20,000-34,000	1475 (23.7%)	1102 (25.9%)	989 (17.7%)	579 (25.1%)
\$35,000-74,000	1887 (30.3%)	1200 (28.2%)	2188 (39.2%)	833 (36.1%)
≥\$75,000	1126 (18.1%)	367 (8.6%)	1671 (29.9%)	412 (17.8%)
Declined to report	928 (14.9%)	496 (11.6%)	445 (8.0%)	188 (8.1%)
Geographic Region, n (%) ^a				

	Women		Men	
Stroke belt	2232 (35.9%)	1390 (32.6%)	1911 (34.2%)	765 (33.1%)
Stroke buckle	1593 (25.6%)	833 (19.6%)	1143 (20.5%)	389 (16.8%)
Non-belt region	2397 (38.5%)	2036 (47.8%)	2534 (45.3%)	1155 (50.0%)
Smoke Status, n (%)				
Current smoker	750 (12.1%)	599 (14.1%)	558 (10.0%)	378 (16.5%)
No current smoker, exposed to secondhand smoke	3468 (55.9%)	2303 (54.3%)	2198 (39.5%)	825 (35.9%)
No current smoker, not exposed to secondhand smoke	1981 (32.0%)	1340 (31.6%)	2815 (50.5%)	1093 (47.6%)
Diabetes, n (%)	680 (11.0%)	1059 (25.0%)	826 (14.9%)	615 (26.8%)
Body mass index, n (%)				
<18.5-24.9 Kg/m ²	2103 (33.9%)	572 (13.5%)	1294 (23.3%)	467 (20.4%)
25-29.9 Kg/m ²	2074 (33.5%)	1259 (29.8%)	2580 (46.5%)	925 (40.4%)
≥30 Kg/m ²	2018 (32.6%)	2397 (56.7%)	1680 (30.2%)	900 (39.3%)
Systolic blood pressure, mmHg, mean (SD)	122.5 (15.4)	128.7 (16.5)	126.2 (14.8)	130.9 (16.0)
Diastolic blood pressure, mmHg, mean (SD)	74.2 (8.9)	77.9 (9.7)	76.3 (9.1)	79.4 (9.7)
Physical Activity, n (%)				
≥4 bouts/week of intense activity	1623 (26.4%)	982 (23.3%)	2129 (38.5%)	720 (31.6%)
1-3 bouts/week of intense activity	2371 (38.6%)	1616 (38.4%)	2121 (38.4%)	948 (41.6%)
0 bouts/week of intense activity	2148 (35.0%)	1615 (38.3%)	1274 (23.1%)	613 (26.9%)
Alcohol consumption, n (%) ^b				
None	3766 (61.3%)	3174 (76.1%)	2491 (45.3%)	1276 (56.6%)

	Women		Men	
Moderate	2069 (33.7%)	927 (22.2%)	2704 (49.2%)	899 (39.9%)
Heavy	311 (5.1%)	69 (1.7%)	306 (5.6%)	78 (3.5%)
Triglycerides, mg/dL, median (25%, 75% percentiles)	120.0 (87.0,169.0)	94.0 (73.0,126.0)	122.0 (88.0,176.0)	97.0 (73.0,137.0)
C-Reactive Protein $\geq$ 2 mg/L, n (%)	3175 (52.4%)	2744 (66.3%)	2077 (37.9%)	1119 (49.3%)
Menopause, n (%)	5505 (90.0%)	3695 (89.4%)	-	-
Antihypertensive therapy, n (%)	2989 (48.0%)	2892 (67.9%)	2808 (50.3%)	1453 (62.9%)
Statin therapy, n (%)	1686 (27.1%)	1144 (26.9%)	2053 (36.7%)	681 (29.5%)
Hormone replacement therapy, n (%)	4183 (67.2%)	2054 (48.2%)	61 (1.1%)	13 (0.6%)
Baseline Six-Item Screener score, mean (SD)	5.9 (0.3)	5.7 (0.4)	5.8 (0.4)	5.7 (0.5)
HDL-C, mg/dL, mean (SD)	58.0 (16.4)	57.3 (15.8)	44.3 (12.9)	48.0 (14.3)
HDL-C categories among women, n (%)				
<40 mg/dL	693 (11.1%)	419 (9.8%)	-	-
40-49 mg/dL	1374 (22.1%)	1044 (24.5%)	-	-
50-59 mg/dL	1586 (25.5%)	1164 (27.3%)	-	-
$\geq$ 60 mg/dL	2569 (41.3%)	1632 (38.3%)	-	-
HDL-C categories among men, n (%)				
<30 mg/dL	-	-	463 (8.3%)	102 (4.4%)
30-39 mg/dL	-	-	1752 (31.4%)	573 (24.8%)
40-49 mg/dL	-	-	1798 (32.2%)	762 (33.0%)
$\geq$ 50 mg/dL	-	-	1575 (28.2%)	872 (37.8%)

