Published in final edited form as:

J Clin Lipidol. 2018 ; 12(4): 1061–1071.e7. doi:10.1016/j.jacl.2018.03.085.

HDL-cholesterol and causes of death in chronic kidney disease

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Abstract

Background—Recent data suggest a U-shaped association between HDL cholesterol (HDL-c) and death in CKD. However, whether the increased mortality in patients with extreme levels is explained by specific causes of death remains unclear.

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Previous presentations

The results of this study was presented as an oral abstract at the 2017 Kidney Week (on November 4, 2017) of the American Society of Nephrology in New Orleans, LA.

Author contributions

Research idea and study design: SDN, JDS, SA; Data acquisition: SA; Data analysis and interpretation: SDN, CPW, JDS, SEJ, SA, SV, WCW, JVN; Statistical analysis: SA, JDS; 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. SDN takes responsibility that this study has been reported honestly, accurately, and transparently; that no important aspects of the study have been omitted, and that any discrepancies from the study as planned have been explained.

Disclosures

SDN is supported by a grant from the National Institutes of Health (NIDDK-R01DK101500). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH. NIH did not had any role in study design; collection, analysis, and interpretation of data; writing the report; and the decision to submit the report for publication. All authors have no relevant financial interest in the contents of this study.

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Objectives—We studied the associations between HDL-c and cause specific deaths in CKD.

Methods—We included 38,377 patients with eGFR 15–59 ml/min/1.73 m². We classified deaths into 3 major categories: a) cardiovascular; b) malignancy; and c) non-cardiovascular/non-malignancy causes. We fitted Cox regression models for overall mortality and separate competing risk models for each major cause of death category to evaluate their respective associations with categories of HDL-c (< 30, 31–40, 41–50 [referent], 51–60, >60 mg/dl). Separate analyses were conducted for men and women.

Results—During a median follow-up of 4.5 years, 9,665 patients died. After adjusting for relevant covariates, in both sexes, HDL-c 31–40 mg/dl and < 30 mg/dl were associated with higher risk of all-cause mortality, cardiovascular mortality, malignancy-related deaths and non-cardiovascular/non-malignancy related deaths. HDL-c >60 mg/dl was associated with lower all-cause (HR 0.75, 95% CI 0.69, 0.81), cardiovascular, malignancy-related, and non-cardiovascular/non-malignancy related deaths among women but not in men. Similar results were noted when HDL-c was examined as a continuous measure.

Conclusions—In a non-dialysis dependent CKD population, HDL-c < 40 mg/dl was associated with risk of higher all-cause, cardiovascular, malignancy and non-cardiovascular/non-malignancy mortality in men and women. HDL >60 mg/dl was associated with lower risk of all-cause, cardiovascular, malignancy and non-cardiovascular non-malignancy mortality in women but not men.

Keywords

HDL-cholesterol; mortality; cardiovascular; malignancy; kidney disease

Background

High-density lipoprotein cholesterol (HDL-c) exerts anti-inflammatory, antioxidant, and antithrombotic effects in addition to its effects on endothelial function and angiogenesis^{1–3}. Several observational studies in the general population reported inverse associations of HDL-c with cardiovascular events and mortality^{4–7}. Lipid abnormalities in chronic kidney disease (CKD) are characterized by elevated serum triglyceride levels, and decreased and dysfunctional HDL-c levels^{8,9}. Thus, it is reasonable to study whether patients with varying levels of HDL-c differ in their health outcomes. In the CKD population, studies examining the associations between HDL-c and outcomes are limited. Zewinger and colleagues examined the associations between HDL-c and mortality among 3307 patients undergoing coronary angiography¹⁰. This report did not find any significant associations between higher levels of HDL-c and mortality in those with CKD. Recently, Bowe and colleagues reported a U-shaped association between HDL-c and all-cause mortality among veterans with and without CKD¹¹.

Ko *et al.* using the Cardiovascular Health in Ambulatory Care Research Team (CANHEART) study noted low HDL-c levels were associated with cardiovascular, cancer and other causes of death while those with higher HDL-c had more non-cardiovascular mortality¹². Hence, in the general population, the higher risk of death with higher HDL-c was attributed to non-cardiovascular causes. Whether the increased mortality in CKD

patients with higher levels of HDL-c demonstrated by Bowe et al is driven by specific causes of death remains unclear. Further, causes of death in CKD among those with lower levels of HDL-c have also not been examined before. Therefore, we examined the associations between HDL-c and cause-specific mortality in a large CKD population.

