Low levels of high-density lipoprotein cholesterol increase the risk of incident kidney disease and its progression

see commentary on page 747

Benjamin Bowe[1], Yan Xie[1], Hong Xian[1,2], Sumitra Balasubramanian[1] and Ziyad Al-Aly[1,3,4]

[1]Clinical Epidemiology Center, VA Saint Louis Health Care System, St. Louis, Missouri, USA; [2]Department of Biostatistics, College for Public Health and Social Justice, Saint Louis University, St. Louis, Missouri, USA; [3]Department of Medicine, Division of Nephrology, VA Saint Louis Health Care System, St. Louis, Missouri, USA; and [4]Department of Medicine, Washington University School of Medicine, St. Louis, Missouri, USA

Available experimental evidence suggests a role for high-density lipoprotein cholesterol (HDL-C) in incident chronic kidney disease (CKD) and its progression. However, clinical studies are inconsistent. We therefore built a cohort of 1,943,682 male US veterans and used survival models to examine the association between HDL-C and risks of incident CKD or CKD progression (doubling of serum creatinine, eGFR decline of 30% or more), or a composite outcome of ESRD, dialysis, or renal transplantation. Models were adjusted for demographics, comorbid conditions, eGFR, body mass index, lipid parameters, and statin use over a median follow-up of 9 years. Compared to those with HDL-C of 40 mg/dl or more, low HDL-C (under 30 mg/dl) was associated with increased risk of incident eGFR under 60 ml/min/1.73 m^2 (hazard ratio: 1.18; confidence interval: 1.17–1.19) and risk of incident CKD (1.20; 1.18–1.22). Adjusted models demonstrate an association between low HDL-C and doubling of serum creatinine (1.14; 1.12–1.15), eGFR decline of 30% or more (1.13; 1.12–1.14), and the composite renal end point (1.08; 1.06–1.11). Cubic spline analyses of the relationship between HDL-C levels and renal outcomes showed a U-shaped relationship, where risk was increased in lowest and highest deciles of HDL-C. Thus, a significant association exists between low HDL-C levels and risks of incident CKD and CKD progression. Further studies are needed to explain the increased risk of adverse renal outcomes in patients with high HDL-C.

Kidney International (2016) **89,** 886–896; http://dx.doi.org/10.1016/j.kint.2015.12.034

KEYWORDS: cholesterol; chronic kidney disease; high-density lipoprotein; incidence of kidney disease; kidney disease progression

Published by Elsevier, Inc., on behalf of the International Society of Nephrology.

Correspondence: *Ziyad Al-Aly, Clinical Epidemiology Center, VA Saint Louis Health Care System, 915 North Grand Boulevard, 151-JC, St. Louis, MO 63106, USA. E-mail: zalaly@gmail.com, ziyad.alaly@va.gov*

Received 25 August 2015; revised 14 November 2015; accepted 3 December 2015; published online 29 January 2016

Experimental evidence suggests that high-density lipoprotein cholesterol (HDL-C) deficiency or dysfunction is mechanistically linked to renal vascular atherosclerosis, glomerulosclerosis, and tubulointerstitial injury.[1–3] Anecdotal observations from human studies suggest that familial lecithin–cholesterol acyltransferase deficiency, a rare genetic disorder of lipid metabolism caused by the absence of familial lecithin–cholesterol acyltransferase activity in plasma and characterized by low HDL-C levels, is associated with risk of renal disease.[4,5] An increasing number of human studies suggest that individuals with low HDL-C levels are at increased risk of renal dysfunction.[1,6–9] In an analysis of the ADVANCE study, Morton *et al.* examined the association between HDL-C and renal events in patients with type 2 diabetes, and reported that patients in the lowest tertile of HDL-C were at increased risk of renal events.[7] In a cohort study of 4483 initially healthy men participating in the Physicians' Health Study, low HDL-C levels were significantly associated with an increased risk of developing renal dysfunction in men with an initial creatinine <1.5 mg/dl.[8] In a study of 2702 dyslipidemic middle-aged men without renal disease participating in the Helsinki Heart Study, patients in the lowest HDL-C group had the greatest decline in kidney function.[9]

Although experimental evidence on the role of HDL-C in chronic kidney disease (CKD) progression is becoming increasingly clear, observations from clinical literature are inconsistent largely because of short duration of follow-up and often very small sample size.[2,10,11] To date, the association between HDL-C and kidney outcomes—incident risk of CKD and risk of CKD progression—has not been examined in large-scale epidemiologic studies spanning a sufficiently prolonged duration of time.[6,12] Also, the question of whether low HDL-C contributes to development of CKD and whether it is associated with CKD progression remains unanswered. Further understanding of the relationship of HDL-C and CKD incidence and progression is important, especially as the field of therapeutic interventions to elevate HDL-C levels expands. We hypothesized that low HDL-C may be associated with increased risk of incident CKD and CKD progression. Because of pronounced biologic differences in HDL-C metabolism between men and women, and because women are generally underrepresented in the United States

Department of Veterans Affairs (VA) datasets, we examined these research questions in a large national cohort of 1,943,682 male US veterans.

RESULTS

The demographic and clinical characteristics of the overall cohort and according to HDL-C levels are presented in Table 1. Among 1,943,682 patients in the overall cohort, 210,023 (10.81%) had low HDL-C, 665,381 (34.23%) had intermediate levels of HDL-C, and 1,068,278 (54.96%) had high HDL-C levels. Over a median follow-up of 9 years (interquartile range: 8.15–9.00), 140,762 (7.24%) experienced doubling of serum creatinine: 19,888 (9.47%), 50,923 (7.65%), and 69,951 (6.55%) were in low, intermediate, and high HDL-C groups,

Table 1 | Demographic and clinical characteristics of overall study cohort, and according to HDL-C levels

