RESEARCH LETTER

Kidney Function and Lipid Levels in Older Adults: The Atherosclerosis Risk in Communities Study

To the Editor:

Cardiovascular disease is a leading cause of mortality among older adults in the United States.[1] Both chronic kidney disease (CKD) and dyslipidemia—important risk factors of cardiovascular disease—are common among older adults.[2,3] Although there have been studies examining dyslipidemia in CKD among young and middle-aged adults, there is a paucity of literature on lipid levels by CKD stage in older adults.

Serum creatinine is the most common filtration marker used for estimated glomerular filtration rate (eGFR), the primary measure of kidney function. However, serum creatinine may overestimate kidney function in older adults because it is affected by nonkidney determinants, such as muscle mass and protein intake.[4] An eGFR determined using both serum creatinine and cystatin C provides more accurate estimates.[4] In this study, we sought to examine the associations between eGFR on the basis of both creatinine and cystatin C and lipid levels in older adults. We conducted a cross-sectional analysis of adults aged 67-89 years during visit 5 (2011-2013) of the Atherosclerosis Risk in Communities study. Among 6,538 individuals from visit 5, those without data on eGFR, statin use, or covariates were excluded. The final study population was 4,965 individuals (Fig S1). The eGFR was calculated using the 2021 CKD Epidemiology Collaboration creatinine-cystatin C equation without a race coefficient.[5] Lipid parameters of interest included total cholesterol; low-density lipoprotein cholesterol (LDL-C), calculated via the Friedewald method; high-density lipoprotein cholesterol (HDL-C); and triglyceride (TG). We plotted adjusted lipid levels by eGFR levels from multivariable linear regression models with linear splines and 3 knots at eGFR 90, 60, and 45 mL/min/1.73 m^2. We also examined binary outcomes (total cholesterol ≥200 mg/dL; LDL-C ≥100 mg/dL; HDL-C <50 mg/dL; and TG ≥150 mg/dL),[1] using multivariable logistic regression with eGFR