Materials and Methods

Patient population

We used the electronic health records (EHR)-based CKD registry developed at the Cleveland Clinic to study the relationship between HDL-c and outcomes. The development and validation of this registry has been described in detail elsewhere¹³. For this analysis, we included patients who had: a) at least one face-to-face outpatient encounter with a Cleveland Clinic health care provider and at least two estimated glomerular filtration rate (eGFR) measures <60 ml/min/1.73 m², >90 days apart, between January 1, 2005 and December 31, 2013 (the second eGFR was 15–59.9 ml/min/1.73 m² and patients were not on dialysis nor had a functioning kidney transplant), b) lipid levels measured within year prior to second eGFR <60 (CKD); and c) who were residents of the State of Ohio (Supplemental Figure 1).

Patient Characteristics

Demographic details (age, sex, race, insurance details) were extracted from the EHR. Comorbid conditions such as diabetes mellitus, hypertension, coronary artery disease, malignancy, congestive heart failure, and hyperlipidemia were defined using prespecified and previously validated criteria¹³. These conditions existed prior to the second eGFR <60 ml/min/1.73 m². We also extracted relevant laboratory data (serum albumin, hemoglobin, and bicarbonate, proteinuria details) from the EHR. For diagnoses of comorbid conditions, any diagnoses prior to inception (including the same day) were considered as presence of that particular co-morbid condition. For laboratory results other than HDL cholesterol, the last outpatient laboratory data obtained within 2 years prior to inception was included.

Kidney function

All serum creatinine measurements were performed in the same clinical laboratory using a Hitachi D 2400 Modular Chemistry Analyzer (Roche Diagnostics, Indianapolis, IN). We calculated eGFR using the CKD-EPI equation¹⁴. CKD was classified into the following stages: stage 3 CKD (eGFR 30–59 ml/min/1.73 m²) and stage 4 CKD (eGFR 15–29 ml/min/1.73 m²). We further categorized stage 3 into CKD stage 3a (eGFR 45–59 ml/min/1.73 m²) and stage 3b (eGFR 30–44 ml/min/1.73 m²). To reflect clinical practice, patients who had a urine dipstick measurement, urine albumin-to-creatinine ratio (UACR), urine protein-to-creatinine ratio (UPR), and 24 hour urine studies were included to assess whether they had proteinuria or not. The following cut-offs were considered in determining whether someone had proteinuria: presence of 1+ proteinuria in dipstick studies, >30 mg/g in those who had UACR and UPR studies and >30 mg proteinuria in 24 hour studies. Other details relating to assessment of proteinuria for this study population have been described previously¹³.

HDL-c

Serum HDL-c was measured using a homogeneous enzymatic calorimetric test run on the Roche cobas c 702 analyzer. Within- and between-run precision of human serum are stated at 1.3% and 1.6%, respectively. In the Cleveland Clinic health system, lipid profiles are obtained in fasting state by standard protocol. HDL-c was classified into following categories: 30, 31–40, 41–50, 51–60 and >60 mg/dl. Lipid profile data obtained within 1 year prior to inception was included.

Ascertainment of death and its causes

We ascertained dates and reported causes of death from the EHR as well as through linkage of the CKD registry with the Ohio Department of Health death records. The underlying cause of death was coded according to the *International Classification of Diseases*, Tenth Revision (ICD-10). We grouped the underlying causes of death according to the National Center for Health Statistics for each coding system, except as defined here. We classified deaths into three categories: a) deaths from cardiovascular causes, b) deaths from malignancy, and c) deaths from other (non-cardiovascular and non-malignancy-related) causes. We defined cardiovascular deaths as deaths reportedly due to diseases of the heart, essential hypertension, cerebrovascular disease, atherosclerosis, or other diseases of the circulatory system (ICD-10 codes I00–I78). We also categorized the cardiovascular deaths into the following clinically meaningful subcategories: ischemic heart disease (I20–I25), heart failure (I50), cerebrovascular diseases (I60s) and all other cardiovascular disease (include all others from I00 to I-78 except I20–I25, I50 and I60). Patients with death noted in the EHR but not found in Ohio death files were included in the analysis of all-cause mortality and excluded from the cause-specific analysis.

Statistical analysis

We compared baseline characteristics between patients with and without HDL data available, and also among patients in defined categories of HDL-c level using Chi-square and ANOVA and Kruskal-Wallis tests for categorical and continuous variables, respectively. We summarized the leading causes of death for various HDL-c categories as percent of total deaths observed. We used Poisson models to estimate age-adjusted mortality rates for each HDL-c group. We evaluated the relationship between HDL-c groups and overall mortality using a Cox proportional hazards models and the relationship between HDL-c and cause specific death categories using competing risks regression models as described by Fine and Gray. We inspected log-log plots for violations of the proportional hazards assumption. We adjusted the models for the following covariates: age, race, smoking, diabetes, hypertension, body mass index (BMI) group, malignancy, cardiovascular disease (any of the following: coronary artery disease, congestive heart failure, cerebrovascular disease, or peripheral vascular disease), log triglycerides, statin use, and eGFR. We also ran similar models while adjusting only for age. Separate analyses were conducted for men and women.

