筑　波　大　学

博 士 （医 学） 学 位 論 文

Constipation and Chronic Kidney Disease

（便秘と慢性腎臓病の関連についての検討）

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Contents

1. Abbreviations

ACEI	angiotensin-converting enzyme inhibitors
AIDS	acquired immunodeficiency syndrome
ARB	angiotensin receptor blockers
BMI	body mass index
CI	confidence interval
CHD	coronary heart disease
CHF	congestive heart failure
CKD	chronic kidney disease
eGFR	estimated glomerular filtration rate
ESRD	end-stage renal disease
HIV	human immunodeficiency virus
HR	hazard ratio
ICD-9-CM	international classification of diseases, ninth revision clinical modification
IQR	interquartile range
MOR	multinomial odds ratio
RCAV	racial and cardiovascular risk anomalies in CKD
SD	standard deviation
TMAO	trimethylamine-N-oxide
US	United States
USRDS	United States Renal Data System
VA	veterans affairs

2. Background

Chronic kidney disease (CKD) is a growing public health problem due to its increasing prevalence and strong association with cardiovascular disease, end-stage renal disease (ESRD), and mortality.[1] Although some risk factors of CKD, such as diabetes mellitus and hypertension,[2] have been established, the identification of novel risk factors and interventions applicable to primary care settings may help to ameliorate the risk for subsequent adverse outcomes and reduce the global burden of CKD.

Constipation is the prototype of functional gastrointestinal disorders and one of the most prevalent conditions encountered in primary care settings. Approximately 30% of the general population experiences problems with constipation during their lifetime,[3] with elderly people and women being mostly affected. Although constipation is usually perceived as a benign, often self-limited condition,[4] its chronic symptoms impair patients' quality-of-life and may impose a substantial economic burden on patients and society.[5, 6] Furthermore, recent observational studies have shown an association of chronic constipation with increased risk of cardiovascular disease,[7, 8] and suggested the possible involvement of chronic inflammation caused by altered gut microbiota as an underlying mechanism for the association.[7, 8] It is plausible that constipation may also be a risk factor for the development of CKD, potentially mediated by altered gut

microbiota, or by other intermediate risk factors such as diabetes, use of nonsteroidal anti-inflammatory drugs, or lack of physical exercise, which have been associated both with constipation[7, 9] and with CKD progression;[2, 10-12] however, to the best of my knowledge, no prior studies have examined the association between constipation and the risk of CKD.

3. Study Objective

In this study, I hypothesized that patients with constipation are at higher risk of incident kidney disease and are more likely to experience rapid decline of kidney function, and that patients with more severe constipation would have a greater risk of such events than those with less severe constipation. To test these hypotheses, I aimed to investigate the association of constipation status and its severity with incident CKD and ESRD, along with change in estimated glomerular filtration rate (eGFR) using a large nationally representative cohort of United States (US) veterans with eGFR of ≥60 mL/min/1.73 m^2.

4. Methods

A) Cohort Definition

I used data from a retrospective cohort study examining risk factors in patients with incident CKD (Racial and Cardiovascular Risk Anomalies in CKD [RCAV] study).[13] **Figure 1** shows the algorithm for cohort definition. All serum creatinine measurements obtained in clinical settings in all US Department of VA health care facilities between October 1, 2004 and September 30, 2006 (baseline period) were used from the national VA Corporate Data Warehouse LabChem data files.[14] Overall, 4,447,691 veterans had at least 1 available serum creatinine measurement, representing ~94% of all US veterans who received VA health care during this time period.[15] The RCAV cohort included 3,582,478 patients with baseline eGFR ≥60 mL/min/1.73 m^2. eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation.[16] After exclusion of patients with missing *International Classification of Diseases, Ninth Revision Clinical Modification* (*ICD-9-CM*) codes (*n* = 11,311) or with erroneous data (*n* = 66,435), 3,504,732 patients were included in the final cohort.

B) Data Collection

Exposures and Covariates

Constipation was defined as either having at least 2 diagnoses for constipation, as identified by the *ICD-9-CM* (**Table 1**), that were >60 days apart; or having ≥2 prescriptions of laxatives of ≥30-day supply each, that were 60–365 days apart during the baseline period, based on information obtained from VA Pharmacy dispensation records.[17] Constipation severity was also quantitatively defined according to the number of different types of laxatives prescribed during the baseline period, and stratified into three groups as follows; absent (no laxative), mild (one type of laxative), or moderate/severe (≥2 types of laxatives). Sociodemographic characteristics, comorbid conditions, medication use, and laboratory characteristics were obtained as previously described.[18, 19] Briefly, data on patients' age, sex, race, marital status (married, single, divorced or widowed), mean per capita income, service connectedness, body mass index (BMI), systolic and diastolic blood pressures, comorbid conditions, and medication use was obtained from various national VA research data files.[20] Prevalent comorbidities were defined as the presence of relevant *ICD-9-CM* and *Current Procedural Terminology* codes recorded from October 1, 2004, to September 30, 2006 (**Table 1**).[18, 19] Prevalent coronary heart disease (CHD) was defined as the presence of diagnostic

codes for coronary artery disease, angina, or myocardial infarction or procedure codes for percutaneous coronary interventions or coronary artery bypass grafting. Bowel disorders were defined as the presence of diagnostic codes for inflammatory bowel disease, irritable bowel syndrome, or diarrhea. In addition to the information derived from VA sources, select socioeconomic indicators using 2004 county typology codes (housing stress, low education, low employment, and persistent poverty; **Table 2**) were included.

Outcomes

The co-primary outcomes of interest were incident CKD, incident ESRD, and change in eGFR. Incident CKD was defined as two eGFR levels <60 mL/min/1.73 m^2 separated by ≥90 days, and a >25% decrease from baseline eGFR.[21] Incident ESRD was defined as initiation of maintenance dialysis or preemptive renal transplantation occurring between the cohort entry date and September 13, 2011, the last date of available event record provided by the United States Renal Data System (USRDS). Change in eGFR (i.e., eGFR slope) was calculated in each patient from an ordinary least squares regression model using all outpatient eGFR measurements available from the cohort entry date to October 13, 2012 (the last date of available serum creatinine

measurement), and stratified into 5 categories as follows: <10, -10 to <-5, -5 to <-1, -1 to 0 (reference), and ≥0 mL/min/1.73 m^2/year. The median (interquartile range [IQR]) number of eGFR measurements used to calculate eGFR slopes was 10 (5 to 17). Information about all-cause mortality was obtained from the VA Vital Status Files.[22]

C) Statistical Analyses

Data are presented as number (percent) for categorical variables and mean±standard deviation (SD) for continuous variables with a normal distribution or median (IQR) for those with a skewed distribution. The start of follow-up was the date of the first eGFR ≥60 mL/min/1.73 m^2 during the baseline period. Patients were followed up until death or until the last date of VA contact. The associations of constipation status and its severity with outcomes were assessed with the Kaplan-Meier method and log-rank tests, and using Cox proportional hazards models (for time-to-event analyses) and multinomial logistic regression models (for change in eGFR). The proportionality assumption was tested by plotting log [-log (survival rate)] against log (survival time) and by scaled Schoenfeld residuals; and showed no violations. For the time-to-event analyses, patients were followed up until death or were censored at the date of the last encounter, or on October 13, 2012 and September 13,

2011 for incident CKD and ESRD, respectively. All associations were examined in unadjusted and multivariable adjusted models. Models were incrementally adjusted for the following confounders based on theoretical considerations: model 1, unadjusted; model 2, adjusted for age, sex, and baseline eGFR; model 3, model 2 variables plus prevalent comorbidities (diabetes mellitus, hypertension, CHD, congestive heart failure [CHF], cerebrovascular disease, peripheral vascular disease, peptic ulcer disease, rheumatic disease, malignancy, depression, liver disease, chronic lung disease, human immunodeficiency virus [HIV]/ acquired immunodeficiency syndrome [AIDS], and bowel disorders); model 4, model 3 variables plus baseline BMI and systolic and diastolic blood pressure; and model 5, model 4 variables plus socioeconomic parameters (mean per capita income, marital status, service connectedness, housing stress, low education, low employment, and persistent poverty), indicators of sickness (number of VA healthcare encounters and cumulative length of hospitalization) and quality of care (receipt of influenza vaccination[s]), and use of angiotensin-converting enzyme inhibitors (ACEIs), or angiotensin II receptor blockers (ARBs), statins, antidepressants, non-opioid analgesics, and opioids at baseline.