	Overall	Low HDL-C	Intermediate HDL-C	High HDL-C
Number (%)	1,943,682	210,023 (10.81)	665,381 (34.23)	1,068,278 (54.96)
Median HDL-C (IQR) (mg/dl)	41.00 (34.00, 49.10)	27.00 (24.50, 28.00)	35.00 (33.00, 37.00)	48.00 (43.10, 56.00)
Race				
White (%)	1,654,798 (85.14)	185,930 (88.53)	579,739 (87.13)	889,129 (83.23)
Black (%)	248,384 (12.78)	19,957 (9.50)	71,261 (10.71)	157,166 (14.71)
Other (%)	40,500 (2.08)	4136 (1.97)	14,381 (2.16)	21,983 (2.06)
Median age in years (IQR)	63.97 (56.01, 72.43)	62.12 (55.28, 71.47)	63.46 (55.89, 72.11)	64.69 (56.26, 72.79)
Cerebrovascular accident (%)	11,489 (0.59)	1699 (0.81)	4423 (0.66)	5367 (0.50)
Cardiovascular disease (%)	645,080 (33.19)	90,128 (42.91)	245,856 (36.95)	309,096 (28.93)
Chronic lung disease (%)	399,125 (20.53)	46,175 (21.99)	131,389 (19.75)	221,561 (20.74)
Diabetes mellitus (%)	603,707 (31.06)	92,632 (44.11)	241,872 (36.35)	269,203 (25.20)
Dementia (%)	59,871 (3.08)	6828 (3.25)	20,386 (3.06)	32,657 (3.06)
HIV (%)	124,735 (6.42)	17,531 (8.35)	44,645 (6.71)	62,559 (5.86)
Hypertension (%)	1,403,193 (72.19)	163,105 (77.66)	496,525 (74.62)	743,563 (69.90)
Hepatitis C (%)	81,842 (4.21)	12,470 (5.94)	26,349 (3.96)	43,023 (4.03)
Peripheral artery disease (%)	61,822 (3.18)	9248 (4.40)	23,321 (3.50)	29,253 (2.74)
Average eGFR at T_0 (SD) (ml/min/1.73 m^2)	74.85 (18.94)	72.49 (20.47)	73.53 (19.15)	76.13 (18.69)
Median number of eGFR measures after T_0 (IQR)	13 (8, 20)	14 (8, 22)	14 (8, 21)	12 (8, 19)
eGFR at T_0 (ml/min/1.73 m^2)				
≥90 (%)	447,325 (23.01)	45,792 (21.80)	141,986 (21.34)	259,547 (24.30)
<90 to ≥60 (%)	1,067,139 (54.90)	106,401 (50.66)	361,030 (54.26)	599,708 (56.14)
<60 to ≥45 (%)	302,954 (15.59)	36,503 (17.38)	11,707 (16.79)	154,744 (14.49)
<45 to ≥30 (%)	103,192 (5.31)	16,576 (7.89)	41,342 (6.21)	45,274 (4.24)
<30 to ≥15 (%)	23,072 (1.19)	4751 (2.26)	9316 (1.40)	9005 (0.84)
Average LDL-C (SD) (mg/dl)	108.82 (35.26)	95.86 (36.73)	107.83 (35.07)	112.18 (34.67)
Average triglycerides (SD) (mg/dl)	162.16 (117.15)	233.60 (171.05)	184.39 (117.79)	134.27 (92.14)
Median microalbumin/creatinine ratio[a] (mg/g)				
0–20 (%)	107,447 (69.69)	14,273 (66.48)	42,247 (68.93)	50,927 (71.32)
20–300 (%)	42,189 (27.37)	6390 (29.76)	17,161 (28.00)	18,638 (26.10)
>300 (%)	4533 (2.94)	806 (3.75)	1884 (3.07)	1843 (2.58)
Body mass index				
Underweight (%)	15,398 (0.79)	718 (0.34)	2282 (0.34)	12,398 (1.16)
Normal (%)	364,960 (18.78)	24,244 (11.54)	87,619 (13.17)	253,097 (23.69)
Overweight (%)	782,436 (40.26)	76,484 (36.42)	258,974 (38.82)	446,978 (41.84)
Obese (%)	780,888 (40.18)	108,577 (51.70)	316,506 (47.57)	355,805 (33.31)
Statin use (%)	1,002,523 (51.58)	109,731 (52.25)	364,127 (54.72)	528,665 (49.49)
Median follow-up time (IQR) (yr)	9.00 (8.15, 9.00)	9.00 (6.75, 9.00)	9.00 (8.20, 9.00)	9.00 (8.43, 9.00)
eGFR less than 60[b] (%)	628,377 (41.49)	70,821 (46.53)	220,984 (43.93)	336,572 (39.17)
Incident CKD[c] (%)	123,775 (31.96)	16,194 (37.03)	43,622 (35.47)	63,959 (29.00)
Doubling of serum creatinine (%)	140,762 (7.24)	19,888 (9.47)	50,923 (7.65)	69,951 (6.55)
≥30% change in eGFR (%)	590,227 (30.37)	75,445 (35.92)	212,156 (31.88)	302,626 (28.33)
ESRD, dialysis, or transplant (%)	62,526 (3.22)	10,262 (4.89)	23,711 (3.56)	28,553 (2.67)
ESRD, dialysis, transplant, or ≥50% decline in eGFR (%)	222,353 (11.44)	31,905 (15.19)	81,686 (12.28)	108,762 (10.18)
Slope (ml/min/1.73 m^2/yr)[d]				
No decline (≥0) (%)	754,193 (40.26)	78,491 (39.26)	256,969 (40.05)	418,733 (40.59)
Mild CKD progression (<0 to ≥ −1) (%)	412,296 (22.01)	40,199 (20.10)	138,913 (21.65)	233,184 (22.60)
Moderate CKD progression (< −1 to ≥ −5) (%)	575,237 (30.71)	63,551 (31.78)	199,889 (31.16)	311,797 (30.22)
Severe CKD progression (< −5) (%)	131,534 (7.02)	17,706 (8.86)	45,821 (7.14)	68,007 (6.59)
Death during follow-up (%)	517,695 (26.63)	67,096 (31.95)	175,351 (26.35)	275,248 (25.77)

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol.
[a]Numbers are for a subset of the cohort where the corresponding data were available (n = 154,169).
[b]Incident eGFR <60 was evaluated in a subcohort of people with eGFR >60 at time of cohort entry (n = 1,514,464).
[c]Incident CKD was evaluated in a subcohort of people with at least 2 eGFR separated by at least 90 days apart who had a T_0 eGFR >60 (n = 387,276).
[d]Numbers are for a subset of the cohort where the corresponding data were available (n = 1,873,260).

respectively (Figure 1a); 590,227 (30.37%) experienced ≥30% decline in eGFR: 75,445 (35.92%), 212,156 (31.88%), and 302,626 (28.33%) were in low, intermediate, and high HDL-C groups, respectively (Figure 1b); 62,526 (3.22%) experienced the composite outcome of end-stage renal disease (ESRD), dialysis, or transplant: 10,262 (4.89%), 23,711 (3.56%), and 28,553 (2.67%) were in low, intermediate, and high HDL-C groups, respectively (Figure 1c).

Adjusted associations of low HDL-C

In multivariate regression models, we examined the adjusted associations of baseline demographic and clinical characteristics with HDL-C categories (Table 2). Low HDL-C was inversely associated with black race and increased age, and also was associated with cardiovascular disease, cerebrovascular disease, diabetes mellitus, HIV, hypertension, hepatitis C, and peripheral artery disease (Table 2). There was a strong and inverse association between increasing low-density lipoprotein cholesterol (LDL-C) levels and low HDL-C category (for every one SD increase in LDL-C levels, the odds of low HDL-C category decreased [odds ratio (OR): 0.73; confidence interval (CI): 0.73–0.73]). There was a strong association between increasing triglycerides levels and low HDL-C category (for every one SD increase in triglycerides levels, the odds of low HDL-C category increased [OR: 2.02; CI: 2.02–2.02]). Statin use was associated with decreased odds of low HDL-C (OR: 0.69; CI: 0.68–0.70). There was no significant association between presence and severity of microalbuminuria and HDL-C levels.

Association between estimated glomerular filtration rate (eGFR) and HDL-C

There was an independent and graded association between the level of HDL-C and eGFR. In models where eGFR was categorized into eGFR >90, 90 to 60, 60 to 45, 45 to 30, 30 to 15 ml/min/1.73 m^2, the odds of low HDL-C increased significantly as eGFR category decreased. Compared with participants with eGFR >90 ml/min/1.73 m^2, the odds of low HDL-C were 1.17 (1.16–1.19), 1.59 (1.56–1.61), 2.08 (2.03–2.13), 2.68 (2.57–2.79) in participants with eGFR 90–60, 60–45,

