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The Association of Statin Use and Statin Type on Cognitive Performance: Analysis of The REasons for Geographic And Racial Differences in Stroke (REGARDS) Study

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SUMMARY

Context—Statin use and type has been variably associated with impaired or improved cognitive performance.

Objective—To assess the association of statin use and type (lipophilic vs hydrophilic) and cognitive impairment

Design—Cross-sectional analysis of 24595 (7191 statin users and 17404 non-users) participants (age ≥45), from a population-based national cohort study (REasons for Geographic And Racial Differences in Stroke) enrolled from January 2003-October 2008 with over-sampling from the southeastern Stroke Belt, and African Americans.

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Main Outcomes—Statin use and type were documented in participants' homes by a trained health professional. Cognitive performance was assessed with a prior validated instrument of global cognitive status (Six-Item Screener). Cognitive impairment was defined as a score of < 4. .

Results—Overall, an association of cognitive impairment and statin use was observed (8.6% of users vs 7.7% or non-users had cognitive impairment p=.014) but, after adjusting for variables known to be associated with cognition (age, gender, race, income, levels of education, and cardiovascular disease) the association was attenuated (OR 0.98, CI; 0.87;1.10). No association was observed between statin type (lipophilic vs hydrophilic) and cognition (OR 1.03, CI; 0.86;1.24), and there were no regional differences in cognitive impairment in statin users (8% in the stroke belt and 7.9% other regions p=0.63).

Conclusions—Statin use and type was marginally associated with cognitive impairment. After adjusting for known variables that affect cognition, no association was observed. No regional differences were observed. This large study found no evidence to support an association between statins and cognitive performance.

Keywords

Statins; Cognition

Cognitive impairment and decrements over time are associated with cardiovascular diseases such as hypertension and diabetes and with cerebrovascular changes such as white matter hyperintensities that are associated with an increased risk for stroke. Research suggests that the prevalence of cognitive impairment is associated with the number and severity of vascular risk factors,[1-4] which include hypercholesterolemia. Individuals with high levels of low density lipoproteins and triglycerides, and/or low levels of high density lipoprotein often receive statins as part of their treatment regimen.

The data are inconsistent as to whether statin use has any association with better or worse cognition. There is also controversy regarding the role of statin type (particularly lipophilic vs non-lipophilic statins, with the hypothesis that lipophilic statins are more likely to cross the blood-brain barrier and thus have more central nervous system effects) in these observations.[5-6] Understanding the relationship between statin use and global cognitive status, and whether this relationship is mediated by statin type, health behaviors, and cardiovascular risk factors, could help delineate the clinical significance of statin use on cognitive function. Questions have been raised regarding the association of cognition and lipid levels, themselves, irrespective of statin use, particularly high density lipoprotein – cholesterol (HDL-C) levels. Specifically, in 3 non-definitive studies, it has been suggested that low HDL-C is associated with cognitive impairment .[7]

It is in the above setting that we evaluated, from the REGARDS data base, the use and type of statin, and HDL-C, and their association with cognition as assessed by the Six-Item Screener of global cognitive status.

METHODS

Study Population

REGARDS is a national cohort of community dwelling individuals over age 45 years recruited with approximately equal representation of whites and blacks, men and women. Twenty percent of the sample was randomly selected from the "buckle" of the Stroke Belt (coastal plain region of North Carolina, South Carolina, and Georgia), 30% from the Stroke Belt states (remainder of North Carolina, South Carolina, and Georgia plus Alabama, Mississippi, Tennessee, Arkansas, and Louisiana), and the remaining 50% from the other 40

contiguous states. Individuals were identified from commercially available lists of residents, and recruited using an initial mailing followed by telephone contact. Defined according to standards recommended by Morton et al,[8] 64.6% of eligible individuals who were reached, agreed to participate (Figure 1).

