The contribution of chronic kidney disease measures to cause-specific mortality and morbidity

Yejin Mok

The Graduate School
Yonsei University
Department of Public Health

The contribution of chronic kidney disease measures to cause-specific mortality and morbidity

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Yejin Mok

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This certifies that the dissertation of Yejin Mok is approved.

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Thesis Supervisor: Sun Ha Jee

_____

Chungmo Nam: Thesis Committee Member #1

_____

Tae Hyun Yoo: Thesis Committee Member #2

_____

Heejin Kimm: Thesis Committee Member #3

_____

Jae Woong Sull: Thesis Committee Member #4

The Graduate School

Yonsei University

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ABSTRACT

The contribution of chronic kidney disease measures to cause-specific mortality and morbidity

Mok, Yejin

Dept. of Public Health

The Graduate School

Yonsei University

Chronic kidney disease (CKD) is increasing common public health problem worldwide. The association of CKD with cardiovascular disease (CVD) mortality is well known, however, the association with other causes mortality such as cancer is unclear. This study assessed the effects of CKD on the cause-specific mortality in a large cohort study.

We studied 367,932 adults (20-93 years old) in the Metabolic Syndrome Mortality Study (health check-up database in Korea with baseline between 1994-2004) and 233,219 adults (30-74 years old) in the Korean Heart Study (baseline between 1996-2004). We assessed the associations of creatinine-based estimated glomerular filtration rate (eGFR) and dipstick proteinuria with mortality and morbidity due to CVD (1,608 cases), cancer (4,035 cases), and non-CVD/cancer (3,152 cases) after adjusting for potential confounders.

Lower eGFR (<60 ml/min/1.73m^2 vs. ≥60 ml/min/1.73m^2) was significantly associated with mortality due to CVD [hazard ratio (HR), 1.49 (95% CI, 1.24-1.78)] and non-CVD/cancer [1.78 (1.54-2.05)]. Adjusted cancer mortality risk was the lowest at GFR 45-59 and reached significance at eGFR <45 ml/min/1.73m^2 [1.62 (1.10-2.39)] with eGFR 45-59 ml/min/1.73m^2 as a reference. Proteinuria (dipstick ≥1+ vs. negative/trace)

was consistently associated with mortality due to CVD [1.93 (1.66-2.25)], cancer [1.49 (1.32-1.68)], and non-CVD/cancer [2.19 (1.96-2.45)]. Examination on causes of deaths suggested that low eGFR was significantly associated with higher mortality due to coronary diabetes, infectious disease, heart disease, oropharyngeal cancer, and renal failure, whereas proteinuria was related to mortality from coronary diabetes, infectious disease, heart disease, liver disease, myeloma, renal failure, stroke, and cancers of the stomach, liver, pancreas, and lung. When examining for morbidity, the study found a similar relationship with the results of mortality. Also, a rapid decline in eGFR inferred significantly greater risk for CVD mortality.

Low eGFR was mainly associated with CVD and non-CVD/cancer mortality, whereas proteinuria was consistently related to mortality due to CVD, cancer, and non-CVD/cancer. These findings suggest the need for multidisciplinary prevention and management strategies in individuals with CKD.

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keywords: eGFR, proteinuria, mortality, morbodity

I. INTRODUCTION

Chronic kidney disease (CKD), which causes reduction in kidney function and/or kidney damage, is a common public health problem worldwide (Coresh et al. 2007; Jha et al. 2013; United States Renal Data System 2014). The prevalence of CKD is 10-15% in Asia, Europe, and the USA (Arora et al. 2013; Coresh et al. 2007; Health 2013; Imai et al. 2009; Zhang et al. 2012). Individuals with CKD are at high risk of cardiovascular disease (CVD) and up to half of this population die due to CVD (Matsushita et al. 2010; Di Angelantonio et al. 2010; Hallan et al. 2007; Hemmelgarn et al. 2010; Nagata et al. 2013; Tonelli et al. 2006; Weiner et al. 2004; Wen et al. 2008). Indeed, numerous studies have reported the significant associations of low estimated glomerular filtration rate (eGFR) and high proteinuria with CVD mortality (Matsushita et al. 2010; Hallan et al. 2007; Nagata et al. 2013).

Several studies also have report the association of CKD with all-cause mortality (Matsushita et al. 2010; Hemmelgarn et al. 2010; Tonelli et al. 2006; Weiner et al. 2004; Wen et al. 2008). This may merely reflect the fact that CVD is a leading cause of deaths in many place of the world (World Health Organization.Causes of death: Mortality and health status. WHO data and statistics). On the other hand, a few studies have reported the link of reduced kidney function to mortality due to cancer, the other worldwide leading cause of death (Fried et al. 2005; Iff et al. 2014; Weng et al. 2011). However, to our knowledge, only one study has simultaneously investigated CKD defined by both eGFR and proteinuria as recommended in clinical guidelines, in this context, and did not observe significant association between CKD and cancer mortality (Di Angelantonio et al. 2010). Thus, further studies are obviously needed, particularly for the potential relation between proteinuria and cancer mortality.

Although CVD and cancer are clearly important as causes of death, other causes account for approximately 30-35% of deaths in developed countries (World Health Organization, 2014) and thus also warrant attention. A few studies have investigated an association of CKD with deaths due to non-CVD/cancer causes (Fried et al. 2005; Wang et al. 2011; Weng et al. 2011). In this context, infection mortality has been most

extensively examined but has demonstrated conflicting results across studies (Fried et al. 2005; Wang et al. 2011; Weng et al. 2011). Moreover, the data on proteinuria are sparse (Wang et al. 2011) and causes of other infectious diseases are in need further investigations (Fried et al. 2005; Wang et al. 2011; Weng et al. 2011).

However, these studies have predominantly considered the kidney function at one point but did not assess the association between changes in the kidney function and future risk. Understanding the dynamics of changes in kidney function using serious measurements may contribute to an additional prognostic beyond a single measurement. Although a limited number of studies has demonstrated an association between change in kidney function over time and adverse outcomes (Al-Aly et al. 2010; Matsushita et al. 2009; Perkins et al. 2011; Rifkin et al. 2008). Also, it focused on cardiovascular disease or all-cause mortality.

Since the prevention and management can be substantially different across diseases, quantifying the associations of CKD measures with cause-specific mortality in a single cohort is important from both clinical and public health perspectives. Therefore, the purpose of our study was to comprehensively assess whether creatinine-based eGFR and dipstick proteinuria are associated with mortality due to CVD, cancer, and other causes in a Korean cohort with data from more than 350,000 adults. The large sample size allowed us to also investigate finer causes of death (e.g., CVD subtypes, organ-specific cancer, and representative individual causes in non-CVD/cancer deaths).

II. OBJECTIVES

The purpose of this study was to assess whether the association eGFR, dipstick proteinuria and cause-specific mortality in a prospective cohort investigation among large population in Korea.

Specifically,

1. To assess CKD attribute the cause-specific mortality
2. To explore the association between CKD and cause-specific mortality
3. To compare the change of eGFR adds additional information beyond that obtained by a single eGFR alone

III. MATERIALS AND METHODS

A. Study population

The Metabolic Syndrome Mortality Study (MSMS) is a retrospective cohort study based on private health examinations. We had collected the data of examinations conducted at 18 centers located in Seoul and six provinces in South Korea from 1994-2004. Of these centers, 14 centers opted in to this cause-specific mortality study. The record linkage for mortality was based on an official personal identification number and resulted in 521,585 study members aged 20 years older at health assessment at baseline. Of these, we excluded participants with missing information on serum creatinine (n=37,196) and dipstick urinary test (n=116,457), leaving the final study population of 367,932 participants.

All Koreans are members of the National Health Insurance Service (NHIS). To ensure anonymity, all linkages were carried out by NHIS staff. The record linkage resulted in 430,920 study members (266,782 men and 164,138 women) aged 30-74 years at health assessment at baseline between 1996 and 2004. We have labeled this study as the Korean Heart Study (KHS) (Jee et al. 2013). Of these we excluded participants with having cancer and cardiovascular at baseline (n=13,092), missing information on serum creatinine (n=126,994) and dipstick urinary test (n=57,615), leaving the final study population of 233,219 participants.

The Institutional Review Board of Human Research of Yonsei University and all the individual health promotion centers participating in the MSMS and KHS approved the investigation.

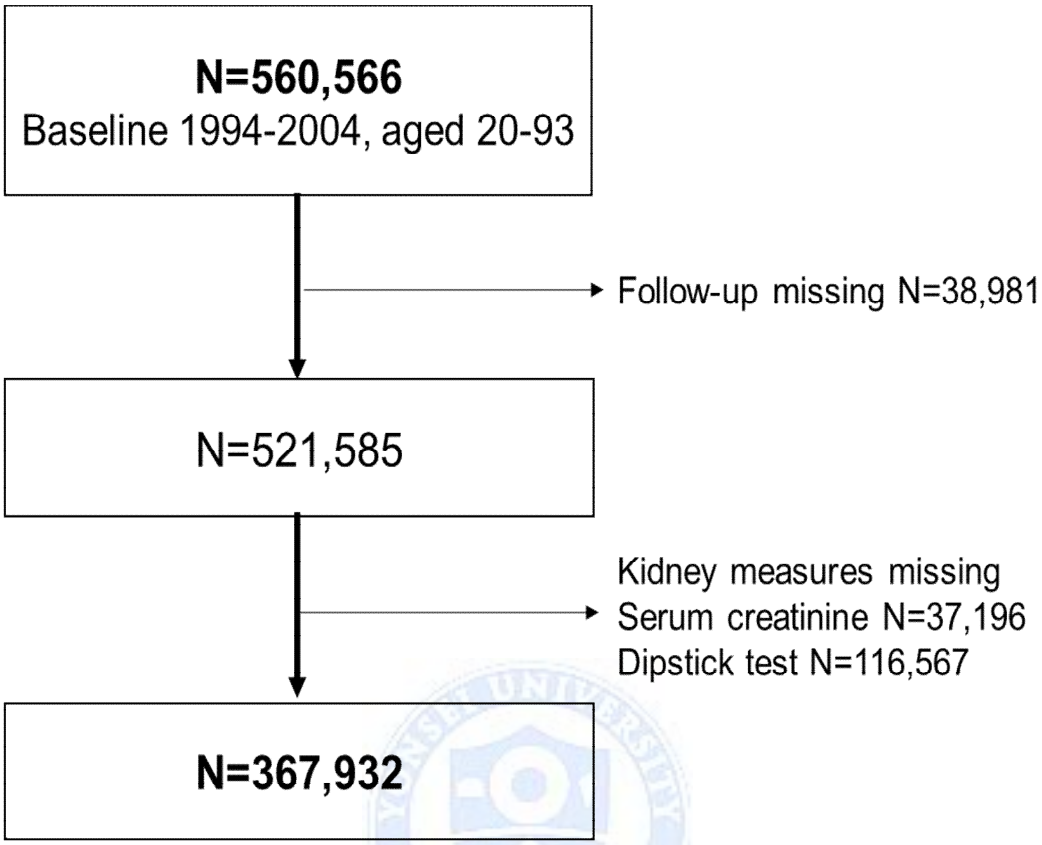

Figure 1. Flow chart describing study population, Metabolic Syndrome Mortality Study

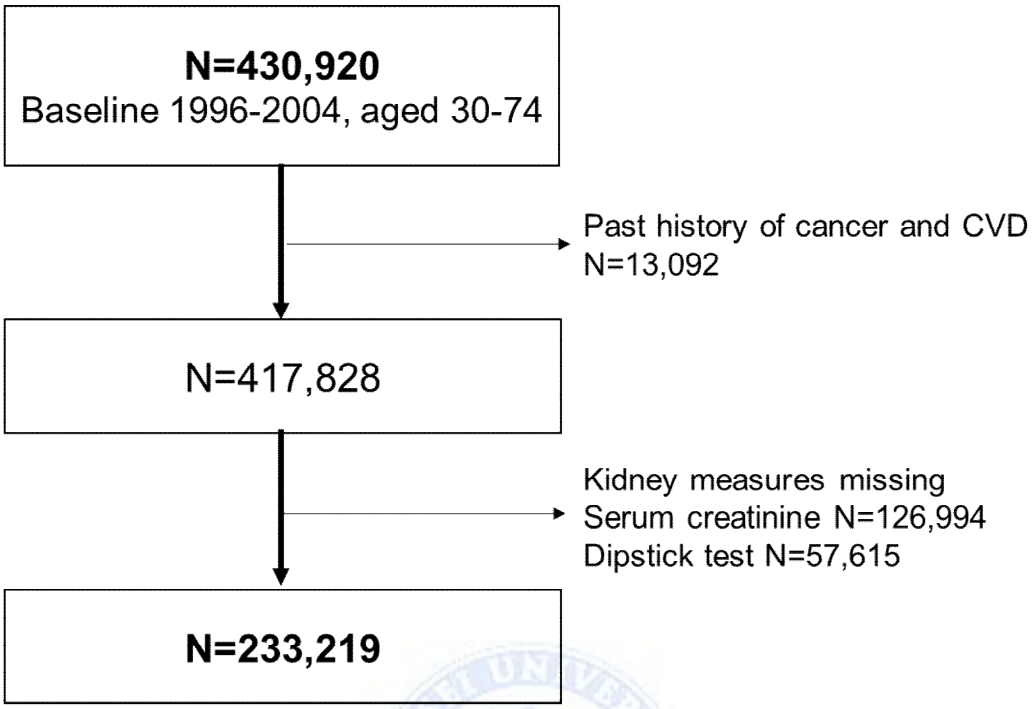

Figure 2. Flow chart describing study population, Korean Heart Study

B. Data collection

Data were collected for demographic information, smoking status (never, past or current), and medical history of comorbidities such as CVD and cancer using a survey. Also, participants' weight (with light clothes worn) and height were collected. Either registered nurses or nurse technicians measured blood pressure. Blood samples were obtained after 12hrs of fasting and serum was stored at -70°C. Total cholesterol, triglyceride, high-density lipoprotein cholesterol, fasting glucose, and liver function (aspartate aminotransferase, alanine aminotransferase) were done across at all centers using the Hitachi-7600 automatic analyzers (Hitachi Ltd, Tokyo, Japan). Viral hepatitis B and hepatitis C were measured in the serum with radioimmunoassay or reverse passive haemagglutination at participating laboratories. Each health center used internal and external quality control procedures as required by the Korean Association of Laboratory Quality Control. Each biomedical marker demonstrated high correlation across all centers (correlations coefficients ranging 0.96-0.99). Diabetes was defined as fasting glucose ≥126 mg/dl, use of glucose-lowering medication, or medical history of diabetes.

C. Assessment of eGFR and dipstick proteinuria

Serum creatinine was measured using he kinetic rate Jaffe method, and eGFR was estimated by the CKD-EPI equation (Levey et al. 2011), in which eGFR ($mL/min/1.73m^2$)= 141 × min(Scr/k, 1)α × max(Scr/k,1)- 1.209 × 0.993age × 1.018 [if patient is female] × 1.159 [if patient is black], where age is in years, k is 0.7 for females and 0.9 for males, α is − 0.329 for females and − 0.411 for males, min indicates the minimum of Scr/k or 1, and max indicates the maximum of Scr/k or 1). Proteinuria was measured by dipstick test using an automated urine analyzer (URiSCAN Pro Ⅱ, YD diagnostics, South Korea), and was recorded as negative, trace, 1+, 2+, 3+, and 4+ across all centers except one health center. It was systematically recorded as negative and trace together as low proteinuria.

D. Change in eGFR

An initial and final eGFR were obtained for a period of one year. This was used to estimate GFR using the CKD-EPI equation and dipstick proteinuria. Change in eGFR was defined as the change in eGFR category with confirmation based on percentage (%) change in eGFR [(last eGFR-first eGFR)/first eGFR X 100]. The groups for change in eGFR was defined as: 'certain drop' (drop in CKD category with ≥25% decrease in eGFR), 'uncertain drop' (drop in CKD category with <25% decrease in eGFR), 'stable' (no change or rise in CKD category). Similar to other studies, a 25% change in the eGFR was used to define certainty of change as this percentage reflect a true change in kidney function rather than variability in creatinine measurements related to the assay or intra-individual serum creatinine variation across measurements (Turin et al. 2012).

E. Follow-up for mortality and morbidity

A computerized search for a death certificate was obtained using the aforementioned official identifier provided by the National Statistical Office in Korea through December 31, 2011. The median follow-up was 9.8 years. Based on the International classification of diseases (ICD) code for primary cause of death and mortality was categorized into CVD (Disease of circulatory system: ICD-10 codes I00-I99 [Coronary Heart Disease: I20-I25, Stroke: I60-I69], Sudden death: R96), cancer (ICD-10 codes C00-C97), and non-CVD/cancer (all causes other than CVD and cancer listed above). To assessment of finer cause of mortality, we also categorized into coronary heart disease (ICD-10 codes I20-I25), stroke (I60-I69), cancer of oropharynx (C00-C14), oesophagus (C15), stomach (C16), colon (C18), rectum (C19-C20), liver (C22), gallbladder (C23), bile duct (C24), pancreas (C25), lung (C34), breast (C50), ovary (C56), urinary tract (C64-C68), brain (C71), unspecified sites (C76-C80), Non-Hodgkin's lymphoma (C82-C85), myeloma (C90) and leukaemia (C91), infectious disease (certain infectious and parasitic diseases:A00-B99; nervous system: G00-G05, G08; circulatory system: I30, I32-I33, I38-I41, I80-I88; respiratory system: J00-J06, J09-J18, J20-J22, J31-J32, J35, J37, J40-J42, J85-J86; digestive system: K05, K29, K65, K67, K73, K80-K81; skin and subcutaneous

tissue: L02-L05, L08; musculoskeletal system and connective tissue: M00-M01, M03), diabetes (E10-E14), Parkinson's disease (G20-G21), chronic obstructive pulmonary disease (J42-J44), Interstitial pulmonary disease (J80-J84), liver disease (K70-K77), renal failure (N17-N19), general symptoms (R50-R69), unknown causes of mortality (R95, R97-R99), accidents (V00-X59) and suicide (X60-X84).

This study conducted to confirm the findings of CVD, cancer, non-CVD/cancer mortality on morbidity data using data from the KHS. Outcomes were ascertained from diagnoses on hospital discharge summaries. For cancer and CVD incidence, one measure was constructed: at least one1 hospitalization for cancer or CVD. For non-CVD/cancer incidence, two measures were constructed: at least one hospitalization or three or more outpatient visits for non-CVD/cancer, then a summary measure was created for having at least one of these indicators.

F. Statistical analysis

i. Descriptive statistic

Descriptive statistic are presented as mean and standard deviation (SD) for continuous variables or percentage for categorical variables across categories of eGFR (≥60 [preserved eGFR], 45-59, 30-44 and <30 ml/min/1.73m^2) and dipstick proteinuria (none/trace [reference], 1+, 2+ and ≥3+). An age-standardized cause-specific mortality rate was calculated for these categories for eGFR and proteinuria using the Korean Population (National Bureau of Statistics, 2010)

ii. Association of eGFR and dipstick proteinuria with cause-specific mortality

Cox proportional hazards models was used to quantify the association of eGFR and proteinuria with cause-specific mortality. For this main analysis, based on clinical guidelines and previous studies (Kidney Disease: Improving Global Outcomes 2013; Levey et al. 2011), we subdivided ≥90 and 60-89ml/min/1.73m^2 into ≥105, 90-104, 75-89

and 60-74. Given that eGFR 75-89 ml/min/1.73m^2 was the most prevalent category in those aged 50 years or older, a group with higher mortality risk than younger individuals, this category was selected as the reference for this analysis, as done in several previous studies (Di Angelantonio et al. 2010; Hallan et al. 2012). We used a restricted cubic spline function with six knots to plot this relationship, which allows for the assessment of non-linear effects of the exposure-outcome relationship. For dipstick proteinuria categories, none/trace was selected due to one center's recording as negative and trace proteinuria for this category. However, using data from 13 centers, we also tested dipstick negative as a reference. Three models were constructed to evaluate the impact of potential confounders. Model 1 incorporated only age and gender. Model 2 further adjusted for the following conventional predictors: smoking status, body mass index, total cholesterol, systolic blood pressure, medication of hypertension, diabetes, and history of CVD and cancer, and each of CKD measures, as appropriate (dipstick proteinuria was accounted for in the analyses for eGFR and vice versa). To assess the robustness of our findings, we repeated our analysis in several subgroups by age (< and ≥60 years), gender, and history of CVD and cancer at baseline. For finer causes of mortality, causes for more than 50 deaths were analyzed. To obtain reliable estimate, we modeled the kidney measures as dichotomous variables (eGFR < vs. ≥60 ml/min/1.73m^2 and dipstick proteinuria ≥1+ vs. none/trace).

iii. Competing risk model

Since competing events can impede the occurrence of the event of interest, competing-risk regression was also considered to evaluate for a possible association between kidney measures and cause-specific mortality. Competing-risks regression is an alternative to Cox regression for survival data in the presence of competing risks. Based on the method of Fine and Gray (1999) (Fine et al, 1999), competing-risks regression posit a model for the sub-hazard function of a failure event of primary interest.

iv. Imputation

The multiple imputations (van Buuren S et al, 1999) were implemented to impute missing values. The method based on conditional specification (FCS) was used, also known as "chained equations". The observed values from the one variable were regressed on the other variables in the imputation model. Missing values in X_1 are replaced by simulated draws from the corresponding posterior predictive distribution of X_1. Then, the next variable with missing values, X_2 say, is regressed on all other variables X_1, X_3, …, X_k, restricted to individuals with the observed X_2, and using the imputed values of X_1. Again, missing values in X_2 are replaced by draws from the posterior predictive distribution of X_2. The process is repeated for all other variables with missing values in turn: this is called a cycle (White IR et al, 2011). Theses regression models were operated under the same assumptions that one would make when performing linear (continuous) or logistic (binary) regression models outside of the context of imputing missing data. The missing values were replaced with predictions (imputations) from the regression model. We implemented multiple imputation (van Buuren S et al, 1999) to impute smoking status (200,887 participant with missing values), diabetes (20 participants), systolic blood pressure (362 participants), and total cholesterol (17 participants) using age, gender, history of cancer and CVD, body mass index, use of anti-hypertensive drugs, eGFR, dipstick proteinuria, death due to CVD, cancer, or other causes, and follow-up time and performed 20 cycles.

All analyses were performed using STATA statistical software version 12. All statistical tests were two-sided and statistical significance was determined as $p<0.05$.

IV. RESULTS

A. General characteristics of study population

The mean age of the study participants was 41.7 (SD, 10.9) years and 41.5% were women. Current smokers were substantially more common in men (54.4%) than in women (5.8%). The average eGFR was 94.2 (SD, 14.4) ml/min/1.73m^2. Among the participants, 1.0% had eGFR below 60 ml/min/1.73m^2 and 3.7% had dipstick proteinuria ≥1+. The participants with lower eGFR (<60 ml/min/1.73m^2) or higher dipstick proteinuria (≥1+) were more likely to be older, men and have diabetes, hypertension, and hypercholesterolemia compared with the participants with higher eGFR (≥60 ml/min/1.73m^2) and lower proteinuria (negative or trace), respectively (Table 1).

Table 2 shows the general characteristics of the study population by cause-specific mortality. Those who died from CVD, cancer and non-CVD/cancer were more likely to be old, men and had higher current smokers status, diabetes and hypertension compared with those who are living. The mean of eGFR by cause-specific mortality was 85.9, 82.3, 86.1 and 94.4 ml/min/1.73m^2 in cancer, CVD, non-CVD/cancer and alive, respectively. The proportion of dipstick proteinuria (≥1+) was 7.68, 13.25, 12.75 and 3.50 % in cancer, CVD, non-CVD/cancer and alive, respectively.