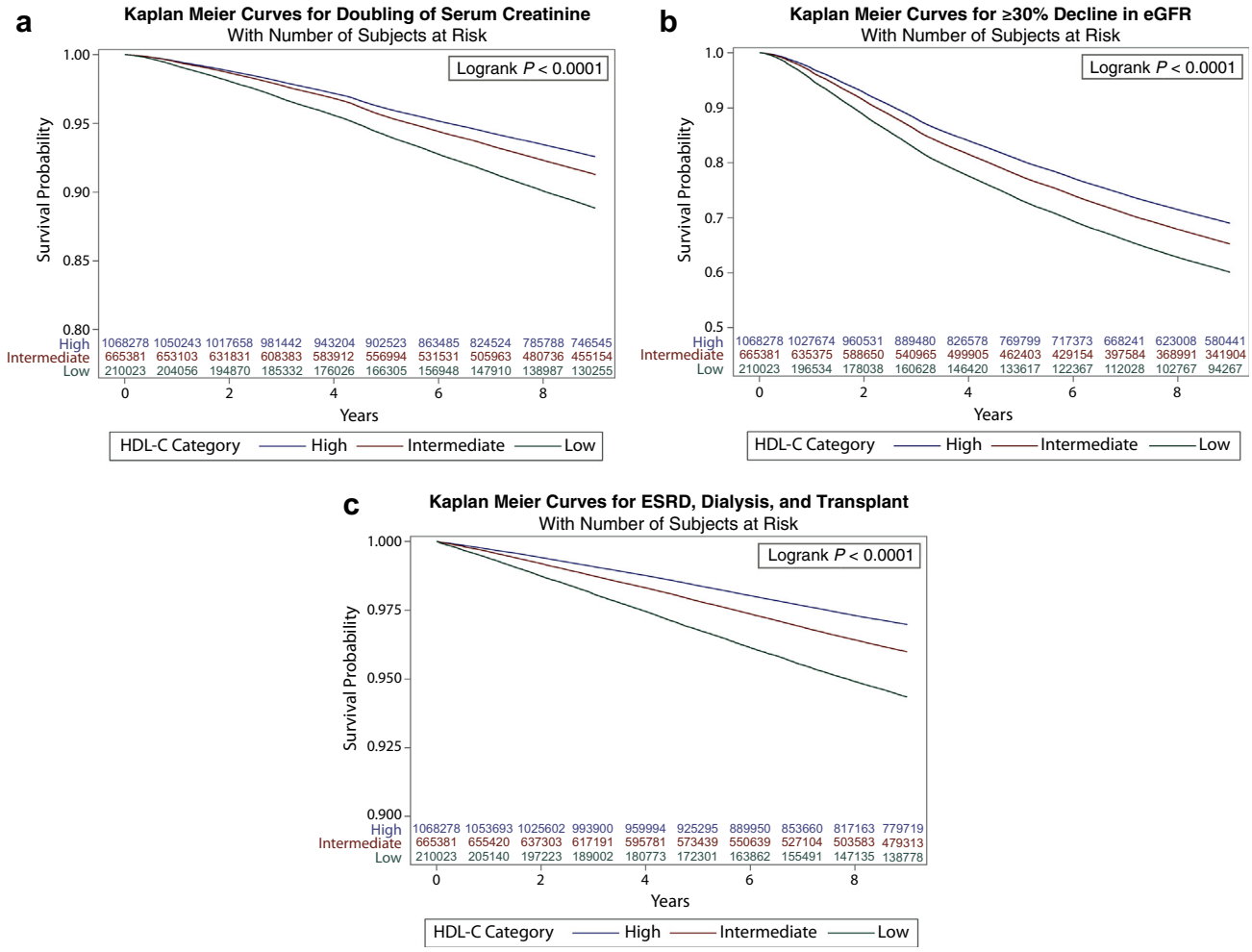

Figure 1 | (a) Kaplan-Meier curves for doubling of serum creatinine by high-density lipoprotein cholesterol category. (**b**) Kaplan-Meier curves for ≥30% decline in estimated glomerular filtration rate (eGFR) by high-density lipoprotein cholesterol category. (**c**) Kaplan-Meier curves for the composite outcome of end-stage renal disease (ESRD), dialysis, or transplant by high-density lipoprotein cholesterol (HDL-C) category.

Table 2 | Adjusted associations of demographic and clinical characteristics with HDL-C categories

	Low HDL-C OR (CI)	Intermediate HDL-C OR (CI)
Race		
White	1	1
Black	0.63 (0.62, 0.64)	0.76 (0.75, 0.76)
Other	0.83 (0.80, 0.86)	0.96 (0.94, 0.99)
Age (yr)	0.98 (0.98, 0.98)	0.99 (0.99, 0.99)
Cerebrovascular accident	1.30 (1.22, 1.37)	1.18 (1.13, 1.23)
Cardiovascular disease	1.70 (1.68, 1.72)	1.34 (1.33, 1.36)
Chronic lung disease	1.00 (0.98, 1.01)	0.93 (0.92, 0.93)
Diabetes mellitus	1.63 (1.62, 1.65)	1.35 (1.34, 1.36)
Dementia	1.04 (1.01, 1.07)	1.02 (1.00, 1.04)
HIV	1.31 (1.29, 1.34)	1.14 (1.12, 1.15)
Hypertension	1.09 (1.07, 1.10)	1.01 (1.00, 1.02)
Hepatitis C	1.57 (1.54, 1.61)	1.13 (1.11, 1.15)
Peripheral artery disease	1.24 (1.21, 1.27)	1.12 (1.10, 1.14)
eGFR at T_0 (ml/min/1.73 m^2)		
≥90	1	1
<90 to ≥60	1.17 (1.16, 1.19)	1.15 (1.14, 1.16)
<60 to ≥45	1.59 (1.56, 1.61)	1.52 (1.50, 1.55)
<45 to ≥30	2.08 (2.03, 2.13)	1.59 (1.56, 1.61)
<30 to ≥15	2.68 (2.57, 2.79)	1.71 (1.65, 1.76)
LDL-C[a] (mg/dl)	0.73 (0.73, 0.73)	0.93 (0.93, 0.93)
Triglycerides[a] (mg/dl)	2.02 (2.02, 2.02)	1.79 (1.79, 1.79)
Body mass index		
Underweight	0.64 (0.59, 0.69)	0.61 (0.58, 0.64)
Normal	1	1
Overweight	1.49 (1.47, 1.52)	1.44 (1.43, 1.45)
Obese	2.03 (2.00, 2.06)	1.88 (1.86, 1.90)
Statin use	0.69 (0.68, 0.70)	0.93 (0.93, 0.94)
Microalbumin/creatinine ratio[b] (mg/g)		
0–20	1	1
20–300	0.98 (0.94, 1.02)	0.97 (0.95, 1.00)
>300	0.95 (0.87, 1.04)	0.95 (0.88, 1.01)

CI, confidence interval; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; OR, odds ratio.
Reference category is high HDL-C.
Models adjusted for age, race, cerebrovascular accident, cardiovascular disease, chronic lung disease, diabetes mellitus, dementia, HIV, hypertension, hepatitis C, peripheral artery disease, T_0 eGFR, LDL-C, triglycerides, BMI, and statin use.
[a]Odds ratios are for every one SD increase in the independent variable.
[b]Model additionally adjusted for microalbumin/creatinine ratio (n = 154,169).

45–30, and 30–15 ml/min/1.73 m^2; respectively. Correspondingly, the odds of intermediate HDL-C levels increased as eGFR category decreased (Table 2).

HDL-C and risk of incident eGFR <60 ml/min/1.73 m^2

We evaluated the risk of incident eGFR <60 ml/min/1.73 m^2 among those with eGFR more than 60 ml/min/1.73 m^2 at time of cohort entry (N = 1, 514, 464). Among those, 628,377 (41.49%) experienced eGFR <60 ml/min/1.73 m^2 during time in cohort; 70,821 (46.53%), 220,984 (43.93%), and 336,572 (39.17%) were in the low, intermediate, and high HDL-C categories, respectively (Supplemental Figure S1A). In adjusted survival models for demographic, comorbid conditions, eGFR, body mass index, LDL-C, triglycerides, and statin use, there was a graded and significant association between HDL-C levels and risk of incident eGFR <60 ml/min/1.73 m^2; compared with patients with high HDL-C, those in the intermediate and low HDL-C categories had a hazard ratio (HR) of 1.10, CI of 1.09–1.10, and HR of 1.18, CI of 1.17–1.19, respectively (Table 3). We evaluated the risk of incident CKD (defined as 2 eGFR <60 ml/min/1.73 m^2 at least 90 days apart) in a cohort of people with at least 2 eGFR measures separated by at least 90 days and whose eGFR at time of cohort entry (T0) was greater than 60 ml/min/1.73 m^2 (N = 387, 276). Among those, 123,775 (31.96%) developed incident CKD: 16,194 (37.03%), 43,662 (35.47%), and 63,959 (29.00%) were in the low, intermediate, and high HDL-C categories, respectively (Supplemental Figure S1B). Compared with patients with high HDL-C, those in the intermediate and low HDL-C categories had a higher risk of CKD with an HR of 1.12 (1.10, 1.13) and an HR of 1.20 (1.18, 1.22), respectively.

HDL-C and risk of CKD progression

In unadjusted models, there was a significant relationship between low HDL-C and doubling of serum creatinine, ≥30% decline in eGFR, and the composite outcome of ESRD, dialysis, or transplantation. Models were adjusted serially for demographic variables, comorbid conditions, baseline eGFR (eGFR at time of cohort entry), vascular disease (cardiovascular disease and peripheral artery disease), body mass index, lipid parameters (LDL-C and triglycerides), and statin use; the association was gradually attenuated and remained significant (Table 4). Cubic spline analyses of the relationship between HDL-C levels and renal outcomes (doubling of serum creatinine, ≥30% decline in eGFR, and composite outcome of ESRD, dialysis, and transplantation) showed a U-shaped relationship (Figure 2a, b, and c).