Approximately 3% of patients were missing BMI data, 12% were missing albumin, 19% were missing hemoglobin, 0.3% were missing cholesterol, 0.8% were missing triglycerides, 12% were missing smoking status, and 3% did not have insurance data. We used multiple imputations (SAS proc MI) with the Markov Chain Monte Carlo method and a single chain

to impute 5 datasets with complete continuous and binary data in a first step, and then in a second step we imputed insurance group on each of the 5 datasets using discriminant function analysis¹⁵. We included the following variables in the imputation: age, sex, race, smoking, diabetes, hypertension, body mass index (BMI), malignancy, coronary artery disease, congestive heart failure, cerebrovascular disease, peripheral vascular disease, insurance group, albumin, hemoglobin, cholesterol, log triglycerides, ACE/ARB use, beta blocker use, statin use, and eGFR. All models were performed on each of the 5 imputed datasets, and parameter estimates were combined using SAS MI analyze.

We also evaluated the association between continuous HDL-c and overall mortality, and each cause-specific mortality category using restricted cubic splines at percentiles 10, 50 and 90 in the Cox models of all-cause mortality, and linear splines at percentiles 10, 50 and 90 in the competing risks regression models. For all-cause mortality, we plotted continuous HDL-c vs. hazard ratio, using data from the first imputation. For each cause-specific mortality, we plotted continuous HDL-c vs. the predicted probability of death at 4 years of follow up using data from the first imputation. The plot estimates were obtained for a hypothetical patient with mean values on all baseline covariates. We evaluated two-way interactions on all-cause mortality between HDL-c category and each of the following: age, African American race, eGFR and cardiovascular disease.

We conducted additional sensitivity analyses to confirm the primary findings by excluding patients with malignancy at the time of CKD diagnosis, excluding those with pre-existing cardiovascular disease (any of the following: coronary artery disease, congestive heart failure, cerebrovascular disease, or peripheral vascular disease), and including only those who had proteinuria details. All analyses were conducted using Linux SAS version 9.4 (SAS Institute, Cary, NC), and graphs were created using R 3.3.2 (The R Foundation for Statistical Computing, Vienna, Austria) and its rms and cmprsk packages. This study and the CKD registry were both approved by the Cleveland Clinic Institutional Review Board.

Results

Patient characteristics

We included 38,377 patients with CKD stage 3 or 4 (Supplemental Figure 1). The mean age was 71.7 ± 11.2 years, 44.2% were men, and 12% were blacks. Mean BMI of the study cohort was 29.9 ± 6.5 kg/m². Prevalences of diabetes, malignancy, and coronary artery disease were 29.8%, 18.6% and 24.2% respectively. Mean eGFR of the study population was 48.7 ml/min/1.73 m². Mean LDL cholesterol was 98 ± 36 mg/dl and median triglyceride concentration was 127 mg/dl (IQR 90 – 180 mg/dl) and 65.8% of the patient were on statins. Of those included in this analysis, 3,628 (9.5%) had been seen by a nephrologist. Table 1 outlines other details of the study population based on HDL-c categories. Supplemental Table 1 and 2 summarizes these details for men and women separately along with comparing to those who didn't have HDL-C data available.

Mortality—During a median follow up of 4.5 years, 9665 (25%) patients died; cause of death was available for 9,544 patients. Among them, 3667 (38.4%) died of cardiovascular causes, 2059 (21.6%) due to malignancy, 3606 (37.8%) due to non-cardiovascular non-

malignancy diseases and 212 due to other causes. Table 2 shows the causes of death based on HDL-c categories.

HDL-c and overall and cause-specific death

Age-adjusted mortality rates of all-cause and cause-specific deaths in men and women are shown in Table 3. Table 4 outlines the age-adjusted and multivariable associations of HDL-c with all-cause and cause specific deaths in men and women. In the multivariable models adjusted for all relevant confounding variables, HDL-c levels of 31–40 mg/dl and <30 mg/dl (vs. HDL-c 41–50 mg/dl) were associated with higher overall mortality, and with higher sub-distribution hazards for cardiovascular, malignancy and non-cardiovascular non-malignancy mortality in both men and women (Table 4). Compared to HDL-c levels of 41–50 mg/dl, HDL-c >60 mg/dl was associated with a lower risk of all-cause death and each of the specific causes in women only. Figure 1 shows the associations between HDL-c (as a continuous measure) and all-cause mortality in men and women. Figure 2 shows the associations between HDL-c (as a continuous measure) and various cause specific deaths in men and women.