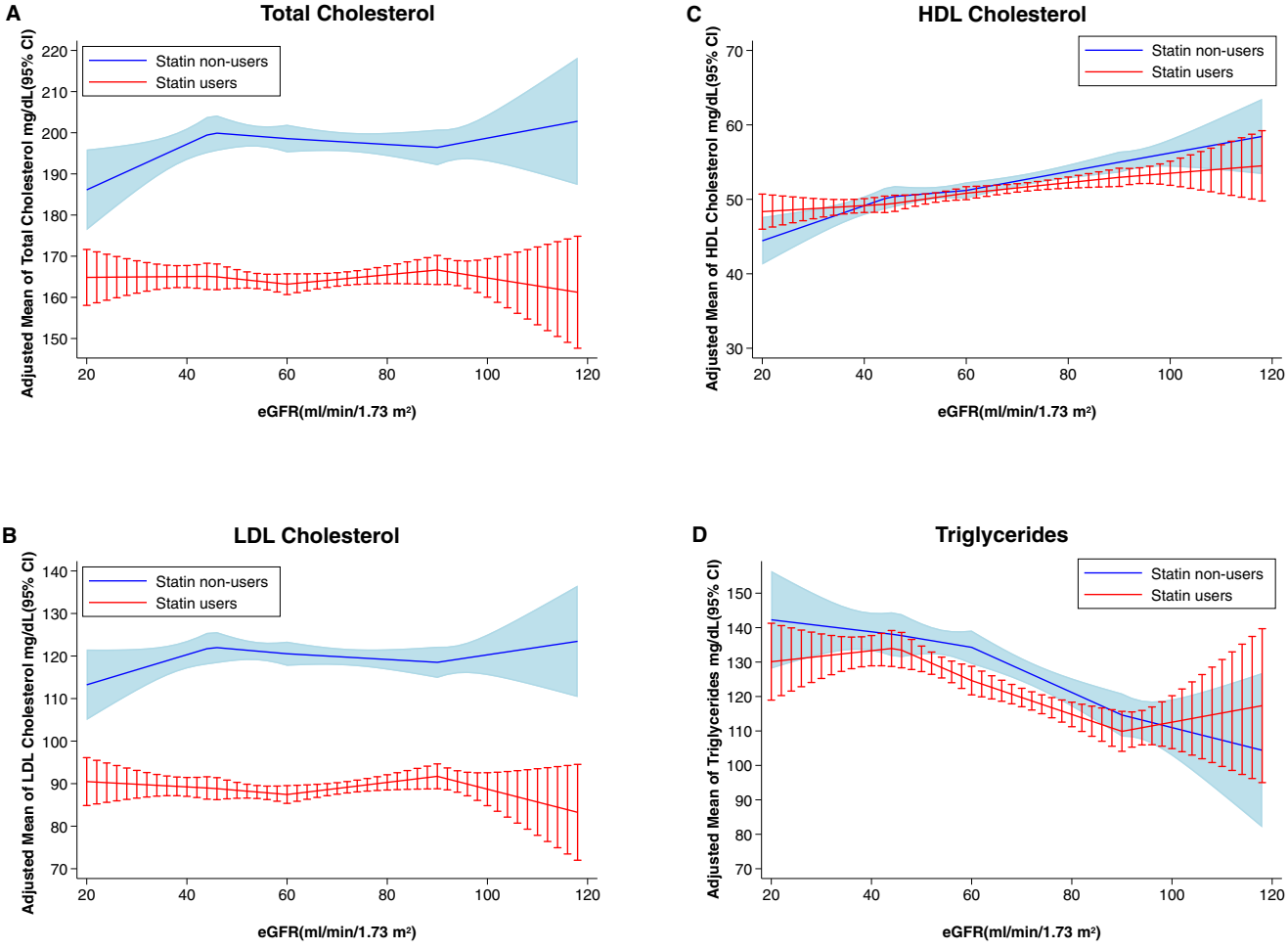

Figure 1. Adjusted associations between eGFR and lipid levels. Conversion factors for units: total cholesterol, LDL-C, and HDL-C in mg/dL to mmol/L, ×0.02586; triglycerides in mg/dL to mmol/L, ×0.01129. Abbreviations: CI, Confidence interval; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Table 1. The Associations Between eGFR and Various Types of Dyslipidemia

Outcome		Statin Users (*N*=2,628)		Statin Nonusers (*N*=2,337)	
		Prevalence	Adjusted OR (95% CI)	Prevalence	Adjusted OR (95% CI)
Total cholesterol ≥200 mg/dL	eGFR category (mL/min/1.73 m^2)				
	>60	218 (14.9%)	1 (Reference)	765 (52.0%)	1 (Reference)
	45-60	79 (11.5%)	0.98 (0.73-1.32)	267 (46.5%)	1.13 (0.92-1.40)
	<45	44 (9.2%)	0.83 (0.56-1.21)	102 (34.9%)	0.79 (0.58-1.06)
LDL-C ≥100 mg/dL					
	>60	451 (30.9%)	1 (Reference)	1,133 (77.0%)	1 (Reference)
	45-60	177 (25.8%)	0.95 (0.76-1.19)	423 (73.7%)	1.04 (0.82-1.32)
	<45	109 (22.7%)	0.91 (0.69-1.19)	193 (66.1%)	0.86 (0.63-1.17)
HDL-C <50 mg/dL					
	>60	695 (47.5%)	1 (Reference)	521 (35.4%)	1 (Reference)
	45-60	417 (60.8%)	1.33 (1.08-1.64)[a]	288 (50.2%)	1.30 (1.03-1.63)[a]
	<45	322 (67.1%)	1.54 (1.19-2.00)[a]	185 (63.4%)	2.03 (1.49-2.78)[a]
Triglycerides ≥150 mg/dL					
	>60	319 (21.8%)	1 (Reference)	317 (21.6%)	1 (Reference)
	45-60	200 (29.2%)	1.59 (1.27-2.00)[a]	166 (28.9%)	1.41 (1.11-1.80)[a]
	<45	152 (31.7%)	1.68 (1.30-2.19)[a]	92 (31.5%)	1.48 (1.08-2.04)[a]

