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Serum triglycerides and mortality risk across stages of chronic kidney disease in 2 million U.S. veterans

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KEYWORDS:
Mortality;
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BACKGROUND: In the general population, elevated triglyceride (TG) levels are an important risk factor for cardiovascular disease and mortality. However, in chronic kidney disease, the association of serum TGs with mortality is less clear.

OBJECTIVE: We sought to examine the association of TGs with mortality across chronic kidney disease (CKD) stages in a large cohort of U.S. veterans.

METHODS: We examined 2,086,904 U.S. veterans with a TG measurement obtained between a baseline period of October 2004 and September 2006, with follow-up until December 2014 (median [interquartile range {IQR}]: 9.2 [6.5, 9.9] years). Associations of TGs with all-cause and cardiovascular mortality across CKD stages were evaluated using Cox proportional hazard models.

RESULTS: Patients were 64 ± 14 years old with a median (IQR) baseline TG of 129 [88, 193] mg/dL and estimated glomerular filtration rate of 76 [61, 91] mL/min/1.73 m^2. More advanced CKD was associated with higher odds of TGs ≥ 240 mg/dL. Low levels of TGs < 80 mg/dL were associated with a higher risk of mortality across all stages, whereas TG levels ≥ 240 mg/dL were only associated with a higher risk of all-cause mortality in non-CKD and CKD stages 3A, 3B, and 4 (reference: TG 120 to <160 mg/dL). The relationship of higher TGs with mortality incrementally attenuated across worsening stages of CKD and attenuated to the null among patients with CKD stage 5/end-stage renal

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disease. Similar results were observed for cardiovascular mortality, in strata by age and diabetes, and further adjustment for high-density lipoprotein and low-density lipoprotein.

CONCLUSION: Associations of elevated TGs with all-cause and cardiovascular mortality were incrementally attenuated across more advanced stages of CKD.
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Introduction

Elevated serum triglycerides (TGs) are a known marker of cardiovascular risk in the general population.[1–3] Mendelian randomization studies further corroborate a potential causal relationship between circulating TGs and atherogenesis by demonstrating an association linking genes determining higher TG levels and coronary heart disease (CHD),[4] and thereby indicate that TGs should be considered as an important cardiovascular risk factor and potential treatment target. A prior study showed that TG levels are elevated in patients with chronic kidney disease (CKD) and increase with advancing disease.[5] Moreover, it has been shown that elevated TGs in CKD is explained by the potential dysregulation of lipid metabolism.[6–8] However, despite the abundant evidence linking CKD to TG dysmetabolism, it is still unclear how elevated TG levels in CKD impact outcomes and translate to cardiovascular endpoints in this population. A better understanding of this relationship may lead to insight of how to address elevated TGs in patients with CKD.

Patients with CKD have an elevated risk of mortality, in which over half of deaths are attributed to cardiovascular disease.[9] It is known that both all-cause and cardiovascular mortality risks increase with advancing CKD.[10] Yet, it is unknown if TG levels are a contributor to the higher all-cause and cardiovascular mortality risks observed across all advancing CKD stages. Prior studies examining the relationship between TGs and mortality outcomes in patients with CKD have shown conflicting results,[11–13] and one study suggested that the TG-mortality relationship in CKD may be age dependent.[11] These studies have primarily examined associations of TGs with mortality in patients with nondialysis-dependent CKD (NDD-CKD) as a collective cohort or in dialysis patients alone.[14–16] However, associations of TGs with mortality have not been evaluated across incrementally advancing CKD stages in a single large cohort. Thus, we hypothesize that the association of elevated TGs with mortality is impacted by advancing stages of CKD.

Material and methods

Study population and data source

LIPROVET (Lipid profiles and management in veterans with CKD) is a retrospective cohort study derived from administrative data sourced by the United States Veterans Affairs (VA) databases. It is composed of all veteran patients who received at least one serum lipid (TG or high-density lipoprotein [HDL], low-density lipoprotein [LDL], or total cholesterol) measurement between the baseline period of October 1, 2004 and September 30, 2006. Patients were followed until December 31, 2014. In the present study, patients were further excluded for missing a TG measurement during baseline, missing an estimated glomerular filtration rate (eGFR) measured within 90 days before the TG measurement, and missing information on censoring. Our final cohort comprised 2,086,904 veteran patients with a TG measurement (Fig. S1).

This study has been approved by the institutional review board of the Tibor Rubin VA Medical Center in Long Beach, CA. The required written consent was waived because of the large sample size, patient anonymity, and nonintrusive nature of the research.

Demographics and clinical measurements

All baseline clinical characteristics were extracted from the combination of VA and Centers for Medicare and Medicaid Services (CMS) databases, with additional supplementation from the United States Renal Data System (USRDS) databases. VA databases solely provided data on marital and smoking status.[17]

Lipid-modulating therapies were predominantly extracted from VA pharmacy records with supplementation from CMS Medicare Part D, using specific drug class codes and names for classification. Statin or nonstatin therapy was defined as having the specific prescription at the time of the TG measurement.

Comorbidity at the time of the TG measurement, including the Deyo Charlson Comorbidity Index (CCI), was derived from combined VA and CMS data sets, using a 2 outpatient or 1 inpatient algorithm of International Classification of Diseases, Ninth Revision (ICD-9) Diagnostic and Current Procedural Terminology codes.[18,19] ICD-9 codes were guided by those included in the Deyo CCI calculation, CMS chronic conditions, and prior studies.[18,20,21]

Laboratory measurements, including the lipid panel, were obtained from the VA Managerial Cost Accounting System Laboratory Results. LDL was also calculated using the Friedewald[22] equation from other lipid measurements taken on the same day, only among patients initially missing an LDL measurement. Other laboratory measurements, including serum creatinine, were obtained from the VA Corporate Data Warehouse LabChem file. The Chronic Kidney Disease Epidemiology Collaboration formula was used to calculate eGFR, which was categorized

into CKD stages (non-CKD, 3A, 3B, 4, and 5) at the time of TG measurement, according to Kidney Disease Improving Global Outcomes guidelines.[23] Patients identified as with end-stage renal disease (ESRD) on renal replacement therapy according to the USRDS records at the time of TG measurement were classified as CKD stage 5, irrespective of eGFR level. Finally, data on body mass index (BMI) and blood pressure were obtained from the VA Corporate Data Warehouse Vital Signs file.[24] For all analyses, the closest single measurement within 90 days before the TG measurement was used.

Exposure measurement

The primary exposure was a single measurement of TGs, categorized into the following groups: <80, 80 to <120, 120 to <160 (reference), 160 to <200, 200 to <240, and ≥ 240 mg/dL, based on the distribution of the cohort, and clinically relevant cut points.

Outcome assessment

The primary outcomes were all-cause and cardiovascular mortality. Censoring for death and lost to follow-up were extracted from VA, National Death Index, CMS, and USRDS data sets. Lost to follow-up was determined by the last date of active use of VA or CMS services (inpatient, outpatient, or pharmacy). Cause of death was obtained from the National Death Index only and was categorized by specific ICD-10 codes for cardiovascular reasons of death (Table S1). Patients were followed up from the date of TG measurement to death, lost to follow-up, or December 31, 2014, whichever occurred first.

Statistical analysis

Patient characteristics were presented as mean (±standard deviation), median (interquartile range [IQR]), or proportion, where appropriate, and across TG groups and CKD stages. Multinomial logistic regression models were used to examine the odds of low TGs (<120 mg/dL) or high TGs (≥240 mg/dL) vs moderate TGs (120 to <240 mg/dL, reference).

Cox proportional hazard models were used to examine the association of TGs with all-cause or cardiovascular mortality stratified by CKD stage. For each CKD stage, TGs 120 to <160 mg/dL was used as the reference.

For our analyses, 4 models were used with hierarchical adjustments: (1) unadjusted, (2) age adjusted, which included age, (3) case-mix adjusted, which included age, gender, race, ethnicity, and the following comorbid conditions: smoking status, CCI, myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, chronic pulmonary disease, dementia, liver disease, cancer, diabetes, atrial fibrillation, hypertension, depression and ischemic heart disease, use of statin therapy, use of nonstatin lipid-lowering drug therapy, and (4) case-mix + lab adjusted, which included the case-mix covariates as well as additionally adjusted for BMI and albumin and we identified as our fully adjusted model. In sensitivity analysis, we further adjusted for HDL and LDL in our case-mix + lab–adjusted model. Adjusted Wald's tests were performed to evaluate the interaction between TGs and CKD stage.

We also used restricted cubic splines to examine the association of continuous TGs with mortality within CKD stage, with best placed knots at the 5th, 35th, 65th, and 95th percentile of TGs per CKD stage. In subgroup analyses, we examined the TGs and mortality association across CKD stage within strata of age and diabetes comorbidity, as well as in males only. In addition, using restricted cubic splines with best-placed knots for eGFR, we evaluated the odds of high or low TGs compared with moderate TGs across continuous eGFR among those not with ESRD (n = 2,074,884) and evaluated the mortality risk associations of low vs moderate TGs and high vs moderate TGs across continuous eGFR in a NDD-CKD (eGFR<60 mL/min/1.73 m^2, n = 496,067) cohort.

Data were missing for <1.4% and 4.2% of the baseline cohort for demographics and smoking status, respectively, and were imputed using a missing category. Baseline albumin and BMI data were missing for 27% and 11%, respectively, and were imputed using means. Data for other laboratory markers were missing at a similar rate. All analyses were performed using SAS Enterprise Guide (7.1) (Cary, NC) and Stata/MP Version 14 (College Station, TX).

Results

The patient cohort was 64 ± 14 years of age, 5% female, and 15% African-American (Table 1). The median [IQR] TG level was 129 [88, 193] mg/dL, along with a median [IQR] lipid panel of 177 [152, 206], 42 [35, 51], and 103 [81, 128] mg/dL for total cholesterol, HDL, and LDL, respectively. The cohort eGFR was 76 [61, 91] mL/min/1.73 m^2, and only 0.8% of the cohort were CKD stage 5 (eGFR <15 mL/min/1.73 m^2) or with ESRD on renal replacement therapy at the time of TG measurement. Among 508,087 patients with CKD, the mean age was 74 ± 10 years and included 3% females and 10% African-Americans (Table S2). The median [IQR] TG level was 133 [93, 196] mg/dL and eGFR was 49 [41, 55] mL/min/1.73 m^2 in this subcohort.

In the total cohort, patients with higher TGs tended to be younger, white, and with a lower prevalence of chronic pulmonary obstructive disorder and anemia, yet a higher proportion of diabetes, depression, post-traumatic stress disorder, current smokers, and nonstatin users. Patients with higher TGs also had a greater BMI and total cholesterol, yet lower HDL.