Sensitivity analyses

We evaluated the robustness and consistency of study findings in a number of sensitivity analyses. We categorized HDL-C in deciles. Compared with decile 8, the risk of doubling of serum creatinine was elevated in the lowest HDL-C decile (HR: 1.17; CI: 1.14–1.20) and the highest HDL-C decile (HR: 1.18; CI: 1.15–1.21) (Supplemental Table S1). The risk of ≥30% decline in eGFR was elevated in the lowest HDL-C decile (HR: 1.15; CI: 1.14–1.16) and the highest HDL-C decile (HR: 1.06; CI: 1.05–1.08). The risk of composite outcome of ESRD, dialysis, or transplantation was increased in the lowest HDL-C decile (HR: 1.10; CI: 1.07–1.14) and the highest HDL-C decile (HR: 1.20; CI: 1.15–1.25). We considered chronic eGFR slope categorized into 4 categories as described in methods (positive slope, mild, moderate, and severe CKD progression) as an alternative outcome to capture chronic CKD progression, and the results were consistent with the primary analyses in that low HDL-C was associated with increased risk of severe CKD progression (eGFR loss < –5 ml/min/1.73 m^2/yr; HR: 1.20; CI: 1.17–1.22) (Supplementary Table S2). Low HDL-C was associated with increased risk of ESRD, kidney transplant, or ≥50% decline in eGFR (HR: 1.12; CI: 1.11–1.14)

Table 3 | Risk of incident eGFR <60 ml/min/1.73 m^2 and risk of incident CKD by HDL-C category

	Incident eGFR less than 60 ml/min/1.73 m^2[d] HR (CI)		Incident CKD[e] HR (CI)	
	Intermediate HDL-C	Low HDL-C	Intermediate HDL-C	Low HDL-C
Model 1	1.16 (1.16, 1.17)	1.28 (1.27, 1.29)	1.28 (1.27, 1.30)	1.40 (1.37, 1.42)
Model 2	1.26 (1.26, 1.27)	1.50 (1.48, 1.50)	1.34 (1.33, 1.36)	1.56 (1.53, 1.59)
Model 3	1.18 (1.17, 1.19)	1.32 (1.31, 1.34)	1.23 (1.21, 1.24)	1.37 (1.34, 1.39)
Model 4	1.15 (1.14, 1.15)	1.29 (1.28, 1.30)	1.18 (1.17, 1.20)	1.31 (1.29, 1.33)
Model 5	1.13 (1.12, 1.14)	1.25 (1.24, 1.26)	1.16 (1.14, 1.17)	1.27 (1.25, 1.29)
Model 6	1.12 (1.11, 1.13)	1.24 (1.23, 1.25)	1.14 (1.12, 1.15)	1.24 (1.22, 1.27)
Model 7	1.09 (1.09, 1.10)	1.17 (1.16, 1.18)	1.12 (1.10, 1.13)	1.19 (1.17, 1.21)
Model 8	1.10 (1.09, 1.10)	1.18 (1.17, 1.19)	1.12 (1.10, 1.13)	1.20 (1.18, 1.22)

BMI, body mass index; CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; Model 1, unadjusted; Model 2, model 1 + demographics[a], Model 3, model 2 + comorbidities[b], Model 4, model 3 + T_0 eGFR; Model 5, model 4 + cardiovascular disease and peripheral artery disease; Model 6, model 5 + BMI; Model 7, model 6 + lipid parameters[c]; Model 8, model 7 + statin use.
[a]Demographics include age and race.
[b]Comorbidities include cerebrovascular accident, chronic lung disease, dementia, diabetes mellitus, hepatitis C, HIV, and hypertension.
[c]Lipid parameters include LDL-C and triglycerides.
[d]Results are for a subset of the cohort where patients had a T_0 eGFR >60 (ml/min/1.73 m^2) (n = 1,514,464).
[e]Results are for a subset of the cohort where patients had a T_0 eGFR >60 (ml/min/1.73 m^2), and two subsequent eGFR at least 90 days apart (n = 387,276); CKD was defined as 2 eGFR <60 ml/min/1.73 m^2 at least 90 days apart.

(Supplemental Table S2). Low HDL-C/triglycerides ratio (categorized into quartiles) was associated with increased risk of doubling of serum creatinine (HR: 1.28; CI: 1.26–1.30), increased risk of ≥30% decline in eGFR (HR: 1.25; CI: 1.24–1.26), and increased risk of composite outcome of ESRD, dialysis, or kidney transplantation (HR: 1.22; CI: 1.19–1.25) (Supplementary Table S3). We evaluated the potential effect that censoring at ESRD, dialysis, or kidney transplant may have had on the HDL-C HRs were the censoring informative; results showed that at both extremes of informative censoring the HRs of HDL-C were consistent with primary analyses (Supplementary Table S4). We built a cohort of women following the same criteria (except for gender selection) used for assembling the primary cohort of male US veterans (n = 92,079) and examined the association between HDL-C and risk of kidney disease progression, and results were consistent with those in the primary analyses (Supplementary Table S5). In a subset of the cohort where data on microalbumin/creatinine ratio were available (n = 154,169), we built serially adjusted models and the results were consistent with those in the primary analyses (Supplemental Table S6).

DISCUSSION

In a longitudinal national cohort study of US veterans spanning almost a decade (median follow-up of 9 years), we show an independent and graded association between the level of HDL-C and eGFR in that low HDL-C levels exhibit a strong association with low eGFR. Results also demonstrate a significant association between low HDL-C and risk of incident CKD and risk of CKD progression defined as doubling of serum creatinine, eGFR decline ≥30%, or the composite renal outcome of ESRD, dialysis, or transplantation. The robustness of study results was examined in a number of sensitivity analyses, and results were consistent.

In an elegant and comprehensive review on dyslipidemias and CKD progression, Cases and Coll note that studies that

Table 4 | Risk of doubling of serum creatinine, ≥30% decline in eGFR, and ESRD, dialysis, or transplantation by HDL-C category

	Doubling of serum creatinine HR (CI)		≥30% decline in eGFR HR (CI)		ESRD, dialysis, or transplant HR (CI)	
	Intermediate HDL-C	Low HDL-C	Intermediate HDL-C	Low HDL-C	Intermediate HDL-C	Low HDL-C
Model 1	1.18 (1.17, 1.19)	1.54 (1.513, 1.56)	1.16 (1.15, 1.16)	1.40 (1.39, 1.41)	1.34 (1.32, 1.36)	1.92 (1.874, 1.96)
Model 2	1.22 (1.21, 1.24)	1.63 (1.60, 1.65)	1.20 (1.19, 1.20)	1.48 (1.17, 1.49)	1.42 (1.40, 1.45)	2.11 (2.07, 2.16)
Model 3	1.06 (1.05, 1.08)	1.27 (1.25, 1.29)	1.08 (1.07, 1.09)	1.23 (1.22, 1.24)	1.20 (1.18, 1.22)	1.57 (1.54, 1.61)
Model 4	1.07 (1.05, 1.08)	1.26 (1.241, 1.28)	1.08 (1.08, 1.09)	1.23 (1.22, 1.24)	1.03 (1.01, 1.05)	1.16 (1.13, 1.18)
Model 5	1.04 (1.03, 1.06)	1.22 (1.20, 1.24)	1.06 (1.06, 1.07)	1.19 (1.18, 1.20)	1.01 (1.00, 1.03)	1.12 (1.10, 1.15)
Model 6	1.05 (1.04, 1.07)	1.23 (1.21, 1.25)	1.07 (1.06, 1.07)	1.20 (1.19, 1.21)	1.03 (1.01, 1.05)	1.14 (1.11, 1.17)
Model 7	1.02 (1.01, 1.04)	1.14 (1.12, 1.16)	1.04 (1.04, 1.05)	1.12 (1.12, 1.13)	1.00 (0.99, 1.02)	1.08 (1.06, 1.11)
Model 8	1.00 (1.01, 1.03)	1.14 (1.12, 1.15)	1.04 (1.04, 1.05)	1.13 (1.12, 1.14)	1.00 (0.98, 1.02)	1.08 (1.06, 1.11)

BMI, body mass index; CI, confidence interval; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; Model 1, unadjusted; Model 2: model 1 + demographics[a]; Model 3: model 2 + comorbidities[b]; Model 4: model 3 + T_0 eGFR; Model 5: model 4 + cardiovascular disease and peripheral artery disease; Model 6: model 5 + BMI; Model 7: model 6 + lipid parameters[c]; Model 8: model 7 + statin use.
[a]Demographics include age and race.
[b]Comorbidities include cerebrovascular accident, chronic lung disease, dementia, diabetes mellitus, hepatitis C, HIV, and hypertension.
[c]Lipid parameters include LDL-C and triglycerides.