Note: Conversion factors for units: total cholesterol, LDL-C, and HDL-C in mg/dL to mmol/L, ×0.02586; triglycerides in mg/dL to mmol/L, ×0.01129.
Abbreviations: CI, Confidence interval; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; OR, odds ratio.[a]
[a]Statistically significant odds ratio with P value < 0.05.

categories (<45, 45-60, >60 mL/min/1.73 m^2).[6] Covariates included age, sex, race-center, body mass index, history of coronary artery disease, diabetes, liver disease, hypertension, alcohol use, smoking, education, physical activity, urine albumin-to-creatinine ratio, and nonstatin lipid-lowering medications. We assessed whether the associations differed by obesity (body mass index ≥30 kg/m^2) and diabetes. All analyses were stratified by statin use.

The mean age of the study population was 75.6 years; 56.1% were women, 22.9% were Black, and 52.9% were using a statin. The mean eGFR of the study population was 64.4 mL/min/1.73 m^2. Individuals with an eGFR of <45 mL/min/1.73 m^2 were older, more likely to be men, less educated, and less physically active, and they had a higher body mass index with more additional comorbid conditions (Table S1).

Overall, neither total cholesterol nor LDL-C levels significantly differed by the levels of eGFR regardless of statin use (Fig 1A and B). Only among statin nonusers with an eGFR of <45 mL/min/1.73 m^2, a lower eGFR was associated with lower total cholesterol levels (−5.6 [95% confidence interval {CI}, −1.0 to −10.3] mg/dL per −10 mL/min/1.73 m^2 in eGFR).

A lower eGFR was linearly associated with lower HDL-C levels in both statin users (−0.7 [95% CI, −0.5 to −1.0] mg/dL per −10 mL/min/1.73 m^2 in eGFR) and nonusers (−1.2 [95% CI, −0.9 to −1.5] mg/dL per −10 mL/min/1.73 m^2 in eGFR) (Fig 1C). A lower eGFR was linearly associated with higher TG levels in both statin users (6.1 [95% CI, 4.0-8.2] mg/dL per −10 mL/min/1.73 m^2 in eGFR) and nonusers (6.5 [95% CI, 4.2-8.7] mg/dL per −10 mL/min/1.73 m^2 in eGFR) when eGFR was 45 to 90 mL/min/1.73 m^2 (Fig 1D). The results were consistent when the outcomes were analyzed as binary variables (Table 1) and when stratified by obesity or diabetes (all P values for interactions were >0.1).

Our study showed a higher burden of other lipid level abnormalities, in particular low HDL-C and high TG levels, among older adults with CKD when compared with those without CKD. Previous studies have demonstrated that an elevated TG or low HDL-C level is associated with higher risk of cardiovascular events and all-cause mortality.[7,8] Patients with CKD, who have low HDL-C and elevated TG levels, may benefit from lifestyle modifications, including regular physical activity, to reduce their risk of mortality.[9] The KDIGO (Kidney Disease Improving Global Outcome) guidelines strongly recommend statin use for older patients with CKD.[10] Indeed, our data showed lower total cholesterol and LDL-C levels among statin users across the entire spectrum of eGFR in comparison to nonusers.

Limitations to our study include the cross-sectional study design because we cannot establish temporality between kidney function and lipid levels. However, the goal of our study was to characterize lipid levels and determine the burden of dyslipidemia by kidney function among older adults using the most accurate estimates of kidney function.

In conclusion, we demonstrated higher burden of low HDL-C and high TG levels among older adults with CKD compared with those without CKD, regardless of statin use. In addition to LDL-C levels, attention to the burden of high TG and low HDL-C levels may be needed to improve clinical outcomes in older adults with CKD.

Shreya Srivastava, MD, MPH, Josef Coresh, MD, PhD, Casey M. Rebholz, PhD, MS, MNSP, MPH, Morgan E. Grams, MD, PhD, Kunihiro Matsushita, MD, PhD, Seth S. Martin, MD, MHS, Jung-Im Shin, MD, PhD

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Figure S1: Derivation of the study population.

Item S1: Detailed Methods.

Table S1: Baseline characteristics of study population by eGFR category.