Demographic information, medical history, and cognitive assessment were obtained by trained interviewers using a computer-assisted telephone interview (CATI). Consent was obtained verbally by telephone and subsequently in writing during a follow-up in-home visit by a healthcare professional. A brief physical exam including anthropometric and blood pressure measurements, blood samples, and an electrocardiogram was conducted in-person, 3-4 weeks after the telephone interview. For the in-home visit, participants were asked to provide bottles of all medications (including over-the-counter ones) taken during the prior two weeks; medication names were recorded by the health professionals and later confirmed for the specific drug name. These were then coded into classes. Participants were followed by telephone at six-month intervals for surveillance of medical events including potential stroke events. The study methods were reviewed and approved by all involved Institutional Review Boards. Additional methodological details are provided elsewhere.[9] As of October 11, 2008, we had data on 24,595 participants. The primary predictor variables were the use of statins (yes, no) and type of statin (lipophilic, non-lipophilic. We considered lovastatin and simvastatin to be lipophilic and atorvastatin, pravastatin, fluvastatin, and rosuvastatin to be hydrophilic.

Cognitive Assessment

Cognitive assessment was conducted during the baseline telephone interview useing The Six-item Screener (SIS) which is designed for either in-person or telephone administration, and is a test of global cognitive function derived from the widely used Mini-Mental State examination.[10] The SIS has been validated against the Mini-1 Mental State examination, other cognitive measures, and diagnoses of dementia and non-dementia cognitive impairment in two populations: in a community-based survey of 344 black adults with a second-stage formal diagnostic evaluation and a clinical sample of 651 adults (16.1% black) with the same diagnostic evaluation.11 Items from the SIS assess recall and temporal orientation. Scores range from 0 to 6; a score of 4 or fewer correct answers indicates cognitive impairment.[5] A cutpoint of 4 or fewer correct had 74.2% sensitivity and 80.2 % specificity to clinically diagnosed CIND (Cognitive Impairment Not Demented). The same cutpoint was 96.8% sensitive and 68.6 specific to a diagnosis of dementia (a cutpoint of 3 or fewer correct had better specificity for dementia diagnosis). The SIS operates about as well as the widely used MMSE for identifying gross (but not subtle) cognitive deficits worthy of further evaluation. The SIS has since been used as an index of cognitive impairment in the context of depression treatment over a two-year period in a sample of 1,684 IMPACT study participants, and it has been validated against the MMSE and the Mini-Cog in two studies of older emergency department patients. [12]

The Six-item Screener used to assess cognitive status likely lacks sensitivity to subtle cognitive changes. Even so, previous findings from REGARDS attest to its utility in detecting broad patterns of association with conditions affecting cognition, such as traditional cardiovascular risk factors[13], chronic kidney disease[14], and congestive heart failure[15]. In addition, the rate of incident cognitive impairment we found using the SIS (approximately 4% annually) is comparable to annual incidence rates reported by studies that used detailed clinical diagnostic assessments for dementia (3.2%)[16,17] and mild cognitive impairment (5.1%)18]. Furthermore, associations of SIS performance with well-established risk factors for cognitive decline, such as age and education, were in the expected direction, lending support to the validity of the SIS. Between January 2003 and October 2008, 30,228 participants were enrolled. We included participants who completed

the REGARDS Medications Inventory, including the Morisky Scale* a measure of medication adherence[19] (audited and recorded by Examination Management Services Inc –EMSI - examiners). The cognitive assessment was not added until January 2004, reducing the sample size to 24, 595 (figure 1).

*In the mid-1980s, Morisky and colleagues developed a brief questionnaire to aid practitioners in prospectively predicting adherence with antihypertensive medications. Subsequently, the instrument was validated in a number of studies and demonstrated to have good psychometric properties. To score the 4 point Morisky Scale, each question that is answered with a NO receives a score of 1. The possible scoring range is herefore 0 to 4. Patients with higher scores are predicted to be more dherent to prescribed medication therapies. Patients with lower scores are at greater risk for nonadherent behavior.

Statistical Analysis

Geographic and ethnic differences in statin use and statin type and their cross-sectional associations with measures of cognition were determined. We excluded individuals who lacked cognitive function measures. We examined frequency distributions of each variable and then examined bivariate relationships between the outcome and each covariate of interest using Pearson's chi-square. Significance was set at $p<0.05$.