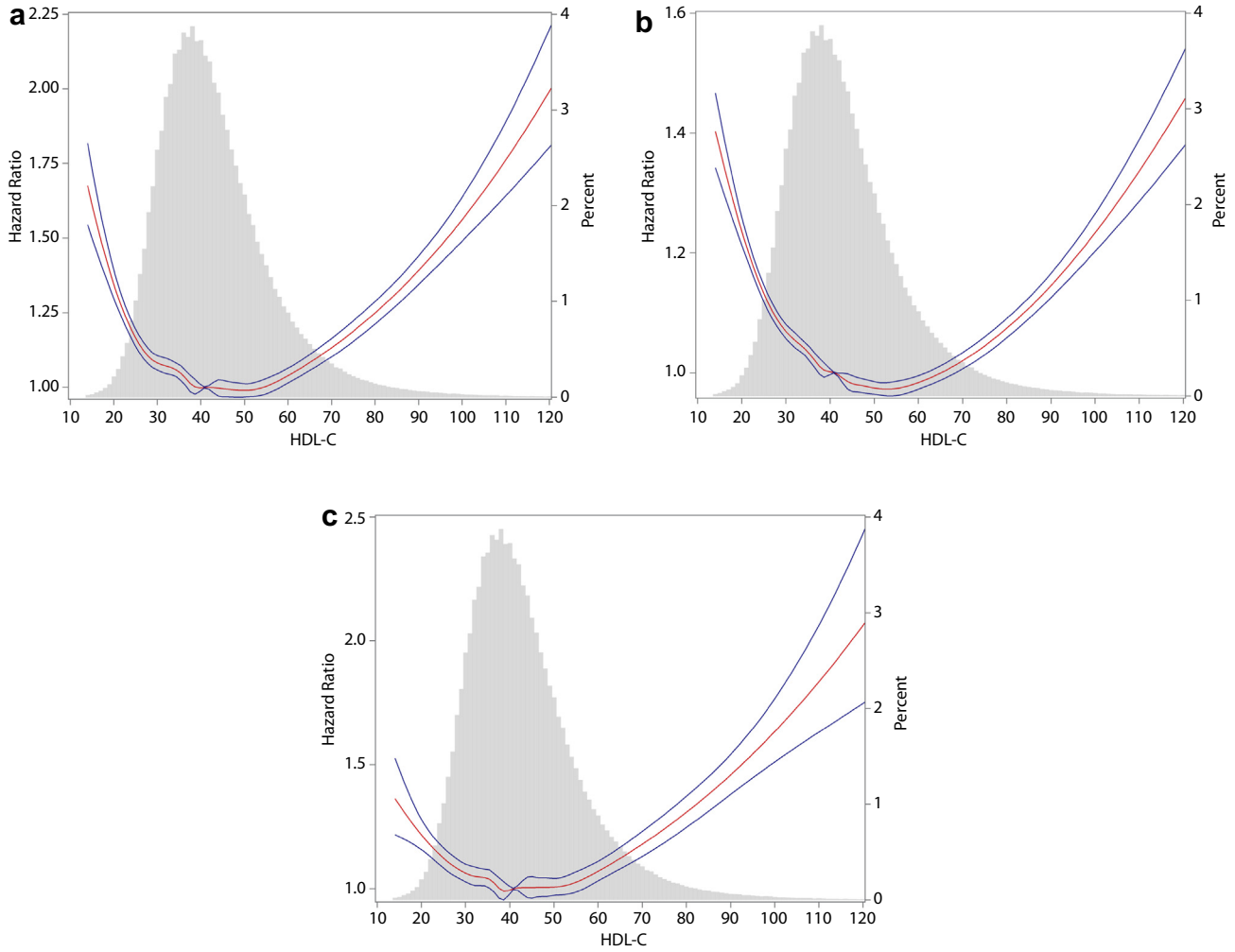

Figure 2 | (a) Cubic spline analyses of risk of doubling of serum creatinine by high-density lipoprotein cholesterol (HDL-C) level (median HDL-C as reference) with HDL-C probability distribution histogram represented by gray bars. (**b**) Cubic spline analyses of risk of ≥30% decline in estimated glomerular filtration rate by HDL-C level (median HDL-C as reference) with HDL-C probability distribution histogram represented by gray bars. (**c**) Cubic spline analyses of risk of composite outcome of end-stage renal disease, dialysis, or transplant by HDL-C level (median HDL-C as reference) with HDL-C probability distribution histogram represented by gray bars.

reported on the association between hyperlipidemia kidney disease development or progression were inconsistent.[1] They also note with prescience that it is "unclear whether dyslipidemia increases the renal risk in those without other risk factors for kidney disease, because most studies that have evaluated the effects of dyslipidemia on renal disease have been performed with patients with pre-existing renal disease or other risk factors for renal disease, such as hypertension and diabetes."[1] In this study, using a large cohort of patients, we show that low HDL-C was associated with increased risk of developing incident CKD and increased risk of CKD progression.

Muntner *et al.* examined the relationship between HDL-C and rise in serum creatinine of more than 0.4 mg/dl in a cohort of 12,728 Atherosclerosis Risk in Communities participants with baseline serum creatinine that was less than 2.0 mg/dl in men and less than 1.8 mg/dl in women.[6] The investigators reported that high HDL-C is associated with reduced risk of renal dysfunction.[6] In a prospective cohort of 3939 adults with CKD and an average eGFR 44.9 ml/min/1.73 m^2 followed up for a median of 4.1 years, Rahman *et al.* reported that none of the lipid parameters—and of particular interest HDL-C—were independently associated with progression of kidney disease defined as composite end point of ESRD or 50% decline in eGFR from baseline.[13] The study population was comprised of patients with relatively advanced CKD (average eGFR 44.9 ml/min/1.73 m^2), and the analytic strategy used by the investigators examined the HR per SD change of the independent variable (HDL-C). Our study was comprised of a cohort of patients with relatively high eGFR (average eGFR 74.85 ml/min/1.73 m^2), and our results suggest that the association seen between HDL-C and kidney disease progression is most evident in those with very low HDL-C (less than 30 mg/dl [10.37% of the overall cohort]). Furthermore, our spline analyses suggest a U-shaped relationship of risk where the risk of renal outcomes may be increased in those with very low and

very high HDL-C levels, and thus the putative effect of HDL-C on renal outcomes may be diluted and might not be visible when examined using the analytic approach devised by Rahman *et al.*[13]

A plausible explanation of the associations reported in this article is that low HDL-C may be a surrogate marker of poor overall metabolic health, and as such the associations may be a mere reflection of residual risk. This interpretation is supported by observations from recent Mendelian randomization analyses showing that some genetic mechanisms that raise plasma HDL-C do not lower risk of myocardial infarction.[14] The findings suggest that the relationship between HDL-C and cardiovascular outcomes may not be causal in nature, and HDL-C might be a mere marker, and as such pharmacologic manipulation of HDL-C levels may not uniformly translate into reduction of cardiovascular risk. In a *post hoc* analysis of the AIM-HIGH trial, which examined the benefits of adding extended-release niacin to simvastatin on eGFR changes in patients with established coronary heart disease, the investigators reported that the addition of niacin resulted in increased HDL-C mean by 11.3 mg/dl (from a baseline of 34.9 mg/dl) over a mean follow-up of 3 years; however, mean change in eGFR among niacin-treated patients was not significantly different from those in the placebo arm. The authors conclude that addition of niacin to simvastatin for secondary prevention of cardiovascular disease improved HDL-C but did not improve kidney function. They also acknowledge that the number of patients in this trial was small.[15] However, lack of therapeutic response to niacin lends further support to the notion that in the context of the association between low HDL-C and kidney outcomes, HDL-C may simply be a marker.

Prior studies suggest that among patients with type 2 diabetes mellitus and retinopathy, microvascular kidney disease is associated with both elevated triglycerides and reduced HDL-C levels, and that the ratio of triglycerides:HDL-C is a useful surrogate marker of insulin resistance or residual microvascular risk in patients with metabolic disease.[16–21] Tsuruya *et al.* evaluated the association of triglycerides:HDL-C ratio and decline in eGFR over a 2-year study and found that the higher quartile of triglycerides:HDL-C ratio at baseline was significantly associated with greater decline in eGFR.[22] In our study, we found a very strong and graded association between HDL-C levels and triglyceride levels (Table 2). Examination of HDL-C:triglycerides ratio (and its inverse ratio) in sensitivity analyses yielded results consistent with those reported by Tsuruya *et al.* and suggests that the association seen may be a reflection of residual microvascular risk in this cohort.

We opted for this study to define—in the primary analyses—outcomes representing kidney disease progression as doubling of serum creatinine and eGFR loss that exceeds 30%. We chose these outcomes as they represent dynamic progression of disease and not terminal end points (e.g., ESRD, dialysis, or transplant), and as such the course of the disease could be potentially reversed, halted, or otherwise stabilized.[23,24] We have, however, also tested the association with the composite renal outcome of ESRD, dialysis, and transplantation, and considered in sensitivity analyses alternative outcomes including chronic eGFR slope (categorized as described previously)[25,26] and the combined end point of ESRD, dialysis, transplantation, and ≥50% decline in eGFR (as described by Rahman *et al.*[13]) and the results were consistent.