Table 1. **Baseline characteristics by eGFR and dipstick in Korean Heart Study, N=367,932**

	eGFR, ml/min/1.73m^2				Dipstick proteinuria			
	≥90 N=227,370	60-89 N=136,920	45-59 N=3,136	<45 N=506	None/trace N=354,433	1+ N=10,090	2+ N=2,545	≥3+ N=864
Age, years	38.2(9.3)	46.9(10.8)	61.2(9.9)	58.1(13.4)	41.6 (10.9)	42.7 (11.8)	44.2 (12.5)	47.1 (12.8)
Female	44.51	36.33	53.09	46.05	41.80	34.07	36.27	34.95
Smoking status								
Ex-smoker	5.34	8.81	14.51	12.85	14.76	14.54	16.54	22.15
Current smoker	14.45	17.00	12.34	15.22	33.39	43.72	39.72	36.97
Cardiovascular disease	0.35	0.79	3.22	3.56	0.51	1.14	1.57	1.50
Cancer	0.19	0.26	0.48	0.59	0.21	0.37	0.24	0.35
Diabetes	3.6	5.72	12.21	21.34	4.04	14.13	20.31	26.62
Diabetes medication	0.57	0.96	3.19	7.51	0.66	2.59	3.50	8.33
Fasting glucose, mg/dl	90.2(20.1)	94.3(21.8)	101.5(31.3)	103.6(35.5)	91.3 (19.6)	103.5 (38.5)	110.3 (46.3)	117.3 (54.4)
Hypertension medication	1.56	3.96	15.05	26.28	2.42	6.40	9.19	14.81
Hypertension	18.85	29.08	54.37	69.57	22.44	35.62	46.40	57.64
SBP, mmHg	116.9(16.0)	122.1(18.1)	134.4(22.2)	142.0(25.6)	118.8 (16.9)	124.2 (20.4)	129.0 (23.2)	137.2 (27.0)
DBP, mmHg	73.9(11.3)	76.5(12.0)	78.4(13.4)	82.4(15.5)	74.8 (11.5)	78.3 (13.3)	80.7 (14.6)	82.0 (15.2)
Hypercholesterolemia	5.32	10.27	20.5	23.32	7.08	11.87	15.60	27.89
Total-C, mmol/l	4.7(0.9)	5.0(0.9)	5.4(1.0)	5.3(1.4)	4.8 (0.8)	5.0 (1.0)	5.2 (1.1)	5.6 (1.3)
HDL-C, mmol/l	1.3(0.3)	1.3(0.3)	1.3(0.3)	1.2(0.3)	1.3 (0.3)	1.3 (0.3)	1.3 (0.3)	1.2 (0.3)
Triglyceride, mmol/l	1.5(1.1)	1.7(1.1)	1.9(1.2)	2.2(1.5)	1.6 (1.1)	1.8 (1.4)	2.0 (1.7)	2.3 (1.9)
LDL-C, mmol/l	2.8(0.8)	3.0(0.8)	3.3(1.0)	3.2(1.2)	2.9 (0.8)	2.9 (0.9)	3.1 (1.0)	3.4 (1.2)
Height, cm	165.3(8.3)	164.9(8.6)	160.1(8.6)	160.9(9.1)	165.1 (8.5)	165.8 (8.1)	164.9 (8.3)	164.4 (8.4)
Weight, kg	63.0(11.5)	65.3(10.8)	63.6(10.4)	62.1(10.5)	63.8 (11.2)	65.4 (12.1)	65.8 (12.9)	65.4 (12.4)
Body mass index, kg/m^2	23.0(3.2)	23.9(3.0)	24.7(3.1)	23.9(3.3)	23.3 (3.1)	23.7 (3.5)	24.1 (3.8)	24.1 (3.7)
Obesity	2.12	2.65	4.91	4.55	2.26	4.05	5.89	6.25
Serum creatinine, mg/dl	0.8(0.1)	1.0(0.1)	1.2(0.2)	2.5(2.2)	0.9 (0.2)	1.0 (0.3)	1.0 (0.5)	1.3 (1.4)
eGFR, ml/min/1.73m^2	103.2(8.9)	80.3(7.1)	55.7(3.5)	32.6(11.5)	94.4 (14.2)	91.3 (16.5)	86.5 (20.6)	77.4 (26.5)

SBP: systolic blood pressure; DBP: diastolic blood pressure; Total-C: Total cholesterol; HDL-C: HDL-cholesterol; LDL-cholesterol: LDL--cholesterol

Table 2. Baseline characteristics by cause-specific mortality

	Cause-specific death			
	Cancer	CVD	Non-CVD/cancer	Alive
	N=4,035	N=1,608	N=3,152	N=359,137
Age, years	55.5 (11.1)	57.8 (12.2)	54.6 (13.5)	41.3 (10.7)
Female	26.62	30.04	28.55	41.87
Smoking status				
Ex-smoker	12.34	12.56	12.21	6.58
Current smoker	30.29	29.1	28.24	15.04
Cardiovascular disease	1.16	3.67	1.4	0.51
Cancer	0.97	0.50	0.22	0.21
Diabetes	12.04	16.29	18.27	4.23
Diabetes medication	2.50	2.80	3.68	0.69
Fasting glucose, mg/dl	100.7 (30.2)	106.1 (40.2)	108.1 (44.8)	91.6 (20.3)
Hypertension medication	5.48	11.26	6.63	2.50
Hypertension	39.33	57.03	43.50	22.52
SBP, mmHg	127.7 (20.9)	138.2(24.0)	128.9 (22.2)	118.8 (16.9)
DBP, mmHg	76.7 (13.0)	80.3(14.3)	77.9 (13.4)	74.9 (11.6)
Hypercholesterolemia	10.16	18.28	12.47	7.19
Total C, mmol/l	4.9 (1.0)	5.2(1.1)	5.0 (1.1)	4.8 (0.9)
HDL-C, mmol/l	1.3 (0.3)	1.2(0.3)	1.3 (0.3)	1.3 (0.3)
Triglyceride, mmol/l	1.7 (1.2)	1.9(1.4)	1.9 (1.6)	1.6 (1.1)
LDL-C, mmol/l	2.9 (0.9)	3.1(1.0)	2.9 (1.0)	2.9 (0.8)
Height, cm	164.1 (8.0)	162.3(9.0)	163.2 (8.5)	165.1 (8.5)
Weight, kg	63.4 (10.2)	63.5(11.1)	61.6 (10.9)	63.9 (11.3)
Body mass index, kg/m^2	23.5 (3.2)	24.0(3.3)	23.1 (3.3)	23.4 (3.1)
Obesity	2.35	3.73	1.94	2.34
Serum creatinine, mg/dl	0.9 (0.3)	1.0(0.4)	1.0 (0.6)	0.9 (0.2)
eGFR, $ml/min/1.73m^2$	85.9 (14.8)	82.3(17.0)	86.1 (18.2)	94.4 (14.3)
Proteinuria (>=1+)	7.68	13.25	12.75	3.50

SBP: systolic blood pressure; DBP: diastolic blood pressure; Total-C: Total cholesterol; HDL-C: HDL-cholesterol; LDL-cholesterol: LDL--cholesterol

B. Age-standardized mortality rate (per 1000 person-years) by eGFR and dipstick proteinuria

During the median follow-up of 9.8 years, 8796 participants died (1,608 from CVD, 4,035 from cancer, and 3,152 from non-CVD/cancer). Age-standardized mortality rate due to CVD, cancer, and non-CVD/cancer largely increased as eGFR decreased (Figure 3). Regarding the proportion of each mortality cause, non-CVD/cancer was the most common cause of death only among those with eGFR above 90 ml/min/1.73m^2 (42.0%), but death due to cancer were most common in eGFR 60-89 ml/min/1.73m^2. Regardless of eGFR categories, CVD accounted least as a cause of mortality (18.9%-30.2%). Similarly, age-standardized mortality rate for CVD, cancer, and non-CVD/cancer tended to increase along with proteinuria. In terms of respective proportion, again, non-CVD/cancer were most common among those with positive proteinuria (dipstick ≥1+) (42.2%-54.0%), but cancer was the most common cause of death among those with none/trace dipstick proteinuria (41.7%).

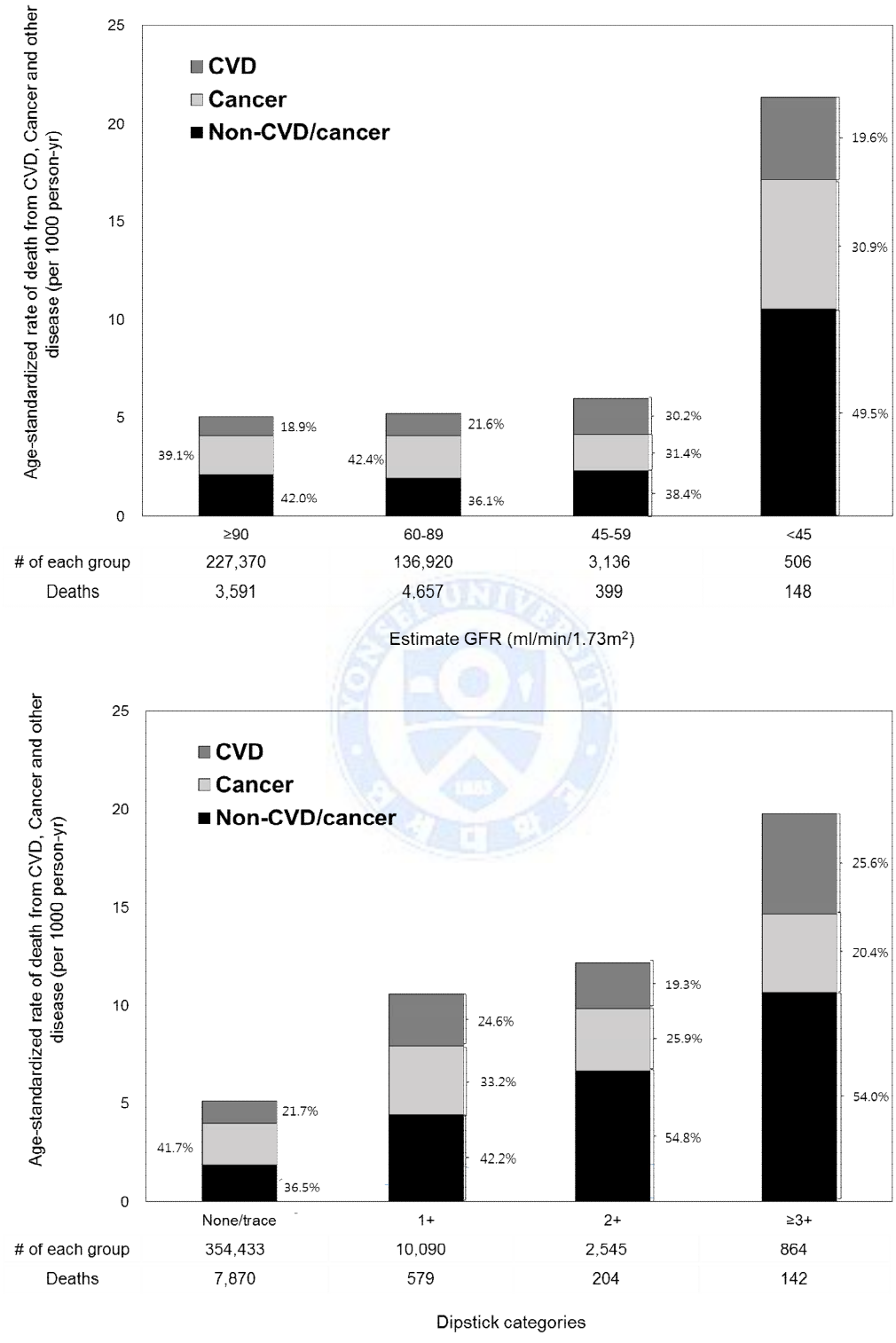

Figure 3. Age-standardized mortality rate (per 100 person-years) by eGFR and dipstick proteinuria categories

C. Cause-specific mortality by eGFR

Crude hazard ratios (HRs) for mortality due to CVD, cancer and non-CVD/cancer were significantly increased as eGFR levels decreased, with eGFR of 75-89 ml/min/1.73m^2 as a reference (Table 3). After adjusting for the potential confounders, eGFR categories below 60 ml/min/1.73m^2 were significantly associated with higher mortality due to CVD and non-CVD/cancer, with higher HR for non-CVD/cancer mortality at a given eGFR category than for CVD mortality [e.g., HR 5.39 (95%CI 3.78-7.70) for non-CVD/cancer mortality and 2.64 (1.42-4.89) in eGFR <30]. Risk of cancer mortality was lowest at eGFR 45-59 after the adjustment for potential confounders and reached at eGFR <45 ml/min/1.73m^2 [1.62 (1.10-2.39)] with eGFR 45-59 as a reference. High eGFR was associated with lower risk of CVD, cancer, and non-CVD/cancer compared to the reference group in the crude model but showed higher risk once age and gender were taken into account. When we tested dichotomous eGFR, eGFR<60ml/min/1.73m^2 was significantly associated with mortality due to CVD [1.49 (1.24-1.78)] and non-CVD/cancer [1.78 (1.54-2.05)] compared to eGFR ≥60 ml/min/1.73m^2 in Model3.

HRs for mortality due to CVD, cancer and non-CVD/cancer were significantly increased as eGFR decline before imputing to missing variable. Compared to imputed model, HRs for mortality due to CVD, cancer and non-CVD/cancer were similar, but slightly lower risk gradient for imputed model over non-imputed model.

To consider failure events of primary interest, we used a competing-risks model. HRs for mortality due to CVD, cancer and non-CVD/cancer were significantly increased as eGFR decline (Table A1). Compared to not competing-risks model, HRs for mortality due to CVD, cancer and non-CVD/cancer were similar, but slightly at lower risk gradient for competing-risks model for CVD and cancer mortality, while higher risk gradient for competing-risks model for non-CVD/cancer mortality in lowest eGFR category

Table 3. Hazard ratios (95%CI) for cause-specific mortality by eGFR

	eGFR, ml/min/1.73m^2					
	≥105 N=87,468	90-104 N=139,902	75-89 N=105,839	60-74 N=31,081	45-59 N=3,136	<45 N=338
Cancer mortality						
Cases	339	1,287	1,507	741	128	33
Crude	0.27 (0.24-0.30)	0.65 (0.60-0.70)	1.0	1.66 (1.52-1.81)	2.94 (2.45-3.52)	5.19 (3.67-7.32)
Model 1	1.28 (1.12-1.45)	1.09 (1.01-1.18)	1.0	0.91 (0.83-1.00)	0.75 (0.63-0.91)	1.46 (1.03-2.07)
Model 2*	1.19 (1.02-1.40)	1.02 (10.93-1.11)	1.0	0.94 (0.84-1.05)	0.82 (0.66-1.02)	1.37 (0.92-2.04)
Model 2 (impute)	1.16 (1.02-1.32)	1.04 (0.97-1.13)	1.0	0.95 (0.87-1.04)	0.78 (0.65-0.94)	1.26 (0.88-1.80)
CVD mortality						
Cases	103	447	570	335	118	35
Crude	0.22 (0.18-0.27)	0.59 (0.53-0.67)	1.0	1.98 (1.73-2.27)	7.17 (5.88-8.74)	14.57 (10.35-20.49)
Model 1	1.19 (0.95-1.49)	1.05 (0.93-1.20)	1.0	1.03 (0.90-1.18)	1.62 (1.32-2.00)	3.59 (2.53-5.07)
Model 2*	1.18 (0.89-1.57)	1.08 (092-1.25)	1.0	0.93 (0.79-1.10)	1.29 (1.00-1.66)	2.21 (1.48-3.30)
Model 2 (impute)	1.17 (0.93-1.46)	1.03 (0.91-1.17)	1.0	0.99 (0.86-1.13)	1.34 (1.90-1.66)	2.09 (1.45-3.01)
Non-CVD/cancer mortality						
Case	396	1,019	992	512	153	80
Crude	0.47 (0.42-0.53)	0.78 (0.71-0.85)	1.0	1.74 (1.56-1.93)	5.32 (4.49-6.31)	19.09 (15.20-23.97)
Model 1	2.01 (1.77-2.29)	1.26 (1.15-1.38)	1.0	0.99 (0.89-1.10)	1.48 (1.24-1.76)	5.86 (4.64-7.39)
Model 2*	1.74 (1.48-2.06)	1.18 (1.06-1.32)	1.0	0.98 (0.86-1.12)	1.37 (1.10-1.69)	3.28 (2.45-4.38)
Model 2 (impute)	1.73 (1.51-1.91)	1.19 (1.09-1.30)	1.0	1.02 (0.92-1.14)	1.41 (1.18-1.68)	3.35 (2.61-4.31)
All-cause mortality						
Case	838	2,753	3,069	1,588	399	148
Crude	0.32 (0.30-0.35)	0.68 (0.64-0.71)	1.0	1.74 (1.64-1.85)	4.50 (4.05-4.90)	11.42 (9.67-13.47)
Model 1	1.53 (1.40-1.66)	1.14 (1.08-1.20)	1.0	0.96 (0.90-1.02)	1.16 (1.04-1.29)	3.24 (2.74-3.83)
Model 2*	1.39 (1.25-1.54)	1.08 (1.01-1.15)	1.0	0.95 (0.88-1.03)	1.12 (0.98-1.27)	2.27 (1.86-2.77)
Model 2 (impute)	1.37 (1.26-1.49)	1.90 (1.03-1.15)	1.0	0.98 (0.92-1.04)	1.11 (1.00-1.24)	2.20 (1.84-2.63)

Model 1: adjusted for age and gender

Model 2: adjusted for age, gender, total cholesterol, diabetes, cardiovascular disease, cancer, current smoker, systolic blood pressure, anti-hypertensive, body mass index and dipstick proteinuria

* used to analyze 166,867 population

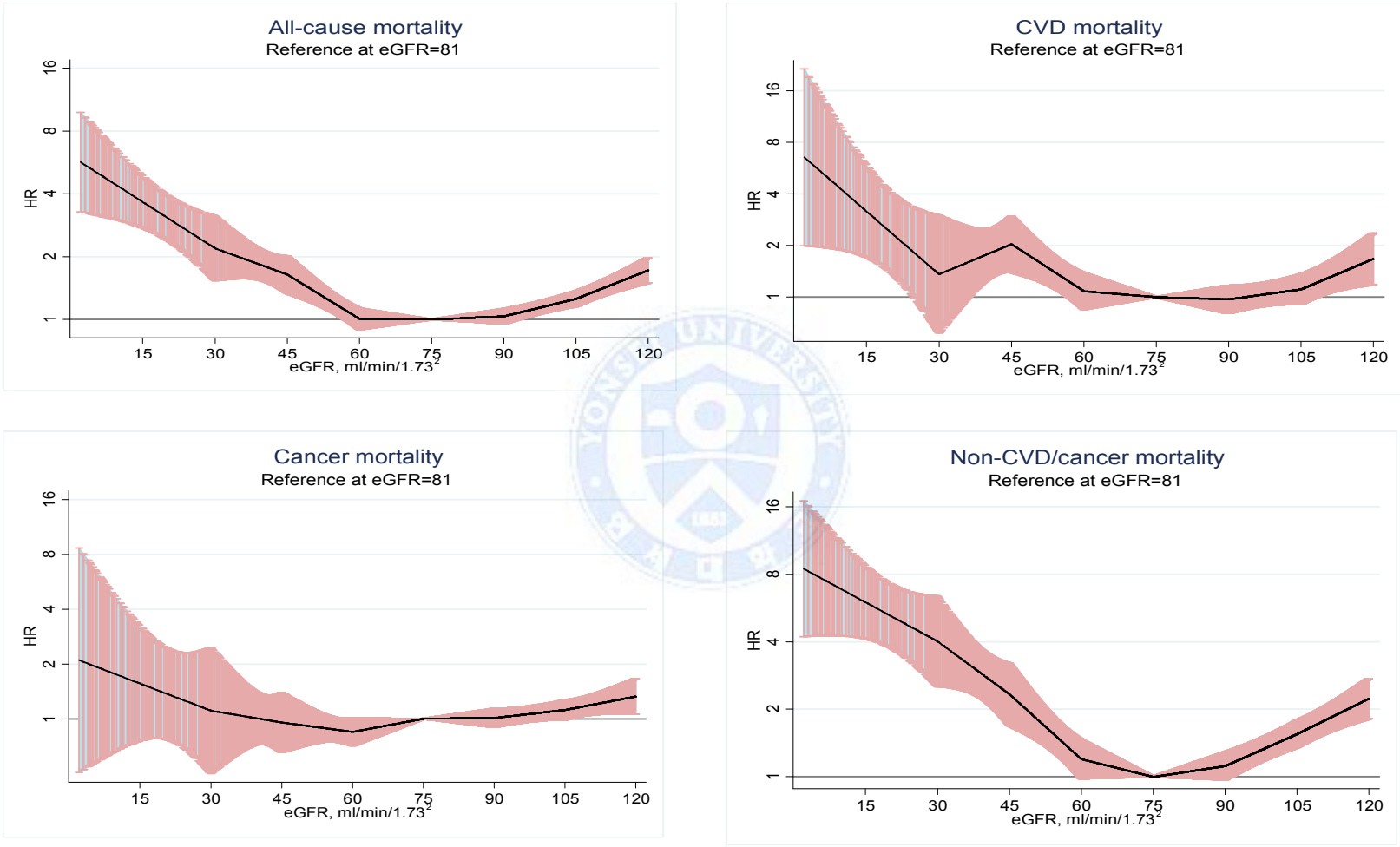

Figure 4. Adjusted hazard ratio of cause-specific mortality by eGFR

D. **Cause-specific mortality by dipstick proteinuria**

In contrast to eGFR, high proteinuria was consistently associated with all of CVD, cancer and non-CVD/cancer mortality outcomes, with robust dose-response relationship (Table 4). HR for non-CVD/cancer mortality was higher at any given proteinuria category followed by CVD and cancer mortality. For all mortality outcomes including cancer, risk was significantly increased even at 1+ proteinuria group [e.g., HR 1.45 (95% CI 1.26-1.66) for cancer]. With available data separating dipstick negative and trace, dipstick trace was significantly associated with increased risk of mortality due to CVD and non-CVD/cancer (Table 5). The association with cancer mortality was borderline significant [1.13 (0.99-1.29), p=0.075]. When we tested dichotomous dipstick proteinuria, positive proteinruia was significantly associated with mortality due to CVD [1.93 (1.66-2.25)], cancer [1.49 (1.32-1.68)] and non-CVD/cancer [2.19 (1.96-2.45)] compared to none/trace.

HRs for mortality due to CVD, cancer and non-CVD/cancer were significantly increased as high proteinuria before imputing to missing variable. Compared to imputed model, HRs for mortality due to CVD, cancer and non-CVD/cancer were similar, but slightly higher risk gradient for imputed model over non-imputed model.

A competing-risks model was used to consider a failure event of primary interest. HRs for mortality due to CVD, cancer and non-CVD/cancer were significantly increased as eGFR decline (Table A2). Compared to not competing-risks model, HRs for mortality due to CVD, cancer and non-CVD/cancer were similar, but slightly at lower risk gradient for competing-risks model for CVD, cancer and non-CVD/cancer mortality.