Compared to non-CKD patients, patients with CKD stages 3A, 3B, 4, and 5/ESRD had a 16%, 29%, 39%, and 11% higher odds of having high TGs ≥ 240 mg/dL, respectively, and a 19%, 29%, 34%, and 32% lower odds of

Table 1 Baseline characteristics of 2,086,904 patients stratified by serum triglycerides level

Characteristic		Serum triglycerides (mg/dL)					
	Total	<80	80–<120	120–<160	160–<200	200–<240	≥240
N (%)	2,086,904	406,564 (19.5%)	531,643 (25.5%)	402,160 (19.3%)	261,928 (12.6%)	164,596 (7.9%)	320,013 (15.3%)
CKD stage (%)							
Non-CKD	76	79	75	74	74	74	75
3A	15	13	15	16	16	16	15
3B	7	5	7	7	7	7	7
4	2	1	2	2	2	2	2
5/ESRD	0.8	0.7	0.8	0.8	0.8	0.8	0.8
eGFR (mL/min/1.73 m^2)*	76 [61, 91]	79 [64, 94]	75 [61, 90]	74 [60, 89]	74 [60, 89]	74 [59, 90]	76 [61, 92]
Age (y)	64 ± 14	64 ± 15	65 ± 14	64 ± 13	63 ± 13	63 ± 13	60 ± 13
Gender (%female)	5	7	5	5	4	4	4
Married (%)	56	53	56	57	57	57	55
Race (%)							
White	82	74	80	83	85	86	86
African-American	15	23	16	13	11	10	9
Other	4	3	4	4	4	4	5
Ethnicity (%)							
Hispanic	4	3	4	4	4	4	4
CCI	1 [0, 2]	1 [0, 2]	1 [0, 2]	1 [0, 2]	1 [0, 2]	1 [0, 2]	1 [0, 2]
Comorbid conditions (%)							
MI	6	6	7	7	7	7	6
CHF	10	11	10	10	10	10	10
PVD	10	9	10	10	10	9	9
Cerebrovascular disease	9	8	9	9	9	8	8
Dementia	3	3	3	3	2	2	2
COPD	18	20	19	18	17	17	16
Rheumatologic disease	2	2	2	2	2	2	2
Renal disease	6	6	6	6	6	7	7
Liver disease	3	4	3	3	3	3	3
Diabetes	29	21	25	29	32	34	39
Cancer	12	12	13	12	12	11	10
Anemia	11	14	12	11	10	10	9
Atrial fibrillation	7	8	7	7	6	6	5
Hyperlipidemia	53	42	51	55	57	58	59
Hypertension	65	59	65	67	68	68	68
ISHD	27	25	28	28	28	28	27
Depression	18	15	16	17	18	20	22
Anxiety	12	10	11	12	12	13	15
Substance abuse	7	8	7	6	6	6	7
PTSD	7	6	6	7	7	8	10

(*continued on next page*)

Table 1 (*continued*)

Characteristic	Serum triglycerides (mg/dL)						
	Total	<80	80–<120	120–<160	160–<200	200–<240	≥240
Smoking (%)							
Never	29	31	30	29	28	28	26
Current	44	42	42	43	44	45	48
Past	27	26	28	28	28	27	26
Laboratory measurements							
Albumin (g/dL)	4.1 ± 0.4	4.0 ± 0.5	4.0 ± 0.4	4.1 ± 0.4	4.1 ± 0.4	4.1 ± 0.4	4.1 ± 0.4
ALP (U/L)	74 [61, 90]	72 [59, 88]	74 [61, 90]	74 [61, 90]	75 [61, 91]	75 [62, 91]	76 [62, 93]
BUN (mg/dL)	17.8 ± 8.9	17.2 ± 8.8	17.7 ± 8.8	17.9 ± 8.7	18.0 ± 8.8	18.1 ± 8.9	18.1 ± 9.2
Glucose (mg/dL)	115.4 ± 44.8	105.7 ± 32.5	109.9 ± 36.2	114.1 ± 40.7	117.8 ± 44.9	121.3 ± 49.0	133.3 ± 64.3
Hemoglobin (g/dL)	14.4 ± 1.7	14.0 ± 1.7	14.3 ± 1.7	14.5 ± 1.6	14.6 ± 1.6	14.7 ± 1.6	14.8 ± 1.6
WBC (x $10^3/mm^3$)	7.2 ± 2.8	6.7 ± 2.7	7.1 ± 2.8	7.3 ± 2.8	7.5 ± 2.8	7.5 ± 2.8	7.6 ± 2.8
SBP (mmHg)	135 ± 19	133 ± 20	134 ± 19	135 ± 19	135 ± 19	135 ± 19	136 ± 19
DBP (mmHg)	75 ± 12	74 ± 12	75 ± 12	75 ± 12	76 ± 12	76 ± 12	77 ± 12
BMI (kg/m^2)	29 ± 6	27 ± 5	28 ± 6	30 ± 6	30 ± 6	31 ± 6	31 ± 6
Lipid panel (mg/dL)							
Triglycerides	129 [88, 193]	63 [53, 72]	99 [89, 109]	138 [128, 148]	177 [168, 188]	217 [208, 228]	313 [269, 400]
HDL	42 [35, 51]	50 [42, 62]	44 [37, 53]	41 [35, 49]	39 [33, 46]	38 [32, 44]	35 [30, 42]
Cholesterol	177 [152, 206]	163 [140, 188]	170 [147, 196]	176 [153, 204]	182 [158, 210]	187 [162, 215]	201 [173, 233]
LDL	103 [81, 128]	97 [78, 119]	104 [84, 128]	107 [85, 132]	107 [85, 134]	106 [83, 133]	99 [73, 128]
Lipid-modulating therapy use (%)							
Statin	33	27	33	35	35	35	33
Ezetimibe	0.4	0.3	0.3	0.4	0.4	0.5	0.5
Nonstatin	6	3	4	5	6	8	11
Fibrate	3	1	2	3	4	5	8
Niacin	2	1	1	2	2	2	3
Fish oil	0.1	0.1	0.1	0.1	0.2	0.2	0.3
Bile acid sequestrants	0.4	0.2	0.4	0.4	0.5	0.5	0.6

Data presented as mean ± standard deviation, median [interquartile range], or percentage, as appropriate.

ALP, alkaline phosphatase; BMI, body mass index; BUN, blood urea nitrogen; CCI, Charlson Comorbidity Index; CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disorder; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HDL, high-density lipoprotein; ISHD, ischemic heart disease; LDL, low-density lipoprotein; MI, myocardial infarction; PTSD, post-traumatic stress disorder; PVD, peripheral vascular disease, SBP, systolic blood pressure; WBC, white blood cell count.

*eGFR provided for only patients classified as CKD stage 5, yet not on ESRD.

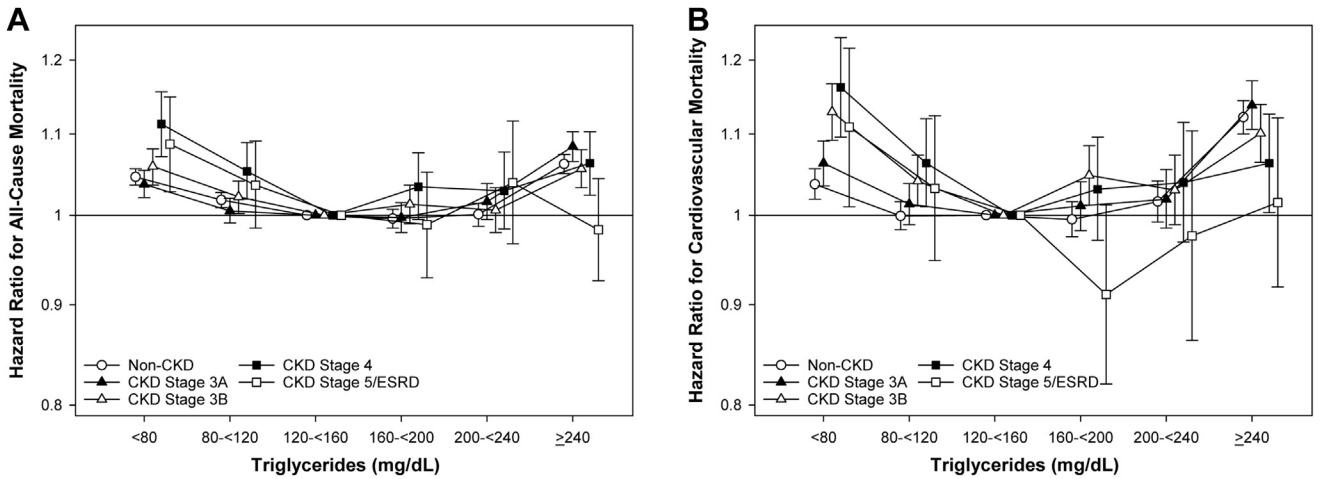

Figure 1 Association of serum triglycerides with (A) all-cause and (B) cardiovascular mortality stratified by CKD stage after case-mix + lab adjustment. CKD, chronic kidney disease; ESRD, end-stage renal disease.

having low TGs < 120 mg/dL, respectively, in case-mix + lab–adjusted models compared with moderate TGs 120 to <240 mg/dL (Table S3). Restricted cubic splines examining the association of continuous eGFR with odds of low or high TGs vs moderate TGs showed similar results (Fig. S2).

Association of serum triglycerides with all-cause and cardiovascular mortality

A total of 726,992 all-cause and 246,530 cardiovascular-related deaths occurred over a median [IQR] follow-up of 9.2 [6.5, 9.9] years for a crude rate of 44.4 [44.3, 44.5] all-cause deaths and 15.1 [15.0, 15.1] cardiovascular deaths per 1000 person-years. Crude all-cause and cardiovascular death rates increased with advancing CKD stages (Table S4). In case-mix adjusted models, the association of TGs with all-cause and cardiovascular mortality appeared to be reverse J-shaped for non-CKD, stage 3A, 3B, and 4 patients (Tables S5 and S6). The relationship then assumed a more U-shaped association after additional adjustment for laboratory covariates. However, the strength of the association between high TGs (≥240 mg/dL) with all-cause and cardiovascular mortality risk appeared to decrease across

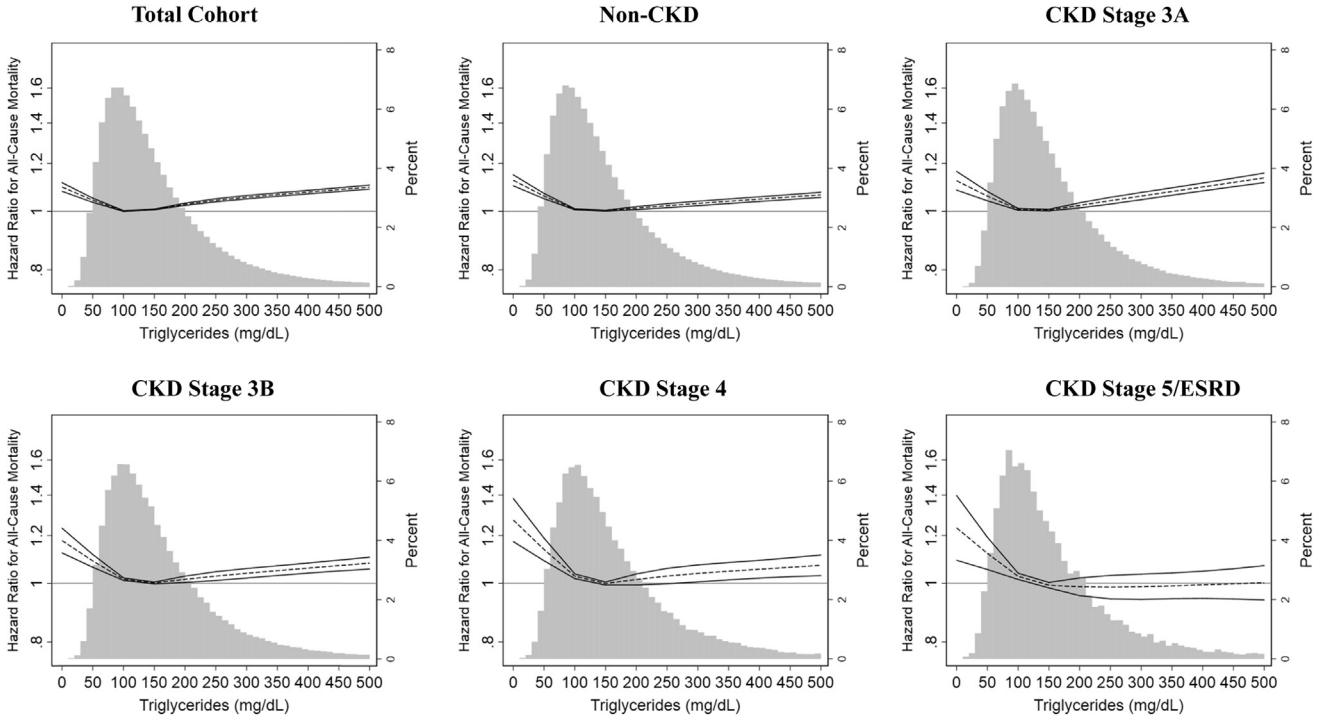

Figure 2 Restricted cubic splines of serum triglycerides with all-cause mortality across CKD stages after case-mix + lab adjustment. CKD, chronic kidney disease; ESRD, end-stage renal disease.

