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

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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.

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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).