Sensitivity analyses

Excluding patients with history of malignancy at baseline: In the analyses excluding patients with malignancy (n=31,228), results were qualitatively similar to the primary analysis. (Supplemental Table 3).

Adjusting for proteinuria: In the analyses restricting to those who had proteinuria data (n=19,919), inclusion of proteinuria in the multivariable model yielded results similar to the primary analyses (Supplemental Table 4).

Excluding patients with history of cardiovascular disease at baseline: In the analyses excluding patients with cardiovascular disease (n=19,919), results were qualitatively similar to the primary analysis (Supplemental Table 5).

Censoring at initiation of dialysis/transplant: In the analyses that censored patients at initiation of dialysis/transplant (as of September 2009), results were qualitatively similar to the primary analyses (Supplemental Table 6)

Interactions—The interaction between age and HDL-c was significant in women, suggesting that the higher mortality risk associated with HDL-c <30 mg/dl was stronger among women <65 years old (HR 2.50, 95% CI: 1.94, 3.21) compared to those ≥65 years (HR 1.76, 95% CI: 1.53, 2.03). No significant interactions with race, and pre-existing cardiovascular disease were noted among either men or women. The interaction with eGFR was significant for males only, suggesting that HDL-c <30 mg/dl was associated with increased mortality only for those with CKD stage 3a (HR 1.78, 95% CI: 1.56, 2.03) and 3b (HR 1.46, 95% CI: 1.24, 1.74). HDL-c >60 mg/dl was associated with significantly decreased mortality only among CKD stage 4.

Discussion

Lipid abnormalities are common in CKD. In this cohort of non-dialysis dependent CKD population, we noted a U-shaped association between HDL-c and all-cause mortality in women but not in men. HDL-c ≤ 40 mg/dl was associated with higher cardiovascular mortality, malignancy related deaths and non-cardiovascular and non-malignancy-related in men and women. HDL-c >60 mg/dl was associated with lower risk of all-cause and various causes of death only in women. Similar results were noted in the models excluding those with pre-existing malignancy and pre-existing cardiovascular disease.

What does this study add to our knowledge? In those with preserved kidney function, data from the Global Lipids Genetics Consortium (n=188,577) and CKD Genetics Consortium (n=133,814) reported that each 17 mg/dl increase in HDL-c was associated with 0.8% higher eGFR¹⁶. Two large observational studies have addressed the associations between HDL-c and mortality in those with pre-existing CKD but their conclusions differed^{10,11}. In a large cohort of patients undergoing coronary angiography (with varying levels of kidney function), authors noted that HDL-c was associated with lower risk of mortality in those with relatively preserved kidney function. However, in those with eGFR <60 ml/min/1.73 m², such an association was not seen¹⁰. In a cohort of US veterans, Bowe *et al.* reported a U-shaped association between HDL-c and mortality both in those with and without kidney disease, but the reasons for increased death risk with higher levels of HDL-c was unclear¹¹. It is plausible that low HDL-c and its associations with overall death could be attributed to factors such as overall poor physical activity and function status, antecedent illnesses and old age of the CKD population. But systematic analysis of the reasons for death was lacking and our data extend and fill this critical knowledge gap about reasons for death in those with different levels of HDL-c in CKD. Further, we also conducted separate analyses for men and women which highlight potential gender differences for various causes of death.

Current Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guidelines recommend the use of statins for all patients aged >50 years with non-dialysis CKD irrespective of LDL-c levels¹⁷. In the general population, among patients with atherosclerotic cardiovascular disease and LDL cholesterol levels <70 mg/dl, there was no incremental clinical benefit with the addition of niacin (to raise HDL-c) to statin therapy despite significant improvements in HDL-c and triglyceride levels¹⁸. In another trial, addition of extended-release niacin-laropiprant to LDL-c lowering therapy with statins did not significantly reduce the risk of major vascular events¹⁹. A recent meta-analysis also noted no benefit with HDL-raising therapy for primary or secondary prevention of cardiovascular disease²⁰. In a secondary analysis of the AIM-HIGH trial, surprisingly, an increased risk of death was noted in the CKD population treated with niacin²¹. It is important to note that the number of cardiovascular events was similar between the groups in this secondary analysis and hence it is unclear if non-cardiovascular and non-malignancy related deaths accounted for the higher all-cause mortality noted in the treatment arm. Further, only stage 3 CKD patients were included in this study, limiting the generalizability of the results. Also, in the trials that examined the impact of increasing HDL-c levels in the general population, the risk of infections was higher in the treatment group and higher HDL-c could have at least partly contributed to this increased risk (through dysfunctional HDL-

c)¹⁹.. More recently, using a national VA cohort, Bowe *et al* reported a U-shaped association with incident CKD with higher HDL-c associated with higher incidence of incident CKD²². It is important to note that majority of patients included in the analysis by Bowe *et al* were men; we didn't observe a similar increased risks for all-cause and various causes of death among men..