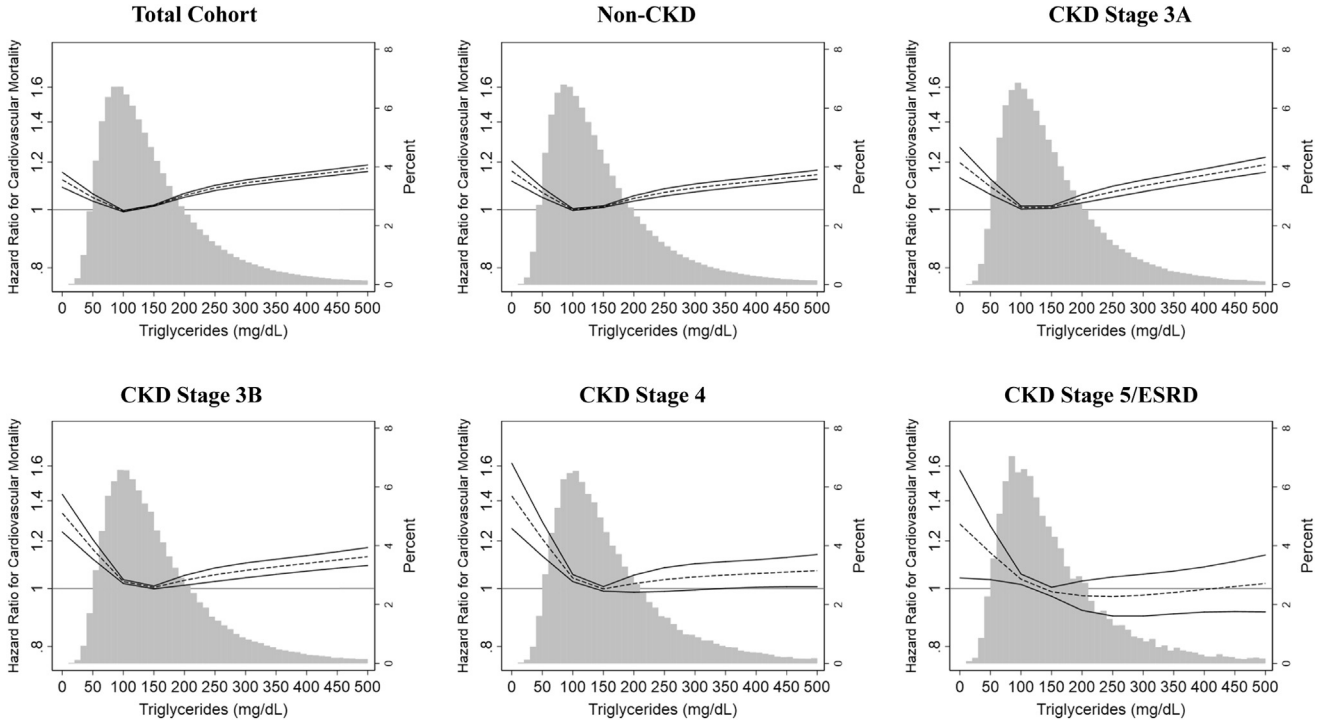

Figure 3 Restricted cubic splines of serum triglycerides with cardiovascular mortality across CKD stages after case-mix + lab adjustment. CKD, chronic kidney disease; ESRD, end-stage renal disease.

worsening stages of CKD (*P*-interaction: <0.0001, Fig. 1, Tables S5 and S6). Notably, among CKD stage 5/ESRD patients, TGs ≥ 240 mg/dL were associated with a lower risk of mortality compared to TGs 120 to <160 mg/dL in the age and case-mix adjusted model, but after additional adjustment for BMI and albumin, the high TG-mortality relationship was null in these CKD stage 5/ESRD patients. Conversely, low TGs < 80 mg/dL were consistently associated with a higher risk of all-cause and cardiovascular mortality across CKD stages and all models of adjustment. Results were similar as illustrated by restricted cubic splines examining the association of continuous TGs with mortality outcomes in case-mix + lab–adjusted models, where the risk of mortality with higher TGs was null among CKD stage 5/ESRD patients (Figs. 2 and 3). Furthermore, among patients with NDD-CKD, the effect of worsening eGFR on the association of high TGs vs moderate TGs with all-cause and cardiovascular mortality is demonstrated in Figure S3B and S3D, where the strength of the associations decreased around an eGFR of 40 mL/min/1.73 m^2. The associations of low vs moderate TGs with all-cause and cardiovascular mortality risk were slightly higher across continuous levels of eGFR (Fig. S3A and S3C).

Subgroup analyses

Associations of TGs with all-cause and cardiovascular mortality across CKD stage were similar in strata of diabetes and age (<65 vs ≥ 65 years) for all-cause (Table S7) and cardiovascular mortality (Table S8). Although, for CKD stage 5/ESRD, low TGs (<80 mg/dL) were associated with a higher mortality risk in patients <65 years; however, there was no difference in mortality risk for low TGs vs the referent in patients aged ≥65 years. Similar associations were evident when examining only male veterans.

Discussion

In a large national cohort of veteran patients, we observed that patients with CKD had a greater odds of having higher TGs (≥240 mg/dL) independent of BMI, age, and comorbidities compared with moderate TGs (120 to <240 mg/dL). We also observed that high TGs ≥ 240 mg/dL levels were associated with a higher risk of all-cause and cardiovascular mortality among non-CKD, stage 3A, 3B, and 4 patients, where the relationship was attenuated among CKD stage 5 and ESRD patients in models adjusted for demographics, comorbidities, lipid-altering therapies, BMI, and albumin. Low TGs < 80 mg/dL levels were also associated with a higher risk of all-cause and cardiovascular mortality across CKD stages. These relationships were consistent under restricted cubic splines analyses and across sensitivity analyses including stratification by age and diabetes, as well as among male veterans.

Elevated TG levels in patients with CKD compared with non-CKD patients have been demonstrated in prior studies.[25,26] In a previous cohort study, more advanced CKD stages were associated with a higher odds of hypertriglyceridemia defined as TGs ≥ 150 mg/dL[5], where CKD stage 4 or 5 patients had a 2.5 times higher odds of

hypertriglyceridemia compared with CKD stage 1. In addition, mechanisms responsible for dysregulation of lipoprotein metabolism leading to hypertriglyceridemia in CKD have previously been characterized.[7,8,27] These mechanisms suggest that a major cause of hypertriglyceridemia in CKD is due to the deficient activity of enzymes involved in the metabolism of the TG-rich lipoproteins, thereby allowing a longer circulatory life span for these particles. In our study, odds of high TGs, defined as TGs $\geq$ 240 mg/dL, were also higher in advanced CKD stages compared with non-CKD patients in models adjusted for demographics, comorbidities, and laboratory markers of nutritional status.

Despite elevated TGs among patients with CKD, studies investigating the associations between TGs and mortality or cardiovascular outcomes in CKD have had conflicting results and were also limited by small size or residual confounding. Kovesdy et al.[12] found no association between TG quartiles and all-cause or cardiovascular mortality risk in a cohort of 986 NDD-CKD male veterans with models adjusted for case-mix variables plus surrogates of the malnutrition-inflammation-cachexia syndrome. Similar findings were observed in a community-based cohort of 1249 elderly patients with CKD.[28] Chawla et al. also examined TG-mortality associations in 840 younger (mean age: 52 $\pm$ 12 years) NDD-CKD patients with fewer comorbidities (5% diabetics)[13] and found no difference in all-cause and cardiovascular mortality risk across TG tertiles.

Alternatively, another small cohort of 807 patients with CKD from the Atherosclerosis Risk in Communities Study showed a positive association between TGs and a composite CHD outcome, although they did not find differences in association across CKD stage.[29] The CKD stage stratified analysis, however, only adjusted for four demographic variables and therefore may be subject to residual confounding, as associations of log TG level with the CHD outcome in the study were attenuated after additional adjustment for comorbid conditions. In our study, higher TG levels were associated with both all-cause and cardiovascular mortality in patients with CKD even after adjustment for a number of potential confounders. In addition, we found that higher TG and mortality associations were modified and incrementally attenuated across worsening CKD stages.

In our study, we also found no effect modification by age group in associations of TGs with mortality across CKD 3A-4 stages. Our findings contrast a prior study by Navaneethan et al.[11] who examined TG-mortality associations in 25,641 Cleveland Clinic NDD-CKD (stages 3 and 4) patients. The authors found TGs were associated with all-cause mortality in patients younger than 65 years but not in older patients ($\geq$65 years old). However, their findings in their younger patients may have been driven by the lower mortality risk observed for patients with lower TGs. While in our cohort, lower TGs were associated with higher all-cause and cardiovascular mortality risk in both younger and older NDD-CKD stage 3 and 4 patients. A trend toward higher all-cause mortality risk for lower TGs has also been observed in a prior veteran cohort.[12] It should be noted that younger VA patients may not be representative of the general population younger than 65 years, such as those treated at the Cleveland Clinic. These younger VA patients are eligible for VA health care due to military service, which may have led to the development of conditions not commonly present in the general younger male population. Therefore, lower TGs observed in our younger patients may represent malnutrition rather than a healthy lipid profile, thus leading to the higher observed mortality rates for lower TGs in our study.

In our cohort, higher TGs were associated with lower mortality risk in CKD stage 5/ESRD patients, which included a majority already on renal replacement therapy (n = 12,020), but the relationship was attenuated to the null in models with adjustment for laboratory measurements including albumin, an important marker of malnutrition and inflammation.[30,31] Low TG levels were associated with higher mortality risk in younger CKD stage 5/ESRD patients; however, there was no association between low TGs and mortality present for older CKD stage 5/ESRD patients.

Prior studies of hemodialysis patients have also shown that higher TGs trended toward[14,15] or were associated[16] with a paradoxically lower mortality risk in case-mix–adjusted models, whereas lower TGs were associated with a higher mortality risk. However, associations for higher TGs were attenuated toward the null in models adjusted for malnutrition-inflammation-cachexia syndrome covariates.[14] Liu et al.[31] hypothesized that malnutrition and inflammation in patients with ESRD may explain this inverse association between lipid markers and mortality in dialysis patients. While they also showed an inverse association between cholesterol and mortality in U.S. dialysis patients overall, they reported a positive cholesterol-mortality relationship in 189 dialysis patients without malnutrition and inflammation. Another study[32] similarly found that higher cholesterol levels were associated with a higher death risk in a subgroup of 128 Japanese dialysis patients with albumin $\geq$4.5 g/dL but not in subgroups with lower albumin levels. Conversely, some authors have criticized that these analyses based on small subsets of patients without inflammation or malnutrition may not be generalizable to all dialysis patients, who are typically afflicted with these conditions.[33,34] Previous studies have not observed effect modification on TG-mortality associations in dialysis patients on the basis on age; however, older patients with ESRD may have a higher prevalence of malnutrition and frailty overall, and therefore low TGs may no longer be as strong an indicator of malnutrition in consideration of other malnutrition factors such as albumin and BMI.

Although we adjusted for albumin, residual confounding by other markers of malnutrition and inflammation may still exist. Although we were unable to fully account for other markers because of high missingness, this possible residual confounding may explain the incrementally lower to null risk of mortality observed for higher TGs across

advancing CKD stages. The underlying pathology explaining the reduced risk of mortality for higher TGs in patients with CKD is still unclear. In addition to potential complications due to malnutrition and inflammation, another possible explanation for this lack of relationship may be due to competing events of cardiovascular causes unrelated to atherosclerosis or TG-related cardiovascular disease, such as cardiomyopathies, left ventricular hypertrophies, or small vessel coronary disease. Tonnelli et al.[35] similarly found an attenuated relationship between LDL and myocardial infarction across worsening CKD stages in 836,060 adults and also postulated that this attenuation may be due to higher risk of cardiovascular outcomes due to malnutrition, inflammation, or competing cardiovascular causes unrelated to lipid levels. However, further studies are needed to assess these hypotheses.

Our study may be useful in demonstrating the type of patients with CKD who may have improved outcomes with treatment with TG-lowering therapies.[36–39] Associations of high TGs with mortality outcomes were present although incrementally attenuated in patients with CKD stage 4 or earlier. In spline models showing continuous effect modification by eGFR in NDD-CKD patients on the association of high TGs with mortality, associations began to attenuate slightly around eGFR 40 mL/min/1.73 m^2. This may be explained by the restriction to a smaller subset of patients with moderate or high eGFR or by the placement of knots in the model. Nonetheless, this study has a number of strengths. It is one of the largest studies to investigate the association of TGs and mortality across CKD stages, especially among late CKD stages. Moreover, we were able to adjust for a number of potential confounders including smoking status and use of lipid-modulating therapies because of the wealth of our combined electronic medical records data sets.

