Appendix 1 (as supplied by the authors): Nephrology consultation and mortality in people with stage 4 chronic kidney disease: a population-based study

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Supplementary Online Content

Appendix to: Liu P, Quinn RR, Karim ME, et al. Nephrology consultation and mortality in people with stage 4 chronic kidney disease: a population-based study. *CMAJ* 2019. doi: 10.1503/cmaj.181372.

eMethods. Supplemental methods

Covariates

Baseline covariates. Demographics included age, sex, First Nations status, and rural or urban location of residence. Health system-related factors included the year of study entry and registration with a primary care network.[1] We measured baseline kidney health in terms of index eGFR, disease duration, eGFR trajectory, prior eGFR, albuminuria, and outpatient nephrology visit >2 years before study entry. We used only outpatient laboratory data to minimize the impact of transient changes in kidney health due to acute or severe illness. We defined disease duration as the number of days between the first eGFR ≥15 and <30 in the episode qualifying for study entry and the index eGFR. We considered eGFR trajectory calculating the slope of eGFR measurements in the episode qualifying for study entry. The prior eGFR was the eGFR immediately before the first eGFR in the episode qualifying for study entry. We used the most recent albuminuria values before study entry, with the following types of measurement in descending order of preference: albumin-to-creatinine ratio, protein-to-creatinine ratio, and urine dipstick, defined as normal, moderate, severe, or unmeasured as in prior work.[2] We employed validated algorithms[3] to identify important comorbidities. We assessed the loss of capacity for independent living as a surrogate of functional status, defined using the first discharge to a public or private long-term care facility following any hospital admission,[4] or the first physician claim of long-term care from nursing homes or auxiliary hospitals.[5] We used the length of hospital stay within the year before study entry as a marker of illness severity. Lastly, we identified exposure to drugs including angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (ACEI/ARBs), statins, and nonsteroidal anti-inflammatory drugs. This was defined as at least one dispensation for these drugs within the year before study entry, using provincial Pharmaceutical databases that capture all prescription drugs dispensed since January 1, 2008 and dispensations occurred before January 1, 2008 for people aged 65 years and older. We created missing categories for patients without drug dispensation data.

Time-varying covariates. We considered laboratory covariates (eGFR and albuminuria), the occurrence of cardiovascular and cerebrovascular events (congestive heart failure, myocardial infarction, stroke, and transient ischemic attack), and measures of functional status (long-term care) and illness severity (length of hospital stay) as time-varying confounders. For eGFR and albuminuria, we averaged the values if multiple measurements were present, or carried forward the most recent value if no new measurement was available in that 90-day period. If participants initiated renal replacement treatment during follow-up, we truncated eGFR at 10 and kept albuminuria constant thereafter. For congestive heart failure, myocardial infarction, stroke, transient ischemic attack, and the receipt of long-term care, we used a binary coding approach that changed post-baseline values from "absence" to "presence" at the time of occurrence and maintained as "presence" for the remaining observations, and we coded as "presence" in case of the associated condition being present at baseline. We separately summed days of hospital stay for each 90-day period.

We accounted for time-varying covariates only before the occurrence of the first outpatient nephrology visit (for the exposed) or the start of renal replacement therapy (for the unexposed). We used this approach because there cannot be confounding in these situations: participants were considered 'exposed' following the first outpatient nephrology visit for the rest of the follow-up; and participants who were still 'unexposed' when they started renal replacement therapy were no longer facing a referral decision.

Alternative definition of stage-4 CKD (moving average eGFR). To decrease the influence of functional changes in eGFR, we repeated all analyses by using a less stringent definition of stage-4 CKD, based on moving average eGFR ≥15 and <30 ml/min/1.73m^2 consistently for more than 90 days.[6] Starting on the date of the first recorded eGFR <30 ml/min/1.73 m^2, we went forward and determined the average eGFR over a period of more than 90 days (requiring at least two outpatient serum creatinine measurements). If the average eGFR over this period was ≥15 and <30 ml/min/1.73 m^2, the individual was considered to have stage-4 CKD. We used the date of the first eGFR after this period as index date, and the calculated average eGFR as index eGFR value.