How does current experimental knowledge about HDL-c support the findings from this study? Dyslipidemia in CKD is accompanied by elevated serum triglycerides, lower HDL-c levels and varying levels of LDL-c⁸. Notably, there are qualitative changes in HDL-c. In CKD, HDL particles may fail to mature, leading to impaired HDL-mediated cholesterol uptake from vascular cells.²³ This process of cholesterol extraction from foam cells and eventual excretion into the liver is known as reverse cholesterol transport. It is important to note that cholesterol efflux capacity, a key step in reverse cholesterol transport, was inversely associated with the incidence of cardiovascular events^{24,25}. Hence, our finding that low HDL-c is associated with cardiovascular deaths is logical. Yet dysfunctional HDL-c and its associations with various causes of death merits further studies in those with non-dialysis dependent CKD, as studies in dialysis populations have not shown an association between HDL-c efflux, and cardiovascular events and other events such as graft failure²⁶⁻²⁸. While it is plausible that antecedent malignancy driving low levels of HDL-C rather than low HDL-C levels leading to a malignancy, we noted that the associations between low HDL and malignancy related deaths remained significant adjusting for other confounders.^{29,30}. Further studies addressing this issue are warranted.

Strengths of this analysis include the large population of patients with CKD, with two eGFR <60 ml/min/1.73 m² from a validated CKD registry, and the availability of cause specific death data which help us fill the knowledge gap about reasons for death in those with different levels of HDL-c. However, the study is subject to limitations. These patients were followed in a health care system and had underlying comorbid conditions. Thus, they might differ from CKD patients in the community thereby limiting the generalizability of these findings. We adjusted for several key confounding variables, but lacked hormone replacement therapy and physical activity data which could influence HDL-c levels. Previous population-based studies have reported alcohol as a key confounder; however, due to the nature of the registry, we also lacked details on alcohol consumption^{31,32}. Since the data were derived from a single health care system, future studies should examine whether such associations are present in other CKD cohorts. Proteinuria data were missing for >50% of the study population but a sensitivity analysis restricting it to those with available urinary data showed similar findings. While HDL-c is associated with inflammation³³, we lacked detailed measures of inflammation to more directly adjust for inflammation as a confounding variable. We lacked details of apoA-I levels to explain potential mechanistic pathways between observed associations³⁴. Cause-specific death data were obtained from the State of Ohio Department of Health mortality files which are collected from death certificates. Similar to others, we validated the reliability of cause specific death data for our earlier publications^{35,36}. Despite their limitations, this is the best available resource to study cause specific deaths.

In a non-dialysis dependent CKD population, HDL-c ≥ 40 mg/dl was associated with higher all-cause, cardiovascular, malignancy-related, non-cardiovascular and non-malignancy related deaths in both men and women. HDL-c >60 mg/dl was associated with lower risk of all-cause, cardiovascular, malignancy-related, non-cardiovascular and non-malignancy related deaths in women but not in men. Additional studies examining the reasons for these different associations between HDL-c and cause-specific mortality, and potential effect modification by sex, are needed.

Acknowledgments

The creation of the Cleveland Clinic CKD registry was funded by an unrestricted grant from Amgen, Inc. to the Department of Nephrology and Hypertension Research and Education Fund, Cleveland Clinic. The authors wish to thank eResearch team, Welf Saupe, and Dr. Anil Jain of Cleveland Clinic who helped in data extraction during the development of the registry.

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Highlights

- Associations between HDL-c and mortality vary based on gender in kidney disease.
- Higher levels of HDL-c are associated with lower risk of death in women with CKD.
- Lower levels of HDL-c are associated with higher risk of death in men and women with CKD.

Figure 1. Associations of HDL-c with all-cause mortality in men and women with CKD examined using a Cox proportional hazards model after adjusting for demographics, comorbid conditions, lipid levels, use of statins and kidney function.

Figure 2.

Associations of HDL-c with cause specific deaths in men and women with CKD examined using a competing risk regression model after adjusting for demographics, comorbid conditions, lipid levels, use of statins and kidney function.