The finding that the relationship between HDL-C levels and risk of kidney disease progression follows a U-shaped curve suggests that at high concentrations, HDL-C loses its protective properties; the mechanism underpinning the observation is not entirely clear. Experimental evidence suggests that HDL-C may have a biphasic effect (at low and high concentrations) and that at high concentrations HDL-C paradoxically enhanced senescence and impaired endothelial progenitor cell tube formation and angiogenesis, suggesting loss of protective effect.[27] Results from recent clinical studies indicate that salutary effect of higher HDL-C levels may be reversed—and cardiovascular risk increased—in patients with high C-reactive protein and high HDL-C; findings from the Thrombogenic Factors and Recurrent Coronary Events, and Prevention of Renal and Vascular End-Stage Disease study demonstrated a subgroup of patients with high C-reactive protein who exhibited increased risk of cardiovascular events with increasing HDL-C levels.[28–32] Findings by Moradi and collaborators show a U-shaped relationship and suggest functional impairment of HDL-C, and higher risk of cardiovascular and all-cause mortality in patients with high HDL-C on maintenance hemodialysis—a state characterized by inflammatory cytokine activation, increased inflammatory burden, and oxidative stress.[33–35] Taken together, the above observations present a framework for a hypothesis that if proven in future studies might help explain the U-shaped relationship observed in this report—mainly that elevated HDL-C–associated risk of CKD progression may be related to inflammation and oxidative stress, which may result in functional impairment of anti-atherogenic properties of HDL-C leading to microvascular disease and renal dysfunction.

Our study has a number of limitations. First, although our study included data on HDL-C levels and other lipid parameters, our data do not allow for qualitative assessment of HDL-C size, composition, functional capacity, or HDL-C subclasses (i.e., HDL_2, which is generally associated with improved cardiovascular outcomes).[36,37] Regardless, we show that quantitative assessment of HDL-C informs risk of renal outcomes. The cohort included older white male US veterans who received care at the VA, thus the results may not be generalizable to less narrowly defined populations. The imperfect nature of administrative data and the retrospective design of the study may also lead to sampling bias and inaccurate measurements of the predictor variables (i.e., variability in the measurement of HDL-C) and outcomes. In order to minimize such measurement bias, we used

definitions of comorbid illnesses that are validated for use in VA administrative data. Low HDL-C may be a surrogate marker of poor overall metabolic health including increased levels of inflammation, oxidative stress, insulin resistance, sedentary lifestyle (or poor physical activity), smoking, and alcohol consumption. Our dataset did not include information on these parameters, and an alternative explanation to the observed risk may simply represent residual confounding, i.e., the existence of factors either unmeasured or unknown that might either partially or fully explain the observed association. We have, however, taken considerable care to test the associations in numerous models using alternative definitions for exposure variable, and evaluated a number of alternative outcomes in sensitivity analyses and the results were consistent.

MATERIALS AND METHODS

Patients

Using administrative data from the VA, we identified users of the VA Healthcare System who had at least one eGFR value between October 1, 2003 and September 30, 2004, where the date of last eGFR during this period was designated as time zero (T_0), with no prior history of ESRD, dialysis, or kidney transplant (n = 2,751,717). Additionally, cohort participants were selected on having complete lipid panel between October 1, 1999 and T_0 (n = 2,233,536), and at least one eGFR subsequent to T_0 (n = 2,035,761). Serum creatinine (and eGFR), HDL-C levels, and other laboratory parameters were acquired during routine outpatient care. The cohort for primary analysis was further restricted to include only men, yielding an analytic cohort of n = 1,943,682. A flowchart and timeline for cohort selection are presented in Figure 3a and b. The study was approved by the Institutional Review Board of the VA Saint Louis Health Care System, St. Louis, Missouri.

Data sources

We used VA databases including inpatient and outpatient medical SAS datasets (which included utilization data related to all inpatient and outpatient encounters within the VA system) to ascertain detailed patient demographic characteristics and comorbidity information based on Current Procedural Terminology codes, and ICD-9-CM diagnostic and procedure codes associated with inpatient and outpatient encounters.[38–41] The VA Managerial Cost Accounting System Laboratory Results (a comprehensive database that includes VA-wide results for selected laboratory tests obtained in the clinical setting) provided information on outpatient and inpatient serum creatinine, HDL-C, LDL-C, triglycerides, and microalbumin/creatinine ratio.[38,39,42] The VA Vital Status and Beneficiary Identification Records Locator Subsystem files provided demographic characteristics and death follow-up through September 30, 2013.[38,39] Corporate Data Warehouse Outpatient Pharmacy datasets were used to obtain

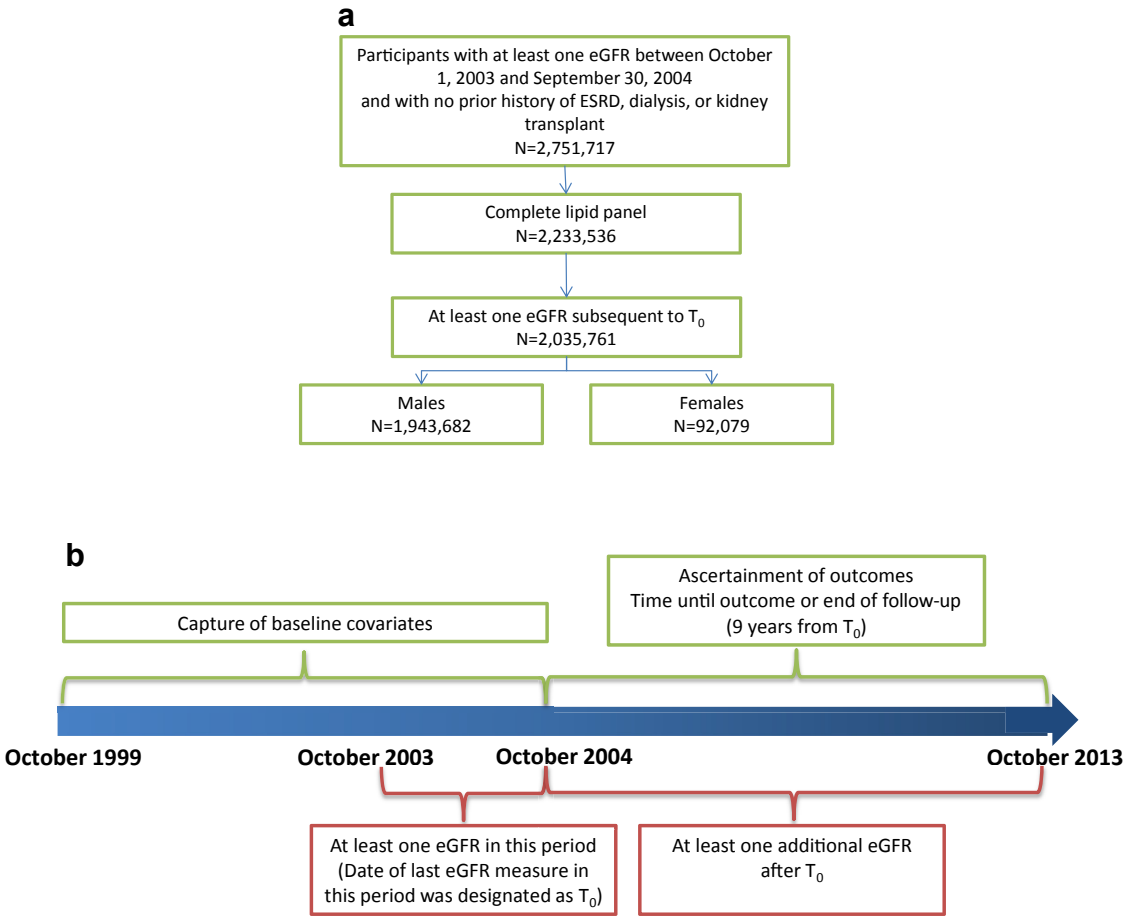

Figure 3 | (a) Flow diagram of cohort assembly. (**b**) Timeline of cohort selection.

data on statin use. Corporate Data Warehouse vital signs datasets were used to obtain height and weight, and to compute body mass index.