Statistical analysis

Sequential Cox approach. We used the sequential Cox approach[7] as the main analysis to control for both immortal

time bias[8] and time-varying confounding,[9] following three steps.

Step 1: Creating a pseudo-dataset of successive mini-trials. Successive mini-trials started on the index-date (first mini-trial) and every 90-day thereafter, and continued until the end of follow-up. We treated each mini-trial as a separate cohort, which consisted of participants received outpatient nephrology care (exposed), and participants unexposed (controls), within the initial 90-day of that minitrial. A control may appear in different mini-trials. Participants who were no longer facing the decision for referral (died, already initiated an outpatient nephrology visit during follow-up, or started renal replacement therapy) were excluded from subsequent mini-trials. Follow-up from the new baseline of each mini-trial terminated by an event (death) or censoring, which was the earliest of the first outpatient nephrology visit (for controls only), out-migration from the province, or study end (March 31, 2015). We obtained the pseudo-dataset by aggregating all mini-trials.

Step 2: Accounting for dependent censoring using the inverse probability of weighting. We estimated the inverse probability of non-censoring weights (IPCW) within 90-day intervals of each mini-trial, using a logistic regression model with censoring as the dependent variable. We adjusted for the exposure history, covariates measured at study entry as well as time-varying covariates updated at the new baseline of each mini-trial and their lagged values. We obtained inverse probabilities of non-censoring from this full model. We stabilized these inverse probabilities multiplying them by the probabilities derived from another logistic regression model that only adjusted for the exposure history and the covariates measured at study entry.

Step 3: Averaging exposure effect estimates by fitting a mini-trial-stratified, IPCW-weighted Cox model. We adjusted each mini-trial for covariates measured at study entry [including age (continuous), sex, First Nations status, rural residence, period of study entry (2002−2004, 2005−2009, 2010−2014), primary care network attachment, index eGFR (continuous), disease duration (continuous), eGFR trajectory (improve >5, improve or decline ≤5, decline >5 to ≤10, decline >10 ml/min/1.73m^2/year), prior eGFR (≥60, ≥30 to <60 ml/min/1.73m^2, unmeasured), albuminuria (normal/mild, moderate, severe, unmeasured), outpatient nephrology visit >2 years before study entry, comorbidities listed in Table 1, long-term care, days of hospital stay within 1 year before study entry (0, 1−7, 8−14, 15−28, >28), and dispensations for ACEI/ARBs, statins, and NSAIDs, respectively (no, yes, data missing)], time-varying covariates updated at the new baseline of each mini-trial, and their lagged values. We used the robust variance estimator to account for correlations of multiple observations per participant.

Marginal structural Cox models. We used marginal structural Cox models[9,10] to evaluate the robustness of the overall association from the sequential Cox model (eFigure 3). First, we calculated stabilized inverse probability of treatment (i.e., the initiation of outpatient nephrology visit) weights (IPTW) within each 90-day interval, obtained as the ratio of two probabilities derived from separate logistic regression models. The denominator model was conditional on measured baseline covariates and history of time-varying covariates (eGFR, albuminuria, the occurrence of congestive heart failure, myocardial infarction, stroke, or transient ischemic attack, long-term care, and length of hospital stay) observed for the current 90-day period and for the previous period. The numerator model only adjusted for baseline covariates. Likewise, we calculated the stabilized inverse probability of non-censoring weights (IPCW) at each 90-day interval, to account for potential selective censoring. We then obtained final stabilized weights multiplying the stabilized IPTW by the stabilized IPCW. Under the assumptions of no unmeasured confounding and correct model specifications,[11] weighting created a pseudo-population in which the distribution of the time-varying covariates was balanced across exposed and unexposed groups. Second, we estimated the effect of nephrology consultation in the weighted population using a Cox proportional hazards model adjusted for baseline covariates.[10]

We did several other sensitivity analyses (eFigure 3). First, we assessed the impact of extreme weights, by which a few participants who were less likely to be exposed could exert undue influence on the results, based on the truncation of stabilized weights at the 0.25 and 99.75 percentiles. Second, we excluded participants who had had any outpatient nephrology visit, i.e. including those who had had an outpatient nephrology visit >2 years before study entry.