I additionally performed several sensitivity analyses. All outcomes were examined in subgroups of patients categorized by baseline age, sex, race, prevalent

diabetes mellitus, hypertension, CHD, CHF, eGFR, and income level. Analyses were repeated in a propensity score-matched cohort to account for baseline differences arising from dissimilarities in clinical and demographic characteristics of patients with and without constipation. Propensity scores for the likelihood of presence versus absence of constipation were calculated by logistic regression using all variables included in multivariable models and performing a 1:1 nearest-neighbor matching without replacement. As death and incident CKD/ESRD are competing events, competing risk regressions were also performed using unadjusted models in the overall cohort, as well as in the propensity-matched cohort. Of the variables included in multivariable adjusted models, data points were missing for race (9.7%), BMI (4.7%), blood pressure (1.4%), per capita income (6.9%), and socioeconomic indicators (4.0%). Missing values were not imputed in primary analyses but were substituted by multiple imputation procedures using the STATA "mi" set of command in sensitivity analyses.

Because of the large sample size, the significance of differences in the main cohort was established based on considerations of biologically or clinically meaningful differences. Differences between variables in the overall and propensity-matched cohorts were examined by calculating standardized differences, and values >0.1 were considered significant. All of the analyses were conducted using Stata/MP version 14

(Stata Corporation, College Station, TX). The study was approved by the institutional review boards at the Memphis and Long Beach VA medical centers.

5. Results

Patients' baseline characteristics overall and those in patients categorized by constipation status are shown in **Table 3**. The mean age at baseline was 60.0 years (SD, 14.1); 93.2% were male; 15.3% were African American; and 24.7% were diabetic. The mean eGFR was 83.8 mL/min/1.73 m^2 (SD, 15.6). Compared to patients without constipation, those with constipation were older and more likely to be African American, had a higher prevalence of comorbidities except HIV/AIDS and a lower per capita income, and were less likely to be married. They also had more frequent healthcare encounters and longer cumulative length of hospitalization during the two-year baseline period. The use of ACEIs/ARBs, statins, antidepressants, non-opioid analgesics, and opioids and the administration of influenza vaccination(s) were more common in patients with constipation. Baseline characteristics were well balanced in the propensity-matched cohort (**Table 3**).

A) Incident CKD

During a median follow-up of 7.0 years, there were a total of 360,541 events of incident CKD (crude rate, 17.2 per 1000 patient-years; 95% CI, 17.2–17.3), including 46,022 (crude rate, 33.9 per 1000 patient-years; 95% CI, 33.6–34.2) and 314,519 (crude

rate, 16.1 per 1000 patient-years; 95% CI, 16.0–16.1) events in patients with and without constipation, respectively. As depicted in **Figure 2(A)a**, patients with constipation had a higher cumulative incidence of CKD (log-rank *P* <0.001). **Figure 3(A)** shows the association between constipation status and incident CKD in unadjusted and adjusted models. In the crude model, the presence of constipation was associated with a higher risk of incident CKD (hazard ratio [HR], 2.08; 95% CI, 2.06–2.10). Although adjustment for covariates resulted in the attenuation of this association, the risk of incident CKD remained significantly higher in patients with constipation (adjusted HR, 1.13; 95% CI, 1.11–1.14). Compared to patients with absent constipation, those with more severe constipation showed incrementally higher associations with the incidence of CKD: log-rank *P* <0.001, **Figure 2(A)b**; fully-adjusted HRs [95% CI], 1.10 [1.09–1.12] and 1.16 [1.14–1.18] for mild and moderate/severe constipation, respectively (**Figure 4(A)**).

B) Incident ESRD

A total of 7,677 patients developed ESRD (crude rate, 0.39 per 1000 patient-years; 95% CI, 0.38–0.40), including 902 (crude rate, 0.65 per 1000 patient-years; 95% CI, 0.61–0.70) and 6,775 (crude rate, 0.37 per 1000 patient-years;

95% CI, 0.36–0.38) events in patients with and without constipation, respectively. Cumulative incidence of ESRD was higher in patients with (versus without) constipation (log-rank *P* <0.001; **Figure 2(B)a**). Patients with constipation had a significantly higher risk of incident ESRD (adjusted HR, 1.09; 95% CI, 1.01–1.18; **Figure 3(B)**). With increasing constipation severity, a higher cumulative incidence of ESRD (**Figure 2(B)b**) as well as a greater risk of incident ESRD (**Figure 4(B)**) was also observed.

C) Change in eGFR

Among 3,242,681 patients in the eGFR slope analysis, 119,165 (3.7%), 189,792 (5.9%), and 905,877 (27.9%) experienced decline in eGFR of <-10, -10 to <-5, and -5 to <-1 mL/min/1.73 m^2/year, respectively, whereas 1,378,842 patients (42.5%) had stable or increasing eGFR (≥0 mL/min/1.73 m^2/year) (**Table 4**). **Figure 3(C)** shows the association between constipation status and change in eGFR. Compared to patients without constipation, those with constipation were at a greater risk of experiencing more progressive eGFR decline, with higher risks seen in patients with faster eGFR decline (adjusted multinomial odds ratios [MORs] [95% CI], 1.17 [1.14–1.20] for eGFR slopes <-10, 1.07 [1.04–1.09] for -10 to <-5, and 1.01 [1.00–1.03] for -5 to <-1 [versus -1 to

<0] mL/min/1.73 m^2/year); and they also had a higher risk of increasing eGFR (adjusted OR [95% CI], 1.09 [1.08–1.11] for eGFR slopes ≥0 [versus -1 to <0] mL/min/1.73 m^2/year). The risk of progressive eGFR decline was higher in patients with mild and moderate/severe constipation than those with absent constipation (adjusted MORs [95% CI] of eGFR slopes <-10 [versus -1 to <0] mL/min/1.73 m^2/year, 1.18 [1.14–1.21] and 1.30 [1.25–1.35], adjusted MORs of eGFR slopes -10 to <-5, 1.07 [1.04–1.10] and 1.12 [1.09–1.16], and adjusted MORs of eGFR slopes -5 to <-1, 1.01 [0.99–1.03] and 1.04 [1.02–1.06], respectively; **Figure 4(C)**). Similarly, the risk of increasing eGFR was incrementally higher in those with more severe constipation (adjusted ORs [95% CI] of eGFR ≥0 [versus -1 to <0] mL/min/1.73 m^2/year, 1.08 [1.06–1.10] and 1.14 [1.12–1.17] for mild and moderate/severe constipation, respectively; **Figure 4(C)**).

D) Sensitivity Analyses

Results were similar in the various sensitivity analyses accounting for confounding by indication, competing risk, and missing data (**Tables 5 and 6**), as well as in select subgroups (**Figures 5 and 6**).