Table 4. Hazard ratios (95%CI) for cause-specific mortality by dipstick proteinuria

	Dipstick proteinuria			
	None/trace	1+	2+	≥3+
	N=354,433	N=10,090	N=2,545	N=864
Cancer mortality				
Case	3,725	219	59	32
Crude	1.0	1.85 (1.61-2.12)	2.18 (1.69-2.82)	3.22 (2.28-4.57)
Model 1	1.0	1.49 (1.30-1.70)	1.47 (1.14-1.91)	1.86 (1.31-2.63)
Model 2*	1.0	1.32 (1.13-1.56)	1.55 (1.15-2.10)	1.82 (1.20-2.75)
Model 2 (impute)	1.0	1.45 (1.26-1.66)	1.47 (1.13-1.91)	1.87 (1.30-2.68)
CVD mortality				
Case	1,395	135	42	36
Crude	1.0	3.07 (2.58-3.66)	4.16 (3.06-5.65)	9.76 (7.01-13.59)
Model 1	1.0	2.40 (2.01-2.87)	2.67 (1.97-3.64)	5.33 (3.82-7.42)
Model 2*	1.0	1.94 (1.58-2.39)	1.84 (1.28-2.65)	2.45 (1.62-3.70)
Model 2 (impute)	1.0	1.86 (1.55-2.24)	1.69 (1.23-2.32)	2.43 (1.68-3.51)
Non-CVD/cancer mortality				
Case	2,750	225	103	74
Crude	1.0	2.56 (2.23-2.93)	5.15 (4.23-6.27)	10.03 (7.96-12.64)
Model 1	1.0	2.13 (1.86-2.44)	3.65 (3.00-4.44)	6.12 (4.85-7.71)
Model 2*	1.0	1.81 (1.55-2.13)	2.66 (2.07-3.41)	2.81 (2.03-3.89)
Model 2 (impute)	1.0	1.77 (1.54-2.03)	2.67 (2.17-3.28)	3.28 (2.52-4.28)
All-cause mortality				
Case	7,870	579	204	142
Crude	1.0	2.31 (2.13-2.58)	3.57 (3.11-4.10)	6.77 (5.73-7.99)
Model 1	1.0	1.88 (1.72-2.04)	2.43 (2.12-2.79)	3.94 (3.33-4.65)
Model 2*	1.0	1.62 (1.47-1.79)	2.03 (1.71-2.40)	2.43 (1.96-3.01)
Model 2 (impute)	1.0	1.65 (1.51-1.80)	1.97 (1.71-2.28)	2.65 (2.20-3.18)

Model 1: adjusted for age and gender

Model 2: adjusted for age, gender, total cholesterol, diabetes, cardiovascular disease, cancer, current smoker, systolic blood pressure, anti-hypertensive, body mass index and eGFR

* used to analyze 166,867 population

Table 5. Hazard ratios (95%CI) for cause-specific mortality by dipstick proteinuria in Korean Heart Study (excluding hospital #7), N=178,603

	Dipstick proteinuria				
	none	trace	+	++	≥+++
	N=154,739	N=14,272	N=7,320	N=1,598	N=674
Cancer mortality					
Crude	1.0	1.46 (1.28-1.68)	1.61 (1.47-1.77)	1.98 (1.60-2.45)	3.31 (2.51-4.36)
Model 1	1.0	1.16 (1.02-1.32)	1.44 (1.24-1.67)	1.52 (1.14-2.03)	1.92 (1.33-2.76)
Model 2 (impute)	1.0	1.13 (0.99-1.29)	1.40 (1.20-1.63)	1.53 (1.14-2.05)	1.89 (1.28-2.77)
CVD mortality					
Crude	1.0	1.87 (1.55-2.26)	3.19 (2.68-3.82)	4.33 (3.18-5.89)	10.17 (7.30-14.17)
Model 1	1.0	1.57 (1.29-1.90)	2.35 (1.93-2.86)	2.81 (1.98-3.98)	5.59 (3.92-7.95)
Model 2 (impute)	1.0	1.39 (1.15-1.69)	1.88 (1.53-2.30)	1.82 (1.27-2.60)	2.61 (1.75-3.88)
Non-CVD/cancer mortality					
Crude	1.0	1.85 (1.62-2.12)	2.67 (2.33-3.06)	5.36 (4.40-6.53)	10.47 (8.30-13.19)
Model 1	1.0	1.58 (1.37-1.81)	2.17 (1.87-2.52)	3.68 (2.94-4.62)	5.65 (4.35-7.32)
Model 2 (impute)	1.0	1.47 (1.28-1.69)	1.84 (1.58-2.14)	2.87 (2.27-3.62)	3.06 (2.27-4.13)
All-cause mortality					
Crude	1.0	1.30 (1.19-1.42)	2.08 (1.90-2.28)	3.20 (2.73-3.75)	5.61 (4.68-6.72)
Model 1	1.0	1.37 (1.26-1.49)	1.85 (1.69-2.03)	2.48 (2.12-2.91)	3.83 (3.20-4.59)
Model 2 (impute)	1.0	1.29 (1.19-1.41)	1.65 (1.50-1.81)	2.08 (1.76-2.44)	2.57 (2.10-3.14)

Model 1: adjusted for age and gender

Model 2: adjusted for age, gender, total cholesterol, diabetes, cardiovascular disease, cancer, current smoker, systolic blood pressure, anti-hypertensive, body mass index and eGFR

E. Stratification by gender and age

Table 6 shows the HRs for cause-specific mortality by eGFR and gender. Adjusted HRs for mortality due to CVD and non-CVD/cancer were significantly increased as eGFR levels decreased both of men and women. Also, High eGFR was associated with higher risk of non-CVD/cancer mortality compared to the reference group. However, HRs for mortality due to cancer was not significantly increased as eGFR levels decreased in both genders.

High proteinuria was consistently associated with all of CVD and non-CVD/cancer mortality outcomes in both genders, with robust dose-response relationship (Table 7). In women, risk of CVD mortality was associated with only ≥3+ proteinuria [HR 3.80 (95%CI 1.94-7.43)]. For cancer mortality, its association was significant in men, but not in women.

Table 6. Hazard ratios (95%CI) for cause-specific mortality by eGFR and gender

	eGFR, ml/min/1.73m^2					
	≥105	90-104	75-89	60-74	45-59	<45
Men (N=215,103)	N=41,958	N=84,219	N=68,605	N=18,577	N=1,471	N=273
Cancer mortality						
Model 1	1.30 (1.11-1.52)	1.09 (1.00-1.20)	1.0	0.86 (0.77-0.95)	0.63 (0.50-0.79)	1.49 (1.00-2.23)
Model 2	1.15 (0.98-1.34)	1.03 (0.94-1.12)	1.0	0.91 (0.82-1.02)	0.66 (0.52-0.83)	1.27 (0.84-1.92)
CVD mortality						
Model 1	1.18 (0.91-1.54)	1.03 (0.88-1.19)	1.0	1.04 (0.88-1.23)	1.70 (1.31-2.21)	3.69 (2.34-5.82)
Model 2	1.12 (0.86-1.45)	1.01 (0.87-1.18)	1.0	1.01 (0.85-1.19)	1.36 (1.04-1.78)	2.08 (1.29-3.38)
Non-CVD/cancer mortality						
Model 1	2.13 (1.82-2.48)	1.32 (1.19-1.47)	1.0	0.98 (0.87-1.12)	1.47 (1.18-1.82)	5.74 (4.30-7.67)
Model 2	1.77 (1.52-2.07)	1.22 (1.10-1.36)	1.0	1.04 (0.92-1.19)	1.44 (1.16-1.79)	3.29 (2.42-4.49)
All-cause mortality						
Model 1	1.56 (1.41-1.73)	1.15 (1.08-1.23)	1.0	0.93 (0.87-1.00)	1.06 (0.93-1.22)	3.12 (2.53-3.83)
Model 2	1.36 (1.23-1.51)	1.09 (1.02-1.16)	1.0	0.97 (0.90-1.05)	1.04 (0.91-1.19)	2.12 (1.71-2.64)
Women (N=152,829)	N=45,510	N=55,683	N=37,234	N=12,504	N=1,665	N=233
Cancer mortality						
Model 1	1.09 (0.86-1.37)	1.09 (0.93-1.27)	1.0	1.06 (0.89-1.27)	1.13 (0.83-1.55)	1.44 (0.71-2.92)
Model 2	1.07 (0.85-1.35)	1.09 (0.93-1.27)	1.0	1.07 (0.90-1.27)	1.13 (0.82-1.54)	1.28 (0.62-2.64)
CVD mortality						
Model 1	1.37 (0.88-2.14)	1.13 (0.89-1.44)	1.0	1.02 (0.80-1.30)	1.46 (1.04-2.05)	3.03 (1.76-5.20)
Model 2	1.38 (0.88-2.17)	1.10 (0.86-1.40)	1.0	0.95 (0.75-1.22)	1.28 (0.91-1.81)	1.19 (0.67-2.11)
Non-CVD/cancer mortality						
Model 1	1.69 (1.33-2.15)	1.10 (0.93-1.31)	1.0	0.98 (0.80-1.20)	1.48 (1.09-2.01)	6.12 (4.14-9.06)
Model 2	1.58 (1.25-2.03)	1.09 (0.91-1.29)	1.0	0.97 (0.79-1.18)	1.32 (0.96-1.80)	3.21 (2.09-4.93)
All-cause mortality						
Model 1	1.39 (1.19-1.62)	1.10 (0.99-1.22)	1.0	1.03 (0.92-1.15)	1.37 (1.14-1.65)	3.58 (2.69-4.76)
Model 2	1.33 (1.14-1.55)	1.09 (0.98-1.21)	1.0	1.01 (0.90-1.14)	1.27 (1.06-1.53)	2.33 (1.72-3.16)

Model 1: adjusted for age

Model 2: adjusted for age, total cholesterol, diabetes, cardiovascular disease, cancer, current smoker, systolic blood pressure, anti-hypertensive, body mass index and dipstick proteinuria

Table 7. Hazard ratios (95%CI) for cause-specific mortality by dipstick and gender

	Dipstick proteinuria			
	None/trace	1+	2+	≥3+
Men (N=215,103)	N=206,267	N=6,652	N=1,622	N=562
Cancer mortality				
Model 1	1.0	1.45 (1.25-1.69)	1.42 (1.07-1.90)	1.87 (1.28-2.73)
Model 2	1.0	1.41 (1.21-1.65)	1.42 (1.06-1.91)	1.84 (1.24-2.72)
CVD mortality				
Model 1	1.0	2.60 (2.13-3.16)	2.75 (1.93-3.91)	5.15 (3.49-7.61)
Model 2	1.0	2.00 (1.63-2.45)	1.82 (1.26-2.61)	2.28 (1.49-3.51)
Non-CVD/cancer mortality				
Model 1	1.0	2.03 (1.74-2.38)	3.48 (2.78-4.37)	5.56 (4.24-7.29)
Model 2	1.0	1.71 (1.45-2.00)	2.70 (2.13-3.41)	3.35 (2.49-4.50)
All-cause mortality				
Model 1	1.0	1.85 (1.68-2.03)	2.34 (2.00-2.75)	3.67 (3.03-4.44)
Model 2	1.0	1.63 (1.48-1.80)	1.97 (1.68-2.32)	2.64 (2.15-3.23)
Women (N=152,829)	N=148,166	N=3,438	N=923	N=302
Cancer mortality				
Model 1	1.0	1.54 (1.12-2.11)	1.60 (0.90-2.82)	1.63 (0.68-3.93)
Model 2	1.0	1.49 (1.08-2.05)	1.51 (0.85-2.69)	1.64 (0.67-4.00)
CVD mortality				
Model 1	1.0	1.92 (1.26-2.92)	2.57 (1.37-4.81)	6.45 (3.45-12.07)
Model 2	1.0	1.52 (0.99-2.32)	1.47 (0.77-2.81)	3.80 (1.94-7.43)
Non-CVD/cancer mortality				
Model 1	1.0	2.48 (1.87-3.30)	4.16 (2.80-6.20)	8.11 (5.20-12.64)
Model 2	1.0	2.07 (1.55-2.75)	2.83 (1.86-4.30)	4.72 (2.91-7.67)
All-cause mortality				
Model 1	1.0	1.96 (1.62-2.36)	2.72 (2.03-3.63)	4.93 (3.53-6.89)
Model 2	1.0	1.71 (1.41-2.07)	2.04 (1.51-2.75)	3.46 (2.43-4.93)

Model 1: adjusted for age

Model 2: adjusted for age, total cholesterol, diabetes, cardiovascular disease, cancer, current smoker, systolic blood pressure, anti-hypertensive, body mass index and eGFR

Table 8 shows the HR for cause-specific mortality by eGFR and age (<60 and ≥ 60 years). Adjusted HRs for mortality due to non-CVD/cancer was significantly increased as eGFR levels decreased in <60 years old, with eGFR of 75-89 ml/min/1.73m^2 as a reference. Risk of cancer mortality was associated with the lowest eGFR levels (<45 ml/min/1.73m^2) in <60 years. In ≥60 years old, adjusted HRs for mortality due to CVD and non-CVD/cancer was significantly increased as eGFR levels decreased, with eGFR of 75-89 ml/min/1.73m^2 as a reference.

High proteinuria was consistently associated with all of CVD, cancer and non-CVD/cancer mortality outcomes in <60 years, with robust dose-response relationship (Table 9). In ≥60 years old, high proteinuria was associated with risk of non-CVD/cancer mortality but not significantly in risk of CVD and cancer mortality.

Table 8. Hazard ratios (95%CI) for cause-specific mortality by eGFR and age

	eGFR, ml/min/1.73m^2					
	≥105	90-104	75-89	60-74	45-59	<45
Age<60 (N=339,855)	N=87,358	N=133,768	N=94,769	N=22,406	N=1,310	N=244
Cancer mortality						
Model 1	1.37 (1.20-1.57)	1.09 (0.99-1.20)	1.0	0.91 (0.80-1.05)	0.91 (0.61-1.37)	3.11 (1.61-6.00)
Model 2	1.26 (1.10-1.45)	1.05 (0.96-1.15)	1.0	0.95 (0.83-1.09)	0.89 (0.59-1.35)	1.99 (1.00-3.96)
CVD mortality						
Model 1	1.13 (0.89-1.45)	1.00 (0.85-1.17)	1.0	1.04 (0.83-1.30)	2.07 (1.25-3.44)	7.63 (3.60-16.15)
Model 2	1.09 (0.86-1.39)	0.99 (0.84-1.17)	1.0	0.96 (0.77-1.21)	1.23 (0.73-2.07)	1.72 (0.76-3.89)
Non-CVD/cancer mortality						
Model 1	1.88 (1.63-2.16)	1.33 (1.19-1.49)	1.0	0.99 (0.83-1.17)	1.32 (0.81-2.14)	14.83 (9.85-22.33)
Model 2	1.67 (1.45-1.93)	1.27 (1.13-1.42)	1.0	0.99 (0.83-1.19)	1.08 (0.66-1.76)	4.72 (2.98-7.49)
All-cause mortality						
Model 1	1.51 (1.38-1.65)	1.15 (1.08-1.23)	1.0	0.96 (0.87-1.06)	1.23 (0.95-1.61)	7.40 (5.41-10.12)
Model 2	1.38 (1.26-1.52)	1.11 (1.04-1.08)	1.0	0.97 (0.88-1.07)	1.05 (0.80-1.37)	2.96 (2.10-4.16)
Age>=60 (N=28,077)	N=110	N=6,134	N=11,070	N=8,675	N=1,826	N=262
Cancer mortality						
Model 1	1.01 (0.42-2.44)	1.09 (0.95-1.25)	1.0	0.94 (0.83-1.06)	0.81 (0.66-1.01)	1.42 (0.94-2.14)
Model 2	0.81 (0.33-1.95)	1.02 (0.89-1.17)	1.0	0.99 (0.88-1.12)	0.88 (0.71-1.09)	1.38 (0.91-2.11)
CVD mortality						
Model 1	0.91 (0.23-3.68)	1.17 (0.96-1.44)	1.0	1.01 (0.85-1.20)	1.48 (1.17-1.87)	2.90 (1.95-4.31)
Model 2	0.77 (0.19-3.10)	1.14 (0.93-1.39)	1.0	0.99 (0.83-1.18)	1.35 (1.06-1.71)	2.20 (1.45-3.33)
Non-CVD/cancer mortality						
Model 1	1.40 (0.58-3.38)	1.18 (1.00-1.38)	1.0	0.92 (0.80-1.05)	1.22 (1.00-1.48)	3.62 (2.72-4.81)
Model 2	0.82 (0.34-2.01)	1.08 (0.92-1.27)	1.0	0.98 (0.85-1.13)	1.27 (1.04-1.56)	2.65 (1.96-3.59)
All-cause mortality						
Model 1	1.12 (0.63-1.97)	1.14 (1.04-1.25)	1.0	0.94 (0.87-1.02)	1.10 (0.98-1.24)	2.56 (2.10-3.12)
Model 2	0.82 (0.46-1.46)	1.07 (0.97-1.17)	1.0	0.98 (0.91-1.07)	1.13 (1.00-1.28)	2.10 (1.70-2.60)

Model 1: adjusted for age

Model 2: adjusted for age, total cholesterol, diabetes, cardiovascular disease, cancer, current smoker, systolic blood pressure, anti-hypertensive, body mass index and dipstick proteinuria

Table 9. Hazard ratios (95%CI) for cause-specific mortality by dipstick and age

	Dipstick proteinuria			
	None/trace	1+	2+	≥3+
Age<60 (N=339,855)	N=327,891	N=9,070	N=2,197	N=697
Cancer mortality				
Model 1	1.0	1.59 (1.33-1.90)	1.65 (1.16-2.36)	2.56 (1.63-4.02)
Model 2	1.0	1.52 (1.26-1.82)	1.58 (1.10-2.27)	2.38 (1.48-3.84)
CVD mortality				
Model 1	1.0	3.03 (2.38-3.85)	3.87 (2.53-5.91)	9.86 (6.45-15.09)
Model 2	1.0	2.19 (1.70-2.80)	2.31 (1.50-3.57)	4.03 (2.48-6.55)
Non-CVD/cancer mortality				
Model 1	1.0	2.19 (1.82-2.63)	4.07 (3.10-5.36)	7.45 (5.38-10.33)
Model 2	1.0	1.83 (1.52-2.21)	3.03 (2.28-4.02)	4.07 (2.81-5.90)
All-cause mortality				
Model 1	1.0	2.02 (1.80-2.26)	2.84 (2.34-3.44)	5.34 (4.27-6.68)
Model 2	1.0	1.76 (1.57-1.97)	2.29 (1.88-2.79)	3.55 (2.77-4.55)
Age>=60 (N=28,077)	N=26,542	N=1,020	N=348	N=167
Cancer mortality				
Model 1	1.0	1.39 (1.13-1.71)	1.31 (0.90-1.90)	1.30 (0.75-2.24)
Model 2	1.0	1.36 (1.10-1.68)	1.31 (0.89-1.92)	1.28 (0.73-2.23)
CVD mortality				
Model 1	1.0	1.91 (1.47-2.48)	1.98 (1.27-3.09)	3.13 (1.84-5.31)
Model 2	1.0	1.54 (1.18-2.02)	1.32 (0.83-2.08)	1.67 (0.96-2.92)
Non-CVD/cancer mortality				
Model 1	1.0	1.94 (1.58-2.38)	3.16 (2.38-4.20)	5.17 (3.72-7.18)
Model 2	1.0	1.63 (1.32-2.01)	2.40 (1.78-3.23)	3.42 (2.40-4.87)
All-cause mortality				
Model 1	1.0	1.69 (1.49-1.92)	2.07 (1.69-2.53)	2.94 (2.30-3.77)
Model 2	1.0	1.50 (1.32-1.71)	1.71 (1.38-2.10)	2.18 (1.68-2.82)

Model 1: adjusted for age and gender

Model 2: adjusted for age, gender, total cholesterol, diabetes, cardiovascular disease, cancer, current smoker, systolic blood pressure, anti-hypertensive, body mass index and eGFR

F. Association of CKD with finer cause of death

Examining finer causes of death, low eGFR (<60 vs. ≥60 ml/min/1.73m^2) was significantly associated with risks of death from oropharyngeal cancer, coronary heart disease, infectious disease, diabetes and renal failure (Figure 2). Given that diabetes and renal failure can be a cause of low eGFR, we repeated the analysis of eGFR and non-CVD/cancer mortality after censoring death due to diabetes and renal failure and confirmed their significant positive relationship [HR 1.36 (95%CI 1.14-1.62) for eGFR <60 vs. ≥60 ml/min/1.73m^2]. Unexpectedly, low eGFR was significantly associated with decreased risk of death from lung cancer and liver disease.

Proteinuria (≥1+ vs. none/trace) was significantly associated with increased risk of death from cancer of various organs (i.e., stomach, liver, pancreas, lung and myeloma), both major CVDs (i.e., coronary heart disease and stroke), infectious disease, diabetes, liver disease and renal failure (Figure 3). Again we confirmed the significant association of proteinuria and non-CVD/cancer mortality after censoring death due to diabetes and renal failure [1.77 (1.54-2.02) for ≥1+ vs. none/trace dipstick proteinuria]. Largely consistent results were observed when we further adjusted for alchol intake, liver function marker (AST, ALT), seropositivity to viral hepatitis B and hepatitis C for liver cancer mortality [1.41 (1.03-1.94) for dipstick 1+ vs. negative/trace] and liver disease [1.38 (0.79-2.38)].

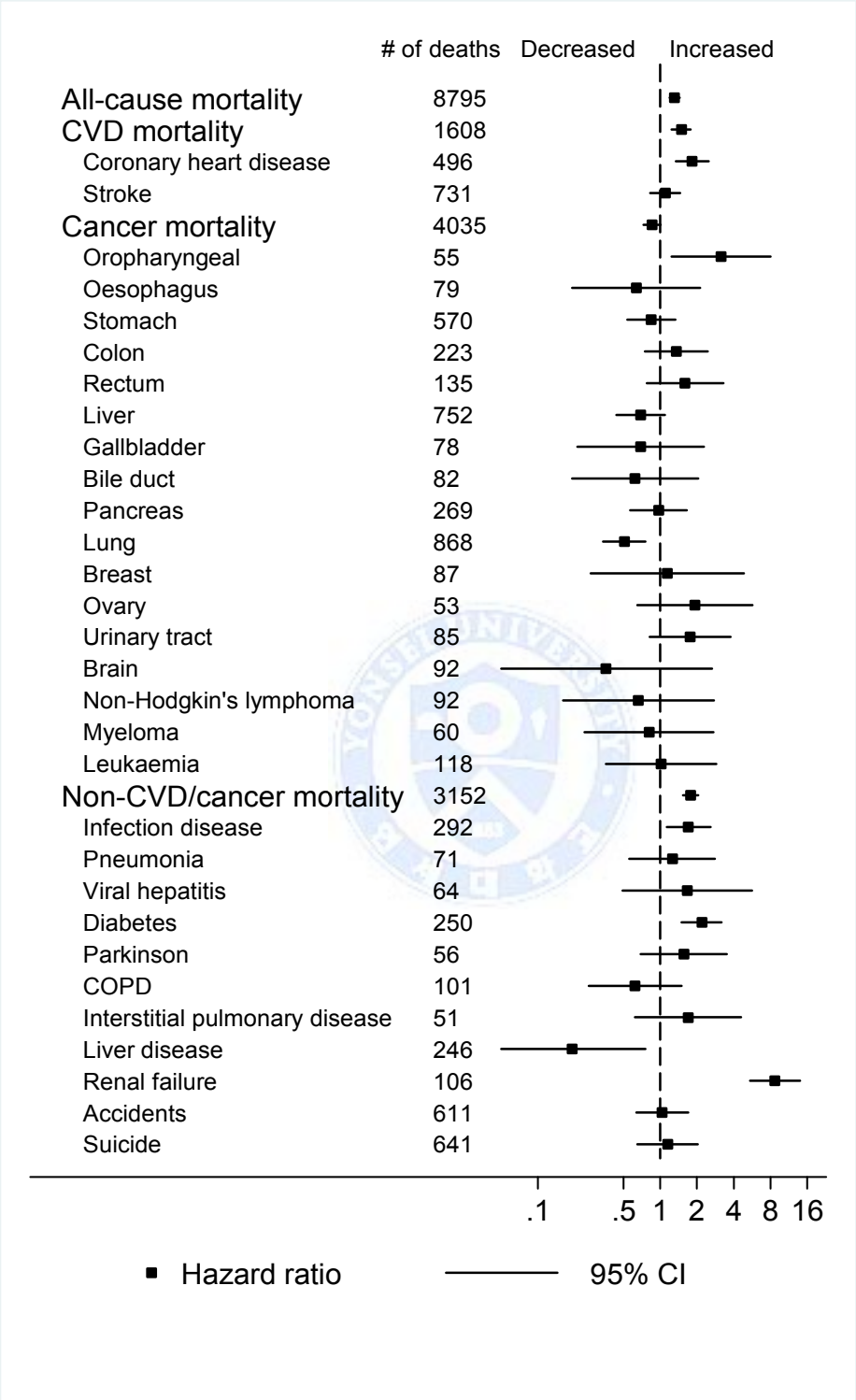

Figure 5. Adjusted hazard ratios of cause-specific mortality for eGFR<60 ml/min/1.73m^2 (vs. ≥60)

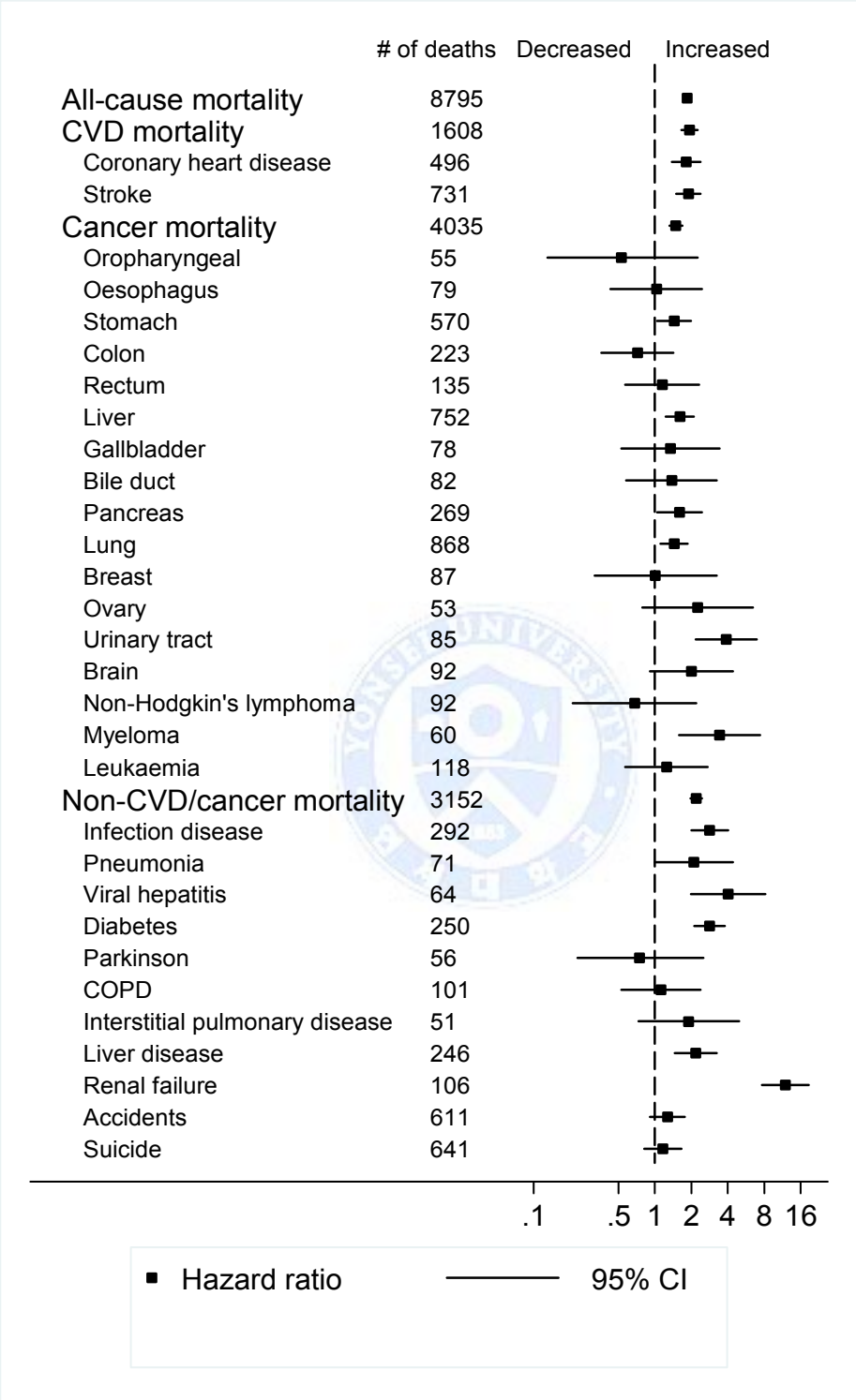

Figure 6. Adjusted hazard ratios of cause-specific mortality for dipstick proteinuria (vs. none/trace)

G. Mortality risk by eGFR and dipstick proteinuria combination

The hazard ratio for each eGFR and dipstick proteinuria combination represents the point estimate from our cohort (Figure 6). As eGFR decreases and proteinuria increases, risk of CVD and non-CVD mortality was increased (HR 4.73 for CVD mortality and 9.07 for non-CVD/cancer mortality in the lowest eGFR and highest proteinuria group). For cancer mortality, risk increases as proteinuria increases in the highest eGFR and lowest eGFR groups.