However, a number of limitations should be noted for our analysis. Due to the observational nature of the study design, we cannot completely eliminate residual confounding nor make causal inferences on the relationship between TGs and mortality by CKD stage. Moreover, we adjusted for only available confounders, yet we were unable to fully account for other potential confounders such as other nutritional or inflammation markers such as C-reactive protein, dietary intake of saturated fat, abdominal adiposity, and alcohol intake. We assume that our TG measurements were drawn after fasting, given that most lipids were drawn in the morning, although we cannot confirm fasting status and a degree of misclassification remains possible. However, a previous study has shown small differences in fasting vs nonfasting levels of lipids,[40] and other studies have demonstrated the utility of nonfasting TGs in cardiovascular risk prediction.[40–42] Finally, the VA population is primarily composed of older white males, and thus, our findings may not be generalizable to the general population, especially among females who may have differences in lipid metabolism.[43]

In conclusion, we observed that high serum TGs were associated with a higher risk of all-cause and cardiovascular mortality among non-CKD, stage 3A, 3B, and 4 patients, however, not among CKD stage 5/ESRD patients. Further studies are needed to examine the mechanism behind these relationships and to better understand how therapies aimed at lowering TGs may impact outcomes among patients with CKD.

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Authors' contributions: E.S., K.K-Z., and C.P.K. contributed to research idea and study design and were responsible for supervision or mentorship; E.S. and M.S. contributed to data acquisition and statistical analysis; M.S., H.M., Y.O., C.P.K., K.K-Z., and E.S. contributed to data analysis/interpretation. 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. E.S. 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 (and, if relevant, registered) have been explained.

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Appendix

Supplemental Table S1 Cardiovascular causes of death

All other forms of chronic ischemic heart disease
Acute myocardial infarction
All other forms of heart disease
Cerebrovascular diseases
Heart failure
Atherosclerotic cardiovascular disease, so described
Hypertensive heart disease
Essential (primary) hypertension and hypertensive renal disease
Aortic aneurysm and dissection
Other diseases of arteries, arterioles, and capillaries
Atherosclerosis
Other acute ischemic heart diseases
Hypertensive heart and renal disease
Other disorders of circulatory system
Acute rheumatic fever and chronic rheumatic heart diseases
Acute and subacute endocarditis
Diseases of the pericardium and acute myocarditis

Supplemental Table S2 Baseline characteristics of 2,086,904 patients stratified by CKD stage

Characteristic	Total	CKD Stage					
		Non-CKD	Total CKD	CKD Stage 3A	CKD Stage 3B	CKD Stage 4	CKD Stage 5/ESRD
N (%)	2,086,904	1,578,817 (75.7%)	508,087 (24.3%)	316,053 (15.1%)	137,688 (6.6%)	37,476 (1.8%)	16,870 (0.8%)
TG group, mg/dL (%)							
<80	19	20	17	17	16	15	18
80–<120	25	25	26	26	25	25	26
120–<160	19	19	20	20	21	20	19
160–<200	13	12	13	13	14	14	13
200–<240	8	8	9	8	9	9	8
≥240	15	15	15	15	16	18	16
eGFR (mL/min/1.73 m^2)*	76 [61, 91]	83 [72, 95]	49 [41, 55]	54 [50, 57]	39 [36, 42]	25 [21, 28]	12 [10, 14]
Age (y)	64 ± 14	60 ± 13	74 ± 10	73 ± 9	76 ± 9	75 ± 10	65 ± 12
Gender (%female)	5	6	3	3	3	3	2
Married (%)	56	54	60	61	60	59	56
Race (%)							
White	82	80	87	88	88	85	64
African-American	15	16	10	9	9	12	29
Other	4	4	3	3	3	4	7
Ethnicity (%)							
Hispanic	4	4	3	3	3	3	4
CCI	1 [0, 2]	1 [0, 2]	2 [1, 4]	2 [0, 3]	3 [1, 4]	4 [2, 6]	5 [3, 6]
Comorbid conditions (%)							
MI	6	5	12	10	14	17	17
CHF	10	6	22	17	28	40	39
PVD	10	6	19	15	23	30	29
Cerebrovascular disease	9	6	16	14	18	22	17
Dementia	3	2	5	4	6	6	4
COPD	18	16	24	23	27	30	25
Rheumatologic disease	2	2	3	2	3	3	2
Renal disease	6	2	21	8	29	66	94
Liver disease	3	4	2	2	2	3	10
Diabetes	29	25	40	35	44	52	58
Cancer	12	10	19	18	21	22	16
Anemia	11	8	23	16	27	44	69
Atrial fibrillation	7	4	13	12	16	17	11
Hyperlipidemia	53	49	66	65	68	66	57
Hypertension	65	59	86	83	91	94	95
ISHD	27	21	46	42	52	57	49
Depression	18	19	14	14	14	15	18
Anxiety	12	13	9	9	8	8	9
Substance abuse	7	8	3	3	3	3	7

(*continued on next page*)

Supplemental Table S2 (*continued*)

Characteristic	Total	CKD Stage					
		Non-CKD	Total CKD	CKD Stage 3A	CKD Stage 3B	CKD Stage 4	CKD Stage 5/ESRD
PTSD	7	8	4	4	3	3	5
Smoking (%)							
Never	29	28	32	32	32	31	31
Current	44	47	33	34	32	33	39
Past	27	25	35	34	36	36	30
Laboratory measurements							
Albumin (g/dL)	4.1 ± 0.4	4.1 ± 0.4	3.9 ± 0.5	4.0 ± 0.4	3.9 ± 0.5	3.8 ± 0.5	3.6 ± 0.6
ALP (U/L)	74 [61, 90]	74 [61, 90]	75 [61, 93]	73 [60, 90]	76 [62, 95]	83 [66, 104]	89 [69, 119]
BUN (mg/dL)	17.8 ± 8.9	15.1 ± 5.1	25.8 ± 12.4	21.2 ± 6.9	28.7 ± 10.2	43.5 ± 16.6	46.4 ± 25.4
Glucose (mg/dL)	115.4 ± 44.8	114.0 ± 43.9	119.5 ± 47.3	117.7 ± 44.3	121.3 ± 49.6	124.5 ± 55.5	125.9 ± 58.9
Hemoglobin (g/dL)	14.4 ± 1.7	14.7 ± 1.5	13.6 ± 1.8	14.0 ± 1.7	13.3 ± 1.8	12.4 ± 1.8	12.3 ± 1.9
WBC (x $10^3/mm^3$)	7.2 ± 2.8	7.2 ± 2.6	7.4 ± 3.2	7.3 ± 3.1	7.5 ± 3.3	7.8 ± 3.6	7.6 ± 3.5
SBP (mmHg)	135 ± 19	134 ± 19	136 ± 21	136 ± 20	135 ± 21	136 ± 23	139 ± 25
DBP (mmHg)	75 ± 12	77 ± 12	72 ± 12	73 ± 12	70 ± 12	69 ± 13	73 ± 15
BMI (kg/m^2)	29 ± 6	29 ± 6	29 ± 5	29 ± 5	29 ± 5	29 ± 6	28 ± 6
Lipid panel (mg/dL)							
Triglycerides	129 [88, 193]	127 [86, 192]	133 [93, 196]	131 [92, 193]	136 [95, 200]	138 [96, 205]	131 [90, 197]
HDL	42 [35, 51]	42 [35, 52]	40 [33, 48]	40 [34, 49]	39 [32, 47]	37 [31, 45]	39 [31, 49]
Cholesterol	177 [152, 206]	181 [155, 209]	166 [143, 193]	168 [146, 195]	163 [140, 190]	159 [134, 188]	154 [127, 185]
LDL	103 [81, 128]	106 [84, 131]	94 [74, 117]	96 [77, 119]	91 [72, 114]	87 [68, 111]	82 [61, 107]
Lipid-modulating therapy use (%)							
Statin	33	29	44	43	46	46	38
Ezetimibe	0.4	0.3	0.5	0.5	0.5	0.7	0.7
Nonstatin	6	5	7	7	8	8	5
Fibrate	3	3	5	4	5	5	3
Niacin	2	2	2	2	2	2	1
Fish oil	0.1	0.1	0.2	0.1	0.2	0.2	0.3
Bile acid sequestrants	0.4	0.4	0.4	0.4	0.5	0.4	0.5

Data presented as mean ± standard deviation, median [interquartile range], or percentage, as appropriate.

ALP, alkaline phosphatase; BMI, body mass index; BUN, blood urea nitrogen; CCI, Charlson Comorbidity Index; CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disorder; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HDL, high-density lipoprotein; ISHD, ischemic heart disease; LDL, low-density lipoprotein; MI, myocardial infarction; PTSD, post-traumatic stress disorder; PVD, peripheral vascular disease; SBP, systolic blood pressure; TG, triglycerides; WBC, white blood cell count.

*eGFR provided for only patients classified as CKD stage 5, yet not on ESRD.

Supplemental Table S3 Association of CKD stage with odds of high (≥240 mg/dL) or low (<120 mg/dL) serum triglycerides compared with moderate serum triglycerides (120 to <240 mg/dL) across levels of adjustment

Unadjusted									
	Non-CKD	CKD stage 3A		CKD stage 3B		CKD stage 4		CKD stage 5/ESRD	
Serum triglycerides (mg/dL)		*P*	OR [95% CI]	*P*	OR [95% CI]	*P*	OR [95% CI]	*P*	OR [95% CI]
Low vs moderate	*Ref*	<.0001	0.87 [0.86, 0.88]	<.0001	0.80 [0.79, 0.81]	<.0001	0.79 [0.77, 0.80]	<.0001	0.92 [0.89, 0.96]
High vs moderate	*Ref*	<.0001	0.90 [0.89, 0.91]	<.0001	0.96 [0.95, 0.98]	0.0002	1.06 [1.03, 1.09]	.81	1.01 [0.96, 1.05]
Case-mix adjusted									
	Non-CKD	CKD stage 3A		CKD stage 3B		CKD stage 4		CKD stage 5/ESRD	
Serum triglycerides (mg/dL)		*P*	OR [95% CI]	*P*	OR [95% CI]	*P*	OR [95% CI]	*P*	OR [95% CI]
Low vs moderate	*Ref*	<.0001	0.81 [0.80, 0.81]	<.0001	0.72 [0.71, 0.73]	<.0001	0.70 [0.69, 0.72]	<.0001	0.88 [0.85, 0.91]
High vs moderate	*Ref*	<.0001	1.15 [1.14, 1.17]	<.0001	1.27 [1.25, 1.29]	<.0001	1.32 [1.28, 1.36]	.27	0.97 [0.93, 1.02]
Case-mix + labs adjusted									
Serum triglycerides (mg/dL)	Non-CKD	CKD stage 3A		CKD stage 3B		CKD stage 4		CKD stage 5/ESRD	
		P	OR [95% CI]	*P*	OR [95% CI]	*P*	OR [95% CI]	*P*	OR [95% CI]
Low vs moderate	*Ref*	<.0001	0.81 [0.80, 0.82]	<.0001	0.71 [0.70, 0.72]	<.0001	0.66 [0.64, 0.67]	<.0001	0.68 [0.66, 0.71]
High vs moderate	*Ref*	<.0001	1.16 [1.15, 1.18]	<.0001	1.29 [1.27, 1.32]	<.0001	1.39 [1.34, 1.43]	<.0001	1.11 [1.05, 1.16]

CKD, chronic kidney disease; ESRD, end-stage renal disease.

Model adjustments.

Unadjusted.

Case-mix adjusted: age, gender, race, ethnicity, smoking status, Charlson Comorbidity Index, myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, chronic pulmonary disease, dementia, liver disease, cancer, diabetes, atrial fibrillation, hypertension, depression, ischemic heart disease, use of statin therapy, and use of nonstatin lipid-lowering drug therapy.

Case-mix + lab adjusted: case-mix adjusted and body mass index and albumin.