Propensity-matched sequential Cox approach. We examined the distribution of initiating outpatient nephrology visit during the initial 90-day period of each mini-trial (eTable 1), and compared means or frequencies of baseline characteristics between exposed and unexposed in the first mini-trial (eTable 2). Exposed and unexposed individuals differed in the vast majority of baseline covariates, which motived matching of the two groups within each mini-trial, using propensity score to enhance group comparability.

We estimated the propensity score using logistic regression to regress the initiation of outpatient nephrology visit on the covariates measured at the new baseline of each mini-trial. We formed pairs of exposed and unexposed individuals within a mini-trial using nearest-neighbour matching without replacement, within 0.2 of the standard deviation of the logit of the propensity score calipers.[12] Given the small number of people initiating outpatient nephrology visit during later mini-trials (eTable 1), we only conducted the propensity-score matching for the first 4 mini-trials. We verified the quality of matching for each matched sample.[13] For example, the standardized differences of the covariates were <0.1 (indicating negligible difference) in the matched sample of the first mini-trial (eTable 2).

We calculated IPCW to account for censoring as a function of patient characteristics at the new baseline of each matched mini-trial. We estimated the association between nephrology consultation and mortality separately for each paired samples[14] of the first four mini-trials. Finally, we examined the association between nephrology consultation and mortality, in an IPCW-weighted-, first four mini-trial-stratified-, and matched-Cox model (eFigure 3).

eTable 1. Distribution of initiating outpatient nephrology visit during the initial 90-day period of selected mini-trials

Time interval of initiating outpatient nephrology visit		Number	%
1	After index date, up to day 90*1	1418	28.3
2	After day 90*1, up to day 90*2	786	15.7
3	After day 90*2, up to day 90*3	466	9.3
4	After day 90*3, up to day 90*4	375	7.5
5	After day 90*4, up to day 90*5	302	6.0
6	After day 90*5, up to day 90*6	234	4.7
7	After day 90*6, up to day 90*7	199	4.0
8	After day 90*7, up to day 90*8	168	3.4
9	After day 90*8, up to day 90*9	151	3.0
10	After day 90*9, up to day 90*10	123	2.5
11	After day 90*10, up to day 90*11	106	2.1
12	After day 90*11, up to day 90*12	87	1.7
13	After day 90*12, up to day 90*13	80	1.6
14	After day 90*13, up to day 90*14	72	1.4
15	After day 90*14, up to day 90*15	52	1.0
16	After day 90*15, up to day 90*16	45	0.9
≥17	After day 90*16	349	7.0
Total		5013	100

eTable 2. Comparison of means or frequencies of baseline characteristics between exposed and unexposed in the first mini-trial, before and after propensity score matching