All-cause mortality

	None/ trace	+1	+2	≥+3
eGFR ≥90	Ref	1.71*	2.45*	3.59*
eGFR 60-89	0.89*	1.50*	1.55*	2.32*
eGFR 45-59	1.08	1.21	1.91*	2.62*
eGFR <45	1.79*	4.21*	4.24*	5.31*

CVD mortality

	None/ trace	+1	+2	≥+3
eGFR ≥90	Ref	1.91*	1.83	3.45*
eGFR 60-89	0.95	1.86*	1.70*	3.16*
eGFR 45-59	1.49*	1.76*	1.49	1.44
eGFR <45	1.84*	4.89*	3.58*	4.73*

Cancer mortality

	None/ trace	+1	+2	≥+3
eGFR ≥90	Ref	1.50*	1.92*	3.61*
eGFR 60-89	0.94	1.35*	1.12	1.11
eGFR 45-59	0.75	1.00	1.08	1.82
eGFR <45	1.23	1.79	2.30*	1.53

Non-CVD/cancer mortality

	None/ trace	+1	+2	≥+3
eGFR ≥90	Ref	1.85*	3.28*	3.51*
eGFR 60-89	0.80*	1.48*	1.89*	3.16*
eGFR 45-59	1.27*	1.11	3.23*	4.17*
eGFR <45	2.55*	6.83*	6.95*	9.07*

Figure 7. Adjusted hazard ratio of cause-specific mortality by combined eGFR with dipstick proteinuria

H. Morbidity risk by eGFR

i. Cancer incidence by eGFR

Table 10 shows HRs of total and site-specific cancer incidence by eGFR. Crude HRs for total cancer incidence was significantly increased as eGFR levels decreased, with eGFR of 75-89 ml/min/1.73m^2 as a reference. After adjusting for the potential confounders, the highest and lowest eGFR were associated with higher risk of incidence of cancer compared to the reference group, but risk of cancer incidence was lowest at eGFR 45-50 ml/min/1.73m^2. Examining finer causes of cancer incidence, lowest eGFR was significantly associated with increased risk of cancer from urinary tract, multiple myeloma and leukemia in both genders, and only ovary cancer for women.

Table 10. Hazard ratios (95%CI) for site-specific cancer incidence by eGFR, Korean Heart Study, N=233,219

	eGFR, ml/min/1.73m^2					
	≥105	90-104	75-89	60-74	45-59	<45
	N=41,032	N=91,204	N=74,913	N=23,646	N=2,116	N=308
All cancers						
Case	1,808	5,230	5,088	2,095	263	53
Crude	0.64 (0.61-0.68)	0.85 (0.81-0.88)	1.0	1.31 (1.24-1.38)	1.90 (1.68-2.15)	3.01 (2.29-3.94)
Model1	1.16 (1.10-1.23)	1.04 (1.00-1.08)	1.0	0.94 (0.89-0.99)	0.94 (0.83-1.06)	1.72 (1.31-2.26)
Model2	1.13 (1.07-1.19)	1.02 (0.98-1.06)	1.0	0.95 (0.90-1.00)	0.91 (0.80-1.02)	1.45 (1.12-1.88)
Oropharinx						
Case	22	68	80	39	8	0
Crude	0.50 (0.31-0.80)	0.70 (0.51-0.97)	1.0	1.53 (1.05-2.25)	3.59 (1.73-7.42)	-
Model1	1.10 (0.67-1.82)	0.91 (0.65-1.26)	1.0	1.10 (0.75-1.63)	1.82 (0.87-3.84)	-
Model2	1.09 (0.67-1.77)	0.89 (0.65-1.23)	1.0	1.03 (0.70-1.50)	1.72 (0.85-3.49)	-
Oesophagus						
Case	8	54	72	26	3	0
Crude	0.20 (0.10-0.42)	0.62 (0.43-0.88)	1.0	1.14 (0.73-1.79)	1.51 (0.48-5.12)	-
Model1	1.15 (0.53-2.49)	1.06 (0.74-1.52)	1.0	0.60 (0.40-0.97)	0.50 (0.18-1.37)	-
Model2	0.91 (0.42-1.96)	1.02 (0.71-1.45)	1.0	0.68 (0.44-1.06)	0.56 (0.20-1.55)	-
Stomach						
Case	260	912	968	361	47	8
Crude	0.49 (0.43-0.56)	0.78 (0.71-0.85)	1.0	1.17 (1.04-1.33)	1.75 (1.31-2.35)	2.29 (1.14-4.60)
Model1	1.14 (0.98-1.31)	1.03 (0.94-1.12)	1.0	0.81 (0.72-0.92)	0.82 (0.61-1.10)	1.21 (0.60-2.44)
Model2	1.09 (0.95-1.26)	1.00 (0.92-1.10)	1.0	0.83 (0.73-0.93)	0.78 (0.58-1.04)	1.22 (0.65-2.32)
Colon						
Case	104	431	417	211	34	4

Crude	0.45 (0.37-0.56)	0.85 (0.75-0.98)	1.0	1.60 (1.35-1.88)	2.94 (2.07-4.17)	2.68 (1.00-7.17)
Model1	1.14 (0.91-1.44)	1.15 (1.01-1.32)	1.0	1.04 (0.88-1.23)	1.19 (0.84-1.70)	1.26 (0.47-3.39)
Model2	1.15 (0.91-1.44)	1.15 (1.01-1.31)	1.0	1.04 (0.88-1.22)	1.07 (0.76-1.52)	0.97 (0.36-2.66)
Rectum						
Case	76	310	313	133	15	1
Crude	0.44 (0.35-0.57)	0.82 (0.70-0.96)	1.0	1.34 (1.09-1.64)	1.72 (1.02-2.89)	0.89 (0.12-6.31)
Model1	1.00 (0.77-1.31)	1.07 (0.91-1.26)	1.0	0.92 (0.75-1.13)	0.79 (0.47-1.33)	0.47 (0.07-3.34)
Model2	0.98 (0.76-1.28)	1.04 (0.89-1.21)	1.0	0.87 (0.71-1.07)	0.84 (0.52-1.34)	0.64 (0.15-2.61)
Liver						
Case	144	528	498	192	19	3
Crude	0.53 (0.44-0.64)	0.88 (0.78-0.99)	1.0	1.21 (1.03-1.43)	1.37 (0.87-2.17)	1.66 (0.53-5.16)
Model1	1.25 (1.03-1.53)	1.16 (1.02-1.32)	1.0	0.85 (0.72-1.00)	0.65 (0.41-1.04)	0.89 (0.29-2.79)
Model2	1.13 (0.93-1.38)	1.11 (0.98-1.25)	1.0	0.83 (0.70-0.98)	0.62 (0.40-0.96)	0.88 (0.35-2.18)
Gallbladder						
Case	9	52	50	29	4	2
Crude	0.33 (0.16-0.66)	0.86 (0.58-1.26)	1.0	1.83 (1.16-2.89)	2.87 (1.04-7.95)	10.88 (2.65-44.70)
Model1	0.92 (0.44-1.95)	1.20 (0.81-1.79)	1.0	1.07 (0.67-1.71)	0.94 (0.33-2.62)	4.15 (1.00-17.21)
Model2	0.97 (0.47-1.98)	1.22 (0.83-1.80)	1.0	1.11 (0.71-1.73)	0.80 (0.29-2.25)	3.76 (0.88-15.99)
Bile duct						
Case	9	83	100	39	7	2
Crude	0.16 (0.08-0.32)	0.68 (0.51-0.91)	1.0	1.23 (0.85-1.78)	2.54 (1.18-5.47)	5.50 (1.36-22.30)
Model1	0.61 (0.30-1.24)	1.03 (0.77-1.39)	1.0	0.71 (0.49-1.03)	0.80 (0.37-1.74)	2.07 (0.51-8.42)
Model2	0.79 (0.41-1.51)	1.09 (0.82-1.46)	1.0	0.70 (0.49-1.01)	0.77 (0.37-1.59)	1.95 (0.47-8.09)
Pancreas						
Case	35	127	155	84	11	0
Crude	0.41 (0.29-0.60)	0.68 (0.54-0.86)	1.0	1.70 (1.31-2.22)	2.54 (1.38-4.69)	-

Model1	1.11 (0.75-1.64)	0.93 (0.74-1.19)	1.0	1.07 (0.82-1.40)	0.96 (0.52-1.79)	-
Model2	1.11 (0.75-1.63)	0.94 (0.74-1.19)	1.0	1.04 (0.80-1.36)	0.91 (0.50-1.65)	-
Lung						
Case	109	508	567	265	26	9
Crude	0.35 (0.28-0.43)	0.74 (0.66-0.83)	1.0	1.47 (1.27-1.70)	1.65 (1.11-2.44)	4.45 (2.31-8.61)
Model1	1.24 (1.00-1.54)	1.11 (0.98-1.25)	1.0	0.87 (0.75-1.00)	0.55 (0.37-0.82)	1.74 (0.90-3.37)
Model2	1.17 (0.94-1.44)	1.08 (0.96-1.21)	1.0	0.92 (0.80-1.06)	0.64 (0.44-0.92)	1.33 (0.67-2.63)
Breast*						
Case	233	345	266	116	13	1
Crude	1.24 (1.04-1.48)	1.01 (0.86-1.18)	1.0	1.11 (0.89-1.38)	1.01 (0.58-1.77)	0.70 (0.10-5.01)
Model1	1.20 (1.00-1.45)	1.00 (0.85-1.17)	1.0	1.13 (0.91-1.42)	1.05 (0.60-1.85)	0.72 (0.10-5.17)
Model2	1.20 (1.00-1.45)	1.00 (0.85-1.17)	1.0	1.14 (0.91-1.42)	1.04 (0.59-1.83)	0.62 (0.08-4.54)
Ovary*						
Case	33	61	49	25	2	1
Crude	0.97 (0.62-1.50)	0.97 (0.67-1.41)	1.0	1.29 (0.80-2.10)	0.84 (0.20-3.45)	3.79 (0.52-27.47)
Model1	1.24 (0.77-2.01)	1.06 (0.73-1.56)	1.0	1.13 (0.69-1.84)	0.65 (0.16-2.69)	3.05 (0.42-22.23)
Model2	1.25 (0.77-2.02)	1.07 (0.73-1.57)	1.0	1.11 (0.68-1.82)	0.61 (0.15-2.55)	2.43 (0.31-18.79)
Urinary tract						
Case	70	256	291	152	24	12
Crude	0.43 (0.33-0.56)	0.72 (0.61-0.86)	1.0	1.65 (1.36-2.01)	2.99 (1.97-4.53)	11.50 (6.45-20.48)
Model1	0.98 (0.75-1.30)	0.95 (0.80-1.12)	1.0	1.18 (0.97-1.44)	1.50 (0.98-2.30)	6.55 (3.66-11.73)
Model2	1.00 (0.76-1.32)	0.96 (0.81-1.14)	1.0	1.16 (0.95-1.41)	1.41 (0.92-2.16)	4.91 (2.62-9.20)
Brain						
Case	24	61	54	26	1	1
Crude	0.81 (0.50-1.31)	0.93 (0.65-1.35)	1.0	1.51 (0.95-2.42)	0.66 (0.09-4.79)	5.03 (0.70-36.35)
Model1	1.53 (0.91-2.58)	1.16 (0.80-1.68)	1.0	1.11 (0.69-1.78)	0.34 (0.05-2.48)	2.93 (0.40-21.31)

Model2	1.40 (0.84-2.34)	1.12 (0.78-1.60)	1.0	1.07 (0.68-1.69)	0.56 (0.13-2.32)	1.95 (0.25-15.45)
Non-Hodgkin's lymphoma						
Case	33	105	103	46	4	0
Crude	0.59 (0.40-0.87)	0.85 (0.64-1.11)	1.0	1.40 (0.99-1.98)	1.38 (0.51-3.76)	-
Model1	0.96 (0.63-1.45)	0.99 (0.76-1.31)	1.0	1.13 (0.79-1.61)	0.88 (0.32-2.43)	-
Model2	0.93 (0.62-1.40)	1.00 (0.76-1.30)	1.0	1.09 (0.77-1.54)	0.97 (0.39-2.42)	-
Multiple myeloma						
Case	6	24	48	17	4	4
Crude	0.23 (0.10-0.53)	0.41 (0.25-0.67)	1.0	1.11 (0.64-1.93)	2.98 (1.08-8.27)	23.33 (8.41-64.71)
Model1	0.62 (0.25-1.51)	0.57 (0.35-0.94)	1.0	0.71 (0.40-1.24)	1.16 (0.41-3.28)	10.60 (3.75-29.98)
Model2	0.61 (0.25-1.49)	0.61 (0.37-0.99)	1.0	0.71 (0.41-1.24)	1.42 (0.58-3.44)	5.16 (1.56-17.05)
Leukemia						
Case	22	77	69	19	2	2
Crude	0.59 (0.36-0.95)	0.93 (0.67-1.28)	1.0	0.86 (0.52-1.43)	1.03 (0.25-4.21)	8.02 (1.97-32.73)
Model1	1.17 (0.70-1.95)	1.17 (0.84-1.62)	1.0	0.61 (0.37-1.03)	0.50 (0.12-2.08)	4.47 (1.09-18.37)
Model2	1.11 (0.66-1.85)	1.22 (0.88-1.69)	1.0	0.62 (0.37-1.04)	0.49 (0.12-2.02)	4.88 (1.15-20.73)

* Only Women

† Only men

Model 1: unadjusted

Model 2: adjusted for age and gender

Model 3: adjusted for age, gender, total cholesterol, diabetes, cardiovascular disease, current smoker, systolic blood pressure, anti-hypertensive, body mass index and dipstick proteinuria

ii. CVD incidence by eGFR

Crude HRs for CVD incidence including ischemic heart diseases and total stroke were significantly increased as eGFR levels decreases, with eGFR of 75-89 ml/min/1.73m^2 as a reference (Table 11). After adjusting for the potential confounders, eGFR categories below 60 ml/min/1.73m^2 were significantly associated with higher CVD incidence. High eGFR was associated with lower risk of CVD including ischemic heart disease and total stroke compared to the reference group in the crude model but showed higher risk once age and gender were taken into account.

Table 11. Hazard ratios (95%CI) for CVD incidence by eGFR

	eGFR, ml/min/1.73m^2					
	≥105	90-104	75-89	60-74	45-59	<45
	N=41,032	N=91,204	N=74,913	N=23,646	N=2,116	N=308
CVD						
Case	5,993	16,569	15,367	6,154	765	198
Crude	0.69 (0.67-0.71)	0.88 (0.86-0.90)	1.0	1.30 (1.26-1.34)	1.94 (1.81-2.09)	4.60 (4.00-5.30)
Model1	1.02 (0.99-1.06)	1.01 (0.99-1.03)	1.0	1.04 (1.01-1.07)	1.18 (1.10-1.27)	3.01 (2.62-3.47)
Model2	1.03 (1.00-1.06)	1.01 (0.99-1.04)	1.0	1.01 (0.98-1.03)	1.05 (0.97-1.13)	1.97 (1.70-2.28)
Coronary heart disease						
Case	377	1,647	1,827	944	154	29
Crude	0.37 (0.33-0.42)	0.74 (0.69-0.79)	1.0	1.64 (1.51-1.77)	3.11 (2.63-3.66)	4.49 (3.11-6.48)
Model1	0.86 (0.76-0.96)	0.97 (0.91-1.04)	1.0	1.12 (1.03-1.21)	1.40 (1.18-1.66)	2.34 (1.62-3.38)
Model2	0.90 (0.80-1.01)	1.00 (0.93-1.07)	1.0	1.05 (0.97-1.14)	1.18 (1.00-1.40)	1.46 (1.00-2.14)
Stroke						
Case	608	2,251	2,508	1,275	208	51
Crude	0.44 (0.40-0.48)	0.74 (0.70-0.78)	1.0	1.61 (1.51-1.73)	3.05 (2.65-3.52)	5.94 (4.50-7.83)
Model1	1.15 (1.04-1.26)	1.01 (0.95-1.07)	1.0	1.00 (0.94-1.08)	1.12 (0.97-1.29)	2.57 (1.95-3.40)
Model2	1.13 (1.03-1.25)	1.00 (0.95-1.06)	1.0	0.97 (0.91-1.04)	0.98 (0.84-1.13)	1.60 (1.20-2.14)

Model 1: unadjusted

Model 2: adjusted for age and gender

Model 3: adjusted for age, gender, total cholesterol, diabetes, cardiovascular disease, current smoker, systolic blood pressure, anti-hypertensive, body mass index and dipstick proteinuria

iii. Non-CVD/cancer disease incidence

Crude HRs for viral hepatitis, pneumonia, diabetes, Parkinson's disease, COPD and pulmonary disease were significantly increased as eGFR levels decreased with eGFR of 75-89 ml/min/1.73m^2 as a reference (Table 12). However, the association of low eGFR with incidence of COPD, diabetes, Parkinson's disease, and pulmonary disease was attenuated after adjusting for the potential confounders.

Table 12. Hazard ratios (95%CI) for Non-CVD/cancer incidence by eGFR

	eGFR, ml/min/1.73m^2					
	≥105	90-104	75-89	60-74	45-59	<45
	N=41,032	N=91,204	N=74,913	N=23,646	N=2,116	N=308
Infectious disease						
Case	39,943	88,743	72,893	22,922	2,041	293
Crude	0.97 (0.95-0.99)	0.99 (0.97-1.00)	1.0	1.01 (0.98-1.03)	1.03 (0.95-1.11)	0.92 (0.76-1.12)
Model1	0.99 (0.97-1.01)	0.99 (0.98-1.01)	1.0	0.98 (0.96-1.01)	0.96 (0.90-1.04)	0.89 (0.74-1.08)
Model2	0.99 (0.97-1.01)	1.00 (0.98-1.01)	1.0	0.99 (0.96-1.01)	0.97 (0.90-1.04)	0.92 (0.76-1.12)
Viral hepatitis						
Case	2,369	5,481	4,578	1,520	141	33
Crude	0.96 (0.90-1.01)	0.97 (0.93-1.01)	1.0	1.07 (1.00-1.14)	1.13 (0.93-1.36)	1.78 (1.17-2.70)
Model1	1.05 (0.99-1.12)	1.00 (0.96-1.05)	1.0	1.02 (0.95-1.09)	1.03 (0.85-1.24)	1.66 (1.09-2.52)
Model2	1.05 (0.99-1.12)	1.00 (0.96-1.05)	1.0	1.02 (0.95-1.09)	1.01 (0.83-1.23)	1.59 (1.03-2.45)
Pneumonia						
Case	3,176	8,186	7,292	2,996	366	61
Crude	0.76 (0.73-0.80)	0.92 (0.89-0.95)	1.0	1.33 (1.27-1.39)	1.90 (1.70-2.13)	2.52 (1.93-3.27)
Model1	1.11 (1.06-1.17)	1.05 (1.02-1.09)	1.0	1.03 (0.99-1.08)	1.08 (0.97-1.21)	1.64 (1.26-2.13)
Model2	1.09 (1.04-1.14)	1.04 (1.01-1.08)	1.0	1.04 (1.00-1.09)	1.09 (0.97-1.22)	1.47 (1.12-1.93)
Diabetes						
Case	4,536	13,642	13,049	5,477	676	127
Crude	0.61 (0.59-0.64)	0.84 (0.82-0.86)	1.0	1.35 (1.30-1.40)	1.85 (1.69-2.03)	2.58 (2.09-3.20)
Model1	1.09 (1.05-1.13)	1.03 (1.00-1.06)	1.0	1.00 (0.96-1.03)	0.95 (0.87-1.04)	1.50 (1.21-1.86)
Model2	1.20 (1.15-1.24)	1.08 (1.05-1.11)	1.0	0.94 (0.91-0.97)	0.78 (0.71-0.86)	0.81 (0.65-1.00)
Renal failure						
Case	143	510	601	549	236	211

Crude	0.44 (0.36-0.53)	0.71 (0.63-0.80)	1.0	2.95 (2.62-3.32)	14.54 (12.42-17.02)	177.71 (149.65-211.03)
Model1	0.74 (0.61-0.89)	0.84 (0.74-0.95)	1.0	2.33 (2.07-2.64)	8.92 (7.55-10.54)	113.55 (94.75-136.09)
Model2	0.72 (0.60-0.88)	0.84 (0.75-0.95)	1.0	2.12 (1.88-2.40)	6.09 (5.13-7.22)	32.28 (26.28-39.64)
Parkinson						
Case	62	358	462	301	77	6
Crude	0.23 (0.18-0.31)	0.63 (0.55-0.73)	1.0	1.98 (1.71-2.31)	5.74 (4.46-7.40)	3.19 (1.32-7.71)
Model1	0.98 (0.73-1.31)	0.98 (0.85-1.13)	1.0	1.05 (0.90-1.22)	1.51 (1.17-1.96)	0.99 (0.41-2.38)
Model2	0.97 (0.72-1.30)	0.98 (0.85-1.13)	1.0	1.05 (0.90-1.22)	1.49 (1.14-1.93)	0.86 (0.35-2.11)
COPD						
Case	2,132	7,037	6,973	3,018	390	44
Crude	0.55 (0.52-0.58)	0.82 (0.79-0.85)	1.0	1.38 (1.32-1.45)	2.00 (1.78-2.24)	1.75 (1.26-2.43)
Model1	1.09 (1.03-1.15)	1.04 (1.00-1.08)	1.0	0.95 (0.90-0.99)	0.88 (0.78-0.99)	0.92 (0.66-1.27)
Model2	1.07 (1.01-1.13)	1.03 (0.99-1.07)	1.0	0.96 (0.91-1.01)	0.90 (0.80-1.01)	0.89 (0.63-1.24)
Pulmonary disease						
Case	76	230	294	157	20	7
Crude	0.47 (0.36-0.60)	0.64 (0.54-0.77)	1.0	1.62 (1.33-1.98)	2.44 (1.54-3.89)	6.96 (3.29-14.73)
Model1	1.31 (0.99-1.72)	0.89 (0.75-1.07)	1.0	1.03 (0.84-1.26)	0.94 (0.59-1.51)	3.15 (1.48-6.68)
Model2	1.25 (0.95-1.66)	0.88 (0.73-1.05)	1.0	1.04 (0.85-1.28)	0.94 (0.59-1.51)	2.20 (0.99-4.89)
Liver disease						
Case	8,717	21,785	18,508	6,361	612	84
Crude	0.85 (0.83-0.88)	0.96 (0.94-0.98)	1.0	1.11 (1.07-1.14)	1.21 (1.11-1.33)	1.19 (0.93-1.53)
Model1	1.08 (1.05-1.11)	1.05 (1.03-1.07)	1.0	0.98 (0.95-1.02)	0.94 (0.86-1.03)	0.98 (0.76-1.26)
Model2	1.12 (1.09-1.15)	1.07 (1.05-1.09)	1.0	0.95 (0.92-0.99)	0.87 (0.80-0.96)	0.89 (0.69-1.14)

Model 1: unadjusted

Model 2: adjusted for age and gender

Model 3: adjusted for age, gender, total cholesterol, diabetes, cardiovascular disease, current smoker, systolic blood pressure, anti-hypertensive, body mass index and dipstick proteinuria

I. Morbidity risk by dipstick proteinuria

i. Cancer incidence by dipstick proteinuria

Table 13 shows HR for total and site-specific cancer incidence by dipstick proteinuria. In contrast to eGFR, high proteinuria was associated with total cancer incidence, with robust dose-response relationship. For total incidence of cancer, outcomes significantly increased even at 1+ proteinuria group. When examining site-specific cancer outcomes, positive proteinuria was significantly associated with increased risk of cancer from oesophagus, stomach, rectum, liver, lung, urinary tract, myeloma in both genders, and ovarian cancer in women. High proteinuria was significantly associated with incidence of cancer due to much broader causes, as compared to low eGFR.