Supplemental Table S4 All-cause and cardiovascular mortality events and rates stratified by serum triglycerides and CKD stage

All-cause mortality

Stage	Total		Non-CKD		CKD stage 3A		CKD stage 3B		CKD stage 4		CKD stage 5/ESRD	
Serum triglycerides group (mg/dL)	N Event	Rate per 1000 person-years [95% CI]	N Event	Rate per 1000 person-years [95% CI]	N Event	Rate per 1000 person-years [95% CI]	N Event	Rate per 1000 person-years [95% CI]	N Event	Rate per 1000 person-years [95% CI]	N Event	Rate per 1000 person-years [95% CI]
<80	153,332	50.2 [49.9, 50.4]	99,400	39.2 [38.9, 39.4]	30,783	84.1 [83.1, 85.0]	15,882	135.3 [133.2, 137.4]	4770	209.9 [203.9, 215.8]	2497	205.2 [197.2, 213.3]
80–<120	196,222	47.9 [47.7, 48.1]	116,493	35.9 [35.7, 36.1]	43,703	74.8 [74.1, 75.5]	24,567	120.1 [118.6, 121.6]	7950	188.8 [184.6, 192.9]	3509	179.7 [173.8, 185.7]
120–<160	140,075	44.1 [43.9, 44.3]	79,451	32.1 [31.9, 32.4]	32,382	68.3 [67.5, 69.0]	19,458	110.4 [108.8, 111.9]	6256	168.5 [164.3, 172.7]	2528	164.6 [158.2, 171.0]
160–<200	87,094	41.5 [41.2, 41.8]	48,410	29.7 [29.5, 30.0]	20,162	63.9 [63.1, 64.8]	12,651	105.8 [103.9, 107.6]	4211	164.9 [160.0, 169.9]	1660	156.0 [148.5, 163.5]
200–<240	52,688	39.6 [39.3, 40.0]	28,674	27.9 [27.5, 28.2]	12,214	61.5 [60.5, 62.6]	8049	102.8 [100.6, 105.1]	2693	158.2 [152.2, 164.2]	1058	150.9 [141.8, 160.0]
≥240	97,581	37.4 [37.1, 37.6]	54,254	26.4 [26.1, 26.6]	21,571	60.4 [59.6, 61.3]	14,524	99.4 [97.7, 101.0]	5265	149.1 [145.1, 153.1]	1967	135.0 [129.0, 140.9]
Total	726,992	44.4 [44.3, 44.5]	426,682	32.9 [32.8, 33.0]	160,815	70.1 [69.7, 70.4]	95,131	112.9 [112.2, 113.7]	31,145	173.2 [171.3, 175.1]	13,219	166.8 [163.9, 169.6]

Cardiovascular mortality

Stage	Total		Non-CKD		CKD stage 3A		CKD stage 3B		CKD stage 4		CKD stage 5/ESRD	
Serum triglycerides group (mg/dL)	N Event	Rate per 1000 person-years [95% CI]	N Event	Rate per 1000 person-years [95% CI]	N Event	Rate per 1000 person-years [95% CI]	N Event	Rate per 1000 person-years [95% CI]	N Event	Rate per 1000 person-years [95% CI]	N Event	Rate per 1000 person-years [95% CI]
<80	50,146	16.4 [16.3, 16.5]	28,794	11.3 [11.2, 11.5]	11,541	31.5 [30.9, 32.1]	6832	58.2 [56.8, 59.6]	2069	91.0 [87.1, 95.0]	910	74.8 [69.9, 79.7]
80–<120	65,352	15.9 [15.8, 16.1]	34,458	10.6 [10.5, 10.7]	16,186	27.7 [27.3, 28.1]	10,079	49.3 [48.3, 50.2]	3355	79.7 [77.0, 82.4]	1274	65.3 [61.7, 68.8]
120–<160	47,664	15.0 [14.9, 15.1]	24,379	9.9 [9.7, 10.0]	11,936	25.2 [24.7, 25.6]	7838	44.5 [43.5, 45.4]	2598	70.0 [67.3, 72.7]	913	59.4 [55.6, 63.3]
160–<200	30,091	14.3 [14.2, 14.5]	15,020	9.2 [9.1, 9.4]	7520	23.8 [23.3, 24.4]	5245	43.9 [42.7, 45.0]	1747	68.4 [65.2, 71.6]	559	52.5 [48.2, 56.9]
200–<240	18,317	13.8 [13.6, 14.0]	9019	8.8 [8.6, 8.9]	4520	22.8 [22.1, 23.4]	3296	42.1 [40.7, 43.5]	1127	66.2 [62.3, 70.1]	355	50.6 [45.4, 55.9]
≥240	34,960	13.4 [13.3, 13.5]	17,690	8.6 [8.5, 8.7]	8345	23.4 [22.9, 23.9]	6032	41.3 [40.2, 42.3]	2165	61.3 [58.7, 63.9]	728	50.0 [46.3, 53.6]
Total	246530	15.1 [15.0, 15.1]	129360	10.0 [9.9, 10.0]	60,048	26.2 [25.9, 26.4]	39,322	46.7 [46.2, 47.1]	13,061	72.6 [71.4, 73.9]	4739	59.8 [58.1, 61.5]

CKD, chronic kidney disease; ESRD, end-stage renal disease.

Supplemental Table S5 Association of serum triglycerides with all-cause mortality across levels of adjustment and CKD stage

Unadjusted

Stage	Non-CKD		CKD stage 3A		CKD stage 3B		CKD stage 4		CKD stage 5/ESRD	
Serum triglycerides group (mg/dL)	*P*	HR [95% CI]	*P*	HR [95% CI]	*P*	HR [95% CI]	*P*	HR [95% CI]	*P*	HR [95% CI]
<80	<.0001	1.23 [1.22, 1.24]	<.0001	1.25 [1.23, 1.27]	<.0001	1.24 [1.22, 1.27]	<.0001	1.26 [1.21, 1.31]	<.0001	1.24 [1.17, 1.31]
80–<120	<.0001	1.12 [1.11, 1.13]	<.0001	1.10 [1.09, 1.12]	<.0001	1.10 [1.08, 1.12]	<.0001	1.13 [1.09, 1.17]	.001	1.09 [1.04, 1.15]
120–<160		*Ref*		*Ref*		*Ref*		*Ref*		*Ref*
160–<200	<.0001	0.92 [0.91, 0.94]	<.0001	0.93 [0.92, 0.95]	<.0001	0.96 [0.93, 0.98]	.28	0.98 [0.94, 1.02]	.10	0.95 [0.89, 1.01]
200–<240	<.0001	0.87 [0.85, 0.88]	<.0001	0.90 [0.88, 0.92]	<.0001	0.93 [0.90, 0.95]	.004	0.94 [0.90, 0.98]	.02	0.92 [0.86, 0.99]
≥240	<.0001	0.82 [0.81, 0.83]	<.0001	0.88 [0.87, 0.90]	<.0001	0.89 [0.88, 0.91]	<.0001	0.88 [0.85, 0.91]	<.0001	0.83 [0.78, 0.88]

Age adjusted

Stage	Non-CKD		CKD stage 3A		CKD stage 3B		CKD stage 4		CKD stage 5/ESRD	
Serum triglycerides group (mg/dL)	*P*	HR [95% CI]	*P*	HR [95% CI]	*P*	HR [95% CI]	*P*	HR [95% CI]	*P*	HR [95% CI]
<80	<.0001	1.16 [1.15, 1.18]	<.0001	1.12 [1.10, 1.14]	<.0001	1.16 [1.14, 1.19]	<.0001	1.24 [1.19, 1.28]	<.0001	1.20 [1.13, 1.27]
80–<120	<.0001	1.06 [1.05, 1.07]	<.0001	1.03 [1.02, 1.05]	<.0001	1.05 [1.03, 1.07]	<.0001	1.10 [1.07, 1.14]	.01	1.07 [1.02, 1.12]
120–<160		*Ref*		*Ref*		*Ref*		*Ref*		*Ref*
160–<200	.0004	0.98 [0.97, 0.99]	.30	0.99 [0.97, 1.01]	.45	0.99 [0.97, 1.01]	.73	1.01 [0.97, 1.05]	.29	0.97 [0.91, 1.03]
200–<240	<.0001	0.97 [0.96, 0.99]	.45	1.01 [0.99, 1.03]	.39	0.99 [0.96, 1.02]	.92	1.00 [0.95, 1.04]	.61	0.98 [0.91, 1.06]
≥240	<.0001	1.07 [1.06, 1.08]	<.0001	1.11 [1.09, 1.13]	<.0001	1.05 [1.03, 1.07]	.30	1.02 [0.98, 1.06]	.02	0.93 [0.88, 0.99]

Case-mix adjusted

Stage	Non-CKD		CKD stage 3A		CKD stage 3B		CKD stage 4		CKD stage 5/ESRD	
Serum triglycerides group (mg/dL)	*P*	HR [95% CI]	*P*	HR [95% CI]	*P*	HR [95% CI]	*P*	HR [95% CI]	*P*	HR [95% CI]
<80	<.0001	1.17 [1.16, 1.19]	<.0001	1.13 [1.12, 1.15]	<.0001	1.15 [1.13, 1.17]	<.0001	1.22 [1.17, 1.26]	<.0001	1.16 [1.10, 1.23]
80–<120	<.0001	1.07 [1.06, 1.08]	<.0001	1.05 [1.03, 1.06]	<.0001	1.06 [1.04, 1.08]	<.0001	1.10 [1.07, 1.14]	.03	1.06 [1.01, 1.12]
120–<160		*Ref*		*Ref*		*Ref*		*Ref*		*Ref*
160–<200	<.0001	0.97 [0.96, 0.98]	.01	0.98 [0.96, 0.99]	.08	0.98 [0.96, 1.00]	.81	1.01 [0.97, 1.05]	.27	0.97 [0.91, 1.03]
200–<240	<.0001	0.95 [0.94, 0.97]	.03	0.98 [0.96, 1.00]	.005	0.96 [0.94, 0.99]	.63	0.99 [0.95, 1.04]	.76	0.99 [0.92, 1.06]
≥240	.33	0.99 [0.98, 1.01]	.002	1.03 [1.01, 1.05]	.71	1.00 [0.98, 1.02]	.46	0.99 [0.95, 1.02]	.004	0.92 [0.86, 0.97]

Case-mix + labs adjusted

Stage	Non-CKD		CKD stage 3A		CKD stage 3B		CKD stage 4		CKD stage 5/ESRD	
Serum triglycerides group (mg/dL)	*P*	HR [95% CI]	*P*	HR [95% CI]	*P*	HR [95% CI]	*P*	HR [95% CI]	*P*	HR [95% CI]
<80	<.0001	1.05 [1.04, 1.06]	<.0001	1.04 [1.02, 1.05]	<.0001	1.06 [1.04, 1.08]	<.0001	1.11 [1.07, 1.16]	.004	1.09 [1.03, 1.15]
80–<120	.00	1.02 [1.01, 1.03]	.48	1.01 [0.99, 1.02]	.03	1.02 [1.00, 1.04]	.002	1.05 [1.02, 1.09]	.17	1.04 [0.99, 1.09]
120–<160		*Ref*		*Ref*		*Ref*		*Ref*		*Ref*

(*continued on next page*)

Supplemental Table S5 (*continued*)

Unadjusted

Stage	Non-CKD		CKD stage 3A		CKD stage 3B		CKD stage 4		CKD stage 5/ESRD	
Serum triglycerides group (mg/dL)	*P*	HR [95% CI]	*P*	HR [95% CI]	*P*	HR [95% CI]	*P*	HR [95% CI]	*P*	HR [95% CI]
160–<200	.47	1.00 [0.99, 1.01]	.75	1.00 [0.98, 1.02]	.27	1.01 [0.99, 1.04]	.09	1.03 [1.00, 1.08]	.72	0.99 [0.93, 1.05]
200–<240	.92	1.00 [0.99, 1.01]	.13	1.02 [1.00, 1.04]	.64	1.01 [0.98, 1.03]	.21	1.03 [0.98, 1.08]	.29	1.04 [0.97, 1.12]
≥240	<.0001	1.06 [1.05, 1.07]	<.0001	1.08 [1.07, 1.10]	<.0001	1.06 [1.03, 1.08]	.002	1.06 [1.02, 1.10]	.58	0.98 [0.93, 1.04]