6. Discussion

In the present study, I examined the association of constipation status and its severity with incident CKD, incident ESRD, and change in eGFR, using a large cohort of US veterans with baseline eGFR ≥60 mL/min/1.73m^2, and found that the presence of constipation and the severity of constipation were associated with increased risk of incident CKD, incident ESRD, and progressive eGFR decline. These findings were similarly observed in selected subgroups and were robust to sensitivity analyses accounting for confounding by indication, competing risk, and missing data.

The prevalence of constipation has been shown to be higher in patients with CKD, particularly among those undergoing dialysis, than the general population,[23] mostly due to their dietary restrictions, medications like phosphate binders, and high prevalence of comorbidities.[24] In recent years, there has been a growing interest in the association between CKD and intestinal environment (often referred to as "CKD-Colonic Axis"), showing that CKD can cause significant quantitative and qualitative alterations of gut environment, which in turn may contribute to the pathogenesis of CKD progression and several CKD-related complications.[25] However, these studies have focused primarily on patients with advanced CKD; and hence, it remains unknown whether the altered gut environment is associated with the development of de-novo kidney disease in patients

with preserved kidney function. Given the fact that gastrointestinal motility and gut environment are interrelated and exert reciprocal effects on each other,[26, 27] it is plausible that constipation, one of the clinical forms of altered gut environment, can be a risk factor for kidney disease progression.

There are several potential mechanisms for the association between constipation and the risk of adverse renal outcomes. Recently, emerging evidence has disclosed a tight and coordinated connection between gut microbiota and host nutrition, metabolism, and immune function,[28] indicating that disturbance of the gut microbiota is linked to the pathogenesis of diverse illnesses, such as metabolic syndrome[29] and cardiovascular disease[30] through chronic inflammation and/or altered metabolite profiles. For example, trimethylamine-N-oxide (TMAO), a gut microbiota-dependent metabolite, has been shown to play a significant role in the development and progression of atherosclerosis and adverse atherosclerotic cardiac events.[31, 32] Furthermore, recent metabolomics data from the Framingham Heart Study highlight that TMAO levels predict the risk of incident CKD in healthy subjects.[33] Alterations in gut microbiota have also been linked to the accumulation of gut-derived uremic toxins such as indoxyl sulfate and p-cresyl sulfate,[10] which in turn appear to accelerate kidney disease progression by causing renal fibrosis, inflammation, and oxidative stress.[34] While a large clinical trial examining the

reduction of systemic toxin absorption through gastrointestinal sequestration via spherical carbon adsorbent AST-120 has failed to show a benefit towards slowing kidney disease progression,[35] adherence to the medication in this clinical trial was poor, and hence it remains unclear if proper administration of this or other similar products could be renoprotective. Considering the possible existence of altered gut microbiota in patient with constipation, these pathophysiologic mechanisms could serve as a potential explanation for the association between constipation and adverse renal outcomes.

Another plausible mechanism for the observed association may be through increased levels of serotonin. Serotonin is synthesized in the gut and incorporated into platelets, which, when activated, release serotonin and enhance vasoconstriction and thrombus formation, resulting in the development of atherosclerotic plaques.[36] Previous studies have also reported an association between elevated plasma levels of serotonin and increased risk of atherosclerotic cardiovascular disease.[37] Since serotonin synthesis and release have been shown to be increased in patients with constipation[38] and in those using certain laxatives,[39] increased serotonin levels could also explain the underlying pathogenesis of kidney disease progression. In addition to these mechanisms, the use of certain types of laxatives may directly (e.g., through drug-induced nephrotoxicity) or indirectly (e.g., through dehydration or electrolyte disturbances) cause kidney damage,

and could potentially contribute to the increased risk of renal events.

Interestingly, I found a significant association between constipation and the risk of increasing eGFR. As previously reported,[40-42] increasing eGFR has been recognized as a predictor of adverse clinical outcomes through loss of muscle mass associated with chronic debilitating conditions, and increasing eGFR may also reflect recovery from acute kidney injury. Although lean body mass was not measured in this cohort and hence precise mechanisms underlying the observed association remain speculative, the greater risk of increasing eGFR might reflect a higher incidence of some chronic illnesses accompanied by a decline in serum creatinine among patients with constipation. Most importantly, however, the associations of constipation with adverse renal outcomes still remained statistically significant even after accounting for various potential confounders including comorbidities, number of VA healthcare encounters, and cumulative length of hospitalization, which highlights the biologically plausible link between the gut and kidney and provides additional insights into the pathogenesis of kidney disease progression.

Given the high prevalence of constipation and the simplicity of its assessment in primary care settings, this study may also have several clinical implications. First, physicians should be aware of the risk of kidney disease progression in patients with

constipation. When evaluating a patient with constipation and reduced kidney function in clinical practice, it is also important for healthcare providers to acknowledge the excess risk of kidney damage caused by dehydration and use (especially over-the-counter use) of nonsteroidal anti-inflammatory drugs. Careful observation of kidney function trajectory may thus be required in those patients, particularly among those with more severe constipation. Furthermore, if the relationships between constipation and renal events are causal, these findings suggest that the treatment of constipation through lifestyle modifications (e.g., exercise and high-fiber diet[43, 44]) and/or use of probiotics[45] rather than laxatives could potentially reduce the risk of adverse renal outcomes and may deserve future clinical trials.

This study is notable for its large sample size and for being representative of veterans in the entire geographic United States; however, several limitations need to be acknowledged. Because the study was observational, the results do not allow us to infer causality. It could be argued that constipation may be merely a non-specific marker of general illness rather than a causative factor; however, the significant association that was robust to adjustment for a wide assortment of confounders, combined with plausible mechanistic explanations, raises the possibility of a causal link between constipation and renal outcomes. Most of the patients were men; hence, the results may

not be generalizable to women or patients from other geographical areas. This cohort was defined on the basis of an eGFR ≥60 mL/min/1.73m^2, but markers of earlier stages of CKD (e.g., proteinuria) were not available. Because information about subjective symptoms of constipation was not available, and constipation status and its severity were defined using the *ICD-9-CM* codes and laxative prescription records during the two-year baseline period, it was unable to assess the impact of lifetime duration of constipation and its status over the entire follow-up period on the outcomes, and patients with constipation might have been misclassified as absent constipation or having less severe constipation. Nevertheless, such misclassification would tend to bias the true effects toward the null, and the results still demonstrated significant associations of constipation with increased risk of renal events. Several statistical methods were applied in the sensitivity analyses to address the effect of confounders, but the possibility of unmeasured confounders cannot be eliminated. Also, we cannot exclude the possibility of nephrotoxicity induced by the long-term use of certain types of laxatives among patients with constipation.

7. Conclusion

In this large nationwide cohort of >3 million US veterans, I found that constipation status and its severity were associated with a higher risk of incident CKD, incident ESRD, and progressive eGFR decline, independent of known risk factors. Further studies are needed to elucidate the underlying mechanisms for the associations and to determine whether the amelioration of constipation can prevent adverse renal outcomes.