Table 13. Hazard ratios (95%CI) for site-specific cancer incidence by dipstick proteinuria

	Dipstick proteinuria			
	None/trace	1+	2+	≥3+
	N=224,973	N=6,331	N=1,421	N=494
All cancers				
Case	13,834	513	128	62
Crude	1.0	1.31 (1.20-1.44)	1.55 (1.31-1.85)	2.13 (1.66-2.73)
Model1	1.0	1.25 (1.15-1.37)	1.33 (1.11-1.58)	1.66 (1.30-2.14)
Model2	1.0	1.23 (1.13-1.34)	1.39 (1.18-1.63)	1.68 (1.32-2.14)
Oropharinx				
Case	202	13	2	0
Crude	1.0	2.27 (1.29-3.97)	1.65 (0.41-6.63)	-
Model1	1.0	1.94 (1.11-3.40)	1.24(0.31-4986)	-
Model2	1.0	1.67 (0.95-2.95)	1.06 (0.26-4.29)	-
Oesophagus				
Case	149	13	1	0
Crude	1.0	3.10 (1.76-5.46)	1.11 (0.16-7.92)	-
Model1	1.0	2.29 (1.30-4.04)	0.65 (0.09-4.65)	-
Model2	1.0	2.04 (1.14-3.63)	1.17 (0.29-4.77)	-
Stomach				
Case	2,416	112	18	10
Crude	1.0	1.64 (1.35-1.98)	1.24 (0.78-1.97)	1.92 (1.03-3.57)
Model1	1.0	1.42 (1.17-1.71)	0.94 (0.59-1.49)	1.29 (0.69-2.40)
Model2	1.0	1.37 (1.13-1.65)	1.04 (0.68-1.60)	1.28 (0.70-2.35)
Colon				
Case	1,152	32	11	6
Crude	1.0	0.98 (0.69-1.39)	1.59 (0.88-2.87)	2.42 (1.08-5.40)
Model1	1.0	0.86 (0.61-1.23)	1.19 (0.66-2.16)	1.60 (0.72-3.57)
Model2	1.0	0.88 (0.63-1.23)	1.33 (0.78-2.26)	1.40 (0.62-3.18)
Rectum				
Case	797	37	12	2
Crude	1.0	1.64 (1.18-2.28)	2.50 (1.42-4.43)	1.16 (0.29-4.66)
Model1	1.0	1.45 (1.04-2.02)	1.94 (1.09-3.42)	0.80 (0.20-3.19)
Model2	1.0	1.45 (1.06-1.99)	1.70 (0.95-3.03)	1.44 (0.53-3.91)
Liver				
Case	1,303	58	14	9
Crude	1.0	1.57 (1.21-2.04)	1.78 (1.05-3.01)	3.20 (1.66-6.16)
Model1	1.0	1.34 (1.03-1.75)	1.34 (0.79-2.26)	2.14 (1.11-4.13)
Model2	1.0	1.29 (0.99-1.67)	1.42 (0.86-2.33)	2.50 (1.31-4.75)
Gallbladder				

Case	137	8	1	0
Crude	1.0	2.07 (1.01-4.21)	1.19 (0.17-8.54)	-
Model1	1.0	1.93 (0.94-3.94)	0.92 (0.13-6.58)	-
Model2	1.0	1.60 (0.78-3.29)	0.63 (0.09-4.63)	-
Bile duct				
Case	225	13	2	0
Crude	1.0	2.05 (1.17-3.58)	1.47 (0.37-5.93)	-
Model1	1.0	1.69 (0.97-2.96)	0.99 (0.25-4.00)	-
Model2	1.0	1.47 (0.84-2.59)	0.76 (0.18-3.10)	-
Pancreas				
Case	390	17	4	1
Crude	1.0	1.53 (0.94-2.49)	1.70 (0.64-4.56)	1.18 (0.17-8.42)
Model1	1.0	1.35 (0.83-2.20)	1.26 (0.47-3.39)	0.76 (0.11-5.40)
Model2	1.0	1.17 (0.72-1.92)	1.07 (0.40-2.89)	0.69 (0.10-4.97)
Lung				
Case	1,387	73	15	9
Crude	1.0	1.85 (1.47-2.35)	1.80 (1.08-2.99)	2.99 (1.55-5.77)
Model1	1.0	1.54 (1.22-1.95)	1.23 (0.74-2.05)	1.71 (0.89-3.29)
Model2	1.0	1.53 (1.21-1.94)	1.20 (0.72-2.01)	2.21 (1.23-3.98)
Breast*				
Case	938	26	7	3
Crude	1.0	1.26 (0.86-1.87)	1.46 (0.69-3.07)	1.58 (0.51-4.91)
Model1	1.0	1.26 (0.86-1.87)	1.47 (0.70-3.10)	1.60 (0.51-4.97)
Model2	1.0	1.29 (0.87-1.90)	1.55 (0.73-3.27)	1.84 (0.58-5.83)
Ovary*				
Case	159	9	3	0
Crude	1.0	2.56 (1.31-5.00)	3.65 (1.17-11.45)	-
Model1	1.0	2.55 (1.30-4.99)	3.50 (1.12-10.98)	-
Model2	1.0	2.55 (1.30-5.02)	3.31 (1.01-10.78)	-
Urinary tract				
Case	744	37	18	6
Crude	1.0	1.76 (1.26-2.44)	4.04 (2.53-6.45)	3.70 (1.66-8.27)
Model1	1.0	1.49 (1.07-2.07)	3.00 (1.88-4.79)	2.43 (1.09-5.43)
Model2	1.0	1.42 (1.02-1.98)	2.45 (1.51-3.99)	1.57 (0.67-3.66)
Brain				
Case	159	5	2	1
Crude	1.0	1.11 (0.45-2.70)	2.08 (0.52-8.38)	2.90 (0.41-20.72)
Model1	1.0	1.02 (0.42-2.48)	1.73 (0.43-6.97)	2.22 (0.31-15.86)
Model2	1.0	1.22 (0.54-2.76)	1.73 (0.42-7.13)	2.13 (0.28-16.43)
Non-Hodgkin's lymphoma				

Case	284	6	0	1
Crude	1.0	0.74 (0.33-1.67)	-	1.64 (0.23-11.69)
Model1	1.0	0.68 (0.30-1.52)	-	1.29 (0.18-9.19)
Model2	1.0	0.64 (0.28-1.44)	-	1.38 (0.19-9.93)
Multiple myeloma				
Case	90	8	2	3
Crude	1.0	3.12 (1.51-6.44)	3.69 (0.91-14.98)	15.29 (4.84-48.31)
Model1	1.0	2.70 (1.31-5.57)	2.66 (0.65-10.81)	9.39 (2.96-29.83)
Model2	1.0	2.42 (1.16-5.04)	1.89 (0.44-8.08)	4.61 (1.22-17.37)
Leukemia				
Case	184	6	1	0
Crude	1.0	1.15 (0.51-2.60)	0.90 (0.13-6.45)	-
Model1	1.0	1.06 (0.47-2.39)	0.74 (0.10-5.31)	-
Model2	1.0	1.01 (0.45-2.30)	0.61 (0.08-4.50)	-

* Only Women

Model 1: unadjusted

Model 2: adjusted for age and gender

Model 3: adjusted for age, gender, total cholesterol, diabetes, cardiovascular disease, current smoker, systolic blood pressure, anti-hypertensive, body mass index and eGFR

ii. **CVD incidence by dipstick proteinuria**

In contrast to eGFR, high proteinuria was consistently associated with CVD including ischemic heart disease and total stroke, with robust dose-response relationship (Table 14). However, the association of highest proteinuria group with incidence of ischemic heart diseases was attenuated after adjusting for the potential confounders.

Table 14. Hazard ratios (95%CI) for CVD incidence by dipstick proteinuria

	Dipstick proteinuria			
	None/trace	1+	2+	≥3+
	N=224,973	N=6,331	N=1,421	N=494
CVD				
Case	42,773	1,568	464	241
Crude	1.0	1.34 (1.27-1.40)	1.93 (1.76-2.12)	3.18 (2.80-3.60)
Model1	1.0	1.29 (1.22-1.35)	1.73 (1.57-1.89)	2.63 (2.32-2.99)
Model2	1.0	1.16 (1.10-1.22)	1.39 (1.27-1.53)	1.76 (1.54-2.01)
Coronary heart disease				
Case	4,615	241	82	40
Crude	1.0	1.86 (1.63-2.11)	3.00 (2.41-3.74)	4.06 (2.98-5.55)
Model1	1.0	1.63 (1.43-1.85)	2.27 (1.83-2.83)	2.70 (1.98-3.69)
Model2	1.0	1.22 (1.07-1.39)	1.37 (1.09-1.71)	1.34 (0.97-1.86)
Stroke				
Case	6,418	321	108	54
Crude	1.0	1.78 (1.59-1.99)	2.86 (2.36-3.46)	3.99 (3.06-5.22)
Model1	1.0	1.62 (1.45-1.82)	2.20 (1.82-2.66)	2.67 (2.04-3.49)
Model2	1.0	1.16 (1.04-1.30)	1.54 (1.26-1.86)	1.50 (1.13-1.98)

Model 1: unadjusted

Model 2: adjusted for age and gender

Model 3: adjusted for age, gender, total cholesterol, diabetes, cardiovascular disease, current smoker, systolic blood pressure, anti-hypertensive, body mass index and eGFR

iii. Non-CVD/cancer incidence by dipstick proteinuria

Crude HRs for incidence of pneumonia, diabetes, renal failure, Parkinson's and pulmonary diseases were significantly increased as higher proteinuria (Table 15). After adjusting for the potential confounders, the association of high proteinuria with diabetes Parkinson's disease, COPD and pulmonary diseases was still remained, but its association of Parkinson's disease was attenuated.

Table 15. Hazard ratios (95%CI) for Non-CVD/cancer incidence by dipstick proteinuria

	Dipstick proteinuria			
	None/trace	1+	2+	≥3+
	N=224,973	N=6,331	N=1,421	N=494
Infectious disease				
Case	218,863	6,131	1,368	473
Crude	1.0	1.00 (0.96-1.04)	0.93 (0.86-1.02)	0.94 (0.82-1.07)
Model1	1.0	1.00 (0.97-1.04)	0.93 (0.85-1.01)	0.93 (0.81-1.06)
Model2	1.0	1.01 (0.97-1.05)	0.94 (0.86-1.02)	0.96 (0.84-1.10)
Viral hepatitis				
Case	13,533	445	106	38
Crude	1.0	1.15 (1.03-1.28)	1.26 (1.01-1.58)	1.15 (0.78-1.70)
Model1	1.0	1.12 (1.01-1.25)	1.22 (0.98-1.53)	1.10 (0.74-1.63)
Model2	1.0	1.10 (0.99-1.23)	1.17 (0.93-1.46)	1.02 (0.68-1.53)
Pneumonia				
Case	21,167	673	164	73
Crude	1.0	1.13 (1.04-1.23)	1.27 (1.08-1.50)	1.66 (1.31-2.12)
Model1	1.0	1.12 (1.03-1.22)	1.16 (0.98-1.37)	1.42 (1.11-1.80)
Model2	1.0	1.12 (1.03-1.22)	1.16 (0.98-1.37)	1.36 (1.06-1.74)
Diabetes				
Case	34,876	1,846	558	227
Crude	1.0	1.96 (1.86-2.06)	2.76 (2.50-3.05)	3.11 (2.64-3.65)
Model1	1.0	1.91 (1.81-2.01)	2.47 (2.23-2.73)	2.55 (2.17-2.99)
Model2	1.0	1.36 (1.29-1.44)	1.47 (1.33-1.63)	1.16 (0.98-1.36)
Renal failure				
Case	1,609	275	205	161
Crude	1.0	6.05 (5.30-6.91)	22.11 (18.98-25.75)	55.42 (46.76 (66.59)
Model1	1.0	5.50 (4.82-6.29)	17.91 (15.36-20.87)	39.53 (33,30-46.92)
Model2	1.0	3.75 (3.27-4.30)	8.26 (7.02-9.73)	7.89 (6.39-9.75)
Parkinson				
Case	1,203	41	14	8
Crude	1.0	1.21 (0.88-1.67)	1.78 (1.01-3.15)	3.25 (1.62-6.51)
Model1	1.0	1.09 (0.79-1.50)	1.27 (0.72-2.24)	1.90 (0.95-3.81)
Model2	1.0	1.02 (0.74-1.40)	1.16 (0.65-2.05)	1.66 (0.81-3.38)
COPD				
Case	18,779	595	167	53
Crude	1.0	1.09 (0.99-1.19)	1.47 (1.25-1.74)	1.33 (0.99-1.78)
Model1	1.0	1.03 (0.94-1.12)	1.22 (1.03-1.44)	0.99 (0.74-1.33)
Model2	1.0	1.06 (0.97-1.16)	1.31 (1.11-1.55)	1.10 (0.82-1.49)
Pulmonary disease				

Case	730	33	14	7
Crude	1.0	1.52 (1.06-2.19)	3.36 (1.98-5.70)	4.58 (2.18-9.65)
Model1	1.0	1.32 (0.92-1.90)	2.46 (1.45-4.17)	2.91 (1.38-6.14)
Model2	1.0	1.25 (0.86-1.80)	2.16 (1.26-3.73)	2.40 (1.10-5.24)
Liver disease				
Case	53,624	1,871	431	141
Crude	1.0	1.29 (1.22-1.35)	1.27 (1.13-1.42)	1.17 (0.96-1.42)
Model1	1.0	1.24 (1.18-1.30)	1.18 (1.05-1.31)	1.06 (0.87-1.28)
Model2	1.0	1.15 (1.10-1.22)	1.04 (0.98-1.09)	0.91 (0.75-1.11)

Model 1: unadjusted

Model 2: adjusted for age and gender

Model 3: adjusted for age, gender, total cholesterol, diabetes, cardiovascular disease, current smoker, systolic blood pressure, anti-hypertensive, body mass index and dipstick proteinuria

J. Summary of morbidity risk by eGFR and dipstick proteinuria

Low eGFR (<60 vs. ≥60 ml/min/1.73m^2) was significantly associated with increased risk of urinary tract cancer, coronary heart disease, viral hepatitis, Parkinson's disease and renal failure (Figure 7). We confirmed a similar relationship with mortality results. Unexpectedly, low eGFR was significantly associated with decreased risk of diabetes when assessing the relationship of eGFR with indicators of incident non-CVD/cancer (Figure A1). Low eGFR was associated with increased risk for hospitalization due to viral hepatitis, pneumonia and Parkinson's disease, but not associated with risk for ≥3 for outpatient visits. For incidence of diabetes, the association of eGFR with hospitalization was not significant, but ≥3 for outpatient visits were significantly decreased.

Proteinuria (≥1+ vs. none/trace) was significantly associated with increased risk of cancer of various organs (i.e., stomach, rectum, liver, ovary, urinary tract and myeloma), both major CVDs (i.e., coronary heart disease and stroke), pneumonia, viral hepatitis, diabetes, pulmonary diseases, liver disease and renal failure (Figure 8). Again, this study confirmed a similar relationship with mortality results. When examining the relationship of positive proteinuria with indicators of incident non-CVD/cancer (Figure A2). Positive proteinuria was associated with increased risk for hospitalization due to infectious diseases including viral hepatitis and pneumonia, pulmonary disease and liver disease. The relationship of positive proteinuria with hospitalization and ≥3 for outpatient visits due to diabetes and renal failure was significantly increased.

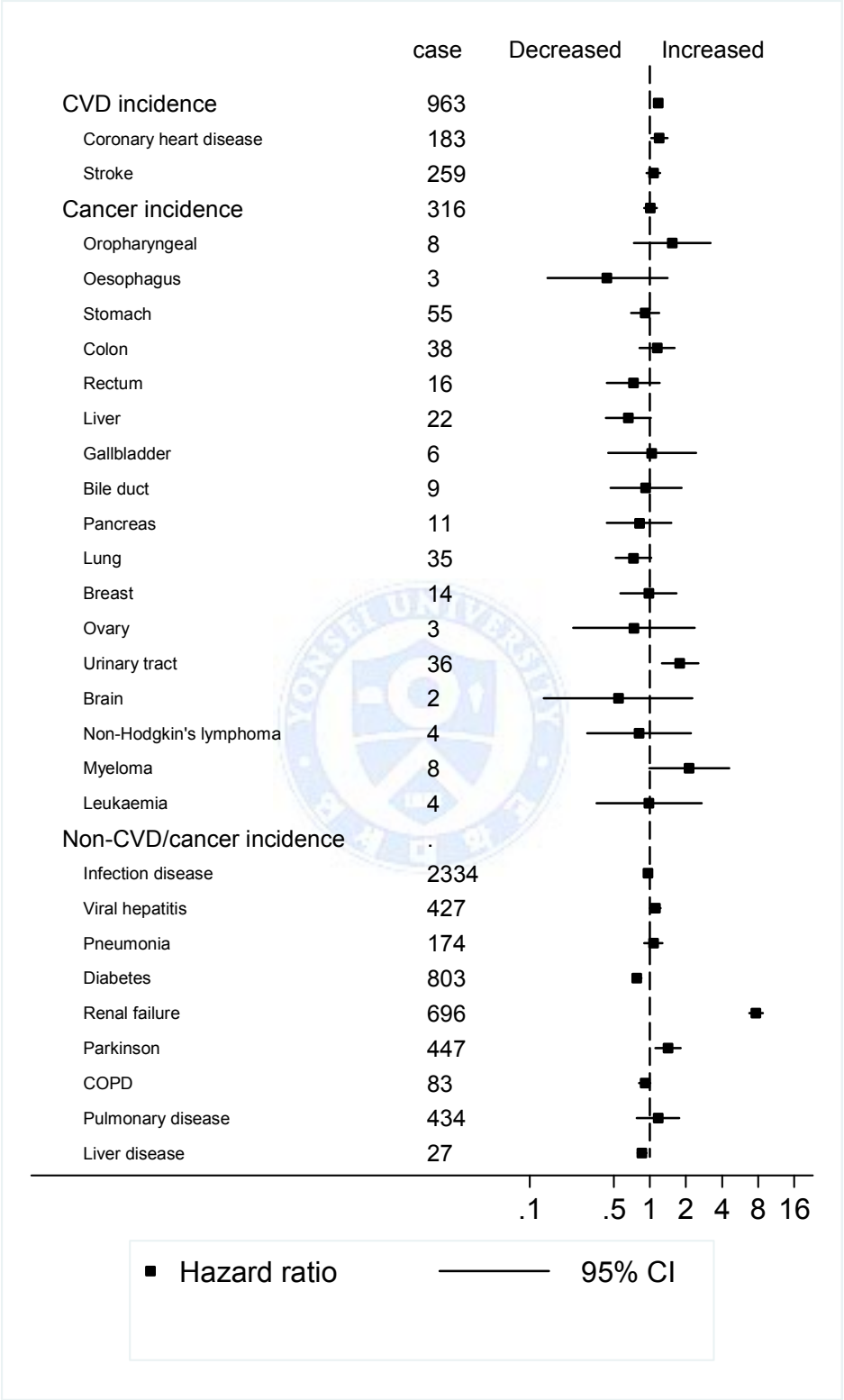

Figure 8. Adjusted hazard ratios of morbidity for eGFR<60 ml/min/1.73m^2 (vs. ≥60)

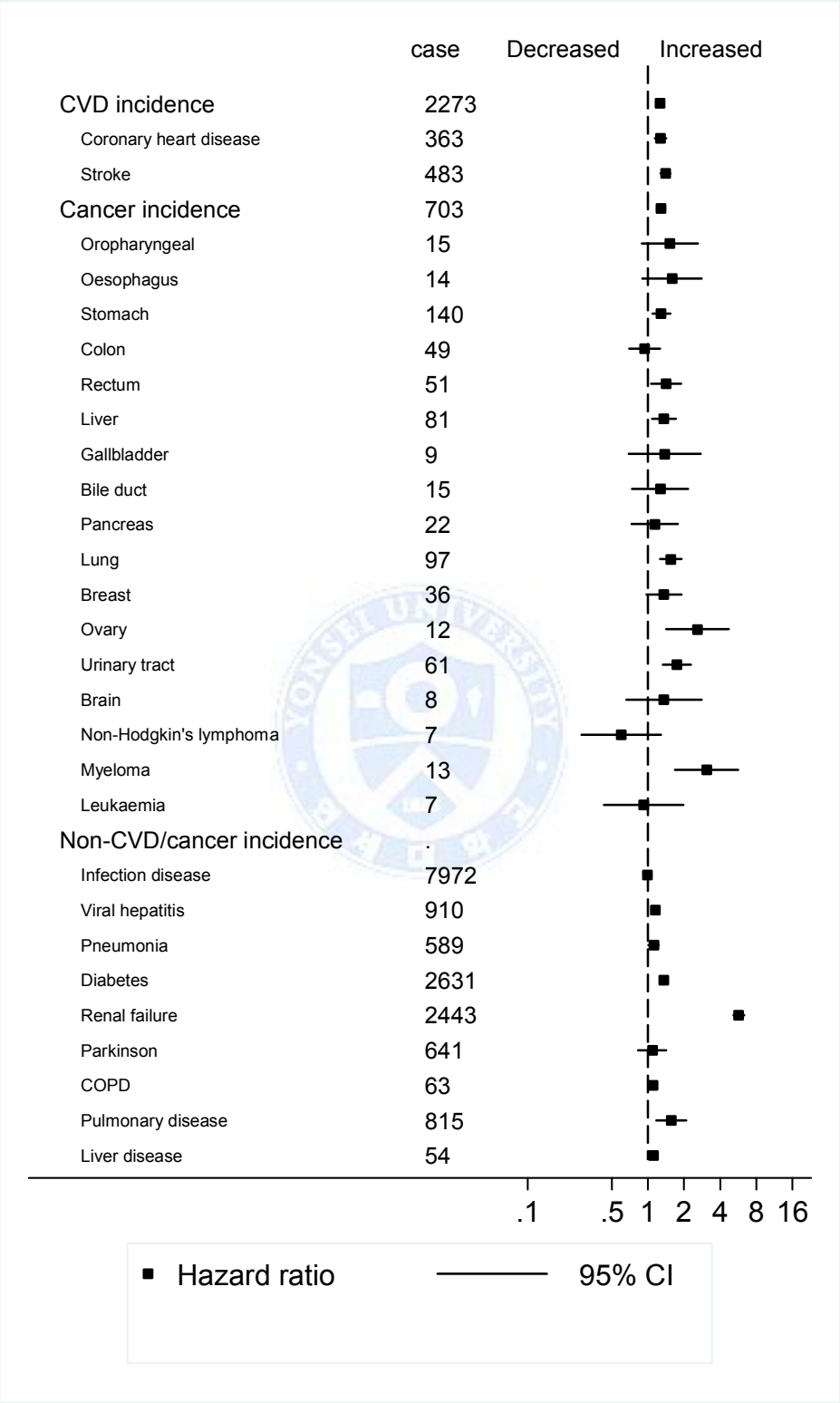

Figure 9. Adjusted hazard ratios of morbidity for dipstick proteinuria (≥ + vs. none/trace)

K. Change in eGFR and cause specific mortality

The distribution of percentage annual change in eGFR between visit 1 and visit 2 is shown in Figure 7. The mean (SD) of percentage annual change was 0.40% (13.39%) with median (inter-quartile range) of -0.70% (-10.62% to 10.32%).