Table 1

Patient characteristics by baseline HDL-c level (in mg/dl) in those with CKD

Variable	Overall (N=38377)	30 (N=2463)	31-40 (N=7530)	41-50 (N=10369)	51-60 (N=8223)	>60 (N=9792)	p-value
Age	71.7±11.2	68.8±12.1	70.3±11.2	71.4±11.1	72.6±10.9	73.1±11.2	<0.001 ^a
Male gender, %	44.2	70.2	64.7	49.6	36.5	22.7	<0.001 ^c
African American, %	12.0	7.1	8.7	10.4	12.5	6.9	<0.001 ^c
Smoking							<0.001 ^c
No	81.3	60.6	76.0	82.1	85.1	86.6	
Yes	7.0	9.0	8.6	7.2	5.9	5.9	
Missing	11.7	30.4	15.4	10.7	9.0	7.6	
BMI							<0.001 ^c
<18.5 kg/m ²	0.88	0.53	0.39	0.56	0.72	1.8	
18.5-24.9 kg/m ²	20.4	13.4	13.6	15.8	20.7	32.1	
25-29.9 kg/m ²	34.9	30.2	33.1	35.8	36.3	35.3	
30-34.9 kg/m ²	22.8	25.2	27.3	24.3	22.6	17.1	
35-39.9 kg/m ²	10.4	13.7	12.8	11.7	9.7	6.8	
>40 kg/m ²	7.3	9.5	8.9	8.2	7.2	4.6	
Missing	3.4	7.6	3.9	3.6	2.7	2.3	
eGFR, ml/min/1.73 m ²	48.7±9.8	45.9±11.0	48.0±10.1	48.7±9.9	49.1±9.5	49.5±9.3	<0.001 ^a
eGFR categories							<0.001 ^c
45-59	71.5	61.2	68.9	71.5	73.3	74.5	
30-44	22.1	27.5	23.5	22.0	21.3	20.5	
15-29	6.4	11.3	7.6	6.4	5.4	5.0	
Diabetes, %	29.8	32.4	37.8	33.2	27.9	20.8	<0.001 ^c
Hypertension, %	87.2	66.1	83.6	88.6	90.2	91.5	<0.001 ^c
CAD, %	24.2	26.3	30.9	26.4	23.0	17.3	<0.001 ^c
CHF, %	7.8	11.2	9.9	7.8	6.4	6.5	<0.001 ^c
Cerebrovascular disease, %	10.4	8.4	10.6	10.8	10.8	9.9	0.002 ^c

Variable	Overall (N=38377)	30 (N=2463)	31–40 (N=7530)	41–50 (N=10369)	51–60 (N=8223)	>60 (N=9792)	p-value
Peripheral vascular disease, %	3.7	4.5	4.2	3.8	3.4	3.2	<0.001 ^c
Hyperlipidemia, %	89.0	75.6	87.0	89.4	90.7	91.9	<0.001 ^c
ACEI/ARBs, %	66.6	58.5	70.4	69.4	67.3	62.1	<0.001 ^c
Statin use, %	65.8	52.6	66.3	69.2	69.3	61.9	<0.001 ^c
Beta-Blocker use, %	55.7	56.4	62.1	57.9	55.2	48.5	<0.001 ^c
Diuretic use, %	67.5	58.3	66.3	69.3	68.2	68.2	<0.001 ^c
SBP (mm Hg)	130.2±19.0	127.5±20.2	129.5±19.2	130.0±19.0	130.4±18.7	131.1±18.7	<0.001 ^a
DBP (mm Hg)	73.1±11.0	71.4±11.8	72.7±11.3	73.1±11.0	73.2±10.7	73.5±10.9	<0.001 ^a
Serum albumin	4.1±0.44	3.8±0.61	4.1±0.45	4.1±0.42	4.2±0.39	4.2±0.39	<0.001 ^a
Hemoglobin	13.0±1.7	12.7±2.0	13.1±1.9	13.1±1.8	13.0±1.6	12.9±1.5	<0.001 ^a
Serum triglycerides	127.0[90.0,180.0]	175.0[118.0,263.0]	160.0[113.0,223.0]	138.0[100.0,187.0]	119.0[88.0,162.0]	97.0[73.0,131.0]	<0.001 ^b
Total cholesterol	179.9±45.0	150.5±49.4	164.6±42.1	175.6±42.0	184.3±41.9	199.9±42.0	<0.001 ^a
LDL cholesterol	98.3±36.1	80.9±40.8	90.9±33.7	98.5±35.1	101.7±36.1	103.7±36.0	<0.001 ^a
Proteinuria, %	24.8	34.4	29.1	25.1	22.6	20.1	<0.001 ^c
Malignancy, %	18.6	14.9	18.1	18.8	19.8	18.9	<0.001 ^c
Insurance							<0.001 ^c
Medicaid	0.30	0.41	0.31	0.36	0.26	0.23	
Medicare	79.4	74.1	76.5	78.7	81.5	82.0	
Missing	3.4	6.2	3.7	3.5	3.1	2.7	
Other	16.9	19.3	19.5	17.5	15.2	15.1	

Values presented as mean±SD, percent, or median [P25, P75]

^a ANOVA,

^b Kruskal-Wallis test,

^c Chi-square test

Table 2

Causes of death based on baseline HDL-c level (mg/dl)