Women	Men
HDL-C: high-density lipoprotein cholesterol.	
Numbers reported in table are n (%) or mean (SD).	
^a Stroke buckle includes coastal North Carolina, South Carolina and Georgia. Stroke belt includes the remaining parts of North Carolina, South Carolina and Georgia, and Tennessee, Mississippi, Alabama, Louisiana and Arkansas. Other US regions includes the remaining 40 contiguous US states and the District of Columbia.	
^b Based on the number of drinks that participants self-reported having per week during their baseline computer-assisted telephone interview and categorized as follows:	
<ul style="list-style-type: none"> • No alcohol consumption: 0 drinks per week. 	
<ul style="list-style-type: none"> • Moderate alcohol consumption: >0 to 7 drinks per week for women and >0 to 14 drinks per week for men. 	
<ul style="list-style-type: none"> • Heavy alcohol consumption: >7 drinks per week for women and >14 drinks per week for men. 	

Table 2
Relative risk for ICI associated with HDL-C levels, stratified by sex and race

HDL-C Level	N (%) with ICI / Total number of participants	Risk ratio (95% confidence interval)					
		Model 1	Model 2	Model 3	Model 4a	Model 4b	Model 4c
White Females							
<40 mg/dL	49 (7.1%) / 693	1.60 (1.16, 2.21)	1.66 (1.20, 2.31)	1.51 (1.06, 2.15)	1.65 (1.16, 2.35)	1.48 (1.04, 2.10)	1.31 (0.89, 1.94)
40-49 mg/dL	76 (5.5%) / 1,374	1.24 (0.94, 1.65)	1.27 (0.96, 1.69)	1.20 (0.89, 1.62)	1.26 (0.93, 1.70)	1.19 (0.88, 1.60)	1.10 (0.80, 1.51)
50-59 mg/dL	87 (5.5%) / 1,586	1.23 (0.94, 1.61)	1.27 (0.97, 1.67)	1.23 (0.92, 1.63)	1.25 (0.94, 1.67)	1.22 (0.92, 1.62)	1.17 (0.88, 1.56)
≥60 mg/dL	114 (4.4%) / 2,569	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Black Females							
<40 mg/dL	61 (14.6%) / 419	1.35 (1.03, 1.76)	1.34 (1.03, 1.75)	1.25 (0.95, 1.65)	1.24 (0.93, 1.64)	1.22 (0.92, 1.62)	1.12 (0.84, 1.51)
40-49 mg/dL	120 (11.5%) / 1,044	1.05 (0.84, 1.30)	1.05 (0.85, 1.30)	0.97 (0.77, 1.22)	0.92 (0.73, 1.17)	0.95 (0.76, 1.20)	0.90 (0.71, 1.15)
50-59 mg/dL	132 (11.3%) / 1,164	1.03 (0.83, 1.27)	1.04 (0.84, 1.29)	1.00 (0.80, 1.25)	1.00 (0.80, 1.25)	1.00 (0.80, 1.25)	0.96 (0.77, 1.20)
≥60 mg/dL	182 (11.2%) / 1,632	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
White Males							
<30 mg/dL	22 (4.8%) / 463	0.96 (0.61, 1.52)	0.99 (0.63, 1.57)	0.89 (0.55, 1.43)	0.92 (0.57, 1.49)	0.87 (0.54, 1.40)	0.82 (0.49, 1.35)
30-39 mg/dL	119 (6.8%) / 1,752	1.34 (1.02, 1.76)	1.38 (1.05, 1.83)	1.25 (0.93, 1.70)	1.29 (0.95, 1.75)	1.23 (0.91, 1.67)	1.19 (0.85, 1.66)
40-49 mg/dL	104 (5.8%) / 1,798	1.14 (0.86, 1.52)	1.16 (0.88, 1.54)	1.05 (0.77, 1.42)	1.07 (0.79, 1.45)	1.04 (0.77, 1.41)	1.02 (0.74, 1.39)
≥50 mg/dL	80 (5.1%) / 1,575	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)