Compared with participants with stable eGFR, the unadjusted risk of CVD was 2-fold higher (HR 3.09, 95% CI 1.34-7.12) for those with a certain drop in 1-year (Table 16). When adjusted for potential confounders, CVD mortality risk was still significant [HR 2.86 (95%CI 1.24-6.62)]. We further assessed the risk of mortality and 2, 3 and 4 years change in kidney measures, but not significantly associated with cause-specific mortality (Table A8-10).

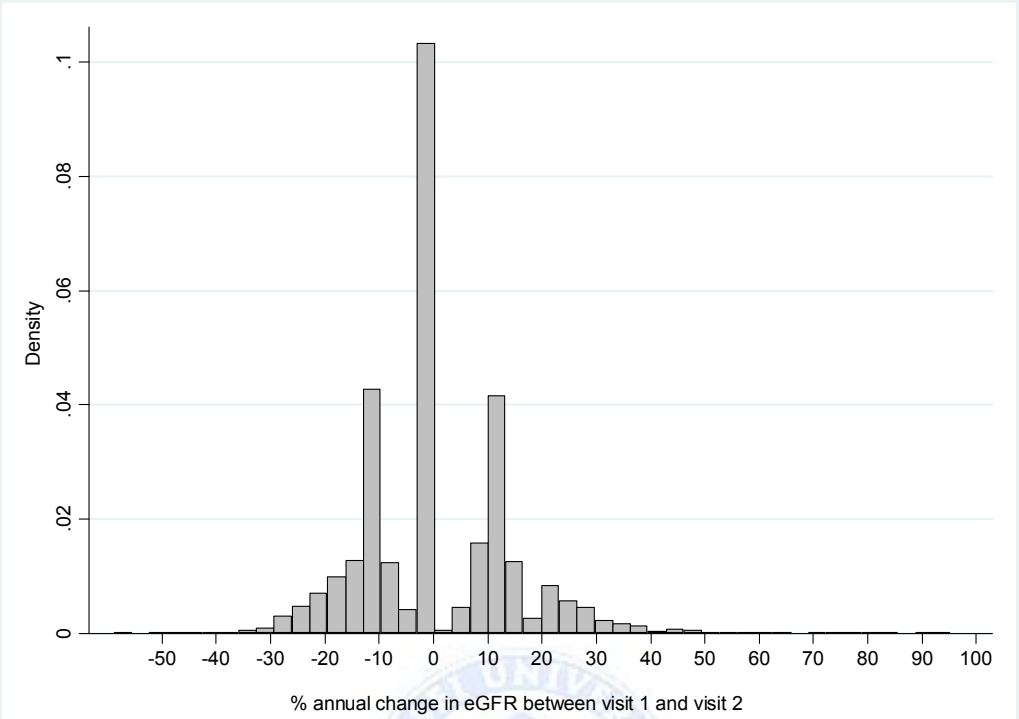

Figure 10. Distribution of percentage annual change in eGFR on the basis of 1-year change among 56,436 participants of MSMS

Table 16. Hazard ratios (95%CI) for cause-specific mortality by 1 year change in eGFR

	1 year change in eGFR		
	Stable N=37,333	Uncertain drop N=16,933	Certain drop N=2,170
Cancer mortality			
Case	205	107	6
Crude	1.0	1.09 (0.87-1.38)	1.04 (0.46-2.33)
Model 1	1.0	1.12 (0.89-1.42)	0.95 (0.42-2.13)
Model 2	1.0	1.10 (0.87-1.40)	0.94 (0.42-2.13)
CVD mortality			
Case	70	40	6
Crude	1.0	1.20 (0.81-1.77)	3.09 (1.34-7.12)
Model 1	1.0	1.23 (0.83-1.81)	2.78 (1.20-6.41)
Model 2	1.0	1.24 (0.84-1.83)	2.86 (1.24-6.62)
Non-CVD/cancer mortality			
Case	67	69	5
Crude	1.0	0.98 (0.73-1.30)	1.19 (0.49-2.91)
Model 1	1.0	0.99 (0.74-1.32)	1.13 (0.46-2.75)
Model 2	1.0	0.99 (0.74-1.31)	1.11 (0.46-2.72)
All-cause mortality			
Case	207	216	17
Crude	1.0	1.07 (0.91-1.26)	1.43 (0.88-2.32)
Model 1	1.0	1.09 (0.93-1.29)	1.32 (0.81-2.14)
Model 2	1.0	1.09 (0.92-1.28)	1.32 (0.81-2.15)

Model 1: adjusted for age and gender

Model 2: adjusted for age, gender, total cholesterol, diabetes, cardiovascular disease, cancer, current smoker, systolic blood pressure, anti-hypertensive, body mass index and dipstick proteinuria

V. DISCUSSION

In this large Korean cohort study, we found that low eGFR and high proteinuria conferred mortality risk due to CVD, cancer, and non-CVD/cancer. Low eGFR was mainly associated with CVD and non-CVD/cancer mortality, whereas high proteinuria was consistently and significantly associated with all of CVD, cancer and non-CVD/cancer mortality outcomes. This pattern was consistent across subgroups by age and gender. Of note, the significant association for proteinuria was observed in trace proteinuria compared to negative proteinuria. In terms of finer causes of death, both kidney markers were commonly associated with increased risk of coronary heart disease, overall infectious disease, diabetes, and renal failure. In addition, high proteinuria was significantly associated with increased mortality due to much broader causes (i.e., stroke, cancer of stomach, liver, pancreas, lung, and urinary tract, myeloma, pneumonia, viral hepatitis, and liver disease), as compared to low eGFR (oropharyngeal cancer). We also explored the association between changes in kidney function over a 1 year period and cause-specific mortality. We found that a certain drop in the eGFR (change in CKD category was accompanied by a 25% decline from the baseline eGFR) was associated with an increased risk of CVD mortality.

As previously reported (Matsushita et al. 2010; Hallan et al. 2007; Nagata et al. 2013; van der Velde et al. 2011), we confirmed the significant associations of low eGFR and high proteinuria with overall CVD mortality, independent of traditional risk factors such as blood pressure and diabetes. High proteinuria was significantly associated with death due to both coronary heart disease and stroke, whereas low eGFR was only significantly associated with coronary mortality. Our finding is consistent with a few previous studies reporting stronger association of stroke with high proteinuria than with low eGFR (Aguilar et al. 2010; Mahmoodi et al. 2014). Although exact mechanisms for the strong association between proteinuria and stroke independently of blood pressure are uncertain, this may reflect the property of proteinuria as an indicator of systemic vascular injury or endothelial dysfunction. Some investigators also raise inflammation and oxidative stress as background of proteinuria-stroke relationship (Aguilar et al. 2010; Mahmoodi et al. 2014).

The association of low eGFR with cancer mortality was weak and not robust in our study (only significant below eGFR 45 ml/min/1.73m^2 in crude or demographically adjusted models with our pre-specified reference of eGFR 75-89 ml/min/1.73m^2 in fully adjusted model with eGFR 45-59 ml/min/1.73m^2 as a reference). This seems to great extent consistent with conflicting results in previous studies (Fried et al. 2005; Iff et al. 2014; Weng et al. 2011). A few studies reported significant associations of reduce kidney function (low eGFR or higher cystatin C levels) and cancer mortality but, of note, did not adjust for some important confounders like blood pressure, diabetes, lipids, obesity or proteinuria (Fried et al. 2005; Iff et al. 2014; Weng et al. 2011). One study accounted for these confounders and actually did not find significant associations of CKD, defined as reduced eGFR and/or elevated proteinuria, with cancer mortality (Di Angelantonio et al. 2010). Unfortunately, this study did not report eGFR- or proteinuria-specific results. Recently, a large cohort study with more than 1 million participants has shown no associations of low eGFR with total cancer incidence (Lowrance et al. 2014). However, this study reports significant associations of low eGFR with kidney urothelial cancer incidences, and the association between low eGFR and kidney cancer mortality was borderline significant in our study. On the other hand, we observed the low eGFR was significantly associated with high risk of oropharyngeal and low risk of lung cancer mortality. A strong U-shaped relationship between eGFR and lung cancer incidence has been shown (Lowrance et al. 2014), with the lowest incidence at eGFR 40-59 ml/min/1.73m^2 and 1.5-2 fold higher incidence in high (90+ ml/min/1.73m^2) and low (<30 ml/min/1.73m^2) eGFR ranges. Thus, the lower risk of lung cancer mortality in eGFR<60 compared to ≥60 might be due to eGFR distribution in our study (few with eGFR<30 and a number of people with higher eGFR). Nevertheless, these results for specific cancer types in our study should be considered with more hypotheses and further investigations. For incidence of cancer, a previous study shared similar results as they reported that there were low eGFR incidences of urinary tract cancer in older people (Wong et al. 2009).

To our knowledge, this is the first study, of its kind, to include reports on significant associations of proteinuria with overall and type-specific cancer mortality: although a previous study did report its association with incidence of cancer (Jorgensen et al. 2008). The associations were evident even at the level of trace or 1+ and observed for cancer of

stomach, liver, pancreas, lung, and urinary tract and myeloma. The significant associations with lung and urinary tract cancer mortality and morbidity are consistent with a previous study examining cancer incidence (Jorgensen et al. 2008). It was of interest that proteinuria was consistently associated with some gastroenterological cancers in our study. Although the exact mechanisms, by which proteinuria is associated with the risk for cancer, are unknown, several mechanisms may be involved. First, albuminuria may reflect prevalent cancer as patients with a large tumor burden or metastatic disease had higher albuminuria levels than less advanced disease (Pedersen and Milman 1998; Sawyer et al. 1988). This particularly relevant to myeloma releasing Bence-Jones proteins, light polypeptide chains of immunoglobulins, in the urine. However, the significant associations were consistent among those without prevalent cancer at baseline and when those who died in 3 years were excluded. Second, proteinuria may be associated with cancer growth or expansion rather than incidence. Indeed, endothelial dysfunction is shown to contribute to invasiveness of cancer cells (Franses et al. 2013). Finally endothelial dysfunction is related with inflammation (Stehouwer et al. 2002), inflammation have been a potential explanation for cancer incidence (Coussens and Werb 2002; Jorgensen et al. 2008). Considering the association of eGFR and proteinuria with cancer mortality and morbidity overall, low eGFR levels are associated with increased risk of urinary tract, whereas proteinuria is associated with much broader site-specific cancer risk.

Unlike report from Western countries (Gansevoort et al. 2013; Stevens et al. 2007), non-CVD/cancer mortality was more common than CVD or cancer mortality in our participants with CVD, which is consistent with other reports from Eastern Asia (Weng et al. 2011). Therefore, health care providers in Eastern Asian countries should pay more attention to non-CVD/cancer causes of death in the CVD care. Whether this applies to Eastern Asian population living in Western Countries warrants further investigation.

In this context, we found that both low eGFR and high proteinuria were strongly associated with non-CVD/cancer mortality, even after excluding death due to diabetes, a potent risk factor of CKD, and renal failure, a direct consequence of CKD. Regarding finer causes, both kidney measures commonly and independently associated with overall infectious disease mortality, which is consistent with a few previous reports (Wang et al. 2011). In addition, proteinuria demonstrated significant associations with two specific

infectious diseases, pneumonia and viral hepatitis. It is known patients with CKD have reduced activities of immune system cell like B-cell, T-cell, monocyte and lymphocyte (Janus et al. 2008).

Taking into consideration the magnitude of changes in kidney function, in addition to the baseline kidney function alone, might provide prognostic information. We found the association between 1-year decline in eGFR and CVD mortality. Other results are consistent with our findings. A rapid decline of eGFR was at significantly greater risk for cardiovascular disease (Al-Aly et al. 2010; Matsushita et al. 2009; Perkins et al. 2011; Rifkin et al. 2008; Turin et al. 2014).

Taken altogether, our findings suggest that person with CKD warrants multidisciplinary care for side range of disease. More specifically, in addition to CVD, special attention would be needed for infectious disease prevention and management such as vaccination programs (Janus et al. 2008; Kidney Disease: Improving Global Outcomes 2013). Although our results need be confirmed in other settings, individuals with proteinuria would deserve further consideration for cancer risk. Although further investigations are clearly needed regarding how to implement cancer screening in the context of CKD, the assessment of proteinuria is already recommended in some clinical populations such as diabetes and hypertension and screening programs for some cancers such as lung cancer (aged 55-80 years with some smoking history) (Davis and Cifu 2014) and stomach cancer (aged ≥40 years) (Leung et al. 2008) is well developed in several countries/regions. Thus, when proteinuria is detected in some clinical scenarios, it seems reasonable to encourage persons with proteinuria to adhere to those cancer screening programs.

A trace of proteinuria is usually regarded as a negative result and the clinical significance is likely to be ignored in the general population. Previous study suggested that trace of proteinuria using a dipstick test could be a useful indicator for microalbuminuria (Konta T et al. 2007). The association of trace of proteinuria and cause-specific mortality was evident in our study; therefore, further investigations are needed.

This study has a few limitations. First, our cohort may not necessarily represent general population in the Korea, since the study participants were in routine health assessments at private health promotion centers, so they have higher socioeconomic

status and relatively small number of older individuals (Jee et al. 2013). Second, our cohort has a small number of participants with severely reduced eGFR (<30ml/min/1.73m^2). Third, cystatin C was not available. Cystatin C is known a stronger predictor of mortality and CVD outcomes than serum creatinine when incorporated in eGFR equations (Herget-Rosenthal et al. 2000; Shlipak et al. 2005). Thus, investigations with cystatins C for cancer and non-CVD/cancer mortality are warranted. Forth, we used semi-quantitative urinary dipstick test as a measure of kidney damage. As it does not account for urine concentration, it is likely that there were some misclassifications of proteinuria. However, this kind of misclassification usually biases the association toward null. Finally, the outcome definition was based on ICD-10 code from death certificates. There have been debates about the accuracy of this approach (Chun and Lee 2000), although this approach is widely used in literature (Harteloh, de Bruin and Kardaun 2010; Lu, Lee and Chou 2000; Winkler, Ott and Becher 2010) and the accuracy of cancer as a cause of death was reported to be high (Lee et al. 2000; Song and Sung 2001).

VI. CONCLUSIONS

Low eGFR was particularly associated with mortality due to CVD and non-CVD/cancer. In contrast, high proteinuria was consistently and robustly associated with deaths due to CVD, cancer, and non-CVD/cancer. Our study provides further evidence that persons with CKD are at high risk for not only CVD but also other causes of deaths such as cancer (particularly when proteinuria is present) and infectious disease. Therefore, multidisciplinary prevention and management strategies need to be encouraged.

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APPENDIX

Table A1. Hazard ratios (95%CI)* for cause-specific mortality by eGFR using competing risk model

	eGFR, ml/min/1.73m^2					
	≥105	90-104	75-89	60-74	45-59	<45
	N=87,468	N=139,902	N=105,839	N=31,081	N=3,136	N=338
Cancer mortality						
Case	339	1,287	1,507	741	128	26
Crude	0.27 (0.24-0.30)	0.65 (0.60-0.70)	1.0	1.64 (1.51-1.80)	2.82 (2.35-3.38)	4.51 (3.18-6.39)
Model 1	1.24 (1.09-1.42)	1.09 (1.01-1.18)	1.0	0.91 (0.83-1.00)	0.72 (0.59-0.86)	1.17 (0.81-1.71)
Model 2 (impute)	1.13 (1.00-1.29)	1.05 (0.97-1.13)	1.0	0.95 (0.87-1.04)	0.74 (0.61-0.89)	0.98 (0.66-1.48)
CVD mortality						
Case	103	447	570	335	118	23
Crude	0.22 (0.18-0.27)	0.60 (0.53-0.68)	1.0	1.96 (1.71-2.24)	6.88 (5.64-8.39)	12.74 (9.02-17.99)
Model 1	1.14 (0.91-1.44)	1.05 (0.92-1.19)	1.0	1.03 (0.90-1.19)	1.59 (1.29-1.96)	2.93 (2.02-4.26)
Model 2 (impute)	1.13 (0.90-1.42)	1.04 (0.91-1.18)	1.0	0.99 (0.86-1.13)	1.31 (1.06-1.63)	1.69 (1.15-2.50)
Non-CVD/cancer mortality						
Case	396	1,019	992	512	153	40
Crude	0.48 (0.42-0.54)	0.78 (0.71-0.85)	1.0	1.72 (1.55-1.91)	5.13 (4.33-6.08)	17.51 (13.92-22.03)
Model 1	1.96 (1.73-2.24)	1.26 (1.15-1.38)	1.0	0.99 (0.88-1.10)	1.44 (1.21-1.71)	5.00 (3.84-6.51)
Model 2 (impute)	1.69 (1.49-1.93)	1.19 (1.09-1.31)	1.0	1.02 (0.92-1.14)	1.38 (1.15-1.65)	2.85 (2.14-3.80)

Model 1: adjusted for age and gender

Model 2: adjusted for age, gender, total cholesterol, diabetes, cardiovascular disease, cancer, current smoker, systolic blood pressure, anti-hypertensive, body mass index and dipstick proteinuria

Table A2. Hazard ratios (95%CI)* for cause-specific mortality by dipstick proteinuria using competing risk model

	Dipstick proteinuria			
	None/trace	1+	2+	≥3+
	N=354,433	N=10,090	N=2,545	N=864
Cancer mortality				
Case	3,725	219	59	32
Crude	1.0	1.83 (1.60-2.10)	2.13 (1.65-2.76)	3.05 (2.15-4.32)
Model 1	1,0	1.43 (1.24-1.64)	1.39 (1.07-1.81)	1.63 (1.14-2.33)
Model 2 (impute)	1.0	1.39 (1.20-1.69)	1.41 (1.08-1.84)	1.70 (1.17-2.46)
CVD mortality				
Case	1,395	135	42	36
Crude	1.0	3.03 (2.54-3.62)	4.05 (2.98-5.51)	9.27 (6.64-12.94)
Model 1	1.0	2.30 (1.92-2.75)	2.47 (1.81-3.38)	4.67 (3.31-6.60)
Model 2 (impute)	1.0	1.79 (1.49-2.16)	1.59 (1.14-2.22)	2.32 (1.56-3.45)
Non-CVD/cancer mortality				
Case	2,750	225	103	74
Crude	1.0	2.54 (2.21-2.91)	5.07 (4.17-6.18)	9.67 (7.67-12.19)
Model 1	1.0	2.06 (1.80-2.37)	3.54 (2.90-4.31)	5.73 (4.53-7.27)
Model 2 (impute)	1.0	1.69 (1.46-1.95)	2.61 (2.11-3.23)	3.40 (2.59-4.48)

Model 1: adjusted for age and gender

Model 2: adjusted for age, gender, total cholesterol, diabetes, cardiovascular disease, cancer, current smoker, systolic blood pressure, anti-hypertensive, body mass index and eGFR

Table A3. Hazard ratios (95%CI) for site-specific cancer incidence by eGFR

	eGFR, ml/min/1.73m^2					
	≥105	90-104	75-89	60-74	45-59	<45
	N=41,032	N=91,204	N=74,913	N=23,646	N=2,116	N=308
Small intestine						
Case	8	18	29	8	2	0
Crude	0.51 (0.23-1.11)	0.52 (0.29-0.93)	1.0	0.86 (0.39-1.89)	2.47 (0.59-10.34)	-
Model1	1.51 (0.64-3.55)	0.73 (0.40-1.32)	1.0	0.54 (0.25-1.20)	0.94 (0.22-4.02)	-
Model2	1.43 (0.61-3.37)	0.75 (0.42-1.34)	1.0	0.51 (0.23-1.13)	1.18 (0.34-4.05)	-
Larynx						
Case	8	30	34	17	2	1
Crude	0.43 (0.20-0.92)	0.73 (0.45-1.19)	1.0	1.57 (0.88-2.81)	2.09 (0.50-8.70)	8.04 (1.10-58.72)
Model1	1.95 (0.85-4.48)	1.18 (0.71-1.94)	1.0	0.91 (0.50-1.64)	0693 (0.16-2.90)	3.03 (0.41-22.38)
Model2	1.94 (0.84-4.44)	1.22 (0.74-1.98)	1.0	0.93 (0.52-1.66)	1.01 (0.30-3.39)	3.70 (0.48-28.46)
Bone and articular cartilage						
Case	4	26	34	13	1	0
Crude	0.21 (0.08-0.60)	0.63 (0.38-1.05)	1.0	1.20 (0.64-2.28)	1.06 (0.14-7.73)	-
Model1	0.42 (0.14-1.22)	0.79 (0.47-1.33)	1.0	0.87 (0.45-1.67)	0.53 (0.07-3.96)	-
Model2	0.42 (0.14-1.22)	0.86 (0.52-1.43)	1.0	0.84 (0.44-1.62)	0.47 (0.06-3.54)	-
Skin						
Case	13	54	58	29	2	1
Crude	0.41 (0.22-0.75)	0.77 (0.53-1.12)	1.0	1.57 (1.00-2.45)	1.24 (0.30-5.07)	4.86 (0.67-35.00)
Model1	0.92 (0.49-1.74)	1.01 (0.69-1.46)	1.0	1.03 (0.65-1.62)	0.51 (0.12-2.09)	2.34 (0.32-16.99)
Model2	0.92 (0.49-1.71)	0.96 (0.66-1.39)	1.0	0.97 (0.62-1.52)	0.42 (0.10-1.74)	1.58 (0.20-12.46)
Soft tissue						
Case	18	56	51	25	0	0

Crude	0.64 (0.37-1.09)	0.90 (0.62-1.32)	1.0	1.55 (0.96-2.50)	-	-
Model1	1.02 (0.58-1.81)	1.06 (0.72-1.56)	1.0	1.17 (0.72-1.90)	-	-
Model2	1.06 (0.60-1.89)	1.08 (0.74-1.59)	1.0	1.14 (0.70-1.86)	-	-
Cervix*						
Case	28	70	52	17	2	0
Crude	0.77 (0.48-1.21)	1.05 (0.73-1.50)	1.0	0.84 (0.48-1.45)	0.80 (0.20-3.29)	-
Model1	1.11 (0.68-1.83)	1.19 (0.83-1.72)	1.0	0.69 (0.40-1.20)	0.56 (0.14-2.33)	-
Model2	1.12 (0.68-1.84)	1.20 (0.83-1.72)	1.0	0.68 (0.39-1.18)	0.50 (0.12-2.09)	-
Unspecified parts of uterus*						
Case	29	55	30	15	2	0
Crude	1.36 (0.82-2.27)	1.42 (0.91-2.22)	1.0	1.27 (0.68-2.36)	1.38 (0.33-5.76)	-
Model1	2.05 (1.17-3.58)	1.64 (1.05-2.58)	1.0	1.03 (0.55-1.93)	0.94 (0.22-3.96)	-
Model2	2.12 (1.21-3.70)	1.65 (1.05-2.59)	1.0	1.01 (0.54-1.89)	0.78 (0.18-3.35)	-
Prostate†						
Case	34	268	323	196	27	3
Crude	0.22 (0.15-0.31)	0.70 (0.60-0.83)	1.0	2.14 (1.79-2.55)	4.50 (3.04-6.66)	3.23 (1.04-10.07)
Model1	0.90 (0.62-1.29)	1.10 (0.94-1.30)	1.0	1.11 (0.93-1.33)	1.01 (0.68-1.51)	1.02 (0.33-3.18)
Model2	0.96 (0.66-1.38)	1.15 (0.97-1.35)	1.0	1.07 (0.89-1.28)	0.95 (0.64-1.42)	0.98 (0.31-3.13)
Kidney						
Case	46	127	143	52	10	9
Crude	0.58 (0.42-0.81)	0.73 (0.58-0.93)	1.0	1.15 (0.83-1.57)	2.52 (1.33-4.78)	17.39 (8.87-34.10)
Model1	0.93 (0.66-1.33)	0.86 (0.67-1.09)	1.0	0.96 (0.70-1.33)	1.78 (0.92-3.42)	13.19 (6.67-26.09)
Model2	0.90 (0.64-1.28)	0.86 (0.68-1.09)	1.0	0.94 (0.69-1.28)	1.50 (0.80-2.82)	10.45 (5.32-20.53)
Ureter						
Case	3	22	19	14	4	2
Crude	0.28 (0.08-0.96)	0.95 (0.52-1.76)	1.0	2.32 (1.16-4.63)	7.54 (2.57-22.18)	29.23 (6.81-125.51)