ARTICLE INFORMATION

Authors' Affiliations: Department of Epidemiology, The Johns Hopkins Bloomberg School of Public Health, Baltimore, MD (SS, JC, CMR, MEG, KM, SSM, JS); Department of Medicine, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, New Hyde Park, NY (SS); Department of Medicine, The Johns Hopkins University School of Medicine, Baltimore, MD (JC, CMR, KM, SSM); and Department of Medicine, New York University Grossman School of Medicine, New York, NY (MEG).

Address for Correspondence: Jung-Im Shin, MD, PhD; Department of Epidemiology, The Johns Hopkins Bloomberg School of Public Health, 2024 E. Monument St, Suite 2-600, Baltimore, MD 21205. Email: jshin19@jhmi.edu

Authors' Contributions: Research idea and study design: SS, JS, MEG; data acquisition: JC; statistical analysis: SS, JS; data interpretation: SS, JC, CMR, MEG, KM, SSM, JS; supervision and mentorship: JS. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

Support: This work was supported by the following grant: K01DK121825 (PI: Shin) from National Institute of Diabetes and Digestive and Kidney Disease. The funders of this study did not have any role in study design, data collection, analysis, interpretation of data, report writing, or decision to submit this report for publication.

Financial Disclosure: The authors declare that they have no relevant financial interests.

Acknowledgements: The Atherosclerosis Risk in Communities (ARIC) study has been funded in whole or in part with federal funds from the National Heart, Lung, and Blood Institute, National Institutes of Health, Department of Health and Human Services, under Contracts HHSN268201700001I, HHSN268201700002I, HHSN268201700003I, HHSN268201700004I, and HHSN26 8201700005I. The authors thank the staff and participants of the ARIC study for their important contributions.

Peer Review: Received January 4, 2022. Evaluated by 1 external peer reviewer, with direct editorial input from the Statistical Editor, an Associate Editor, and the Editor-in-Chief. Accepted in revised form April 24, 2022.

 Published online May 27, 2022 with doi 10.1016/j.xkme.2022.100494

REFERENCES

1. Virani SS, Alonso A, Aparicio HJ, et al. Heart disease and stroke statistics—2021 update: a report from the American Heart Association. *Circulation*. 2021;143(8):e254-e743.
2. Chronic Kidney Disease in the United States, 2021. US Department of Health and Human Services, Centers for Disease Control and Prevention. Accessed November 22, 2021. https://www.cdc.gov/kidneydisease/publications-resources/ckd-national-facts.html
3. McDonald M, Hertz RP, Unger AN, Lustik MB. Prevalence, awareness, and management of hypertension, dyslipidemia, and diabetes among United States adults aged 65 and older. *J Gerontol A Biol Sci Med Sci*. 2009;64(2):256-263.
4. Inker LA, Schmid CH, Tighiouart H, et al. Estimating glomerular filtration rate from serum creatinine and cystatin C. *N Engl J Med*. 2012;367(1):20-29.
5. Inker LA, Eneanya ND, Coresh J, et al. New creatinine- and cystatin C–based equations to estimate GFR without race. *N Engl J Med*. 2021;385(19):1737-1749.
6. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppl*. 2013;3(1):30-130.
7. Zhong GC, Huang SQ, Peng Y, et al. HDL-C is associated with mortality from all causes, cardiovascular disease and cancer in a J-shaped dose-response fashion: a pooled analysis of 37 prospective cohort studies. *Eur J Prev Cardiol*. 2020;27(11):1187-1203.
8. Sandesara PB, Virani SS, Fazio S, Shapiro MD. The forgotten lipids: triglycerides, remnant cholesterol, and atherosclerotic cardiovascular disease risk. *Endocr Rev*. 2019;40(2):537-557.
9. Ricardo AC, Anderson CA, Yang W, et al. Healthy lifestyle and risk of kidney disease progression, atherosclerotic events, and death in CKD: findings from the Chronic Renal Insufficiency Cohort (CRIC) study. *Am J Kidney Dis*. 2015;65(3):412-424.
10. Wanner C, Tonelli M; Kidney Disease: Improving Global Outcomes Lipid Guideline Development Work Group Members. KDIGO clinical practice guideline for lipid management in CKD: summary of recommendation statements and clinical approach to the patient. *Kidney Int*. 2014;85(6):1303-1309.