HDL-C Level	N (%) with ICI / Total number of participants	Risk ratio (95% confidence interval)					
		Model 1	Model 2	Model 3	Model 4a	Model 4b	Model 4c
Black Males							
<30 mg/dL	8 (7.8%) / 102	0.80 (0.40, 1.61)	0.81 (0.40, 1.64)	0.75 (0.37, 1.53)	0.78 (0.39, 1.59)	0.74 (0.36, 1.51)	0.73 (0.35, 1.52)
30-39 mg/dL	53 (9.2%) / 573	0.95 (0.68, 1.31)	0.93 (0.68, 1.29)	0.88 (0.63, 1.24)	0.86 (0.61, 1.22)	0.87 (0.62, 1.23)	0.87 (0.60, 1.26)
40-49 mg/dL	67 (8.8%) / 762	0.90 (0.66, 1.22)	0.93 (0.68, 1.25)	0.83 (0.60, 1.15)	0.82 (0.59, 1.14)	0.82 (0.59, 1.14)	0.82 (0.59, 1.15)
≥50 mg/dL	85 (9.7%) / 872	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Data are presented as relative risks and 95% confidence intervals.							
ICI: Incident cognitive impairment; HDL-C: high-density lipoprotein cholesterol							
ICI was defined by a score 1.5 standard deviations below the age, sex, and education adjusted mean on at least two of the three tests in the Three Test Battery: Word List Learning, Word List Delayed Recall, and Animal Naming Tests at any time during follow-up.							
Model 1 adjusts for age and geographic region of residence.							
Model 2 adjusts for the components of Model 1 plus income and education.							
Model 3 adjusts for the components of Model 2 plus smoking, second-hand smoke, body mass index, physical activity, alcohol consumption, use of hormone replacement therapy, and menopausal status among women.							
Model 4a adjusts for variables in Model 3 plus C-reactive protein.							
Model 4b adjusts for variables in Model 3 plus systolic blood pressure and hypertension medication use.							
Model 4c adjusts for variables in Model 3 plus the log of triglycerides.							

Discussion:

In this large prospective, population-based study of White and Black women and men, low HDL-C (<40 mg/dL) was associated with an increased risk for ICI in White and Black women, but not in men. The higher risk of ICI was present before and after adjustment for factors known to contribute to HDL-C. However, adjustment for triglycerides attenuated these associations in both White women and Black women. Examination of race-sex differences is important because of well-known differences in levels of HDL-C between women and men and triglyceride levels between White and Black people (11).

Multiple prospective population-based studies, (1, 3, 4) and a pooled analysis of 11 cohort studies including 5,658 participants, reported that lower levels of HDL-C were associated with cognitive decline (10). These studies included participants with a history of stroke. In contrast, there was no association between HDL-C and cognitive function in an analysis of 5,033 stroke-free women and men who participated in the Tromso study (5). The results from the current study are consistent with the findings from the Tromso study.