Model1	1.29 (0.36-4.64)	1.53 (0.82-2.85)	1.0	1.28 (0.64-2.59)	2.24 (0.74-6.76)	10.14 (2.32-44.44)
Model2	1.05 (0.30-3.74)	1.48 (0.82-2.65)	1.0	1.27 (0.66-2.44)	1.81 (0.60-5.46)	9.92 (2.24-43.97)
Bladder						
Case	18	110	136	94	14	2
Crude	0.24 (0.15-0.39)	0.66 (0.52-0.85)	1.0	2.19 (1.68-2.84)	3.74 (2.16-6.48)	4.10 (1.01-16.54)
Model1	0.74 (0.44-1.23)	0.95 (0.74-1.23)	1.0	1.39 (1.06-1.82)	1.48 (0.84-2.59)	1.88 (0.46-7.64)
Model2	0.70 (0.42-1.17)	1.03 (0.81-1.31)	1.0	1.35 (1.05-1.75)	1.28 (0.74-2.21)	1.20 (0.29-5.02)
Thyroid gland						
Case	572	1,142	880	267	25	3
Crude	1.19 (1.07-1.32)	1.07 (0.98-1.17)	1.0	0.95 (0.83-1.09)	1.02 (0.69-1.52)	0.96 (0.31-2.97)
Model1	0.94 (0.84-1.05)	1.00 (0.91-1.09)	1.0	0.95 (0.82-1.09)	0.94 (0.63-1.41)	0.91 (0.29-2.82)
Model2	0.92 (0.83-1.03)	0.99 (0.91-1.08)	1.0	0.92 (0.80-1.05)	0.94 (0.65-1.36)	0.73 (0.23-2.31)
Other endocrine gland						
Case	10	15	17	10	0	0
Crude	1.08 (0.50-2.37)	0.73 (0.36-1.46)	1.0	1.86 (0.85-4.05)	-	-
Model1	2.04 (0.86-4.82)	0.91 (0.45-1.84)	1.0	1.28 (0.58-2.84)	-	-
Model2	2.12 (0.89-5.03)	0.93 (0.46-1.87)	1.0	1.24 (0.56-2.77)	-	-
Unspecified sites						
Case	393	1,272	1,325	594	70	15
Crude	0.54 (0.48-0.61)	0.79 (0.73-0.86)	1.0	1.41 (1.28-1.56)	1.90 (1.49-2.42)	3.15 (1.89-5.24)
Model1	1.22 (1.08-1.38)	1.04 (0.96-1.12)	1.0	0.94 (0.85-1.03)	0.79 (0.62-1.01)	1.54 (0.93-2.57)
Model2	1.17 (1.04-1.32)	1.02 (0.94-1.10)	1.0	0.96 (0.87-1.05)	0.82 (0.64-1.05)	1.43 (0.85-2.42)

* Only Women; † Only men

Model 1: unadjusted

Model 2: adjusted for age and gender
Model 3: adjusted for age, gender, total cholesterol, diabetes, cardiovascular disease, current smoker, systolic blood pressure, anti-hypertensive, body mass index and dipstick proteinuria

Table A4. Hazard ratios (95%CI) for site-specific cancer incidence by dipstick proteinuria

	Dipstick proteinuria			
	None/trace	1+	2+	≥3+
	N=224,973	N=6,331	N=1,421	N=494
Small intestine				
Case	59	4	1	1
Crude	1.0	2.37 (0.86-6.52)	2.83 (0.39-20.43)	7.73 (1.07-55.83)
Model1	1.0	2.03 (0.74-5.59)	2.06 (0.28-14.91)	4.90 (0.67-35.51)
Model2	1.0	1.78 (0.64-4.98)	1.82 (0.25-13.38)	4.69 (0.62-35.38)
Larynx				
Case	87	4	1	0
Crude	1.0	1.62 (0.59-4.42)	1.89 (0.26-13.57)	-
Model1	1.0	1.19 (0.44-3.25)	1.12 (0.16-8.08)	-
Model2	1.0	1.03 (0.37-2.83)	0.80 (0.11-6.07)	-
Bone and articular cartilage				
Case	73	4	1	0
Crude	1.0	1.91 (0.70-5.24)	2.28 (0.32-16.39)	-
Model1	1.0	1.72 (0.63-4.72)	1.80 (0.25-12.95)	-
Model2	1.0	1.53 (0.55-4.24)	1.58 (0.22-11.52)	-
Skin				
Case	148	7	1	1
Crude	1.0	1.66 (0.78-3.55)	1.13 (0.16-8.07)	3.09 (0.43-22.11)
Model1	1.0	1.55 (0.72-3.31)	0.90 (0.13-6.46)	2.21 (0.31-15.85)
Model2	1.0	1.60 (0.78-3.29)	0.77 (0.11-5.60)	1.77 (0.23-13.73)
Soft tissue				
Case	143	4	3	0
Crude	1.0	0.99 (0.37-2.68)	3.46 (1.10-10.87)	-
Model1	1.0	0.96 (0.36-2.60)	3.06 (0.97-9.61)	-
Model2	1.0	1.01 (0.37-2.74)	3.45 (1.09-10.96)	-
Cervix*				
Case	161	6	1	1
Crude	1.0	1.70 (0.75-3.84)	1.19 (0.17-8.53)	3.09 (0.43-22.06)
Model1	1.0	1.69 (0.72-3.82)	1.13 (0.16-8.04)	2.86 (0.40-20.42)
Model2	1.0	1.64 (0.72-3.71)	1.17 (0.16-8.45)	3.30 (0.45-24.10)
Unspecified parts of uterus*				
Case	124	2	4	1
Crude	1.0	0.74 (0.18-2.98)	6.39 (2.36-17.29)	4.00 (0.56-28.66)
Model1	1.0	0.73 (0.18-2.97)	6.08 (2.24-16.46)	3.78 (0.53-27.05)
Model2	1.0	0.67 (0.16-2.71)	5.42 (1.97-14.92)	3.54 (0.48-26.09)
Prostate†				

Case	799	39	8	5
Crude	1.0	1.54 (1.11-2.12)	1.55 (0.77-3.10)	2.72 (1.13-6.55)
Model1	1.0	1.24 (0.90-1.71)	0.95 (0.48-1.92)	1.28 (0.53-3.09)
Model2	1.0	1.28 (0.92-1.77)	0.98 (0.48-1.99)	1.35 (0.55-3.31)
Kidney				
Case	358	16	10	3
Crude	1.0	1.58 (0.96-2.61)	4.64 (2.48-8.70)	3.84 (1.23-11.98)
Model1	1.0	1.41 (0.85-2.33)	3.85 (2.05-7.23)	3.00 (0.96-9.37)
Model2	1.0	1.25 (0.76-2.04)	2.80 (1.51-5.18)	1.42 (0.48-4.15)
Ureter				
Case	59	5	0	0
Crude	1.0	2.96 (1.19-7.39)	-	-
Model1	1.0	2.31 (0.93-5.78)	-	-
Model2	1.0	2.30 (0.97-5.41)	-	-
Bladder				
Case	345	19	7	3
Crude	1.0	1.94 (1.22-3.08)	3.38 (1.60-7.15)	3.97 (1.28-12.38)
Model1	1.0	1.56 (0.98-2.47)	2.24 (1.06-4.74)	2.21 (0.71-6.90)
Model2	1.0	1.40 (0.89-2.21)	2.39 (1.21-4.69)	1.79 (0.56-5.73)
Thyroid gland				
Case	2,810	58	13	8
Crude	1.0	0.73 (0.56-0.94)	0.77 (0.45-1.33)	1.32 (0.66-2.65)
Model1	1.0	0.81 (0.62-1.05)	0.85 (0.49-1.46)	1.42 (0.71-2.83)
Model2	1.0	0.80 (0.62-1.03)	1.01 (0.62-1.63)	1.32 (0.65-2.66)
Other endocrine gland				
Case	50	2	0	0
Crude	1.0	1.41 (0.34-5.81)	-	-
Model1	1.0	1.37 (0.33-5.63)	-	-
Model2	1.0	1.35 (0.33-5.63)	-	-
Unspecified sites				
Case	3,473	150	32	14
Crude	1.0	1.53 (1.30-1.80)	1.53 (1.08-2.16)	1.87 (1.11-3.16)
Model1	1.0	1.40 (1.19-1.65)	1.22 (0.86-1.73)	1.32 (0.78-2.23)
Model2	1.0	1.39 (1.18-1.64)	1.20 (0.85-1.71)	1.29 (0.75-2.21)

* Only Women

† Only men

Model 1: adjusted for age and gender

Model 2: adjusted for age, gender, total cholesterol, diabetes, cardiovascular disease, current smoker, systolic blood pressure, anti-hypertensive, body mass index and eGFR

Table A5. Hazard ratios (95%CI) for indicators of incident non-CVD/cancer by eGFR

	eGFR, ml/min/1.73m^2					
	≥105	90-104	75-89	60-74	45-59	<45
	N=41,032	N=91,204	N=74,913	N=23,646	N=2,116	N=308
Infectious disease						
Inpatients						
Crude	0.87 (0.84-0.90)	0.96 (0.94-0.99)	1.0	1.21 (1.17-1.25)	1.76 (1.62-1.92)	3.17 (2.65-3.80)
Model1	1.21 (1.17-1.25)	1.08 (1.06-1.11)	1.0	0.98 (0.95-1.02)	1.11 (1.02-1.21)	2.17 (1.81-2.59)
Model2	1.20 (1.16-1.24)	1.08 (1.05-1.11)	1.0	0.98 (0.95-1.02)	1.10 (1.01-1.20)	1.87 (1.55-2.26)
Outpatients						
Crude	0.97 (0.95-0.98)	0.99 (0.97-1.00)	1.0	1.01 (0.98-1.03)	1.02 (0.94-1.09)	0.89 (0.74-1.08)
Model1	0.98 (0.96-1.00)	0.99 (0.98-1.01)	1.0	0.99 (0.96-1.01)	0.96 (0.89-1.03)	0.87 (0.72-1.05)
Model2	0.98 (0.96-1.00)	0.99 (0.98-1.01)	1.0	0.99 (0.96-1.01)	0.96 (0.89-1.04)	0.90 (0.74-1.10)
Viral hepatitis						
Inpatients						
Crude	1.10 (0.98-1.24)	1.02 (0.92-1.12)	1.0	0.98 (0.85-1.13)	1.39 (0.96-2.00)	3.19 (1.65-6.15)
Model1	1.23 (1.09-1.39)	1.05 (0.96-1.16)	1.0	0.95 (0.82-1.10)	1.33 (0.92-1.92)	3.07 (1.59-5.94)
Model2	1.21 (1.07-1.36)	1.04 (0.95-1.15)	1.0	0.96 (0.83-1.11)	1.32 (0.91-1.92)	2.48 (1.24-4.95)
Outpatients						
Crude	0.95 (0.89-1.00)	0.97 (0.93-1.02)	1.0	1.06 (0.99-1.13)	1.07 (0.87-1.30)	1.45 (0.90-2.34)
Model1	1.03 (0.97-1.10)	1.00 (0.96-1.05)	1.0	1.02 (0.95-1.09)	0.98 (0.80-1.20)	1.36 (0.85-2.20)
Model2	1.04 (0.97-1.10)	1.00 (0.96-1.05)	1.0	1.01 (0.94-1.09)	0.97 (0.79-1.19)	1.34 (0.82-2.18)
Pneumonia						
Inpatients						
Crude	0.54 (0.49-0.60)	0.84 (0.79-0.90)	1.0	1.57 (1.45-1.71)	3.04 (2.56-3.60)	6.59 (4.82-9.02)
Model1	1.40 (1.26-1.55)	1.14 (1.07-1.22)	1.0	0.99 (0.91-1.07)	1.14 (0.96-1.35)	2.92 (2.13-4.00)

Model2	1.29 (1.16-1.44)	1.11 (1.03-1.18)	1.0	1.01 (0.93-1.10)	1.16 (0.98-1.38)	2.04 (1.47-2.85)
Outpatients						
Crude	0.80 (0.76-0.84)	0.93 (0.90-0.96)	1.0	1.27 (1.21-1.34)	1.56 (1.37-1.78)	1.43 (0.99-2.08)
Model1	1.06 (1.01-1.12)	1.03 (1.00-1.07)	1.0	1.03 (0.98-1.08)	0.96 (0.84-1.10)	1.00 (0.69-1.45)
Model2	1.05 (1.00-1.10)	1.03 (0.99-1.07)	1.0	1.04 (0.99-1.09)	0.98 (0.86-1.12)	1.02 (0.70-1.48)
Diabetes						
Inpatients						
Crude	0.64 (0.60-0.69)	0.89 (0.85-0.93)	1.0	1.46 (1.37-1.55)	2.44 (2.12-2.81)	6.16(4.78-7.94)
Model1	1.48 (1.37-1.59)	1.17 (1.12-1.23)	1.0	0.96 (0.90-1.02)	1.01 (0.87-1.17)	2.94 (2.28-3.79)
Model2	1.45 (1.34-1.56)	1.17 (1.11-1.23)	1.0	0.93 (0.87-0.99)	0.91 (0.79-1.05)	1.62 (1.24-2.11)
Outpatients						
Crude	0.61 (0.59-0.63)	0.84 (0.82-0.86)	1.0	1.35 (1.30-1.40)	1.83 (1.67-2.01)	2.45 (1.96-3.06)
Model1	1.08 (1.04-1.12)	1.02 (1.00-1.05)	1.0	1.00 (0.96-1.04)	0.95 (0.87-1.04)	1.44 (1.16-1.80)
Model2	1.19 (1.14-1.24)	1.08 (1.05-1.11)	1.0	0.94 (0.91-0.98)	0.77 (0.70-0.85)	0.77 (0.61-0.96)
Renal failure						
Inpatients						
Crude	0.51 (0.39-0.66)	0.78 (0.66-0.93)	1.0	2.63 (2.19-3.15)	13.82 (10.93-17.48)	243.44 (198.67-298.31)
Model1	0.97 (0.74-1.27)	0.97 (0.81-1.16)	1.0	1.94 (1.61-2.33)	7.23 (5.65-9.25)	135.20 (108.85-167.92)
Model2	0.92 (0.70-1.21)	0.96 (0.80-1.14)	1.0	1.74 (1.45-2.10)	4.68 (3.64-6.02)	31.77 (24.63-40.97)
Outpatients						
Crude	0.41 (0.33-0.51)	0.69 (0.60-0.79)	1.0	3.13 (2.74-3.57)	16.57 (13.99-19.63)	213.30 (178.39-255.05)
Model1	0.62 (0.50-0.77)	0.79 (0.69-0.91)	1.0	2.66 (2.32-3.04)	11.93 (9.96-14.29)	159.77 (132.27-193.00)
Model2	0.62 (0.49-0.77)	0.80 (0.69-0.91)	1.0	2.37 (2.07-2.71)	7.65 (6.36-9.20)	39.31 (31.65-48.82)
Parkinson						
Inpatients						
Crude	0.16 (0.09-0.28)	0.62 (0.48-0.79)	1.0	2.36 (1.84-3.01)	9.80 (6.91-13.90)	3.80 (0.94-15.32)

Model1	0.95 (0.53-1.72)	1.05 (0.82-1.35)	1.0	1.14 (0.89-1.46)	2.12 (1.48-3.04)	0.96 (0.24-3.90)
Model2	0.94 (0.52-1.71)	1.05 (0.81-1.34)	1.0	1.14 (0.88-1.46)	2.12 (1.48-3.05)	0.93 (0.22-3.85)
Outpatients						
Crude	0.22 (0.16-0.29)	0.63 (0.55-0.73)	1.0	1.96 (1.67-2.28)	5.47 (4.19-7.14)	2.71 (1.01-7.25)
Model1	0.91 (0.67-1.24)	0.99 (0.85-1.14)	1.0	1.03 (0.88-1.21)	1.44 (1.10-1.89)	0.84 (0.31-2.25)
Model2	0.91 (0.67-1.24)	0.99 (0.85-1.14)	1.0	1.03 (0.88-1.20)	1.41 (1.07-1.86)	0.71 (0.26-1.93)
COPD						
Inpatients						
Crude	0.39 (0.32-0.47)	0.79 (0.71-0.89)	1.0	1.65 (1.44-1.89)	2.70 (1.99-3.65)	0.46 (0.06-3.24)
Model1	1.80 (1.47-2.21)	1.27 (1.13-1.43)	1.0	0.88 (0.77-1.02)	0.74 (0.55-1.01)	0.14 (0.02-1.03)
Model2	1.55 (1.27-1.91)	1.19 (1.06-1.34)	1.0	0.96 (0.84-1.11)	0.88 (0.65-1.20)	0.14 (0.02-1.01)
Outpatients						
Crude	0.55 (0.52-0.58)	0.82 (0.79-0.85)	1.0	1.37 (1.31-1.44)	1.97 (1.75-2.21)	1.76 (1.27-2.46)
Model1	1.06 (1.00-1.12)	1.03 (0.99-1.07)	1.0	0.94 (0.90-0.99)	0.88 (0.78-0.99)	0.94 (0.67-1.31)
Model2	1.04 (0.99-1.11)	1.02 (0.98-1.06)	1.0	0.96 (0.91-1.00)	0.89 (0.79-1.01)	0.90 (0.64-1.26)
Pulmonary disease						
Inpatients						
Crude	0.54 (0.39-0.75)	0.67 (0.53-0.84)	1.0	2.04 (1.59-2.62)	2.82 (1.57-5.07)	10.80 (4.78-24.41)
Model1	1.89 (1.32-2.70)	0.99 (0.78-1.26)	1.0	1.19 (0.92-1.54)	0.92 (0.51-1.67)	4.16 (1.83-9.46)
Model2	1.80 (1.26-2.58)	0.97 (0.77-1.23)	1.0	1.18 (0.92-1.53)	0.87 (0.48-1.57)	2.36 (0.98-5.68)
Outpatients						
Crude	0.45 (0.33-0.62)	0.66 (0.53-0.82)	1.0	1.46 (1.13-1.89)	1.76 (0.90-3.43)	4.56 (1.46-14.26)
Model1	1.17 (0.83-1.65)	0.89 (0.72-1.11)	1.0	0.96 (0.74-1.25)	0.73 (0.37-1.44)	2.22 (0.71-6.98)
Model2	1.14 (0.81-1.61)	0.88 (0.70-1.09)	1.0	0.99 (0.76-1.28)	0.78 (0.40-1.54)	2.11 (0.64-6.93)
Liver disease						
Inpatients						

Crude	0.89 (0.83-0.96)	1.04 (0.98-1.10)	1.0	1.06 (0.98-1.15)	1.23 (0.97-1.55)	2.73 (1.78-4.20)
Model1	1.31 (1.21-1.42)	1.19 (1.12-1.26)	1.0	0.88 (0.81-0.96)	0.83 (0.66-1.05)	2.02 (1.31-3.11)
Model2	1.30 (1.20-1.40)	1.18 (1.12-1.25)	1.0	0.88 (0.81-0.96)	0.82 (0.65-1.03)	1.65 (1.06-2.57)
Outpatients						
Crude	0.85 (0.83-0.88)	0.96 (0.94-0.98)	1.0	1.11 (1.08-1.15)	1.21 (1.10-1.33)	1.02 (0.78-1.35)
Model1	1.07 (1.04-1.10)	1.04 (1.02-1.07)	1.0	0.99 (0.96-1.03)	0.95 (0.87-1.04)	0.85 (0.64-1.11)
Model2	1.11 (1.08-1.15)	1.06 (1.04-1.09)	1.0	0.96 (0.93-1.00)	0.88 (0.80-0.96)	0.77 (0.58-1.02)

Model 1: adjusted for age and gender
Model 2: adjusted for age, gender, total cholesterol, diabetes, cardiovascular disease, current smoker, systolic blood pressure, anti-hypertensive, body mass index and dipstick proteinuria

Table A6. Hazard ratios (95%CI) for indicators of incident non-CVD/cancer by dipstick proteinuria

	Dipstick proteinuria			
	None/trace	1+	2+	≥3+
	N=224,973	N=6,331	N=1,421	N=494
Infectious disease				
Inpatients				
Crude	1.0	1.21 (1.14-1.28)	1.38 (1.23-1.55)	2.10 (1.78-2.48)
Model1	1.0	1.18 (1.11-1.25)	1.28 (1.14-1.43)	1.82 (1.54-2.15)
Model2	1.0	1.16 (1.10-1.23)	1.22 (1.09-1.38)	1.67 (1.41-1.98)
Outpatients				
Crude	1.0	1.00 (0.96-1.03)	0.93 (0.85-1.01)	0.93 (0.81-1.06)
Model1	1.0	1.00 (0.96-1.04)	0.92 (0.85-1.00)	0.92 (0.80-1.05)
Model2	1.0	1.00 (0.97-1.04)	0.93 (0.85-1.01)	0.95 (0.83-1.09)
Viral hepatitis				
Inpatients				
Crude	1.0	1.35 (1.10-1.67)	1.46 (0.95-2.25)	2.19 (1.21-3.95)
Model1	1.0	1.31 (1.06-1.62)	1.41 (0.92-2.17)	2.11 (1.17-3.82)
Model2	1.0	1.30 (1.05-1.60)	1.35 (0.88-2.09)	1.95 (1.05-3.62)
Outpatients				
Crude	1.0	1.15 (1.03-1.29)	1.23 (0.97-1.55)	1.03 (0.67-1.58)
Model1	1.0	1.13 (1.01-1.26)	1.19 (0.95-1.50)	0.99 (0.64-1.52)
Model2	1.0	1.11 (0.99-1.25)	1.15 (0.91-1.45)	0.95 (0.61-1.47)
Pneumonia				
Inpatients				
Crude	1.0	1.56 (1.36-1.79)	2.37 (1.86-3.01)	4.43 (3.30-5.94)
Model1	1.0	1.43 (1.25-1.65)	1.84 (1.44-2.34)	3.05 (2.27-4.09)
Model2	1.0	1.39 (1.21-1.60)	1.72 (1.34-2.20)	2.60 (1.91-3.54)
Outpatients				
Crude	1.0	1.02 (0.93-1.12)	1.07 (0.88-1.30)	0.98 (0.70-1.37)
Model1	1.0	1.02 (0.93-1.12)	1.00 (0.82-1.21)	0.86 (0.62-1.21)
Model2	1.0	1.04 (0.95-1.15)	1.04 (0.86-1.27)	0.91 (0.65-1.28)
Diabetes				
Inpatients				
Crude	1.0	2.60 (2.39-2.83)	4.09 (3.55-4.73)	6.38 (5.23-7.78)
Model1	1.0	2.43 (2.24-2.64)	3.36 (2.91-3.87)	4.83 (3.96-5.89)
Model2	1.0	1.38 (1.27-1.51)	1.54 (1.33-1.78)	2.14 (1.74-2.63)
Outpatients				
Crude	1.0	2.01 (1.90-2.12)	2.84 (2.57-3.14)	3.15 (2.68-3.71)
Model1	1.0	1.95 (1.85-2.06)	2.53 (2.29-2.80)	2.58 (2.20-3.04)