Case-mix + labs adjusted + HDL + LDL

Stage	Non-CKD		CKD stage 3A		CKD stage 3B		CKD stage 4		CKD stage 5/ESRD	
Serum triglycerides group (mg/dL)	*P*	HR [95% CI]	*P*	HR [95% CI]	*P*	HR [95% CI]	*P*	HR [95% CI]	*P*	HR [95% CI]
<80	.005	0.99 [0.98, 1.00]	.0003	1.03 [1.01, 1.05]	<.0001	1.06 [1.04, 1.08]	<.0001	1.12 [1.08, 1.16]	.05	1.06 [1.00, 1.12]
80–<120	.73	1.00 [0.99, 1.01]	.66	1.00 [0.99, 1.02]	.02	1.02 [1.00, 1.04]	.002	1.06 [1.02, 1.09]	.33	1.03 [0.97, 1.08]
120–<160		*Ref*		*Ref*		*Ref*		*Ref*		*Ref*
160–<200	.45	1.00 [0.99, 1.02]	.81	1.00 [0.98, 1.02]	.31	1.01 [0.99, 1.04]	.11	1.03 [0.99, 1.07]	.88	1.00 [0.94, 1.06]
200–<240	.07	1.01 [1.00, 1.03]	.13	1.02 [1.00, 1.04]	.78	1.00 [0.98, 1.03]	.28	1.03 [0.98, 1.07]	.19	1.05 [0.98, 1.13]
≥240	<.0001	1.07 [1.06, 1.08]	<.0001	1.08 [1.06, 1.10]	<.0001	1.05 [1.03, 1.07]	.01	1.05 [1.01, 1.09]	.60	0.98 [0.93, 1.05]

CKD, chronic kidney disease; ESRD, end-stage renal disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Model adjustments

Unadjusted

Age adjusted: age

Case-mix adjusted: age, gender, race, ethnicity, smoking status, Charlson Comorbidity Index, myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, chronic pulmonary disease, dementia, liver disease, cancer, diabetes, atrial fibrillation, hypertension, depression, ischemic heart disease, use of statin therapy, and use of nonstatin lipid-lowering drug therapy.

Case-mix + lab adjusted: case-mix adjusted + body mass index and albumin.

Case-mix + lab adjusted + HDL + LDL: case-mix + lab adjusted + HDL + LDL.

Supplemental Table S6 Association of serum triglycerides with cardiovascular mortality across levels of adjustment and CKD stage

Unadjusted

Stage	Non-CKD		CKD stage 3A		CKD stage 3B		CKD stage 4		CKD stage 5/ESRD	
Serum triglycerides group (mg/dL)	*P*	HR [95% CI]	*P*	HR [95% CI]	*P*	HR [95% CI]	*P*	HR [95% CI]	*P*	HR [95% CI]
<80	<.0001	1.16 [1.14, 1.18]	<.0001	1.27 [1.24, 1.30]	<.0001	1.33 [1.28, 1.37]	<.0001	1.31 [1.24, 1.39]	<.0001	1.25 [1.14, 1.37]
80–<120	<.0001	1.08 [1.06, 1.10]	<.0001	1.11 [1.08, 1.13]	<.0001	1.12 [1.08, 1.15]	<.0001	1.14 [1.09, 1.20]	.04	1.10 [1.01, 1.19]
120–<160		*Ref*		*Ref*		*Ref*		*Ref*		*Ref*
160–<200	<.0001	0.93 [0.92, 0.95]	.0001	0.95 [0.92, 0.97]	.35	0.98 [0.95, 1.02]	.47	0.98 [0.92, 1.04]	.02	0.88 [0.80, 0.98]
200–<240	<.0001	0.89 [0.87, 0.91]	<.0001	0.90 [0.87, 0.93]	.004	0.94 [0.91, 0.98]	.11	0.95 [0.88, 1.01]	.01	0.85 [0.76, 0.97]
≥240	<.0001	0.87 [0.85, 0.89]	<.0001	0.92 [0.90, 0.95]	<.0001	0.92 [0.89, 0.95]	<.0001	0.87 [0.83, 0.92]	.0008	0.85 [0.77, 0.93]

Age adjusted

Stage	Non-CKD		CKD stage 3A		CKD stage 3B		CKD stage 4		CKD stage 5/ESRD	
Serum triglycerides group (mg/dL)	*P*	HR [95% CI]	*P*	HR [95% CI]	*P*	HR [95% CI]	*P*	HR [95% CI]	*P*	HR [95% CI]
<80	<.0001	1.08 [1.06, 1.10]	<.0001	1.13 [1.10, 1.16]	<.0001	1.23 [1.19, 1.27]	<.0001	1.28 [1.21, 1.36]	<.0001	1.21 [1.10, 1.32]
80–<120	.35	1.01 [0.99, 1.02]	.01	1.03 [1.01, 1.06]	<.0001	1.07 [1.04, 1.10]	<.0001	1.11 [1.06, 1.17]	.11	1.07 [0.99, 1.17]
120–<160		*Ref*		*Ref*		*Ref*		*Ref*		*Ref*
160–<200	.91	1.00 [0.98, 1.02]	.67	1.01 [0.98, 1.04]	.16	1.03 [0.99, 1.06]	.73	1.01 [0.95, 1.07]	.06	0.90 [0.81, 1.00]
200–<240	.14	1.02 [0.99, 1.04]	.27	1.02 [0.99, 1.06]	.53	1.01 [0.97, 1.06]	.65	1.02 [0.95, 1.09]	.17	0.92 [0.81, 1.04]
≥240	<.0001	1.19 [1.16, 1.21]	<.0001	1.18 [1.15, 1.22]	<.0001	1.10 [1.07, 1.14]	.26	1.03 [0.98, 1.10]	.53	0.97 [0.88, 1.07]

Case-mix adjusted

Stage	Non-CKD		CKD stage 3A		CKD stage 3B		CKD stage 4		CKD stage 5/ESRD	
Serum triglycerides group (mg/dL)	*P*	HR [95% CI]	*P*	HR [95% CI]	*P*	HR [95% CI]	*P*	HR [95% CI]	*P*	HR [95% CI]
<80	<.0001	1.12 [1.10, 1.13]	<.0001	1.14 [1.11, 1.17]	<.0001	1.21 [1.17, 1.25]	<.0001	1.25 [1.18, 1.33]	.0006	1.18 [1.07, 1.29]
80–<120	.0007	1.03 [1.01, 1.05]	.0003	1.04 [1.02, 1.07]	<.0001	1.07 [1.04, 1.10]	.0002	1.10 [1.05, 1.16]	.23	1.05 [0.97, 1.15]
120–<160		*Ref*		*Ref*		*Ref*		*Ref*		*Ref*
160–<200	.03	0.98 [0.96, 1.00]	.66	0.99 [0.97, 1.02]	.29	1.02 [0.98, 1.06]	.84	1.01 [0.95, 1.07]	.03	0.89 [0.80, 0.99]
200–<240	.28	0.99 [0.96, 1.01]	.46	0.99 [0.95, 1.02]	.69	0.99 [0.95, 1.03]	.87	1.01 [0.94, 1.08]	.27	0.93 [0.83, 1.06]
≥240	<.0001	1.08 [1.06, 1.10]	<.0001	1.09 [1.06, 1.12]	.007	1.05 [1.01, 1.08]	.99	1.00 [0.94, 1.06]	.35	0.96 [0.87, 1.05]

Case-mix + labs adjusted

Stage	Non-CKD		CKD stage 3A		CKD stage 3B		CKD stage 4		CKD stage 5/ESRD	
Serum triglycerides group (mg/dL)	*P*	HR [95% CI]	*P*	HR [95% CI]	*P*	HR [95% CI]	*P*	HR [95% CI]	*P*	HR [95% CI]
<80	<.0001	1.04 [1.02, 1.06]	<.0001	1.06 [1.04, 1.09]	<.0001	1.13 [1.09, 1.17]	<.0001	1.16 [1.10, 1.23]	.03	1.11 [1.01, 1.22]
80–<120	.95	1.00 [0.98, 1.02]	.28	1.01 [0.99, 1.04]	.01	1.04 [1.01, 1.07]	.02	1.06 [1.01, 1.12]	.47	1.03 [0.95, 1.12]
120–<160		*Ref*		*Ref*		*Ref*		*Ref*		*Ref*

(*continued on next page*)

Supplemental Table S6 (*continued*)

Unadjusted

Stage	Non-CKD		CKD stage 3A		CKD stage 3B		CKD stage 4		CKD stage 5/ESRD	
Serum triglycerides group (mg/dL)	*P*	HR [95% CI]	*P*	HR [95% CI]	*P*	HR [95% CI]	*P*	HR [95% CI]	*P*	HR [95% CI]
160–<200	.66	1.00 [0.98, 1.02]	.48	1.01 [0.98, 1.04]	.01	1.05 [1.01, 1.09]	.32	1.03 [0.97, 1.10]	.08	0.91 [0.82, 1.01]
200–<240	.20	1.02 [0.99, 1.04]	.28	1.02 [0.99, 1.06]	.16	1.03 [0.99, 1.07]	.28	1.04 [0.97, 1.12]	.70	0.98 [0.86, 1.10]
≥240	<.0001	1.12 [1.10, 1.14]	<.0001	1.14 [1.11, 1.17]	<.0001	1.10 [1.06, 1.14]	.04	1.06 [1.00, 1.13]	.77	1.02 [0.92, 1.12]

Case-mix + labs adjusted + HDL + LDL

Stage	Non-CKD		CKD stage 3A		CKD stage 3B		CKD stage 4		CKD stage 5/ESRD	
Serum triglycerides group (mg/dL)	*P*	HR [95% CI]	*P*	HR [95% CI]	*P*	HR [95% CI]	*P*	HR [95% CI]	*P*	HR [95% CI]
<80	.05	1.02 [1.00, 1.04]	<.0001	1.10 [1.07, 1.13]	<.0001	1.16 [1.12, 1.20]	<.0001	1.20 [1.13, 1.27]	.06	1.10 [1.00, 1.21]
80–<120	.37	0.99 [0.98, 1.01]	.05	1.02 [1.00, 1.05]	.001	1.05 [1.02, 1.08]	.006	1.08 [1.02, 1.13]	.53	1.03 [0.94, 1.12]
120–<160		*Ref*		*Ref*		*Ref*		*Ref*		*Ref*
160–<200	.97	1.00 [0.98, 1.02]	.75	1.01 [0.98, 1.03]	.02	1.04 [1.01, 1.08]	.43	1.03 [0.97, 1.09]	.10	0.91 [0.82, 1.02]
200–<240	.04	1.03 [1.00, 1.05]	.50	1.01 [0.98, 1.05]	.36	1.02 [0.98, 1.06]	.47	1.03 [0.96, 1.10]	.75	0.98 [0.87, 1.11]
≥240	<.0001	1.14 [1.12, 1.17]	<.0001	1.13 [1.10, 1.16]	<.0001	1.09 [1.05, 1.12]	.17	1.04 [0.98, 1.10]	.84	1.01 [0.91, 1.12]

CKD, chronic kidney disease; ESRD, end-stage renal disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Model adjustments

Unadjusted

Adjusted: age

Case-mix adjusted: age, gender, race, ethnicity, smoking status, Charlson Comorbidity Index, myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, chronic pulmonary disease, dementia, liver disease, cancer, diabetes, atrial fibrillation, hypertension, depression, ischemic heart disease, use of statin therapy, and use of nonstatin lipid-lowering drug therapy.

Case-mix + lab adjusted: case-mix adjusted and body mass index and albumin.

Case-mix + lab adjusted + HDL + LDL: case-mix + lab adjusted + HDL + LDL.