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10. Tables and Figures

Table 1. ICD-9 and procedure (CPT) codes used to define prevalent comorbid conditions

ICD-9 codes

Comorbid condition	ICD-9 code
Constipation	564.0x
Hypertension	401-405
Diabetes mellitus	250.x
Coronary artery disease	414.0, 414.8, 414.9
Angina	411, 413
Myocardial infarction	410-410.9, 412
PCI	36.03, 36.04, 36.06, 36.07, 36.09
CABG	36.10-36.17, 36.19
Congestive heart failure	428-428.9
Cerebrovascular disease	430-438
Peripheral arterial disease	440.0-440.9, 443, 443.x, 38.0, 38.1, 39.50, 39.22, 39.24, 39.25, 39.26, 39.28
Chronic lung disease	490-496, 500-505, 506.4
Dementia	290-290.9
Rheumatologic disease	710.0, 710.1, 710.4, 714.0-714.2, 714.81, 725
Peptic ulcer disease	531-534.9, 531.4-531.7, 532.4-532.7, 533.4-533.7, 534.4-534.7
Liver disease	571.x, 572.x, 456.0-456.21
Malignancy	140-172.9, 174-195.8, 200-208.9, 196-199.1
HIV/AIDS	042, V08, 795.71
Depression	296.x
Bowel disorders	555.x, 556.x, 564.1x, 564.5x, 787.91, 009.x

Procedure (CPT) codes

Procedure	CPT code
PCI	92980 92981 92982 92984 92985 92986 92987 92988 92989 92990 92991 92992 92993 92994 92995 92996
CABG	33510 33511 33512 33513 33514 33515 33516 33517 33518 33519 33521 33522 33523 33533 33534 33535 33536

Abbreviations: AIDS = acquired immunodeficiency syndrome; CABG = coronary artery bypass grafting; HIV = human immunodeficiency virus; PCI = percutaneous coronary intervention

Table 2. Area-based socio-economic indicators

Indicators	Definition
Housing stress	30 percent or more of households had one or more of these housing conditions in 2000: lacked complete plumbing, lacked complete kitchen, paid 30 percent or more of income for owner costs or rent, or had more than 1 person per room.
Low-education	25 percent or more of residents 25 through 64 years old had neither a high school diploma nor General Educational Development in 2000.
Low-employment	Less than 65 percent of residents 21 through 64 years old were employed in 2000.
Persistent poverty	20 percent or more of residents were poor as measured by each of the last 4 censuses: 1970, 1980, 1990 and 2000.

Note: The Area Health Resources Files (AHRF, http://ahrf.hrsa.gov/) system is issued by the National Center for Health Workforce Analysis, Bureau of Health Workforce, Health Resources and Services Administration. Within the AHRF, we used select **2004 County Typology Codes** from the Economic Research Service (ERS), U.S. Department of Agriculture, www.ers.usda.gov. The 2004 County Typology Codes were developed for all 3,141 counties, county equivalents, and independent cities in the United States.

Table 3. Baseline patient characteristics in the overall cohort and propensity-matched cohort

Characteristics	Overall cohort				Propensity-matched cohort		
	Total	Constipation		Std. Diff.	Constipation		Std. Diff.
		No	Yes		No	Yes	
	(*n* = 3,504,732)	(*n* = 3,251,291)	(*n* = 253,441)		(*n* = 208,979)	(*n* = 208,979)	
Mean age (SD), *y*	60.0 (14.1)	59.6 (14.1)	64.1 (13.0)	0.33	63.9 (12.3)	63.5 (12.8)	-0.031
Mean eGFR (SD), *mL/min/1.73m^2*	83.8 (15.6)	83.9 (15.5)	82.8 (15.8)	-0.08	82.9 (15.5)	83.1 (15.8)	0.01
Male, *n (%)*	3,267,365 (93.2)	3,030,680 (93.2)	236,685 (93.4)	0.028	195,507 (93.6)	195,626 (93.6)	-0.002
African American, *n (%)*	537,191 (15.3)	487,079 (15.0)	50,112 (20.0)	0.096	44,180 (21.1)	43,716 (20.9)	-0.005
Hypertension, *n (%)*	2,079,730 (59.3)	1,899,132 (58.4)	180,598 (71.3)	0.25	151,774 (72.6)	150,044 (71.8)	-0.018
Diabetes mellitus, *n (%)*	831,043 (24.7)	749,118 (23.0)	81,925 (32.3)	0.19	69,389 (33.2)	68,462 (32.8)	-0.009
CHD, *n (%)*	399,833 (11.4)	353,552 (10.9)	46,281 (18.3)	0.21	39,716 (19.0)	39,293 (18.8)	-0.005
CHF, *n (%)*	152,126 (4.3)	125,624 (3.9)	26,502 (10.5)	0.25	21,680 (10.4)	22,215 (10.6)	0.008
CVD, *n (%)*	212,024 (6.1)	180,585 (5.6)	31,439 (12.4)	0.23	26,544 (12.7)	26,203 (12.5)	-0.005
PAD, *n (%)*	190,548 (5.4)	162,877 (5.0)	27,671 (10.9)	0.21	23,452 (11.2)	23,357 (11.2)	-0.001
Chronic lung disease, *n (%)*	637,350 (18.2)	558,622 (17.2)	78,728 (31.1)	0.32	67,551 (32.3)	66,434 (31.8)	-0.011
Dementia, *n (%)*	28,646 (0.8)	22,741 (0.7)	5,905 (2.3)	0.13	4,284 (2.1)	4,487 (2.2)	0.007
Rheumatologic disease, *n (%)*	49,021 (1.4)	43,098 (1.3)	5,923 (2.3)	0.075	5,167 (2.5)	4,998 (2.4)	-0.005
Peptic ulcer disease, *n (%)*	64,990 (1.9)	55,294 (1.7)	9,696 (3.8)	0.13	8,010 (3.8)	8,224 (3.9)	0.005
Liver disease, *n (%)*	14,795 (0.4)	10,061 (0.3)	4,734 (1.9)	0.15	3,476 (1.7)	4,042 (1.9)	0.02
Malignancies, *n (%)*	355,185 (10.1)	307,105 (9.5)	48,080 (19.0)	0.28	40,777 (19.5)	39,979 (19.1)	-0.01
HIV/AIDS, *n (%)*	21,247 (0.6)	19,637 (0.6)	1,610 (0.6)	-0.001	1,330 (0.6)	1,389 (0.7)	0.004
Depression, *n (%)*	323,221 (9.2)	279,955 (8.6)	43,266 (17.1)	0.24	37,499 (17.9)	37,310 (17.9)	-0.002
Bowel disorders, *n (%)*	145,811 (4.2)	122,835 (3.8)	22,976 (9.1)	0.21	19,212 (9.2)	19,499 (9.3)	0.005
Median per capita income (IQR), *$*	22971 (11725-36048)	23258 (11866-37111)	19061 (10647-30613)	-0.20	18856 (10606-30453)	19119 (10717-30588)	0.029
Married, *n (%)*	1,880,248 (53.7)	1,758,279 (54.1)	121,969 (48.1)	0.096	107,179 (51.3)	106,522 (51.0)	-0.006
Service connected, *n (%)*	1,426,273 (40.7)	1,301,738 (40.0)	124,535 (49.1)	0.14	107,187 (51.3)	105,723 (50.6)	-0.014
Mean BMI (SD), *kg/m^2*	29.2 (5.7)	29.2 (5.7)	29.2 (6.2)	0.008	29.3 (6.1)	29.3 (6.3)	0.004
Mean systolic BP (SD), *mmHg*	135.4 (19.1)	135.5 (19.1)	134.1 (19.8)	-0.075	134.2 (19.2)	134.2 (19.8)	-0.002