Primary predictor variable

The primary predictor variable for all survival analyses was HDL-C level. HDL-C was measured using enzyme-based chromogenic assays. The value for HDL-C was taken as the outpatient HDL-C value prior to and most proximal to T_0. HDL-C was then categorized by means of the following criteria: low HDL-C when <30 mg/dl, intermediate HDL-C from 30 to <40 mg/dl, and high as greater than or equal to 40 mg/dl.

Outcomes

We evaluated the risk of incident eGFR <60 ml/min/1.73 m^2 in those with eGFR >60 ml/min/1.73 m^2 at time of cohort entry, and risk of CKD among those with at least two eGFR values no less than 90 days apart. CKD was defined as 2 eGFR <60 ml/min/1.73 m^2 at least 90 days apart. The primary outcomes in survival analyses consisted of time until doubling of serum creatinine, time until greater than or equal to 30% decline in eGFR, and time until ESRD, dialysis, or transplant from the T_0 creatinine.[24,43] eGFR values were censored after onset of ESRD or at first record of dialysis or kidney transplant. All patients were followed up until a maximum of 9 years from time of cohort entry (T_0).

Covariates

Baseline covariates were ascertained from October 1, 1999 until cohort entry (T_0 between October 1, 2003 and September 30, 2004). Covariates included T_0 eGFR, age, race, diabetes mellitus, hypertension, cardiovascular disease (defined as diagnosis of coronary artery disease, myocardial infarction, coronary artery bypass graft, angioplasty, or congestive heart failure), peripheral artery disease (defined as diagnosis of peripheral artery disease, lower extremity amputation, or revascularization procedure), cerebrovascular disease (defined as diagnosis of stroke or transient ischemic attack), chronic lung disease (defined as chronic obstructive pulmonary disease or chronic bronchitis), hepatitis C, HIV, dementia, LDL-C, triglycerides, microalbumin/creatinine ratio, body mass index, and statin use (defined as cumulative exposure to any statin drug for more than 90 days during the baseline period). Race/ethnicity was categorized as white, black, or other (Latino, Asian, Native American, or other racial/ethnic minority groups). T_0 eGFR (ml/min/1.73 m^2) was categorized into groups as 90 or greater, less than 90 to 60, less than 60 to 45, less than 45 to 30, and less than 30 to 15. Covariates were treated as continuous variables where appropriate and unless otherwise specified. Comorbidities were assigned on the basis of relevant ICD-9-CM diagnostic and procedures codes and Current Procedural Terminology codes in the VA Medical SAS datasets.[25,44,45]

Statistical analysis

Association of HDL-C category with covariates was assessed through use of a multinomial logistic regression model, where high HDL-C was set as the reference category. Kaplan Meier curves were generated to show the survival of doubling of serum creatinine, greater than 30% decline in eGFR, and occurrence of ESRD, dialysis, or transplant by HDL-C category. Because of the censoring of eGFR values by occurrence of ESRD, dialysis, transplant, and death, competing risk Cox proportional hazard regression models were used in the assessment of survival outcomes. Specifically, ESRD, dialysis, transplant, and death were treated as competing risks in models where the outcomes were doubling of serum creatinine or greater than a 30% decline in eGFR, whereas death was treated as a competing risk in models where the outcome was ESRD, dialysis, or transplant. Such censoring was considered noninformative.[46] Multiple models were built to assess the relationship between HDL-C category and outcomes while controlling for different covariates. The proportional hazard assumption was assessed through use of log-negative log plots. Cubic spline analyses of the association between HDL-C and outcomes were performed with knots placed at HDL-C decile cutoffs, where 50 mg/dl, the cutoff used for the high HDL-C category, was used as the reference value.[47] Cubic spline analyses were plotted with an HDL-C probability distribution histogram. In survival analyses, a 95% CI of an HR that does not include unity was considered statistically significant. In all analyses, a P value of 0.05 or less was considered statistically significant. All analyses were performed, and graphs made, using SAS Enterprise Guide version 6.1 and SAS 9.4 (SAS Institute, Cary, NC).

Sensitivity analyses

We evaluated the consistency of study findings by undertaking a number of sensitivity analyses where we:

(i) categorized HDL-C into deciles, where the range of deciles was 14.00 to 29.00, 29.01 to 33.00, 33.01 to 36.00, 36.01 to 39.00, 39.01 to 41.00, 41.01 to 44.00, 44.01 to 48.00, 48.01 to 53.00, 53.01 to 61.00, and 61.01 to 121.00 mg/dl for deciles 1 to 10, respectively; (ii) considered chronic eGFR slope as an alternative outcome; chronic eGFR slope captures longitudinal eGFR changes and was categorized into 4 groups: positive slope, mild decline (eGFR slope 0 to –1 ml/min/1.73 m^2/yr); moderate decline (eGFR slope –1 to –5 ml/min/1.73 m^2/yr), and severe decline (eGFR slope < –5 ml/min/1.73 m^2/yr)[25,48]; (iii) considered time until ESRD, dialysis, kidney transplant, or eGFR decline ≥50% as another alternative outcome[13]; (iv) created an HDL-C/triglycerides ratio variable to examine a potential combined effect; this ratio was categorized into quartiles as low (Q1) when 0.01–0.19, medium low (Q2) when 0.19 to 0.32, medium high (Q3) when 0.32 to 0.52, and high (Q4) when 0.52 to 4.60; (v) assessed potential effects on the HRs for HDL-C category by treating the censoring of ESRD, dialysis, and kidney transplant as informative[46]; (vi) conducted analyses in a separate cohort of women (n = 92,079), where HDL-C was categorized as low HDL-C when <30 mg/dl, intermediate HDL-C from 30 to <50 mg/dl, and high as greater than or equal to 50 mg/dl; and (vii) examined the association in a subcohort where data on microalbumin/creatinine ratio were available (n = 154,169).

DISCLOSURE

All the authors declared no competing interests.

ACKNOWLEDGMENT

This work was funded by a grant from the US Department of Veterans Affairs (for ZAA).

DISCLAIMER

The contents do not represent the views of the US Department of Veterans Affairs or the United States Government.

SUPPLEMENTARY MATERIAL

Figure S1. (**A**) Kaplan-Meier curves for estimated glomerular filtration rate less than 60 ml/min/1.73 m^2 by high-density lipoprotein

cholesterol category. (**B**) Kaplan-Meier curves for incident chronic kidney disease by high-density lipoprotein cholesterol category.
Table S1. Risk of doubling of serum creatinine, ≥30% decline in estimated glomerular filtration rate, or end-stage renal disease, dialysis, or transplant by high-density lipoprotein cholesterol deciles.
Table S2. Sensitivity analyses for alternate outcomes.
Table S3. Risk of doubling of serum creatinine, or ≥30% decline in estimated glomerular filtration rate by high-density lipoprotein cholesterol/triglycerides ratio.
Table S4. Sensitivity analyses for informative censoring of end-stage renal disease, dialysis, or kidney transplant.
Table S5. Risk of doubling of serum creatinine, ≥30% decline in estimated glomerular filtration rate, or end-stage renal disease, dialysis, or transplant by high-density lipoprotein cholesterol level in women (N = 92,079).
Table S6. Risk of doubling of serum creatinine, ≥30% decline in estimated glomerular filtration rate, or end-stage renal disease, dialysis, or transplant by high-density lipoprotein cholesterol level in a subcohort where data on microalbuminuria are available (N = 154,169).
Supplementary material is linked to the online version of the paper at www.kidney-international.org.