Characteristics	Before matching				After matching		
	Exposed* (n=1418)	Unexposed* (n=12,964)	Standardized differences†		Exposed* (n=1409)	Unexposed* (n=1409)	Standardized differences†
Demographics							
Age, year, mean	75	82	-0.71		75	75	-0.02
18−64	0.19	0.06	0.40		0.18	0.18	0.00
65−79	0.44	0.28	0.33		0.44	0.42	0.04
≥80	0.38	0.66	-0.60		0.38	0.40	-0.04
Men	0.47	0.36	0.22		0.47	0.49	-0.04
First Nations	0.03	0.01	0.11		0.03	0.02	0.04
Rural residence	0.14	0.17	-0.09		0.14	0.14	0.01
Health system factors							
Period of study entry							
2002−2004	0.17	0.24	-0.18		0.17	0.17	0.00
2005−2009	0.40	0.41	-0.01		0.40	0.41	-0.01
2010−2014	0.43	0.36	0.15		0.43	0.42	0.01
Primary care network attachment	0.56	0.51	0.10		0.56	0.56	0.00
Renal factors							
Index eGFR, ml/min/1.73m^2, mean	23.5	24.7	-0.34		23.5	23.4	0.02
25−29	0.41	0.54	-0.26		0.41	0.40	0.02
20−24	0.37	0.33	0.08		0.37	0.37	-0.01
15−19	0.22	0.13	0.24		0.22	0.23	-0.02
Disease duration, days, mean	183	231	-0.26		183	183	0.00
91−180	0.73	0.56	0.35		0.73	0.67	0.14
181−365	0.20	0.29	-0.21		0.20	0.26	-0.14
366−730	0.06	0.12	-0.21		0.06	0.07	-0.05
>730	0.02	0.03	-0.09		0.02	0.01	0.08
eGFR trajectory, ml/min/1.73m^2/year							
Improve >5	0.15	0.16	-0.02		0.15	0.15	0.01
Improve or decline ≤5	0.38	0.52	-0.29		0.38	0.39	-0.03
Decline >5 to ≤10	0.17	0.15	0.07		0.17	0.17	0.01
Decline >10	0.29	0.17	0.29		0.29	0.29	0.01
Prior eGFR, ml/min/1.73m^2							
Unmeasured	0.17	0.21	-0.10		0.17	0.18	-0.02
≥60	0.03	0.02	0.07		0.03	0.03	-0.01
≥30 to <60	0.80	0.77	0.07		0.80	0.79	0.03

eTable 2. (Continued)

Characteristics	Before matching				After matching		
	Exposed* (n=1418)	Unexposed* (n=12,964)	Standardized differences†		Exposed* (n=1409)	Unexposed* (n=1409)	Standardized differences†
Albuminuria							
Normal/mild	0.42	0.56	-0.27		0.43	0.41	0.02
Moderate	0.23	0.20	0.08		0.23	0.23	0.00
Severe	0.33	0.17	0.39		0.33	0.34	-0.02
Unmeasured	0.02	0.08	-0.31		0.02	0.02	-0.01
Outpatient nephrology visit >2 years before study entry	0.15	0.11	0.12		0.15	0.16	-0.01
Comorbidities							
Alcohol misuse	0.04	0.03	0.04		0.04	0.05	-0.04
Atrial fibrillation	0.22	0.29	-0.17		0.22	0.22	-0.01
Cancer, lymphoma	0.01	0.01	0.00		0.01	0.01	0.03
Cancer, metastatic	0.02	0.02	-0.01		0.02	0.02	0.01
Cancer, non-metastatic (breast, cervical, colorectal, lung, prostate)	0.08	0.09	-0.04		0.08	0.09	-0.03
Congestive heart failure	0.31	0.44	-0.28		0.31	0.31	0.01
Chronic pain	0.07	0.07	0.01		0.07	0.06	0.03
Chronic pulmonary disease	0.32	0.36	-0.08		0.32	0.34	-0.03
Cirrhosis	0.01	0.01	0.02		0.01	0.01	0.01
Dementia	0.06	0.18	-0.37		0.06	0.07	-0.03
Depression	0.10	0.12	-0.06		0.10	0.10	0.01
Diabetes	0.52	0.41	0.21		0.52	0.53	-0.02
Hypertension	0.90	0.92	-0.07		0.90	0.90	0.01
Myocardial infarction	0.12	0.13	-0.03		0.12	0.12	-0.01
Peripheral vascular disease	0.08	0.07	0.04		0.08	0.09	-0.02
Stroke	0.19	0.22	-0.08		0.19	0.18	0.01
TIA	0.11	0.16	-0.15		0.11	0.10	0.03

eTable 2. (Continued)