Mean diastolic BP (SD), *mmHg*	77.2 (11.8)	77.3 (11.8)	75.2 (12.0)	-0.19	75.3 (11.9)	75.4 (12.0)	0.011
ACEI/ARB use, *n (%)*	773,938 (22.1)	703,531 (21.6)	70,407 (27.8)	0.14	58,796 (28.1)	57,888 (27.7)	-0.01
Statin use, *n (%)*	506,980 (14.5)	459,218 (14.1)	47,762 (18.9)	0.13	39,531 (18.9)	39,086 (18.7)	-0.005
Antidepressants use, *n (%)*	622,543 (17.8)	538,862 (16.6)	83,681 (33.0)	0.36	71,663 (34.3)	69,854 (33.4)	-0.018
Non-opioid analgesics use, *n (%)*	827,856 (23.6)	725,729 (22.3)	102,127 (40.3)	0.37	87,710 (42.0)	85,186 (40.8)	-0.025
Opioids use, *n (%)*	385,838 (11.0)	316,038 (9.7)	69,800 (27.5)	0.46	60,782 (29.1)	59,486 (28.5)	-0.014
Influenza vaccination, *n(%)*	1,032,254 (29.5)	920,070 (28.3)	112,184 (44.3)	0.33	96,629 (46.2)	93,828 (44.9)	-0.027
Living in area with high housing stress, *n (%)*	1,181,986 (33.7)	1,090,152 (33.5)	91,834 (36.2)	0.067	79,956 (38.3)	80,040 (38.3)	0.001
Living in area with low education, *n (%)*	364,485 (10.4)	334,018 (10.3)	30,467 (12.0)	0.05	26,885 (12.9)	26,407 (12.6)	-0.007
Living in area with low employment, *n (%)*	318,669 (9.1)	292,720 (9.0)	25,949 (10.2)	0.035	22,829 (10.9)	22,374 (10.7)	-0.007
Living in area of persistent poverty, *n (%)*	166,638 (4.8)	152,459 (4.7)	14,179 (5.6)	0.036	12,603 (6.0)	12,190 (5.8)	-0.008
Healthcare encounters, *n (IQR)*	20 (10-38)	19 (10-35)	51 (28-85)	0.77	45 (24-81)	54 (31-88)	0.053
Cumulative length of hospitalization (IQR), *days*	0 (0-0)	0 (0-0)	0 (0-6)	0.23	0 (0-3)	0 (0-7)	0.017

Note: Data are presented as number (percentage), mean ± standard deviation, or median (interquartile range).

Abbreviations: ACEI = angiotensin-converting enzyme inhibitors; AIDS = acquired immunodeficiency syndrome; ARB = angiotensin receptor blockers; BMI = body mass index; BP = blood pressure; CHD = coronary heart disease; CHF = congestive heart failure; CVD = cerebrovascular disease; DM = diabetes mellitus; eGFR = estimated glomerular filtration rate; HIV = human immunodeficiency virus; PAD = peripheral arterial disease; Std. Diff. = standardized difference

Table 4. Number of patients across categories of change in eGFR stratified by constipation status

	Total	**Constipation**	
		No	**Yes**
	(*n* = 3,242,681)	**(*n* = 2,996,125)**	**(*n* = 246,556)**
Change in eGFR, *mL/min/1.73 m^2/year*			
<-10	119,165 (3.7)	106,111 (3.5)	13,054 (5.3)
-10 to <-5	189,792 (5.9)	171,691 (5.7)	18,101 (7.3)
-5 to <-1	905,877 (27.9)	834,744 (27.9)	71,133 (28.9)
-1 to <0	649,005 (20.0)	606,329 (20.2)	42,676 (17.3)
≥0*	1,378,842 (42.5)	1,277,250 (42.6)	101,592 (41.2)

Note: Data are presented as number (percentage).

*~82% of patients in this category had eGFR <3 mL/min/1.73 m^2

Abbreviation: eGFR = estimated glomerular filtration rate

Table 5. Incident CKD and incident ESRD outcomes associated with (A) constipation status and (B) constipation severity in Cox models censored for mortality and in competing risk regression models

(A) Constipation status (present vs. absent constipation)

	Primary events (*n*, %)	**Competing events (deaths; *n*, %)**	**HR (95% CI)**	**SHR (95% CI)**
Unmatched (*n* = 3,504,732)				
Incident CKD	360,541 (10.3)	595,643 (17.1)	2.08 (2.06–2.10)	1.96 (1.94–1.98)
Incident ESRD	7,674 (0.2)	703,419 (20.1)	1.77 (1.65–1.90)	1.61 (1.50–1.73)
PS-matched (*n* = 417,958)				
Incident CKD	77,518 (18.5)	100,089 (23.9)	1.12 (1.10–1.13)	1.10 (1.08–1.11)
Incident ESRD	1,471 (0.4)	128,884 (30.8)	1.15 (1.04–1.28)	1.12 (1.01–1.24)

(B) Constipation severity

	Primary events (*n*, %)	**Competing events (deaths; *n*, %)**	**Constipation Severity**	**HR (95% CI)**	**SHR (95% CI)**
Unmatched (*n* = 3,504,732)					
Incident CKD	360,541 (10.3)	595,643 (17.1)	Mild	1.99 (1.96–2.02)	1.89 (1.86–1.91)
			Moderate/Severe	2.38 (2.34–2.41)	2.18 (2.14–2.21)
Incident ESRD	7,674 (0.2)	703,419 (20.1)	Mild	1.73 (1.58–1.90)	1.60 (1.45–1.75)
			Moderate/Severe	2.08 (1.88–2.31)	1.82 (1.64–2.02)
PS-matched (*n* = 417,958)					
Incident CKD	77,518 (18.5)	100,089 (23.9)	Mild	1.09 (1.07–1.11)	1.08 (1.06–1.09)
			Moderate/Severe	1.28 (1.26–1.30)	1.22 (1.20–1.25)
Incident ESRD	1,471 (0.4)	128,884 (30.8)	Mild	1.15 (1.02–1.30)	1.13 (1.01–1.28)
			Moderate/Severe	1.38 (1.21–1.57)	1.27 (1.12–1.45)

Abbreviations: CKD = chronic kidney disease; ESRD = end-stage renal disease; HR = hazard ratio; SHR = subhazard ratio

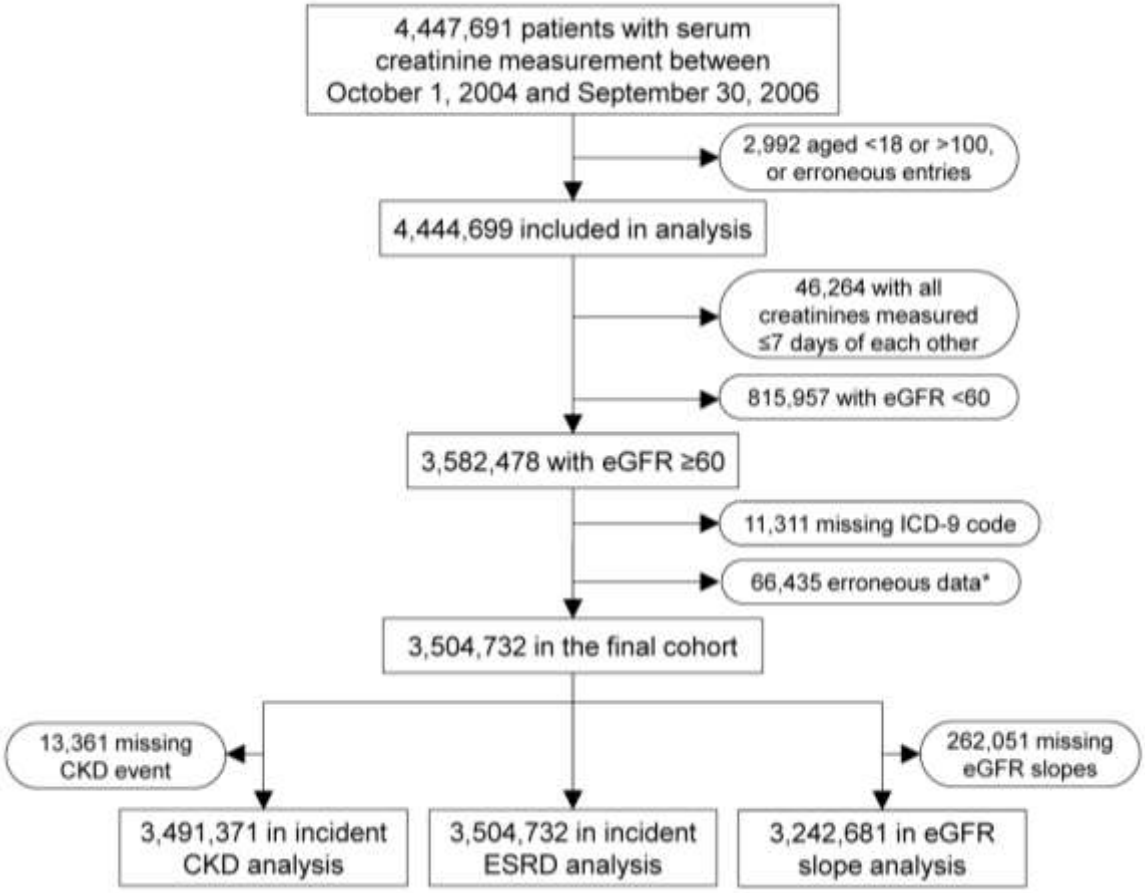
Table 6. Renal outcomes associated with constipation status and constipation severity in Cox models (for incident CKD and ESRD) and multinomial logistic regression models (for change in eGFR) after fully-adjustment with multiple imputations for missing data (*n* = 3,504,732)