Model2	1.0	1.38 (1.31-1.46)	1.48 (1.34-1.64)	1.15 (0.97-1.36)
Renal failure				
Inpatients				
Crude	1.0	8.00 (6.70-9.55)	25.17 (20.34-31.15)	92.11 (75.56-112.28)
Model1	1.0	7.28 (6.10-8.70)	19.71 (15.91-24.42)	62.60 (51.21-76.53)
Model2	1.0	4.68 (3.90-5.63)	6.92 (5.46-8.77)	10.87 (8.36-14.12)
Outpatients				
Crude	1.0	7.05 (6.12-8.13)	27.62 (23.59-32.35)	70.47 (59.26-83.80)
Model1	1.0	6.44 (5.59-7.43)	22.76 (19.42-26.67)	52.13 (43.77-62.10)
Model2	1.0	4.29 (3.71-4.96)	9.96 (8.40-11.80)	9.13 (7.32-11.39)
Parkinson				
Inpatients				
Crude	1.0	1.03 (0.58-1.84)	1.24 (0.40-3.86)	3.35 (1.08-10.42)
Model1	1.0	0.91 (0.51-1.63)	0.85 (0.27-2.64)	1.82 (0.58-5.68)
Model2	1.0	0.78 (0.43-1.38)	0.66 (0.21-2.07)	1.24 (0.39-3.97)
Outpatients				
Crude	1.0	1.13 (0.80-1.59)	1.91 (1.08-3.37)	3.48 (1.73-6.97)
Model1	1.0	1.01 (0.72-1.42)	1.35 (0.77-2.39)	2.03 (1.10-4.07)
Model2	1.0	0.95 (0.68-1.35)	1.26 (0.71-2.24)	1.85 (0.91-3.76)
COPD				
Inpatients				
Crude	1.0	1.12 (0.85-1.48)	2.28 (2.78-8.76)	1.15 (0.43-3.07)
Model1	1.0	0.93 (0.70-1.22)	1.51 (0.99-2.30)	0.62 (0.23-1.65)
Model2	1.0	1.00 (0.76-1.33)	1.94 (1.27-2.97)	0.83 (0.31-2.23)
Outpatients				
Crude	1.0	1.09 (0.99-1.19)	1.43 (1.20-1.70)	1.38 (1.03-1.85)
Model1	1.0	1.03 (0.94-1.13)	1.19 (1.00-1.41)	1.04 (0.77-1.39)
Model2	1.0	1.06 (0.97-1.17)	1.27 (1.07-1.52)	1.15 (0.85-1.55)
Pulmonary disease				
Inpatients				
Crude	1.0	2.11 (1.40-3.18)	4.93 (2.78-8.76)	6.75 (3.01-15.12)
Model1	1.0	1.80 (1.19-2.72)	3.48 (1.96-6.19)	4.05 (1.81-9.08)
Model2	1.0	1.60 (1.06-2.44)	2.77 (1.53-5.03)	2.98 (1.27-7.02)
Outpatients				
Crude	1.0	1.00 (0.58-1.74)	2.21 (0.99-4.94)	2.01 (0.50-8.04)
Model1	1.0	0.87 (0.50-1.50)	1.63 (0.73-3.66)	1.30 (0.32-5.23)
Model2	1.0	0.8 (0.50-1.53)	1.63 (0.71-3.71)	1.29 (0.31-5.36)
Liver disease				
Inpatients				
Crude	1.0	1.61 (1.43-1.82)	1.80 (1.41-2.28)	1.96 (1.33-2.88)
Model1	1.0	1.52 (1.35-1.71)	1.60 (1.26-2.04)	1.68 (1.14-2.47)

Model2	1.0	1.48 (1.32-1.67)	1.53 (1.20-1.94)	1.58 (1.06-2.35)
Outpatients				
Crude	1.0	1.29 (1.22-1.36)	1.23 (1.10-1.38)	1.09 (0.89-1.33)
Model1	1.0	1.24 (1.18-1.31)	1.14 (1.02-1.29)	0.99 (0.80-1.21)
Model2	1.0	1.15 (1.09-1.22)	1.01 (0.90-1.13)	0.86 (0.70-1.06)

Model 1: adjusted for age and gender
Model 2: adjusted for age, gender, total cholesterol, diabetes, cardiovascular disease, current smoker, systolic blood pressure, anti-hypertensive, body mass index and dipstick proteinuria

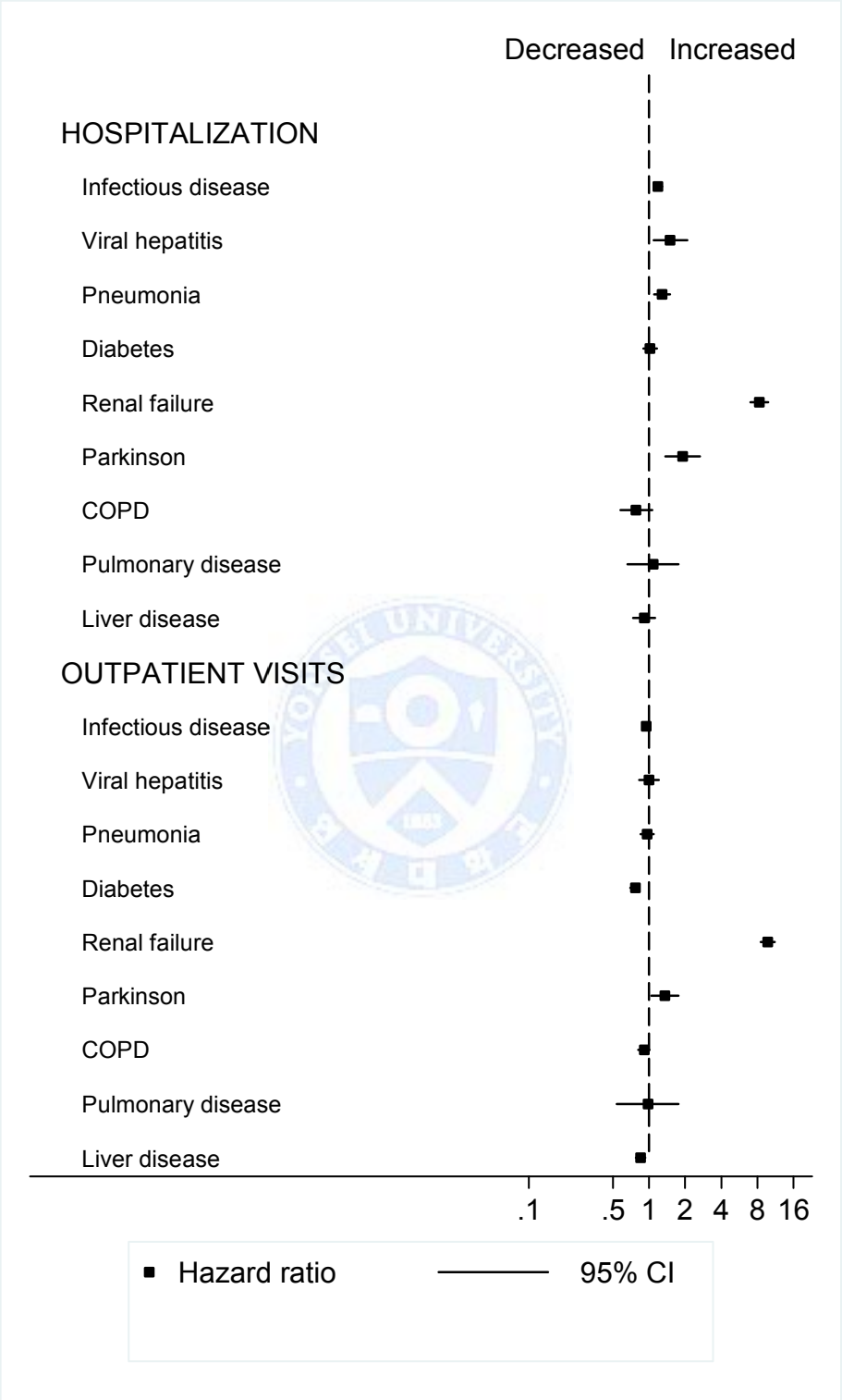

Figure A1. Adjusted hazard ratios (95%CI) for indicators of incident non-CVD/cancer for eGFR<60 ml/min/1.73m^2 (vs. ≥ 60)

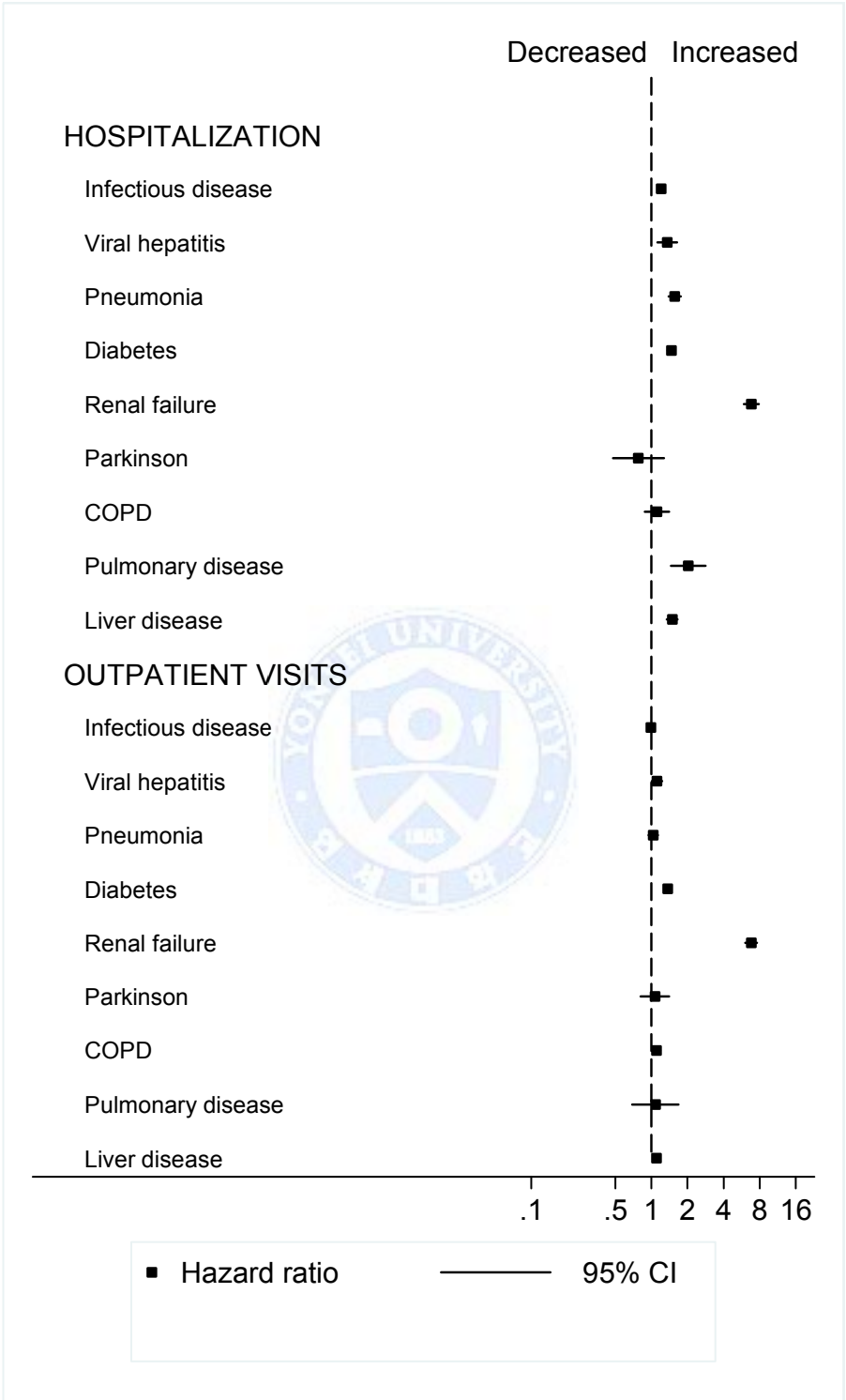

Figure A2. Adjusted hazard ratios (95%CI) for indicators of incident non-CVD/cancer for positive proteinuria (vs. none/trace)

Table A7. Hazard ratios (95%CI) for cause-specific mortality by 1 year change in eGFR

	Quartile of 1 year change in eGFR			
	Q1 (-58.83 to -10.61) N=14,468	Q2 (-10.62 to -0.70) N=13,307	Q3 (-0.71 to 10.31) N=13,445	Q4 (10.32 to 95.34) N=15,212
Cancer mortality				
Case	81	82	85	70
Crude	0.88 (0.65-1.19)	0.96 (0.71-1.30)	1.0	0.76 (0.55-1.04)
Model 1	0.97 (0.72-1.32)	1.00 (0.74-1.35)	1.0	0.80 (0.58-1.10)
Model 2	0.97 (0.71-1.32)	0.98 (0.72-1.32)	1.0	0.80 (0.58-1.10)
CVD mortality				
Case	36	33	24	23
Crude	1.38 (0.82-2.32)	1.37 (0.81-2.31)	1.0	0.89 (0.50-1.57)
Model 1	1.61 (0.95-2.70)	1.42 (0.84-2.41)	1.0	0.98 (0.55-1.74)
Model 2	1.58 (0.94-2.66)	1.37 (0.81-2.33)	1.0	0.96 (0.54-1.70)
Non-CVD/cancer mortality				
Case	51	60	72	39
Crude	0.65 (0.45-0.93)	0.83 (0.59-1.17)	1.0	0.50 (0.34-0.74)
Model 1	0.74 (0.51-1.06)	0.86 (0.61-1.21)	1.0	0.54 (0.37-0.80)
Model 2	0.74 (0.51-1.05)	0.83 (0.59-1.18)	1.0	0.54 (0.36-0.79)
All-cause mortality				
Case	168	175	181	132
Crude	0.86 (0.69-1.05)	0.96 (0.78-1.18)	1.0	0.67 (0.54-0.84)
Model 1	0.96 (0.78-1.19)	1.00 (0.81-1.23)	1.0	0.72 (0.58-0.91)
Model 2	0.96 (0.78-1.18)	0.97 (0.79-1.20)	1.0	0.72 (0.57-0.90)

Model 1: adjusted for age and gender

Model 2: adjusted for age, gender, total cholesterol, diabetes, cardiovascular disease, cancer, current smoker, systolic blood pressure, anti-hypertensive, body mass index and dipstick proteinuria

Table A8. Hazard ratios (95%CI) for cause-specific mortality by 2 year change in eGFR

	2 years change in eGFR		
	Stable N=19,009	Uncertain drop N=30,630	Certain drop N=1,094
Cancer mortality			
Case	144	198	12
Crude	1.0	0.81 (0.66-1.01)	1.15 (0.64-2.07)
Model 1	1.0	0.93 (0.75-1.16)	1.21 (0.67-2.19)
Model 2	1.0	0.95 (0.76-1.18)	1.30 (0.72-2.35)
CVD mortality			
Case	42	65	0
Crude	1.0	0.96 (0.65-1.42)	0.00 (0.00-0.00)
Model 1	1.0	1.10 (0.75-1.63)	0.00 (0.00-0.00)
Model 2	1.0	1.16 (0.78-1.71)	0.00 (0.00-0.00)
Non-CVD/cancer mortality			
Case	75	122	9
Crude	1.0	0.97 (0.73-1.39)	1.70 (0.85-3.41)
Model 1	1.0	1.10 (0.82-1.47)	1.82 (0.91-3.64)
Model 2	1.0	1.13 (0.84-1.51)	1.73 (0.85-3.49)
All-cause mortality			
Case	261	385	21
Crude	1.0	0.88 (0.75-1.03)	1.13 (0.72-1.76)
Model 1	1.0	1.01 (0.86-1.18)	1.20 (0.77-1.87)
Model 2	1.0	1.03 (0.88-1.21)	1.22 (0.78-1.92)

Model 1: adjusted for age and gender

Model 2: adjusted for age, gender, total cholesterol, diabetes, cardiovascular disease, cancer, current smoker, systolic blood pressure, anti-hypertensive, body mass index and dipstick proteinuria

Table A9. Hazard ratios (95%CI) for cause-specific mortality by 3 year change in eGFR

	3 years change in eGFR		
	Stable N=20,329	Uncertain drop N=13,147	Certain drop N=407
Cancer mortality			
Case	203	99	6
Crude	1.0	0.97 (0.69-1.38)	0.98 (0.48-2.03)
Model 1	1.0	0.98 (0.69-1.38)	1.00 (0.49-2.06)
Model 2	1.0	0.98 (0.69-1.39)	1.06 (0.51-2.20)
CVD mortality			
Case	52	34	2
Crude	1.0	0.84 (0.45-1.55)	1.39 (0.45-4.24)
Model 1	1.0	0.83 (0.45-1.54)	1.35 (0.44-4.09)
Model 2	1.0	0.83 (0.44-1.54)	1.25(0.40-3.86)
Non-CVD/cancer mortality			
Case	106	65	2
Crude	1.0	1.01 (0.60-1.70)	1.18 (0.44-3.19)
Model 1	1.0	1.01 (0.60-1.71)	1.17 (0.44-3.16)
Model 2	1.0	1.02 (0.61-1.72)	1.23 (0.45-3.36)
All-cause mortality			
Case	361	198	10
Crude	1.0	0.96 (0.74-1.24)	1.11 (0.66-1.85)
Model 1	1.0	0.96 (0.74-1.24)	1.11 (0.66-1.86)
Model 2	1.0	0.97 (0.74-1.25)	1.15 (0.69-1.94)

Model 1: adjusted for age and gender

Model 2: adjusted for age, gender, total cholesterol, diabetes, cardiovascular disease, cancer, current smoker, systolic blood pressure, anti-hypertensive, body mass index and dipstick proteinuria

Table A10. Hazard ratios (95%CI) for cause-specific mortality by 4 year change in eGFR

	4 years change in eGFR		
	Stable N=13,533	Uncertain drop N=7,837	Certain drop N=491
Cancer mortality			
Case	167	82	5
Crude	1.0	1.21 (0.82-1.79)	0.84 (0.40-1.78)
Model 1	1.0	1.15 (0.78-1.70)	0.92 (0.44-1.94)
Model 2	1.0	1.16 (0.78-1.71)	0.96 (0.46-2.03)
CVD mortality			
Case	49	26	0
Crude	1.0	0.67 (0.29-1.54)	1.29 (0.35-4.79)
Model 1	1.0	0.65 (0.29-1.50)	1.28 (0.34-4.73)
Model 2	1.0	0.69 (0.30-1.59)	1.37 (0.36-5.17)
Non-CVD/cancer mortality			
Case	82	56	3
Crude	1.0	0.88 (0.49-1.60)	1.08 (0.41-2.86)
Model 1	1.0	0.84 (0.46-1.53)	1.19 (0.45-3.13)
Model 2	1.0	0.83 (0.45-1.52)	1.08 (0.41-2.84)
All-cause mortality			
Case	298	164	8
Crude	1.0	1.04 (0.77-1.40)	0.97 (0.56-1.66)
Model 1	1.0	0.99 (0.73-1.34)	1.05 (0.61-1.79)
Model 2	1.0	1.00 (0.74-1.35)	1.03 (0.60-1.76)

Model 1: adjusted for age and gender

Model 2: adjusted for age, gender, total cholesterol, diabetes, cardiovascular disease, cancer, current smoker, systolic blood pressure, anti-hypertensive, body mass index and dipstick proteinuria

Table A11. STATA command for analysis

Imputation	mi set wide mi register regular age female hx_cvd hx_can antihtn egfr dpr event_cvd1 event_can event_othe1 fu_death logflup mi register imputed cursmk sbp chol drink diabetes mi describe mi impute chained (regress) sbp chol (logit) drink cursmk diabetes=age female hx_cvd hx_can bmi antihtn event_cvd1 event_can event_othe1 fu_death egfr dpr logflup, add(20) rseed(1) force
Cox regression using multiple imputation	capture program drop miPH_45 program miPH_45 syntax [if] global full "age female chol diabetes hx_cvd hx_can cursmk sbp antihtn bmi" foreach v in cvd1 can1 othe1 death { mi stset fu_death, failure(event_`v'==1) mi estimate, dots: stcox ib2.egfr3 i.dpr1 $full `if', nolog } end
Competing risks model	capture program drop PH_com1 program PH_com1 syntax [if] foreach v in can1 cvd1 othe1 { mi stset fu_death, failure(event_`v'==1) replace oth_death=0 if event_`v'==1 stcrreg ib2.egfr3 `if', nolog compete(oth_death==1) stcrreg i.dpr1 `if', nolog compete(oth_death==1) replace oth_death=event_death } end

Spline with multiple imputation	mkspline segfr1 30 segfr2 45 segfr3 60 segfr4 75 segfr5 90 segfr6 105 segfr7=egfr
	
	mi stset fu_death, failure(event_death==1) id(id)
	mi estimate, vartable saving(miestfile, replace): stcox egfr? age female chol diabetes hx_cvd hx_can cursmk sbp antihtn bmi,nolog
	foreach v in age female chol diabetes hx_cvd hx_can cursmk sbp antihtn bmi {
	replace `v'=0
	}
	mi predict hr using miestfile
	mi predict stderr using miestfile, stdp
	
	gen hr1=exp(hr)
	gen lci=exp(hr-1.96*stderr)
	gen uci=exp(hr+1.96*stderr)
	
	twoway ///
	rarea lci uci egfr, color(ltblue) graphregion(fcolor(white)) ///
	title("all-cause mortality") subtitle("Reference at eGFR=95") ytitle("HR") ///
	xtitle("eGFR, ml/min/1.73{superscript:2}") xlabel(15 30 45 60 75 90 105 120) ///
	ylabel(0.5 1 2 4 8) yscale(log) xscale() yline(1, lcolor(gray)) || ///
	line hr1 egfr, clw(0.3) lcolor(black)|| ///
	rcap lci uci egfr, lcolor("230 170 170") lwidth(0.3)

ABSTRACT IN KOREAN

만성신장질환 요인이 특정원인질환 사망 및 발생에 미치는 영향

연세대학교 대학원 보건학과

목 예 진

만성신장질환은 동서양 지역 모두 10-15%의 유병률을 차지하고 있는 전 세계적으로 증가하고 있는 질환 중 하나이며, 보건학적으로 문제가 대두되고 있다. 이전의 많은 연구들은 사구체 여과율의 저하와 단백뇨에 따른 사망, 특히 모든 원인에 의한 사망과 심장병으로 인한 사망과의 관련성을 보고하였다. 하지만 신장질환과 암을 비롯한 그 외의 원인으로 인한 사망에 대한 연구는 미비한 실정이다. 따라서 본 연구에서는 신장질환과 특정원인에 의한 사망과의 관련성을 보고 신장질환이 사망을 예측함에 있어서 얼마나 기여하는지 보고자 하였다.

본 연구는 1994 년부터 2004 년까지 건강검진센터에서 검진을 받은 367,932 명(20~93 세)의 대사증후군 사망연구(Metabolic Syndrome Mortality Study, MSMS)와 1996 년부터 2004 년까지 검진을 받은 233,219 명(30~74 세)의 한국인 심장병 연구(Korean Heart Study, KHS)의 자료를 이용하였다. 사구체 여과율(estimated glomerular filtration rate, eGFR)은 크레아티닌 수치를 이용한 CKD-EPI 공식을 사용하였으며, dipstick 단백뇨(proteinuria)는 negative/trace, 1+, 2+, 3+이상 군으로 나누었다. eGFR 과 proteinuria 와 특정원인 사망과의 관련성을 보기 위해 Cox proportional hazard model 을 이용하였다.

낮은 eGFR(<60ml/min/1.73m^2 vs. ≥60ml/min/1.73m^2)수치와 심장병[hazard ratio (HR)1.49(95%CI, 1.24-1.78)], 비심장병/암[1.78(1.54-2.05)]으로 인한 사망위험과 통계적으로 유의한 관련성을 나타내었다. 암으로 인한 사망의 경우 eGFR 이

45-59 ml/min/1.73m^2 인 군에서 가장 낮은 위험을 보였고, 이 군을 기준으로 하였을 때 eGFR 이 45 ml/min/1.73m^2 미만인 군에서 암으로 인한 사망의 위험이 높게 나타났다 [1.62(1.10-2.39)]. 단백뇨(dipstick≥1+ vs. negative/trace)는 심장병[1.93(1.66-2.25)], 암[1.49(1.32-1.68)], 비심장병/암[2.19(1.96-2.45)]으로 인한 사망위험 모두 통계적으로 유의한 관련성을 보였다. 좀 더 세부적인 사망원인을 보았을 때, 낮은 eGFR 수치는 허혈성심장병, 구인두암, 감염병, 당뇨병과 신부전으로 인한 사망위험과 관련이 있었고, 단백뇨는 허혈성심장병, 뇌혈관질환, 위암, 간암, 췌장암, 폐암, 골수종, 감염병, 당뇨병, 간질환과 신부전으로 인한 사망위험과 관련이 있었다. 위의 결과를 질병발생 데이터에 적용하여서 살펴보았을 때 비슷한 결과를 나타내었다. 또한, eGFR 수치의 1 년 이내 급속한 감소는 심장병으로 인한 사망과 관련이 있었지만 다른 질환으로 인한 사망과 관련은 없었다.

낮은 eGFR 수치는 심장병과 비 심장병/암으로 인한 사망위험과 관련성이 있는 반면에 단백뇨는 심장병, 암, 비 심장병/암으로 인한 사망위험과 관련성을 나타내었다. 이러한 연구결과는 신장질환환자에게 다 학문적 예방과 관리전략의 필요성을 제시한다.

핵심되는 말: 사구체여과율, 단백뇨, 사망, 질환발생