Characteristics	Before matching				After matching		
	Exposed* (n=1418)	Unexposed* (n=12,964)	Standardized differences†		Exposed* (n=1409)	Unexposed* (n=1409)	Standardized differences†
Long-term care	0.08	0.19	-0.33		0.08	0.08	0.00
Days of hospital stay 1year before index							
0	0.64	0.63	0.03		0.64	0.63	0.03
1−7	0.12	0.12	0.00		0.12	0.12	0.01
8−14	0.08	0.07	0.03		0.08	0.09	-0.04
15−28	0.07	0.07	-0.02		0.07	0.07	-0.03
>28	0.09	0.10	-0.06		0.09	0.08	0.01
Drugs dispensed							
ACEI/ARBs							
No	0.17	0.26	-0.23		0.17	0.18	-0.02
Yes	0.77	0.71	0.13		0.77	0.76	0.01
Data missing	0.06	0.02	0.19		0.06	0.06	0.01
Statins							
No	0.44	0.60	-0.33		0.44	0.42	0.03
Yes	0.50	0.38	0.24		0.50	0.51	-0.02
Data missing	0.07	0.03	0.19		0.07	0.07	-0.01
NSAIDs							
No	0.73	0.76	-0.07		0.73	0.74	-0.01
Yes	0.18	0.21	-0.06		0.19	0.18	0.02
Data missing	0.08	0.03	0.22		0.08	0.09	-0.01

ACEI/ARBs=angiotensin-converting enzyme inhibitor or angiotensin receptor blockers; eGFR=estimated glomerular filtration rate; NSAIDs=nonsteroidal anti-inflammatory drugs; TIA=transient ischemic attack.
*Exposed: those eventually had an outpatient nephrology visit during follow-up; unexposed: those never had an outpatient nephrology visit before renal replacement treatment.
†Standardized differences > 0.1 are considered clinically important.

eTable 3. HRs (95% CIs) for death associated with covariates in the sequential Cox modelling the association between nephrology consultation and mortality

	Hazard ratio	95% confidence interval
Nephrology consultation yes vs. no	0.88	0.82 to 0.93
Baseline covariates:		
Age, years	1.05	1.04 to 1.06
Male	1.31	1.22 to 1.40
First Nations	0.80	0.56 to 1.14
Rural residence	0.99	0.91 to 1.07
Period of study entry		
2002−2004	1	Reference
2005−2009	0.95	0.87 to 1.04
2010−2014	0.88	0.79 to 0.99
Primary care network attachment	1.08	0.99 to 1.17
Index eGFR, ml/min/1.73m^2	0.98	0.97 to 0.99
Disease duration, days	1.00	1.00 to 1.00
eGFR trajectory, ml/min/1.73m^2/year		
Improve >5	1	Reference
Improve or decline ≤5	0.87	0.79 to 0.95
Decline >5 to ≤10	0.90	0.80 to 1.01
Decline >10	0.93	0.83 to 1.05
Prior eGFR, ml/min/1.73m^2		
≥60	1.25	0.97 to 1.60
≥30 to <60	1.09	1.00 to 1.19
Unmeasured	1	Reference
Albuminuria		
Normal or mild	1	Reference
Moderate	1.09	0.99 to 1.20
Severe	1.18	1.04 to 1.35
Unmeasured	Omitted	
Outpatient nephrology visit >2 years before study entry	0.91	0.82 to 1.01
Alcohol misuse	0.98	0.78 to 1.24
Atrial fibrillation	1.17	1.09 to 1.26
Cancer, lymphoma	1.53	1.14 to 2.04
Cancer, metastatic	1.39	1.11 to 1.74
Cancer, non-metastatic (breast, cervical, colorectal, lung, prostate)	1.16	1.04 to 1.30
Congestive heart failure	1.12	0.99 to 1.26
Chronic pain	1.07	0.97 to 1.19
Chronic pulmonary disease	1.17	1.09 to 1.25
Cirrhosis	3.12	2.24 to 4.33
Dementia	1.37	1.25 to 1.50
Depression	0.99	0.90 to 1.09
Diabetes	1.19	1.12 to 1.28
Hypertension	0.98	0.83 to 1.15