	Incident CKD HR (95% CI)	Incident ESRD HR (95% CI)	Rapid eGFR decline* OR (95% CI)
Constipation status			
Presence of constipation	1.13 (1.12–1.14)	1.07 (1.00–1.16)	1.15 (1.13–1.18)
Constipation Severity			
Mild	1.11 (1.10–1.13)	1.08 (0.98–1.19)	1.16 (1.13–1.20)
Moderate/Severe	1.15 (1.13–1.17)	1.12 (1.01–1.25)	1.29 (1.25–1.34)

*eGFR slope (mL/min/1.73 m^2/year); <-10 versus -1 to <0 (reference)

Abbreviations: CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; HR = hazard ratio; OR = odds ratio

Figure 1.



Algorithm used to define the study cohort

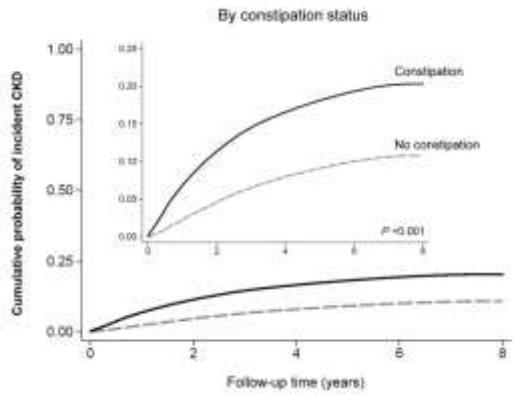
*Patients with the date of cohort entry later than the date of last encounter (*n* = 32,038), those with the date of incident ESRD later than the date of last encounter (*n* = 2,236), or those with an eGFR slope <-55 (0.5th percentile) or ≥40 (99.5th percentile) mL/min/1.73 m^2/year (*n* = 32,161).

Abbreviations: eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; ICD = International Classification of Diseases

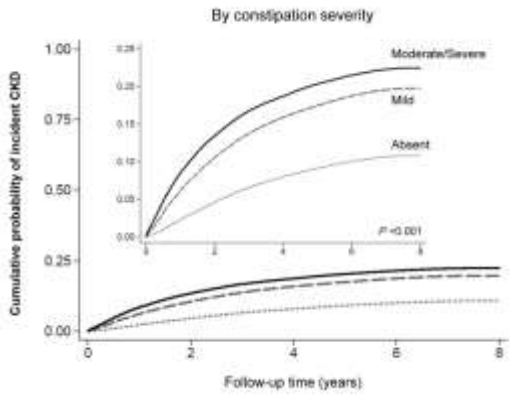
Figure 2.

(A)

a.

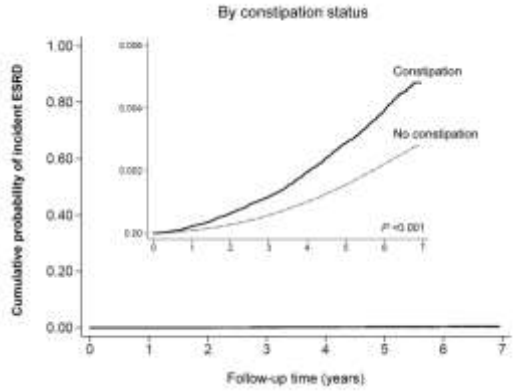


b.



(B)

a.



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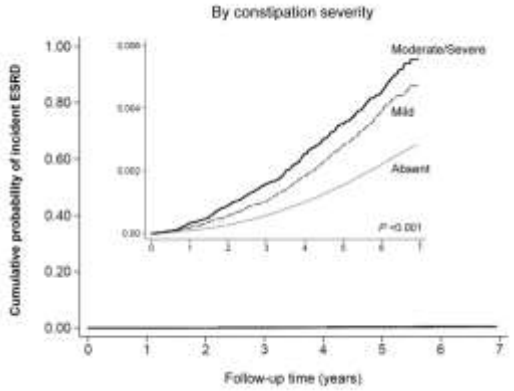
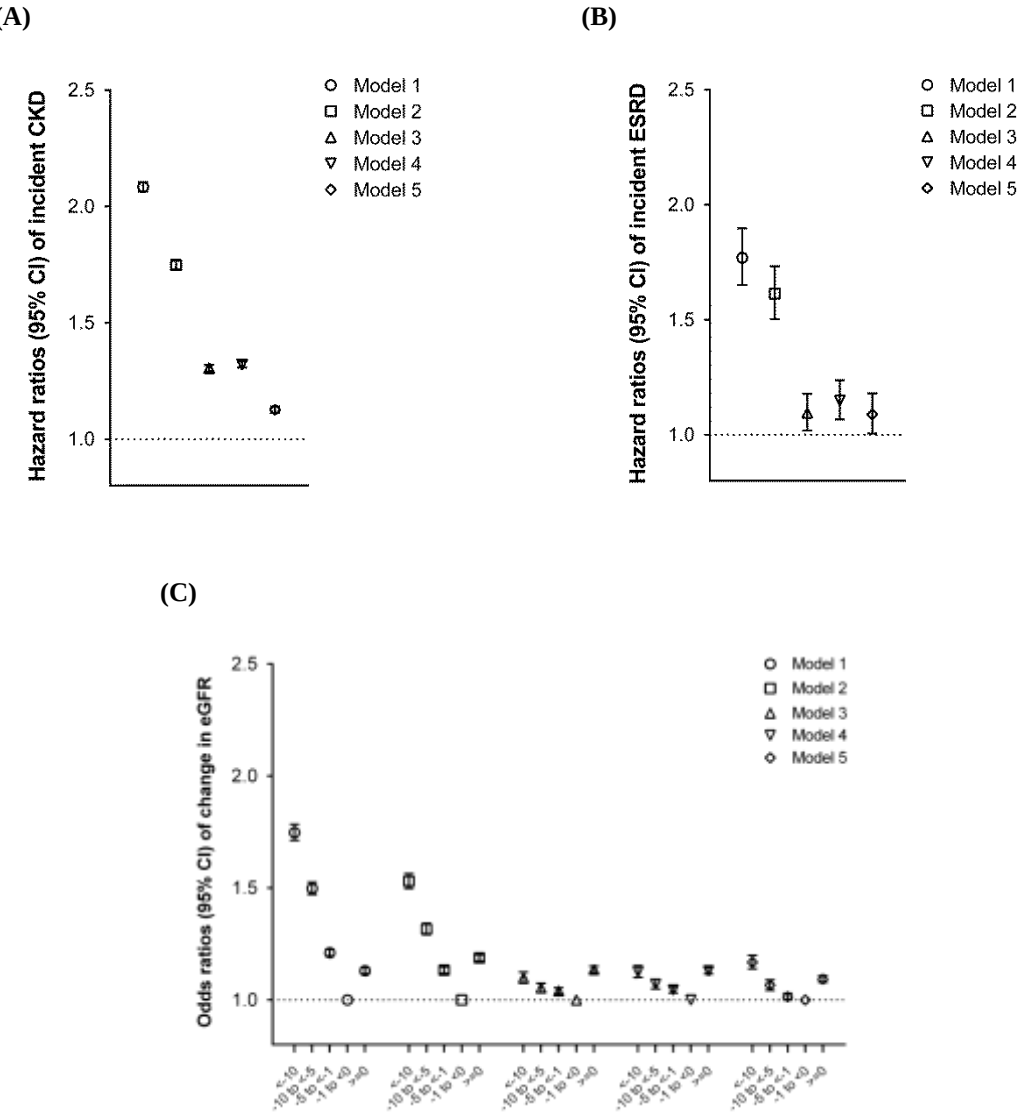