Logistic regression (PROC LOGISTIC in SAS 9.1 Cary, NC) was used to calculate odds ratios (ORs) and 95% confidence intervals (CI) for our multivariable models. Examining the potential for interaction by race, a p value of 0.34 was observed so stratified analyses were not performed. it should be noted that although race is a significant predictor of cognitive function, and the analysis has been adjusted for race, estimated racial differences in cognition are not provided as they do not affect the conclusions drawn in the paper. Variables were considered in a series of incremental models, first adjusting for demographic factors and then the other concomitant variables and diseases potentially associated with the outcome variable. Both a summary variable reflecting any use of a statin as well as a variable stratified by statin type was analyzed. Covariates included ethnicity, age, geographic location, race, urban/rural location, income, level of education, sex, Framingham Coronary Disease Risk (REF), or history of heart disease (MI, vascular disease, or vascular intervention; and EKG evidence of MI), and prior history of stroke (self-reported stroke or TIA). In addition we included systolic blood pressure, pulse pressure, total cholesterol, LDL-C and HDL-C as both continuous and discreet quartiles as covariates.

We prespecified a logistic model based on previous analyses examining cognitive decline in REGARDS. We conducted the Cox proportional Hazards model and mixed linear model. After the final logistic model was determined (n=21317), we performed a series of sensitivity analyses to examine model robustness. We first stratified the results by Morisky score considering perfect adherers (n=4590, 64%). Morisky score was not a statistically significant effect modifier or confounder. We also examined the association between statin use and cognition in those who did not report income and did not find a difference compared with the models presented.

Results

As shown in Tables 1 and 2, there were 7191 participants who were receiving statins, and 17,404 participants who were not The proportion of participants receiving statins was similar by region (29% in the stroke belt vs 30% in other regions (p=011). Overall, cognitive impairment was observed in 8.6% of users vs 7.7% of non-users, (p=0.014), but there were no regional differences (8% in the stroke belt and 7.9% in other regions demonstrated

cognitive impairment p=0.63). However, cognitive impairment was also a function of type of statin use, male sex, age, urban dwelling, lower income, lower educational status, presence of heart disease or stroke, elevated systolic blood pressure (SBP) and pulse pressure (PP), diabetes mellitus, and higher Framingham Coronary Risk.

As seen in Table 3, when the above variables were entered into the multivariable model, cognitive impairment was not associated with statin use. We also found no association between cognitive impairment and HDL-C levels. Imputation of the income status and sensitivity analysis using the Morisky score of medication adherence (among only the 64% of the cohort that reported perfect adherence) did not change the lack of association between cognitive impairment and either statin use or HDL-C level.

Lipophilic vs Non-lipophilic Statins: (Table 4)

The majority of statin use was simvastatin (n=2700) and atorvastatin (n=3102), accounting for 81% of all statin use. Thus, any comparison of lipophilic vs non-lipophilic statin use was primarily driven by these two statins. As a result, we did not feel that stratification by the degree of lipophilicity was appropriate and just compared atorvostatin to simvastin. With univariate analysis there was at best a trend toward more cognitive impairment with lipophilic vs hydrophilic statins (simvastatin vs atorvastatin), but upon adjustment there was no apparent difference.

Discussion

Our aim was to determine associations of cognitive impairment and statin use and type, as well as HDL-C levels. These aims were a result of the inconsistent literature which has reported an association of statin use with impaired or improved cognitive performance along with studies that have reported a neutral effect. The REasons for Geographic And Racial Differences in Stroke (REGARDS) study allowed us to perform a cross-sectional analysis in a large population-based cohort (n=24595) to address this question. Overall, without adjustment for potential confounders, a small but significantly higher rate of cognitive impairment was found in statin users with a trend toward lipophilic statins being more likely to be associated with cognitive impairment than hydrophilic statins. When adjusted for factors that would likely affect cognitive performance, no association with statin use or type, nor with HDL-C was demonstrated. As expected, there were associations of cognitive impairment with age, lower level of education and income, sex, urban dwelling, CVD, diabetes mellitus, FRS, SBP, and PP.