Few studies have analyzed sex-specific differences in HDL-C and ICI. The China Health and Retirement Longitudinal Study (CHARLS) investigated ICI in 6,792 Chinese stroke-free adults aged 45 years and older, and paradoxically reported a higher HDL-C level was associated with a higher risk of cognitive decline in women, but a lower risk of cognitive decline in men (12). Among women <60 years of age, the adjusted odds ratio for cognitive decline associated with HDL-C levels of 40-59 mg/dL and ≥ 60 mg/dL versus <40 mg/dL was 1.37 (95% CI 1.04, 1.80) and 1.29 (95% CI 0.94, 1.77), respectively. Episodic memory loss was also associated with a higher HDL-C in women (adjusted odds ratio associated with HDL-C 40-59 mg/dL and ≥ 60 mg/dL versus <40 mg/dL 1.55 [95% CI 1.18, 2.03] and 1.55 [95% CI 1.13, 2.13], respectively). Fasting triglyceride levels were not associated with cognitive decline in participants in CHARLS. In the REGARDS study, an increased risk of ICI in Black and White women with low HDL-C concentrations was present after multivariate adjustment with the exception of triglycerides. Elevated triglycerides were associated with an increased risk of non-Alzheimer's dementia and stroke in a prospective study of 125,727 individuals participating in the Copenhagen General Population Study and Copenhagen City Heart Study (13). Triglyceride-rich lipoproteins increase atherosclerosis contributing to increased risk of stroke and non-Alzheimer's dementia in Blacks and Whites, but not apparently in Chinese.

HDL-C is a common metric for HDL; however, the cholesterol content of HDL is an inadequate metric for the multifarious functions of HDL (14). Emerging evidence from genetic, clinical and experimental studies supports the involvement of surface protein components of HDL in cognitive function (15). In the current study, we were unable to determine the association of HDL-C with the plethora of anti-oxidant and anti-inflammatory properties of specific HDL subspecies that may have important physiological involvement in mitigating the risk of cognitive decline (14). However, the association between a low level of HDL-C in White women remained present after adjustment for the systemic inflammatory marker CRP.

LIMITATIONS:

CI and dementia have various etiologies. Specific causes of CI or dementia were unavailable in this cohort analysis. The REGARDS study is limited to Black and White Americans; therefore, the results may not be generalizable to other race/ethnic groups including Asians or Hispanics. We used data on HDL-C as a surrogate marker for HDL, while recognizing the importance of HDL proteins in cholesterol efflux and mitigating inflammation. An ongoing analysis of REGARDS (NIH R01AG061186) is evaluating the HDL proteome in ICI and Alzheimer's dementia. Other limitations include the lack of data on triglyceride-rich lipoproteins, which also contribute to vascular inflammation. Markers of inflammation were limited to CRP.

Conclusion:

In conclusion, low HDL-C was associated with ICI in White and Black women. Adjustment for lifestyle factors partially attenuated the association between low HDL-C and ICI. Triglyceride-rich lipoproteins share many of the same determinants as HDL-C, but have distinct properties that may contribute to ICI.

Declarations

Ethics approval and consent to participate

Study methods were approved by the institutional review boards at participating institutions and all participants provided written informed consent for the storage of their clinical data for research purposes as part of the Reasons for Geographic and Racial Differences in Stroke (REGARDS) project.

Consent for publication:

Not applicable

Availability of data and materials

Qualified researchers trained in human subject confidentiality protocols may request access to the data that support the findings of this study by contacting the REGARDS Study at REGARDS@uab.edu

Competing interests:

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RSR, MC, PM, TV, SJ, and LDC.

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Authors' contributions

The individual contributions of authors to the manuscript should be specified in this section. Guidance and criteria for authorship can be found in our editorial policies.

RSR, MC, PM, LDC, JH obtained funding for this research. RSR, MC, EM, PM, TV, CT, SJ, LDC analyzed and interpreted the data and wrote the manuscript, ZW conducted the statistical analyses. All authors read and approved the final manuscript.

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<https://www.uab.edu/soph/regardsstudy/>

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