Unadjusted Kaplan-Meier cumulative-event curves for (A) incidence of CKD and (B) incident ESRD according to (a) constipation status and (b) its severity

Cumulative incidences of (A) CKD and (B) ESRD were higher in patients with (versus without) constipation and with more severe constipation.

Abbreviations: CKD = chronic kidney disease; ESRD = end-stage renal disease

Figure 3.



Association of the presence of constipation with renal events: (A) incident CKD, (B) incident ESRD, and (C) change in eGFR

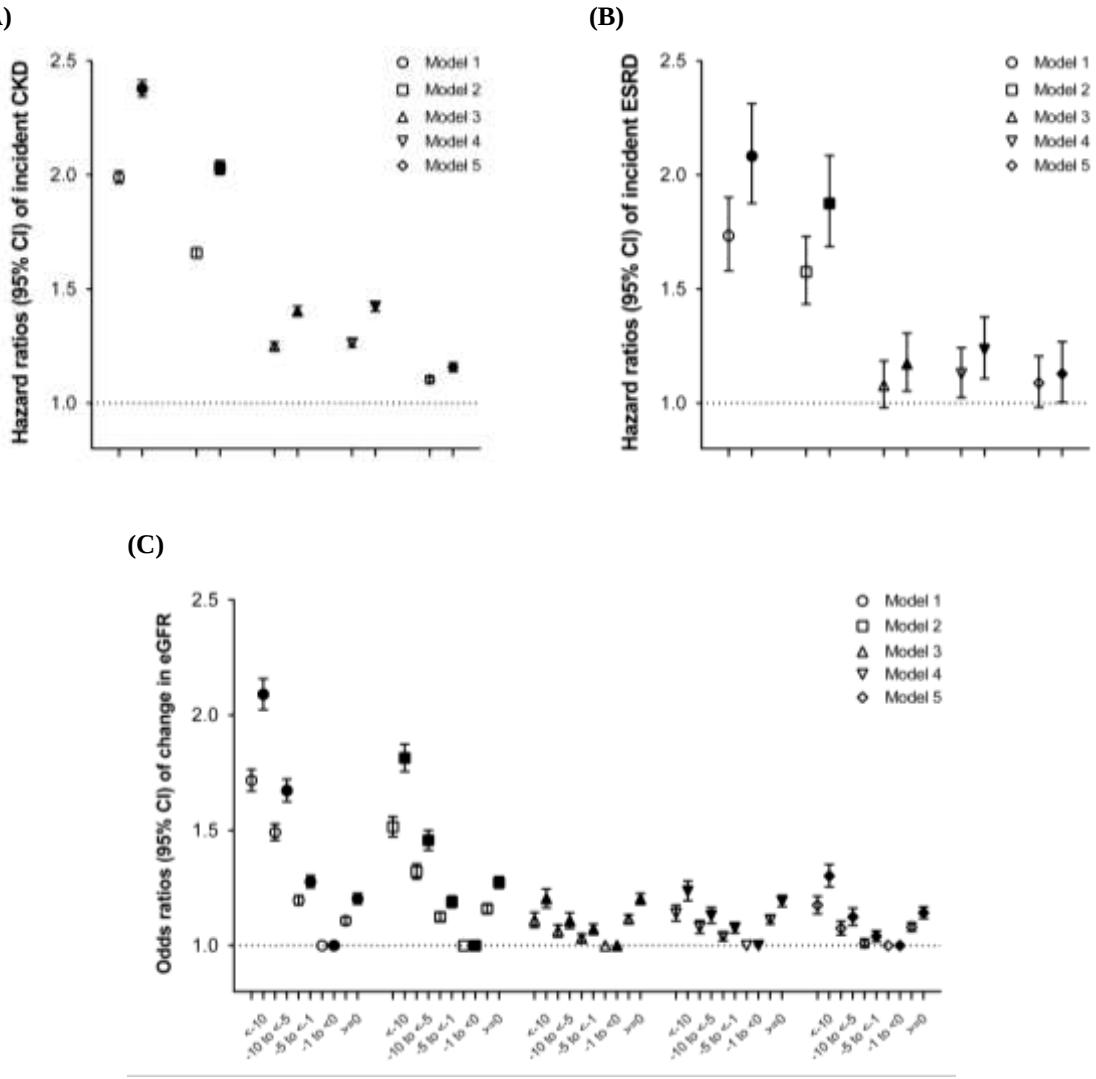
The presence of constipation was associated with higher risk of incident CKD and ESRD and faster eGFR decline, compared with the absence of constipation.

Estimates were calculated using Cox-proportional models (for incident CKD and ESRD) and multinomial logistic regression models (for change in eGFR). Models represent unadjusted association (model 1) and associations after adjustment for age, gender, race, and baseline eGFR (model 2); model 2 variables plus comorbidities (diabetes mellitus, hypertension, coronary heart disease, congestive heart failure,

cerebrovascular disease, peripheral arterial disease, peptic ulcer disease, rheumatic disease, malignancy, depression, liver disease, chronic lung disease, human immunodeficiency virus/acquired immunodeficiency syndrome, and bowel disorders) (model 3); model 3 plus baseline body mass index, systolic blood pressure, and diastolic blood pressure (model 4); model 4 plus socioeconomic parameters (mean per capita income, marital status, service connectedness, housing stress, low education, low employment, persistent poverty), number of VA healthcare encounters, cumulative length of hospitalization, receipt of influenza vaccination(s), and use of angiotensin-converting enzyme inhibitors/angiotensin-receptor blockers, statins, antidepressants, non-opioid analgesics, and opioids (model 5).

Abbreviations: CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; VA = Veterans Affairs

Figure 4.



Association of constipation severity with renal events: (A) incident CKD, (B) incident ESRD, and (C) change in eGFR. Mild (blank symbols) and moderate/severe (filled symbols) constipation vs. absent constipation (reference).