Many of the studies exploring the relationship between statins and cognition have been conducted on either clinical populations[8,20] or on populations that were relatively homogenous with respect to age (mostly ages 60 years and above)[21] and race (predominantly non-African American)[22]. It has been suggested that statin use is associated with improved cognition although some studies have suggested that statins have no effect or may even be detrimental. A review of PubMed by one of the coauthors (Dr. Kana) using the search terms “statins and cognitive assessment”, “statins and cognitive function”, “statins and cognition” and the references sited within the resulting papers, found 79 review papers and 120 studies examining the association between statins and cognition. These studies ranged from case studies[5-8] to randomized controlled studies[23]. We excluded from consideration studies without human subjects, studies of children, studies in a language other than English, studies without a focus on statins and cognitive function. We also excluded ongoing studies without published results with respect to impact on cognition, conceptual and design papers, opinion papers and studies of special populations (for example of airline crews, traumatic brain injury patients) resulting in 63 total reviews and studies. These studies yielded varying results with respect to the effect of statins on

cognition, with some studies showing no effect[9,23 , a few showing worsening of cognitive function[5-7] some demonstrating small benefits[24) and the rest inconclusive[25,26]

It was hypothesized that there were a number of variables that could affect the association between stains use and cognitive impairment, including increasing age, SES, geographic location, vascular disease etc. (See Table 2). What is clearly evident from our analysis is that age "drove" the univariate association of statin use and cognitive function; and, when any other model with age adjustment was used, no association was observed between statin use or HDL-C level and cognitive impairment.

Limitations

The REGARDS study relied on in home evaluation of statin use. During the in-home visit participants were asked to show the bottles of all prescribed and over the counter medications they were taking in order to be certain that participants were actually complying with that therapy, although it is still possible that some participants may not have taken their statins as prescribed. However, a sensitivity analysis of those who indicated perfect adherence (as assessed by the Morisky scale) did not change the results. While we did not have long-term adherence data, the Morisky score has been shown to be a valid measure of medication adherence.[19] This cross-sectional study did not have information on duration of statin exposure, nor baseline cognitive status prior to statin use. Nevertheless, our study can be compared with the findings of other cross-sectional studies. The Six Item Screener we used to evaluate cognitive impairment, has been validated, but the use of a more formal and complete evaluation of cognitive performance might be more sensitive to subtle differences in cognitive function. Finally, specific dosage information is not available.

In conclusion, this analysis provides for a greater understanding of the relationship and frequency of statin use to global cognitive status, and whether this relationship is mediated by statin type, health behaviors, and cardiovascular risk factors. When adjusted for variables that have been related to cognitive impairment, we found no association between statin use and cognitive impairment.

CONDENSED ABSTRACT

In this cross-sectional analysis of 24595 (7191 statin users) participants from a population-based national cohort study we assessed the association of statin use and type, and cognitive impairment. Overall, an association of cognitive impairment and statin use was observed but, after adjusting for variables known to be associated with cognition the association was attenuated. No association was observed between statin type and cognition, and there were no regional differences in cognitive impairment in statin users. This large study found no evidence to support an association between statins and cognitive performance.

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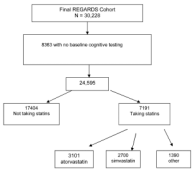