Supplemental Table S7 Association of serum triglycerides with all-cause mortality across strata of age and diabetes and male gender under case-mix + lab adjustment

Age<65 y (N = 1,083,489)

Stage	Non-CKD		CKD stage 3A		CKD stage 3B		CKD stage 4		CKD stage 5/ESRD	
Serum triglycerides group (mg/dL)	*P*	HR [95% CI]	*P*	HR [95% CI]	*P*	HR [95% CI]	*P*	HR [95% CI]	*P*	HR [95% CI]
<80	<.0001	1.10 [1.08, 1.11]	.002	1.10 [1.04, 1.16]	.04	1.09 [1.00, 1.19]	.01	1.18 [1.05, 1.33]	<.0001	1.22 [1.11, 1.33]
80–<120	<.0001	1.05 [1.03, 1.06]	.57	1.01 [0.97, 1.07]	.003	1.12 [1.04, 1.21]	.10	1.10 [0.98, 1.22]	.16	1.06 [0.98, 1.16]
120–<160		*Ref*		*Ref*		*Ref*		*Ref*		*Ref*
160–<200	.53	0.99 [0.98, 1.01]	.46	0.98 [0.93, 1.03]	.24	1.05 [0.97, 1.14]	.10	1.10 [0.98, 1.24]	.67	1.02 [0.93, 1.13]
200–<240	.15	0.99 [0.96, 1.01]	.21	0.96 [0.91, 1.02]	.73	1.02 [0.93, 1.11]	.36	1.06 [0.93, 1.21]	.34	1.06 [0.94, 1.19]
≥240	<.0001	1.05 [1.03, 1.06]	.01	1.06 [1.01, 1.11]	.22	1.04 [0.97, 1.12]	.03	1.12 [1.01, 1.24]	.84	0.99 [0.91, 1.09]

Age ≥65 y (N = 1,003,415)

Stage	Non-CKD		CKD stage 3A		CKD stage 3B		CKD stage 4		CKD stage 5/ESRD	
Serum triglycerides group (mg/dL)	*P*	HR [95% CI]	*P*	HR [95% CI]	*P*	HR [95% CI]	*P*	HR [95% CI]	*P*	HR [95% CI]
<80	.0001	1.02 [1.01, 1.04]	.003	1.03 [1.01, 1.04]	<.0001	1.05 [1.03, 1.08]	<.0001	1.10 [1.06, 1.15]	.96	1.00 [0.93, 1.08]
80–<120	.63	1.00 [0.99, 1.01]	.95	1.00 [0.99, 1.02]	.12	1.02 [1.00, 1.04]	.009	1.05 [1.01, 1.09]	.56	1.02 [0.96, 1.09]
120–<160		*Ref*		*Ref*		*Ref*		*Ref*		*Ref*
160–<200	.79	1.00 [0.98, 1.01]	.91	1.00 [0.98, 1.02]	.35	1.01 [0.99, 1.04]	.17	1.03 [0.99, 1.07]	.53	0.98 [0.90, 1.06]
200–<240	.19	1.01 [0.99, 1.03]	.05	1.02 [1.00, 1.05]	.77	1.00 [0.98, 1.03]	.30	1.03 [0.98, 1.08]	.38	1.04 [0.95, 1.15]
≥240	<.0001	1.06 [1.05, 1.08]	<.0001	1.07 [1.05, 1.09]	<.0001	1.06 [1.03, 1.08]	.01	1.05 [1.01, 1.10]	.71	0.99 [0.91, 1.07]

Nondiabetics (N = 1,488,299)

Stage	Non-CKD		CKD stage 3A		CKD stage 3B		CKD stage 4		CKD stage 5/ESRD	
Serum triglycerides group (mg/dL)	*P*	HR [95% CI]	*P*	HR [95% CI]	*P*	HR [95% CI]	*P*	HR [95% CI]	*P*	HR [95% CI]
<80	<.0001	1.06 [1.04, 1.07]	.07	1.02 [1.00, 1.04]	<.0001	1.06 [1.04, 1.09]	<.0001	1.13 [1.07, 1.19]	.81	1.01 [0.93, 1.11]
80–<120	.0009	1.02 [1.01, 1.03]	.78	1.00 [0.98, 1.02]	.14	1.02 [0.99, 1.05]	.003	1.08 [1.03, 1.13]	.60	1.02 [0.94, 1.11]
120–<160		*Ref*		*Ref*		*Ref*		*Ref*		*Ref*
160–<200	.28	0.99 [0.98, 1.01]	.75	1.00 [0.98, 1.03]	.64	1.01 [0.98, 1.04]	.04	1.06 [1.00, 1.13]	.73	1.02 [0.92, 1.13]
200–<240	.10	0.99 [0.97, 1.00]	.77	1.00 [0.98, 1.03]	.65	1.01 [0.97, 1.05]	.11	1.06 [0.99, 1.13]	.24	1.07 [0.95, 1.21]
≥240	<.0001	1.05 [1.03, 1.06]	<.0001	1.07 [1.04, 1.10]	.18	1.02 [0.99, 1.06]	.0005	1.11 [1.05, 1.18]	.57	0.97 [0.88, 1.08]

Diabetics (N = 597,958)

Stage	Non-CKD		CKD stage 3A		CKD stage 3B		CKD stage 4		CKD stage 5/ESRD	
Serum triglycerides group (mg/dL)	*P*	HR [95% CI]	*P*	HR [95% CI]	*P*	HR [95% CI]	*P*	HR [95% CI]	*P*	HR [95% CI]
<80	.22	0.99 [0.97, 1.01]	.0002	1.05 [1.02, 1.08]	.05	1.03 [1.00, 1.07]	.002	1.09 [1.03, 1.15]	0.0006	1.13 [1.06, 1.22]
80–<120	.44	1.01 [0.99, 1.02]	.95	1.00 [0.98, 1.03]	.14	1.02 [0.99, 1.05]	.21	1.03 [0.98, 1.08]	.21	1.04 [0.98, 1.12]
120–<160		*Ref*		*Ref*		*Ref*		*Ref*		*Ref*

(*continued on next page*)

Supplemental Table S7 (*continued*)

Age<65 y (N = 1,083,489)										
Stage	Non-CKD		CKD stage 3A		CKD stage 3B		CKD stage 4		CKD stage 5/ESRD	
Serum triglycerides group (mg/dL)	*P*	HR [95% CI]	*P*	HR [95% CI]	*P*	HR [95% CI]	*P*	HR [95% CI]	*P*	HR [95% CI]
160–<200	.84	1.00 [0.98, 1.02]	.55	0.99 [0.97, 1.02]	.19	1.02 [0.99, 1.06]	.70	1.01 [0.96, 1.07]	.48	0.97 [0.90, 1.05]
200–<240	.13	1.02 [1.00, 1.04]	.07	1.03 [1.00, 1.06]	.58	1.01 [0.97, 1.05]	.91	1.00 [0.95, 1.07]	.64	1.02 [0.93, 1.12]
≥240	<.0001	1.06 [1.04, 1.08]	<.0001	1.08 [1.06, 1.11]	<.0001	1.07 [1.04, 1.11]	.30	1.03 [0.98, 1.08]	.71	0.99 [0.92, 1.06]
Males (N = 1,983,095)										
Stage	Non-CKD		CKD stage 3A		CKD stage 3B		CKD stage 4		CKD stage 5/ESRD	
Serum triglycerides group (mg/dL)	*P*	HR [95% CI]	*P*	HR [95% CI]	*P*	HR [95% CI]	*P*	HR [95% CI]	*P*	HR [95% CI]
<80	<.0001	1.05 [1.04, 1.06]	<.0001	1.04 [1.02, 1.06]	<.0001	1.06 [1.04, 1.08]	<.0001	1.12 [1.07, 1.16]	.005	1.08 [1.03, 1.15]
80–<120	<.0001	1.02 [1.01, 1.03]	.44	1.01 [0.99, 1.02]	.03	1.02 [1.00, 1.04]	.001	1.06 [1.02, 1.09]	.18	1.04 [0.98, 1.09]
120–<160		*Ref*		*Ref*		*Ref*		*Ref*		*Ref*
160–<200	.21	0.99 [0.98, 1.00]	.76	1.00 [0.98, 1.02]	.20	1.02 [0.99, 1.04]	.08	1.04 [1.00, 1.08]	.68	0.99 [0.93, 1.05]
200–<240	.69	1.00 [0.98, 1.01]	.14	1.02 [1.00, 1.04]	.67	1.01 [0.98, 1.03]	.18	1.03 [0.99, 1.08]	.39	1.03 [0.96, 1.11]
≥240	<.0001	1.06 [1.05, 1.07]	<.0001	1.08 [1.06, 1.10]	<.0001	1.06 [1.04, 1.08]	.0006	1.07 [1.03, 1.11]	.55	0.98 [0.92, 1.04]

CKD, chronic kidney disease; ESRD, end-stage renal disease.

Model adjustments

Case-mix + lab adjusted: age, gender, race, ethnicity, smoking status, Charlson Comorbidity Index, myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, chronic pulmonary disease, dementia, liver disease, cancer, diabetes, atrial fibrillation, hypertension, depression, ischemic heart disease, use of statin therapy, use of nonstatin lipid-lowering drug therapy, body mass index, and albumin.

Supplemental Table S8 Association of serum triglycerides with cardiovascular mortality across strata of age and diabetes and male gender under case-mix + lab adjustment

Age<65 y (N = 1,083,489)

Stage	Non-CKD		CKD stage 3A		CKD stage 3B		CKD stage 4		CKD stage 5/ESRD	
Serum triglycerides group (mg/dL)	*P*	HR [95% CI]	*P*	HR [95% CI]	*P*	HR [95% CI]	*P*	HR [95% CI]	*P*	HR [95% CI]
<80	.02	1.04 [1.01, 1.07]	.002	1.15 [1.05, 1.26]	.05	1.15 [1.00, 1.32]	.15	1.16 [0.95, 1.42]	.01	1.21 [1.04, 1.41]
80–<120	.95	1.00 [0.97, 1.03]	.53	1.03 [0.95, 1.11]	.04	1.14 [1.01, 1.29]	.10	1.16 [0.97, 1.39]	.71	1.03 [0.89, 1.19]
120–<160		*Ref*		*Ref*		*Ref*		*Ref*		*Ref*
160–<200	.92	1.00 [0.97, 1.04]	.48	0.97 [0.89, 1.06]	.33	1.07 [0.94, 1.22]	.23	1.13 [0.93, 1.36]	.19	0.89 [0.75, 1.06]
200–<240	.47	0.99 [0.95, 1.03]	.15	0.93 [0.84, 1.03]	.22	1.09 [0.95, 1.26]	.15	1.16 [0.95, 1.43]	.31	0.90 [0.73, 1.10]
≥240	<.0001	1.10 [1.07, 1.13]	.02	1.10 [1.02, 1.18]	.28	1.06 [0.95, 1.19]	.68	1.04 [0.88, 1.22]	.38	1.07 [0.92, 1.24]

Age ≥65 y (N = 1,003,415)

Stage	Non-CKD		CKD stage 3A		CKD stage 3B		CKD stage 4		CKD stage 5/ESRD	
Serum triglycerides group (mg/dL)	*P*	HR [95% CI]	*P*	HR [95% CI]	*P*	HR [95% CI]	*P*	HR [95% CI]	*P*	HR [95% CI]
<80	.01	1.03 [1.01, 1.05]	.002	1.05 [1.02, 1.07]	<.0001	1.12 [1.08, 1.16]	<.0001	1.16 [1.09, 1.23]	.46	1.05 [0.93, 1.18]
80–<120	.60	1.00 [0.98, 1.02]	.58	1.01 [0.98, 1.03]	.03	1.03 [1.00, 1.07]	.05	1.06 [1.00, 1.12]	.57	1.03 [0.93, 1.15]
120–<160		*Ref*		*Ref*		*Ref*		*Ref*		*Ref*
160–<200	.46	0.99 [0.97, 1.02]	.31	1.02 [0.99, 1.05]	.01	1.05 [1.01, 1.09]	.43	1.03 [0.96, 1.09]	.24	0.92 [0.81, 1.06]
200–<240	.07	1.03 [1.00, 1.06]	.11	1.03 [0.99, 1.07]	.30	1.02 [0.98, 1.07]	.50	1.03 [0.95, 1.11]	.65	1.04 [0.89, 1.21]
≥240	<.0001	1.09 [1.07, 1.12]	<.0001	1.12 [1.09, 1.16]	<.0001	1.10 [1.06, 1.14]	.03	1.07 [1.01, 1.14]	.57	0.96 [0.84, 1.10]

Nondiabetics (N = 1,488,299)