REFERENCES

1. Cases A, Coll E. Dyslipidemia and the progression of renal disease in chronic renal failure patients. *Kidney Int Suppl*. 2005;Dec(99):S87–S93.
2. Vaziri ND, Navab M, Fogelman AM. HDL metabolism and activity in chronic kidney disease. *Nat Rev Nephrol*. 2010;6:287–296.
3. Ganda A, Magnusson M, Yvan-Charvet L, et al. Mild renal dysfunction and metabolites tied to low HDL cholesterol are associated with monocytosis and atherosclerosis. *Circulation*. 2013;127:988–996.
4. Homma S, Murayama N, Yoshida I, et al. Marked atherosclerosis in a patient with familiar lecithin: cholesterol acyltransferase deficiency associated with end-stage renal disease and diabetes mellitus. *Am J Nephrol*. 2001;21:415–419.
5. Gjone E. Familial lecithin:cholesterol acyltransferase deficiency - a new metabolic disease with renal involvement. *Adv Nephrol Necker Hosp*. 1981;10:167–185.
6. Muntner P, Coresh J, Smith JC, et al. Plasma lipids and risk of developing renal dysfunction: the atherosclerosis risk in communities study. *Kidney Int*. 2000;58:293–301.
7. Morton J, Zoungas S, Li Q, et al. Low HDL cholesterol and the risk of diabetic nephropathy and retinopathy: results of the ADVANCE study. *Diabetes Care*. 2012;35:2201–2206.
8. Schaeffner ES, Kurth T, Curhan GC, et al. Cholesterol and the risk of renal dysfunction in apparently healthy men. *J Am Soc Nephrol*. 2003;14:2084–2091.
9. Manttari M, Tiula E, Alikoski T, et al. Effects of hypertension and dyslipidemia on the decline in renal function. *Hypertension*. 1995;26:670–675.
10. Vaziri ND. Causes of dysregulation of lipid metabolism in chronic renal failure. *Semin Dial*. 2009;22:644–651.
11. Wang F, Zheng J, Ye P, et al. Association of high-density lipoprotein cholesterol with the estimated glomerular filtration rate in a community-based population. *PloS One*. 2013;8:e79738.
12. Baragetti A, Norata GD, Sarcina C, et al. High density lipoprotein cholesterol levels are an independent predictor of the progression of chronic kidney disease. *J Int Med*. 2013;274:252–262.
13. Rahman M, Yang W, Akkina S, et al. Relation of serum lipids and lipoproteins with progression of CKD: The CRIC study. *Clin J Am Soc Nephrol*. 2014;9:1190–1198.
14. Voight BF, Peloso GM, Orho-Melander M, et al. Plasma HDL cholesterol and risk of myocardial infarction: a mendelian randomisation study. *Lancet*. 2012;380:572–580.
15. Kalil RS, Wang JH, de Boer IH, et al. Effect of extended-release niacin on cardiovascular events and kidney function in chronic kidney disease: a post hoc analysis of the AIM-HIGH trial. *Kidney Int*. 2015;87:1250–1257.
16. Fioretto P, Dodson PM, Ziegler D, et al. Residual microvascular risk in diabetes: unmet needs and future directions. *Nat Rev Endocrinol*. 2010;6:19–25.
17. Tsuruya K, Yoshida H, Nagata M, et al. Association of the triglycerides to high-density lipoprotein cholesterol ratio with the risk of chronic kidney disease: analysis in a large Japanese population. *Atherosclerosis*. 2014;233:260–267.
18. Giannini C, Santoro N, Caprio S, et al. The triglyceride-to-HDL cholesterol ratio: association with insulin resistance in obese youths of different ethnic backgrounds. *Diabetes Care*. 2011;34:1869–1874.
19. Sacks FM, Hermans MP, Fioretto P, et al. Association between plasma triglycerides and high-density lipoprotein cholesterol and microvascular kidney disease and retinopathy in type 2 diabetes mellitus: a global case-control study in 13 countries. *Circulation*. 2014;129:999–1008.
20. Gasevic D, Frohlich J, Mancini GB, et al. The association between triglyceride to high-density-lipoprotein cholesterol ratio and insulin resistance in a multiethnic primary prevention cohort. *Metabolism*. 2012;61:583–589.
21. Mostafa SA, Davies MJ, Morris DH, et al. The association of the triglyceride-to-HDL cholesterol ratio with insulin resistance in White European and South Asian men and women. *PloS One*. 2012;7:e50931.
22. Tsuruya K, Yoshida H, Nagata M, et al. Impact of the triglycerides to high-density lipoprotein cholesterol ratio on the incidence and progression of CKD: a longitudinal study in a large Japanese population. *Am J Kidney Dis*. 2015;66:972–983.
23. Al-Aly Z, Balasubramanian S, McDonald JR, et al. Greater variability in kidney function is associated with an increased risk of death. *Kidney Int*. 2012;82:1208–1214.
24. Al-Aly Z. Prediction of renal end points in chronic kidney disease. *Kidney Int*. 2013;83:189–191.
25. Al-Aly Z, Zeringue A, Fu J, et al. Rate of kidney function decline associates with mortality. *J Am Soc Nephrol*. 2010;21:1961–1969.
26. Xie Y, Bowe B, Xian H, et al. Rate of kidney function decline and risk of hospitalizations in stage 3A CKD. *Clin J Am Soc Nephrol*. 2015;10:1946–1955.
27. Huang CY, Lin FY, Shih CM, et al. Moderate to high concentrations of high-density lipoprotein from healthy subjects paradoxically impair human endothelial progenitor cells and related angiogenesis by activating Rho-associated kinase pathways. *Arterioscler Thromb Vasc Biol*. 2012;32:2405–2417.
28. Corsetti JP, Ryan D, Rainwater DL, et al. Cholesteryl ester transfer protein polymorphism (TaqIB) associates with risk in postinfarction patients with high C-reactive protein and high-density lipoprotein cholesterol levels. *Arterioscler Thromb Vasc Biol*. 2010;30:1657–1664.
29. Corsetti JP, Zareba W, Moss AJ, et al. Elevated HDL is a risk factor for recurrent coronary events in a subgroup of non-diabetic postinfarction patients with hypercholesterolemia and inflammation. *Atherosclerosis*. 2006;187:191–197.
30. Corsetti JP, Gansevoort RT, Sparks CE, et al. Inflammation reduces HDL protection against primary cardiac risk. *Eur J Clin Invest*. 2010;40:483–489.
31. deGoma EM, Leeper NJ, Heidenreich PA. Clinical significance of high-density lipoprotein cholesterol in patients with low low-density lipoprotein cholesterol. *J Am Coll Cardiol*. 2008;51:49–55.
32. van der Steeg WA, Holme I, Boekholdt SM, et al. High-density lipoprotein cholesterol, high-density lipoprotein particle size, and apolipoprotein A-I: significance for cardiovascular risk: the IDEAL and EPIC-Norfolk studies. *J Am Coll Cardiol*. 2008;51:634–642.
33. Moradi H, Streja E, Kashyap ML, et al. Elevated high-density lipoprotein cholesterol and cardiovascular mortality in maintenance hemodialysis patients. *Nephrol Dial Transplant*. 2014;29:1554–1562.
34. Al-Aly Z. Arterial calcification: a tumor necrosis factor-alpha mediated vascular Wnt-opathy. *Transl Res*. 2008;151:233–239.
35. Al-Aly Z. Phosphate, oxidative stress, and nuclear factor-kappaB activation in vascular calcification. *Kidney Int*. 2011;79:1044–1047.
36. de Boer IH, Brunzell JD. HDL in CKD: how good is the "good cholesterol?". *J Am Soc Nephrol*. 2014;25:871–874.
37. Muller-Deile J, Schmitt R. HDL in CKD: not protective any longer? *Kidney Int*. 2014;85:712.
38. Murphy PA, Cowper DC, Seppala G, et al. Veterans Health Administration inpatient and outpatient care data: an overview. *Eff Clin Pract*. 2002;5:E4.
39. Oddone EZ, Eisen S. Veterans Affairs Research and Development: using science to improve health care for veterans. *N C Med J*. 2008;69:35–37.
40. VIReC Research User Guide: VHA Medical SAS Outpatient Datasets FY2006. U.S. Department of Veterans Affairs. VA Information Resource Center: Hines I, September 2007.
41. VIReC Research User Guide: VHA Medical SAS Inpatient Datasets FY2006. U.S. Department of Veterans Affairs. VA Information Resource Center: Hines I, September 2007.

42. VIReC Research User Guide: Veterans Health Administration Decision Support System Clinical National Data Extracts H, IL, U.S. Department of Veterans Affairs. VA Information Resource Center, September 2009.
43. Coresh J, Turin TC, Matsushita K, et al. Decline in estimated glomerular filtration rate and subsequent risk of end-stage renal disease and mortality. *JAMA*. 2014;311:2518–2531.
44. O'Hare AM, Bertenthal D, Covinsky KE, et al. Mortality risk stratification in chronic kidney disease: one size for all ages? *J Am Soc Nephrol*. 2006;17:846–853.
45. Xie Y. Renal function trajectories in patients with prior improved eGFR slopes and risk of death. *PloS One*. 2015.
46. Kleinbaum DG, Klein M. *Survival Analysis*. New York, NY: Springer; 2005.
47. Heinzl H, Kaider A. Gaining more flexibility in Cox proportional hazards regression models with cubic spline functions. *Comput Methods Programs Biomed*. 1997;54:201–208.
48. Turin TC, Coresh J, Tonelli M, et al. Change in the estimated glomerular filtration rate over time and risk of all-cause mortality. *Kidney Int*. 2013;83:684–691.