Figure 1.
Exclusionary Cascade For Analysis of the Subpopulation

Table 1

Demographic characteristics of sample population

	Sample Size	Cognitive Performance Impaired		*p* value	Statin Use Taking Statin		*p* value
		No	%		No	%	
All	**24595**	**1958**	**8.0%**		**7191**	**29%**	
Statin Use							
No	17404	1338	7.7%		0	0%	
Yes	7191	620	8.6%	0.014	7191	100%	
Type of Statin							
atorvastatin	3101	255	8.2%	0.560	3101	100%	
simvastatin	2700	251	9.3%	0.007	2700	100%	
Lipophilic[a]	3415	316	9.3%	0.003	3415	100%	
Region (missing 9)							
Other regions	10663	839	7.9%		3174	30%	
Stroke Belt	13923	1119	8.0%	0.63	4014	29%	0.11
Race (missing 3)							
White	14349	753	5.2%		4379	30.5%	
Black	10246	1205	11.8%	<0.001	2812	27.4%	<0.001
Gender							
Male	9862	899	9.1%		3289	33.4%	
Female	14733	1059	7.2%	<0.001	3902	26.5%	<0.001
Age group							
40–54	3753	160	4.3%		570	15.2%	
55–64	9057	505	5.6%		2452	27.1%	
65–74	7690	694	9.0%		2728	35.5%	
75–84	3620	493	13.6%		1301	35.9%	
85+	475	106	22.3%	<0.001	140	29.5%	<0.001
Rural/urban (missing 9)							
Non-urban*	7302	511	7.0%		2158	29.6%	
Urban	17284	1447	8.4%	<0.001	5030	29.1%	0.47

	Sample Size	Cognitive Performance Impaired		p value	Statin Use Taking Statin		p value
		No	%		No	%	
All	**24595**	**1958**	**8.0%**		**7191**	**29%**	
Income (missing 3228)							
$20K	4362	565	13.0%		1303	29.9%	
$20K–$34K	5792	543	9.4%		1741	30.1%	
$35K–74K	7244	394	5.4%		2151	29.7%	
$75+	3969	121	3.0%	0.001	1060	26.7%	0.001
Years of education (missing 22)							
<High school	2915	505	17.3%		960	32.9%	
High school	6443	590	9.2%		1970	30.6%	
Some college	6669	444	6.7%		1879	28.2%	
College+	8546	412	4.8%	<0.001	2373	27.8%	<0.001

[a] Includes lovastatin and simvastatin

Table 2

Concurrent health conditions

	Sample Size	Cognitive Performance Impaired		*p* value	Statin Use Taking Statin		*p* value
		No	%		No	%	
All	**24595**	**1958**	**8.0%**		**7191**	**29%**	
History of heart disease (missing 592)							
No	18607	1347	7.2%		4489	24.1%	
Yes	5396	538	10.0%	<0.001	2520	46.7%	<0.001
History of stroke (missing 39)							
No	22165	1640	7.4%		6132	27.7%	
Yes	2391	315	13.2%	<0.001	1040	43.5%	<0.001
History of hypertension (missing 356)							
No	9795	631	6.4%		1977	20.2%	
Yes	14444	1299	9.0%	<0.001	5141	35.6%	<0.001
History of diabetes (missing 1338)							
No	18128	1299	7.2%		4515	24.9%	
Yes	5129	556	10.8%	<0.001	2341	45.6%	<0.001
Framingham cardiac risk score (missing 6663)							
Q1	4490	193	4.3%		876	19.5%	
Q1–Median	4491	278	6.2%		1155	25.7%	
Median–Q3	4491	359	8.0%		1235	27.5%	
Q3 or higher	4490	494	11.0%	<0.001	1118	24.9%	<0.001
Systolic blood pressure (missing 659)							
Q1 (70.0-117.0 mmHg)	6116	369	6.0%		1616	26.4%	
Q2 (117.5-125.0 mmHg)	6006	423	7.0%		1726	28.7%	
Q3 (125.5-137.0 mmHg)	5970	523	8.8%		1918	32.1%	
Q4 (137.5-245.0 mmHg)	5844	598	10.2%	<0.001	1744	29.8%	<0.001
Pulse pressure (missing 661)							
Q1(14.5-40.5 mmHg)	5150	322	6.3%		1221	23.7%	
Q2 (41.0-48.5 mmHg)	6065	378	6.2%		1703	28.1%	
Q3 (49.0-57.5 mmHg)	6397	538	8.4%		1987	31.1%	