Stage	Non-CKD		CKD stage 3A		CKD stage 3B		CKD stage 4		CKD stage 5/ESRD	
Serum triglycerides group (mg/dL)	*P*	HR [95% CI]	*P*	HR [95% CI]	*P*	HR [95% CI]	*P*	HR [95% CI]	*P*	HR [95% CI]
<80	<.0001	1.06 [1.03, 1.08]	.01	1.04 [1.01, 1.08]	<.0001	1.14 [1.09, 1.19]	<.0001	1.19 [1.10, 1.29]	.68	1.03 [0.89, 1.19]
80–<120	.41	1.01 [0.99, 1.03]	.47	1.01 [0.98, 1.04]	.01	1.05 [1.01, 1.10]	.008	1.10 [1.03, 1.19]	.96	1.00 [0.88, 1.15]
120–<160		*Ref*		*Ref*		*Ref*		*Ref*		*Ref*
160–<200	.87	1.00 [0.97, 1.03]	.59	1.01 [0.97, 1.05]	.04	1.05 [1.00, 1.11]	.06	1.09 [1.00, 1.19]	.15	0.88 [0.74, 1.05]
200–<240	.74	1.00 [0.96, 1.03]	.88	1.00 [0.95, 1.05]	.64	1.01 [0.96, 1.08]	.17	1.08 [0.97, 1.20]	.71	0.96 [0.79, 1.18]
≥240	<.0001	1.11 [1.08, 1.14]	<.0001	1.11 [1.06, 1.15]	.007	1.07 [1.02, 1.13]	.02	1.12 [1.02, 1.22]	.35	0.92 [0.78, 1.09]

Diabetics (N = 597,958)

Stage	Non-CKD		CKD stage 3A		CKD stage 3B		CKD stage 4		CKD stage 5/ESRD	
Serum triglycerides group (mg/dL)	*P*	HR [95% CI]	*P*	HR [95% CI]	*P*	HR [95% CI]	*P*	HR [95% CI]	*P*	HR [95% CI]
<80	.13	0.98 [0.95, 1.01]	.001	1.07 [1.03, 1.12]	.0003	1.10 [1.04, 1.16]	.005	1.13 [1.04, 1.23]	.02	1.16 [1.02, 1.30]
80–<120	.08	0.98 [0.95, 1.00]	.66	1.01 [0.97, 1.05]	.37	1.02 [0.98, 1.07]	.49	1.03 [0.95, 1.11]	.45	1.04 [0.93, 1.17]
120–<160		*Ref*		*Ref*		*Ref*		*Ref*		*Ref*

(*continued on next page*)

Supplemental Table S8 (*continued*)

Age<65 y (N = 1,083,489)

Stage	Non-CKD		CKD stage 3A		CKD stage 3B		CKD stage 4		CKD stage 5/ESRD	
Serum triglycerides group (mg/dL)	*P*	HR [95% CI]	*P*	HR [95% CI]	*P*	HR [95% CI]	*P*	HR [95% CI]	*P*	HR [95% CI]
160–<200	.49	0.99 [0.96, 1.02]	.55	1.01 [0.97, 1.06]	.08	1.05 [1.00, 1.10]	.72	0.99 [0.91, 1.07]	.27	0.93 [0.81, 1.06]
200–<240	.08	1.03 [1.00, 1.07]	.11	1.04 [0.99, 1.09]	.12	1.05 [0.99, 1.11]	.95	1.00 [0.91, 1.10]	.92	0.99 [0.85, 1.16]
≥240	<.0001	1.11 [1.08, 1.14]	<.0001	1.15 [1.10, 1.19]	<.0001	1.11 [1.06, 1.16]	.71	1.02 [0.94, 1.10]	.34	1.06 [0.94, 1.20]

Males (N = 1,983,095)

Stage	Non-CKD		CKD stage 3A		CKD stage 3B		CKD stage 4		CKD stage 5/ESRD	
Serum triglycerides group (mg/dL)	*P*	HR [95% CI]	*P*	HR [95% CI]	*P*	HR [95% CI]	*P*	HR [95% CI]	*P*	HR [95% CI]
<80	<.0001	1.04 [1.02, 1.06]	<.0001	1.07 [1.04, 1.09]	<.0001	1.14 [1.10, 1.17]	<.0001	1.17 [1.10, 1.24]	.03	1.11 [1.01, 1.22]
80–<120	.87	1.00 [0.99, 1.02]	.16	1.02 [0.99, 1.04]	.005	1.04 [1.01, 1.08]	.02	1.07 [1.01, 1.12]	.45	1.03 [0.95, 1.13]
120–<160		*Ref*		*Ref*		*Ref*		*Ref*		*Ref*
160–<200	.60	0.99 [0.97, 1.02]	.41	1.01 [0.98, 1.04]	.005	1.05 [1.02, 1.09]	.25	1.04 [0.98, 1.10]	.11	0.92 [0.82, 1.02]
200–<240	.24	1.02 [0.99, 1.04]	.27	1.02 [0.99, 1.06]	.17	1.03 [0.99, 1.07]	.22	1.05 [0.97, 1.12]	.73	0.98 [0.87, 1.11]
≥240	<.0001	1.12 [1.10, 1.14]	<.0001	1.14 [1.11, 1.17]	<.0001	1.11 [1.07, 1.15]	.03	1.07 [1.01, 1.13]	.79	1.01 [0.92, 1.12]

Model adjustments

Case-mix + lab adjusted: age, gender, race, ethnicity, smoking status, Charlson Comorbidity Index, myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, chronic pulmonary disease, dementia, liver disease, cancer, diabetes, atrial fibrillation, hypertension, depression, ischemic heart disease, use of statin therapy, use of nonstatin lipid-lowering drug therapy, body mass index, and albumin.

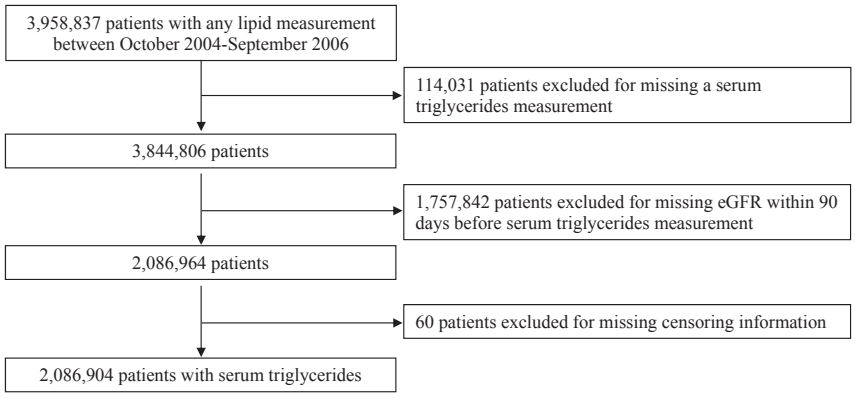

Figure S1 Cohort construction.

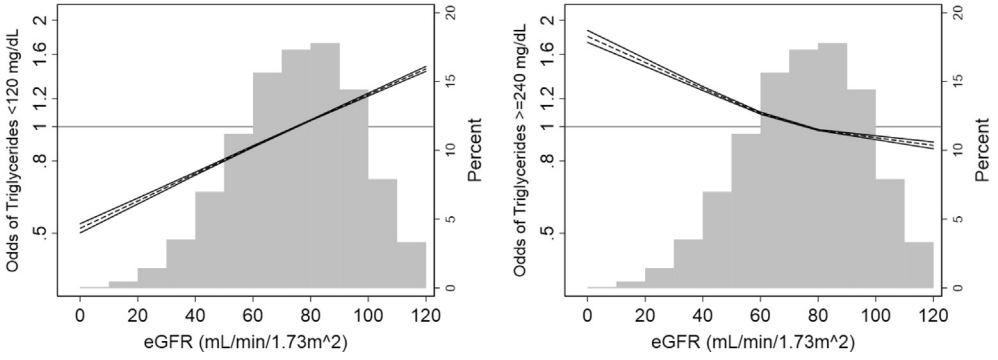

Figure S2 Restricted cubic splines of the association of continuous eGFR with odds of low (<120 mg/dL) or high (≥240 mg/dL) serum triglycerides compared with moderate serum triglycerides (120 to <240 mg/dL) among those not on ESRD (n = 2,074,884) under case-mix + lab adjustment. Model adjustments: case-mix + lab adjusted: age, gender, race, ethnicity, smoking status, CCI, myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, chronic pulmonary disease, dementia, liver disease, cancer, diabetes, atrial fibrillation, hypertension, depression, ischemic heart disease, use of statin therapy, use of nonstatin lipid-lowering drug therapy, BMI, and albumin. eGFR, estimated glomerular filtration rate; CCI, Charlson Comorbidity Index; ESRD, end-stage renal disease; BMI, body mass index.

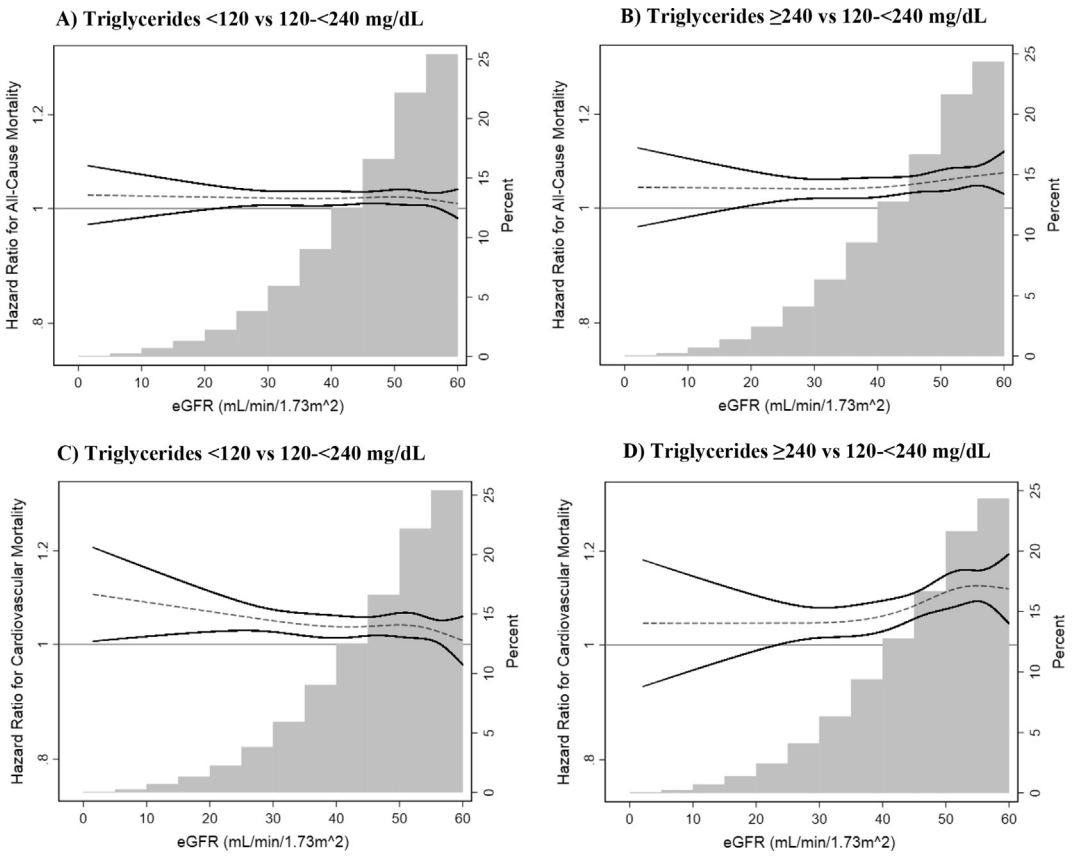

Figure S3 Restricted cubic splines for the effect modification of continuous eGFR on low (<120 mg/dL) vs moderate (120 to <240 mg/dL) serum triglycerides with (A) all-cause and (C) cardiovascular mortality and high (≥240 mg/dL) vs moderate (120 to <240 mg/dL) serum triglycerides with (B) all-cause and (D) cardiovascular mortality under case-mix + lab adjustment among 496,067 patients with NDD-CKD. Model adjustments: case-mix + lab adjusted: age, gender, race, ethnicity, smoking status, CCI, myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, chronic pulmonary disease, dementia, liver disease, cancer, diabetes, atrial fibrillation, hypertension, depression, ischemic heart disease, use of statin therapy, use of nonstatin lipid-lowering drug therapy, BMI, and albumin. CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; CCI, Charlson Comorbidity Index; BMI, body mass index; NDD-CKD, nondialysis-dependent CKD.