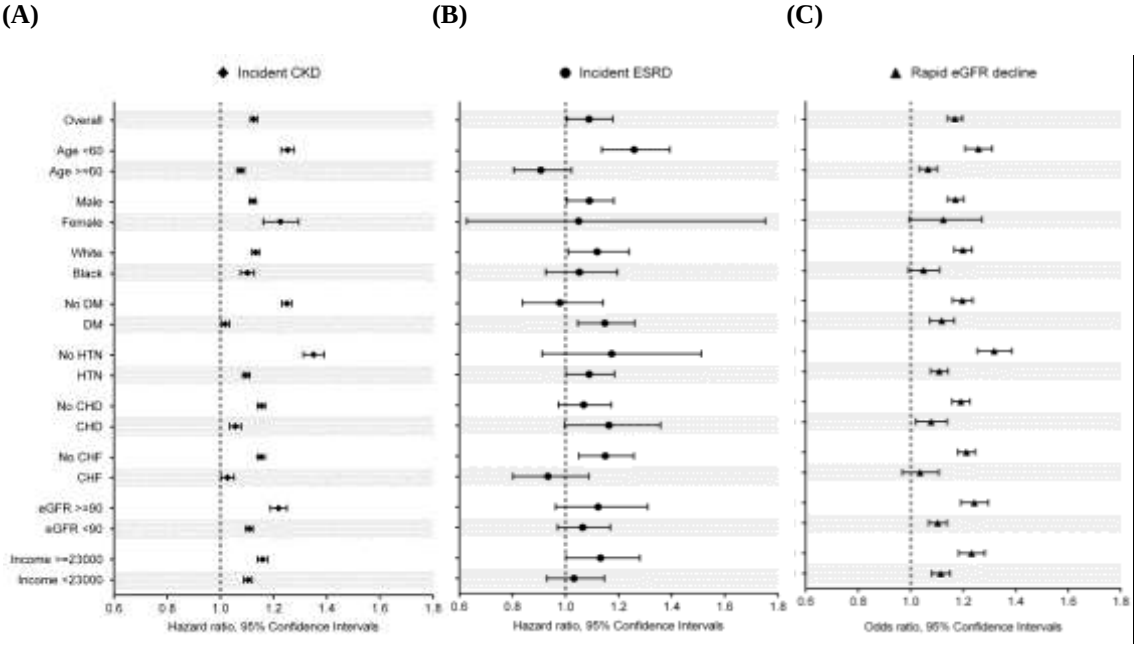
More severe constipation was associated with incrementally higher risk of incident CKD and ESRD and faster eGFR decline, compared with the absence of constipation.

Estimates were calculated using Cox-proportional models (for incident CKD and ESRD) and multinomial logistic regression models (for change in eGFR). Models represent unadjusted association (model 1) and associations after adjustment for age, gender, race, and baseline eGFR (model 2); model 2 variables plus comorbidities (diabetes mellitus, hypertension, coronary heart disease, congestive heart failure,

cerebrovascular disease, peripheral arterial disease, peptic ulcer disease, rheumatic disease, malignancy, depression, liver disease, chronic lung disease, human immunodeficiency virus/acquired immunodeficiency syndrome, and bowel disorders) (model 3); model 3 plus baseline body mass index, systolic blood pressure, and diastolic blood pressure (model 4); model 4 plus socioeconomic parameters (mean per capita income, marital status, service connectedness, housing stress, low education, low employment, persistent poverty), number of VA healthcare encounters, cumulative length of hospitalization, receipt of influenza vaccination(s), and use of angiotensin-converting enzyme inhibitors/angiotensin-receptor blockers, statins, antidepressants, non-opioid analgesics, and opioids (model 5).

Abbreviations: CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease, VA = Veterans Affairs

Figure 5.



Association of the presence of constipation with (A) incident CKD, (B) incident ESRD, and (C) change in eGFR in predefined subgroups of the overall cohort

The presence (versus absence) of constipation was associated with higher risk of incident CKD and ESRD and faster eGFR decline in most subgroups.

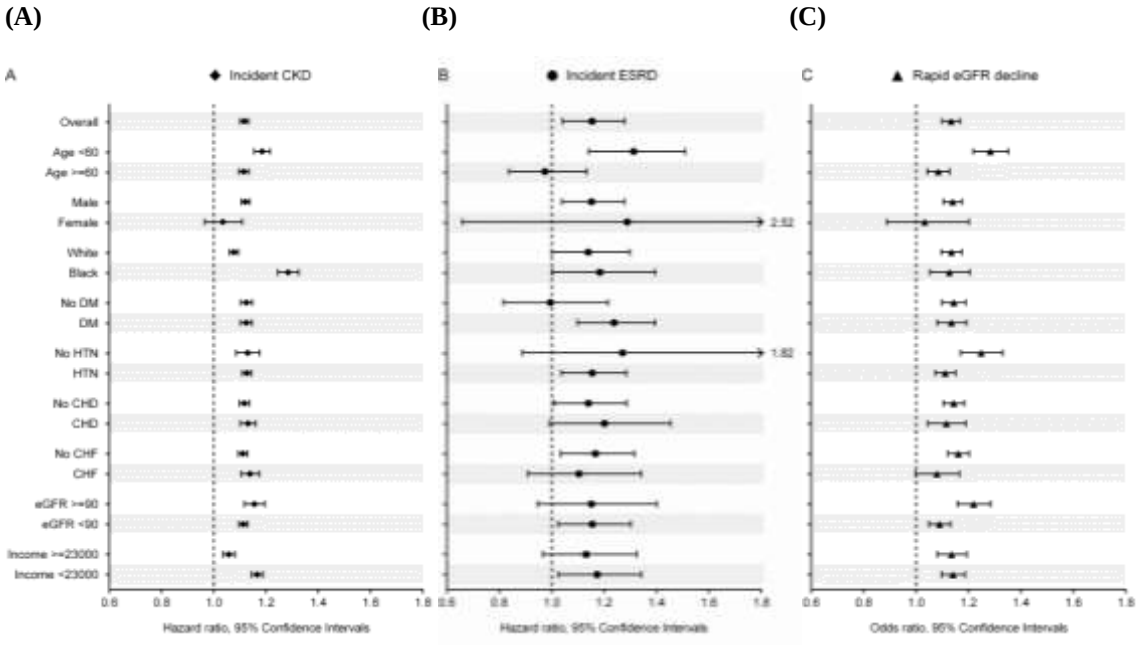
Estimates were calculated using Cox-proportional models (for incident CKD and ESRD) and multinomial logistic regression models (for eGFR slope [mL/min/1.73 m^2/year]; <-10 vs. -1 to <0 [reference]).

Data were adjusted for age, gender, race, baseline eGFR, comorbidities (diabetes mellitus, hypertension, coronary heart disease, congestive heart failure, cerebrovascular disease, peripheral arterial disease, peptic ulcer disease, rheumatic disease, malignancy, depression, liver disease, chronic lung disease, human immunodeficiency virus/acquired immunodeficiency syndrome, and bowel disorders), baseline body mass index, systolic blood pressure, diastolic blood pressure, socioeconomic parameters (mean per capita income, marital status, service connectedness, housing stress, low education, low employment, persistent poverty), number of VA healthcare encounters, cumulative length of hospitalization, receipt of influenza vaccination(s), and use of angiotensin-converting enzyme inhibitors/angiotensin-receptor blockers, statins, antidepressants, non-opioid analgesics, and opioids.

Abbreviations: CHD = coronary heart disease; CHF = congestive heart failure; CKD = chronic kidney disease; DM = diabetes mellitus; eGFR = estimated glomerular filtration rate; ESRD = end-stage renal

disease; HTN = hypertension; VA = Veterans Affairs

Figure 6.



Association of the presence of constipation with (A) incident CKD, (B) incident ESRD, and (C) change in eGFR in predefined subgroups in a propensity-matched cohort

The presence (versus absence) of constipation was associated with higher risk of incident CKD and ESRD and faster eGFR decline in most subgroups.

Estimates were calculated using Cox-proportional models (for incident CKD and ESRD) and multinomial logistic regression models (for eGFR slope [mL/min/1.73 m^2/year]; <-10 vs. -1 to <0 [reference]).

Abbreviations: CHD = coronary heart disease; CHF = congestive heart failure; CKD = chronic kidney disease; DM = diabetes mellitus; eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; HTN = hypertension