	Overall	30	31–40	41–50	51–60	>60
Females	(N=4846)	(N=348)	(N=707)	(N=1183)	(N=1111)	(N=1497)
<i>All Cardiovascular Diseases, (%)</i>	37.5	40.2	35.6	36.9	37.0	38.5
Ischemic Heart Diseases, (%)	17.0	20.7	18.7	16.8	16.2	16.2
Heart Failure, (%)	3.0	4.0	2.7	3.0	3.1	2.7
Cerebrovascular disease, (%)	5.2	4.6	4.1	5.0	5.9	5.7
All Other CV diseases, (%)	12.3	10.9	10.2	12.1	11.9	14.0
<i>Malignant Neoplasms, (%)</i>	20.0	18.7	21.1	19.9	21.0	19.0
<i>Non-cancer Non-malignancy, (%)</i>	40.6	40.2	40.9	41.2	40.1	40.5
Chronic lower respiratory diseases, (%)	5.7	6.3	6.1	5.5	5.3	5.9
Diabetes mellitus, (%)	5.1	7.5	6.6	6.5	4.7	3.0
Nephritis, nephrotic syndrome and nephrosis, (%)	2.3	0.57	3.1	2.7	1.9	2.2
Alzheimer's disease, (%)	3.1	1.4	1.7	3.4	3.6	3.5
Influenza and pneumonia, (%)	1.8	2.0	2.0	2.4	1.5	1.5
Septicemia, (%)	2.1	2.0	2.3	2.1	2.2	2.1
Chronic liver disease and cirrhosis, (%)	0.99	2.9	1.6	0.93	0.18	0.94
Pneumonitis due to solids and liquids, (%)	0.74	1.1	0.71	0.68	1.3	0.33
Parkinson's disease, (%)	0.31	0.0	0.28	0.34	0.27	0.40
All other diseases, (%)	18.4	16.4	16.5	16.7	19.3	20.6
Non-Disease related deaths, (%)	1.9	0.86	2.4	2.0	1.9	1.9
Males	(N=4698)	(N=644)	(N=1306)	(N=1310)	(N=805)	(N=633)
<i>All Cardiovascular Diseases, (%)</i>	39.4	41.1	43.0	39.2	35.8	35.4
Ischemic Heart Diseases, (%)	22.5	26.9	25.5	22.5	17.8	18.0
Heart Failure, (%)	3.0	2.8	2.9	3.0	3.2	3.0
Cerebrovascular disease, (%)	3.8	2.3	4.4	3.4	4.1	4.4
All Other CV diseases, (%)	10.1	9.2	10.2	10.2	10.7	10.0
<i>Malignant Neoplasms, (%)</i>	23.2	23.6	23.6	22.4	23.5	23.4
<i>Non-cancer Non-malignancy, (%)</i>	34.9	33.5	30.9	35.7	37.8	39.0

	Overall	30	31–40	41–50	51–60	>60
Females	(N=4846)	(N=348)	(N=707)	(N=1183)	(N=1111)	(N=1497)
Chronic lower respiratory diseases, (%)	4.4	3.0	3.8	4.1	5.1	7.0
Diabetes mellitus, (%)	5.1	6.8	4.9	5.1	5.3	3.6
Nephritis, nephrotic syndrome and nephrosis, (%)	2.8	2.8	2.6	3.1	3.0	2.2
Alzheimer's disease, (%)	1.3	0.47	0.77	1.4	1.2	2.8
Influenza and pneumonia, (%)	2.0	2.2	1.6	2.1	2.5	2.2
Septicemia, (%)	1.7	2.0	1.7	2.0	1.4	1.6
Chronic liver disease and cirrhosis, (%)	0.81	1.6	0.54	0.61	0.75	1.1
Pneumonitis due to solids and liquids, (%)	1.1	0.93	0.92	1.3	1.1	1.4
Parkinson's disease, (%)	0.68	0.16	0.61	0.99	0.62	0.79
All other diseases, (%)	14.9	13.7	13.4	15.1	16.8	16.3
Non-Disease related deaths, (%)	2.5	1.7	2.6	2.7	3.0	2.2