	Sample Size	Cognitive Performance Impaired		*p* value	Statin Use Taking Statin		*p* value
		No	%		No	%	
All	**24595**	**1958**	**8.0%**		**7191**	**29%**	
Q4 (58.0-143.0 mmHg)	6322	675	10.7%	<0.001	2092	33.1%	<0.001
HDL (missing 1127)							
Q1 (7.0-40.0 mg/dL)	5656	461	8.2%		1875	33.2%	
Q2 (41.0-50.0 mg/dL)	6359	502	7.9%		2089	32.9%	
Q3 (51.0-61.0 mg/dL)	5475	395	7.2%		1579	28.8%	
Q4 (62.0-199.0 mg/dL)	5978	480	8.0%	0.26	1310	21.9%	<0.001

Table 3

Univariate and multivariate logistic models for predicting cognitive impairment

	Univariate Associations		Model 2[a]		Model 3 [a]		Model 4[a]	
	OR	**95%CI**	**OR**	**95%CI**	**OR**	**95%CI**	**OR**	**95%CI**
Statin Use								
Yes vs No	1.13	(1.03, 1.25)	1.03	(0.93, 1.14)	0.99	(0.89, 1.12)	0.98	(0.87, 1.10)
Gender								
Male vs Female	1.30	(1.18, 1.42)	1.38	(1.25, 1.52)	1.57	(1.41, 1.75)	1.56	(1.39, 1.74)
Age group								
55–64 vs 40–54	1.33	(1.11, 1.59)	1.36	(1.13, 1.63)	1.34	(1.10, 1.64)	1.34	(1.09, 1.64)
65–74 vs 40–54	2.23	(1.87, 2.66)	2.37	(1.98, 2.84)	1.95	(1.60, 2.39)	1.94	(1.59, 2.37)
75–84 vs 40–54	3.54	(2.94, 4.26)	3.99	(3.31, 4.82)	2.94	(2.38, 3.64)	2.91	(2.35, 3.61)
85+ vs 40–54	6.45	(4.94, 8.43)	7.59	(5.77, 9.98)	5.06	(3.67, 6.98)	4.98	(3.61, 6.88)
Income								
<$20K vs >$75K	4.73	(3.87, 5.79)			2.48	(1.97, 3.13)	2.47	(1.96, 3.12)
$20K–$34K vs >$75K	3.29	(2.69, 4.02)			2.02	(1.62, 2.52)	2.02	(1.62, 2.52)
$35K–74K vs >$75K	1.83	(1.49, 2.25)			1.46	(1.18, 1.81)	1.46	(1.17, 1.81)
Years of education								
<High school vs college+	4.14	(3.60, 4.75)			1.80	(1.51, 2.15)	1.79	(1.50, 2.14)
High school vs college+	1.99	(1.75, 2.27)			1.35	(1.16, 1.58)	1.35	(1.15, 1.57)
Some college vs college+	1.41	(1.23, 1.62)			1.12	(0.96, 1.31)	1.12	(0.95, 1.31)
History of heart disease								
Yes vs No	1.42	(1.28, 1.58)					1.09	(0.96, 1.23)
History of stroke								
Yes vs No	1.90	(1.67, 2.16)			1.41	(1.21, 1.64)	1.40	(1.20, 1.63)

[a]All models control for race in addition to other covariates Model 3 is the final model.

Hypertension, diabetes, systolic blood pressure, pulse pressure, HDL, and Framingham cardiac risk score were considered as covariates, but were not significant predictors in the fully adjusted model. The results were similar to those presented in Model 4.

Table 4

Subanalyses comparing specific statins (n=7191)

	Univariate		Multivariate	
	OR	**95% CI**	**OR**	**95% CI**
Use of lipophyllic vs hydrophyllic statin (multivariate n= 6237) Yes vs No	1.17	(0.99, 1.37)	1.03	(0.86, 1.24)
Use of simvastatin vs other statins (multivariate n= 6237) Yes vs No	1.15	(0.97, 1.35)	1.05	(0.87, 1.27)
Use of atorvastatin vs other statins (multivariate n= 6237) Yes vs No	0.91	(0.77, 1.08)	1.01	(0.83, 1.22)
Use of simvastatin vs atorvastatin (multivariate n= 5018) Yes vs No	1.14	(0.95, 1.37)	1.03	(0.84, 1.26)

[a] All models control for race, age, gender, income, education, and history of stroke