Table 3

Age-adjusted mortality per 1,000 years

HDL (mg/dl)	Female Estimate (95% CI)	Male Estimate (95% CI)
<u>All-cause</u>		
30	110 (99, 122)	89 (83, 96)
31–40	56 (52, 60)	58 (55, 62)
41–50	46 (44, 49)	52 (49, 55)
51–60	40 (38, 43)	52 (49, 56)
60	36 (34, 38)	56 (52, 61)
<u>Cardiovascular</u>		
30	40 (34, 47)	35 (31, 39)
31–40	18 (16, 20)	23 (21, 25)
41–50	15 (14, 16)	19 (17, 21)
51–60	13 (11, 14)	17 (15, 19)
60	12 (11, 13)	18 (16, 20)
<u>Malignancy</u>		
30	21 (17, 27)	21 (18, 25)
31–40	12 (11, 15)	14 (12, 16)
41–50	10 (9, 11)	12 (11, 13)
51–60	9 (8, 11)	13 (11, 15)
60	8 (7, 9)	13 (11, 16)
<u>Non-cardiovascular non-malignancy</u>		
30	44 (38, 52)	30 (27, 35)
31–40	23 (21, 26)	18 (17, 20)
41–50	19 (17, 21)	19 (18, 21)
51–60	16 (15, 18)	21 (18, 23)
60	15 (14, 16)	23 (20, 26)

Mortality rates adjusted to mean age of 72 for females, and mean age of 71 for males

Table 4

Associations of HDL-c (in mg/dl) with all-cause and cause-specific deaths in men and women with CKD.

HDL level	Women			Men		
	N/N events	HR (95% CI)*	HR (95% CI)**	N/N events	HR (95% CI)*	HR (95% CI)**
<u>All-cause death</u>						
30	735/352	2.24 (1.99, 2.52)	1.93 (1.70, 2.18)	1728/652	1.70 (1.55, 1.87)	1.55 (1.41, 1.72)
31–40	2658/712	1.20 (1.09, 1.32)	1.14 (1.03, 1.25)	4872/1320	1.12 (1.04, 1.21)	1.08 (1.00, 1.17)
41–50	5227/1201	ref	ref	5142/1322	ref	ref
51–60	5222/1133	0.85 (0.79, 0.93)	0.86 (0.80, 0.94)	3001/814	0.99 (0.91, 1.08)	0.99 (0.90, 1.08)
60	7570/1517	0.76 (0.70, 0.81)	0.75 (0.69, 0.81)	2222/642	1.04 (0.95, 1.15)	0.97 (0.88, 1.07)
<u>Cardiovascular death[^]</u>						
30	731/140	2.27 (1.86, 2.77)	1.80 (1.46, 2.21)	1720/265	1.67 (1.44, 1.95)	1.46 (1.24, 1.72)
31–40	2653/252	1.18 (1.01, 1.38)	1.10 (0.94, 1.29)	4858/561	1.23 (1.09, 1.39)	1.17 (1.03, 1.32)
41–50	5209/436	ref	ref	5130/513	ref	ref
51–60	5200/411	0.86 (0.75, 0.98)	0.88 (0.76, 1.00)	2992/288	0.89 (0.77, 1.02)	0.91 (0.79, 1.05)
60	7550/577	0.80 (0.71, 0.91)	0.82 (0.71, 0.93)	2213/224	0.92 (0.79, 1.08)	0.90 (0.76, 1.06)
<u>Malignancy death[^]</u>						
30	731/65	1.89 (1.44, 2.49)	1.81 (1.34, 2.43)	1720/152	1.63 (1.34, 1.98)	1.67 (1.35, 2.06)
31–40	2653/149	1.24 (1.01, 1.52)	1.21 (0.98, 1.50)	4858/308	1.15 (0.98, 1.35)	1.17 (0.99, 1.37)
41–50	5209/236	ref	ref	5130/294	ref	ref
51–60	5200/233	0.96 (0.80, 1.15)	0.94 (0.79, 1.14)	2992/189	1.07 (0.89, 1.28)	1.03 (0.85, 1.24)
60	7550/285	0.81 (0.68, 0.96)	0.77 (0.64, 0.94)	2213/148	1.14 (0.94, 1.39)	1.10 (0.89, 1.35)
<u>Non-cardiovascular non-malignancy death[^]</u>						
30	731/140	1.92 (1.58, 2.33)	1.65 (1.34, 2.03)	1720/216	1.43 (1.21, 1.68)	1.27 (1.06, 1.51)
31–40	2653/289	1.18 (1.02, 1.36)	1.09 (0.93, 1.26)	4858/403	0.94 (0.83, 1.08)	0.90 (0.79, 1.03)
41–50	5209/487	ref	ref	5130/468	ref	ref
51–60	5200/446	0.85 (0.75, 0.97)	0.89 (0.78, 1.01)	2992/304	1.07 (0.92, 1.23)	1.08 (0.94, 1.25)
60	7550/606	0.78 (0.69, 0.88)	0.82 (0.72, 0.94)	2213/247	1.16 (0.99, 1.35)	1.11 (0.94, 1.31)

* Model adjusted for age

** Model adjusted for age, AA, eGFR, diabetes, hypertension, history of cardiovascular disease (coronary artery disease, congestive heart failure, cerebrovascular disease, peripheral vascular disease), malignancy, BMI group, statin use, log triglycerides and smoking