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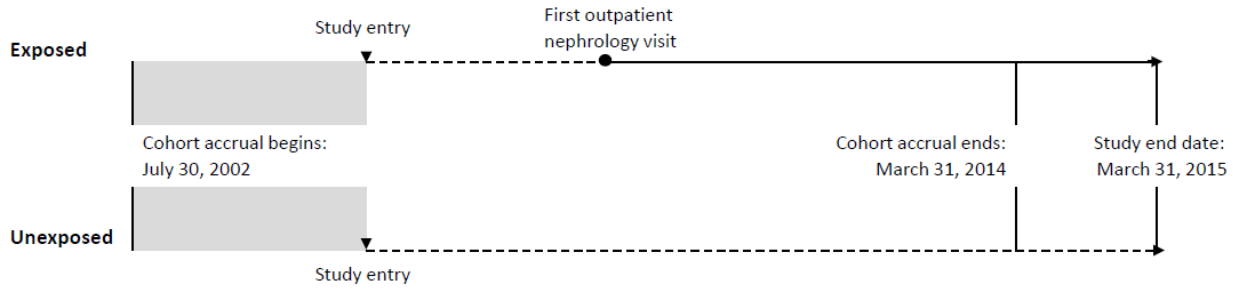
Myocardial infarction	0.83	0.67 to 1.02
Peripheral vascular disease	1.22	1.09 to 1.37
Stroke	0.85	0.74 to 0.98
TIA	1.00	0.84 to 1.20
Long-term care	0.80	0.71 to 0.90
Days of hospital stay within 1 year before study entry		
0	1	Reference
1–7	1.02	0.93 to 1.12
8–14	0.96	0.85 to 1.09
15–28	1.05	0.92 to 1.19
>28	1.05	0.94 to 1.17
ACEI or ARBs		
No	1	Reference
Yes	0.90	0.84 to 0.97
Data missing	0.63	0.33 to 1.20
Statins		
No	1	Reference
Yes	0.81	0.76 to 0.88
Data missing	1.46	0.70 to 3.02
NSAIDs		
No	1	Reference
Yes	0.91	0.85 to 0.99
Data missing	1.29	0.78 to 2.11
Time-varying covariates: updated at the new baseline of each mini-trial		
eGFR, ml/min/1.73m^2	0.989	0.986 to 0.991
Albuminuria		
Normal or mild	1	Reference
Moderate	1.05	0.99 to 1.10
Severe	1.19	1.10 to 1.29
Unmeasured	1.73	1.50 to 1.99
Myocardial infarction	1.16	0.99 to 1.36
Congestive heart failure	1.30	1.19 to 1.43
Stroke	1.18	1.06 to 1.32
TIA	0.99	0.86 to 1.14
Long-term care	1.47	1.37 to 1.58
Days of hospital stay within 1 year before study entry		
0	1	Reference
1–7	1.34	1.29 to 1.39
8–14	1.45	1.38 to 1.53
15–28	1.59	1.51 to 1.68
>28	1.77	1.68 to 1.87
Time-varying covariates: lagged values		
eGFR, ml/min/1.73m^2	0.9995	0.997 to 1.002
Albuminuria		

Normal or mild	1	Reference
Moderate	1.07	1.03 to 1.11
Severe	1.07	1.01 to 1.14
Unmeasured	Omitted	
Myocardial infarction	1.15	0.98 to 1.34
Congestive heart failure	0.98	0.90 to 1.06
Stroke	1.03	0.94 to 1.14
TIA	1.10	0.97 to 1.24
Long-term care	1.22	1.14 to 1.31
Days of hospital stay within 1 year before study entry		
0	1	Reference
1–7	1.15	1.11 to 1.20
8–14	1.18	1.12 to 1.24
15–28	1.14	1.08 to 1.20
>28	1.09	1.04 to 1.15

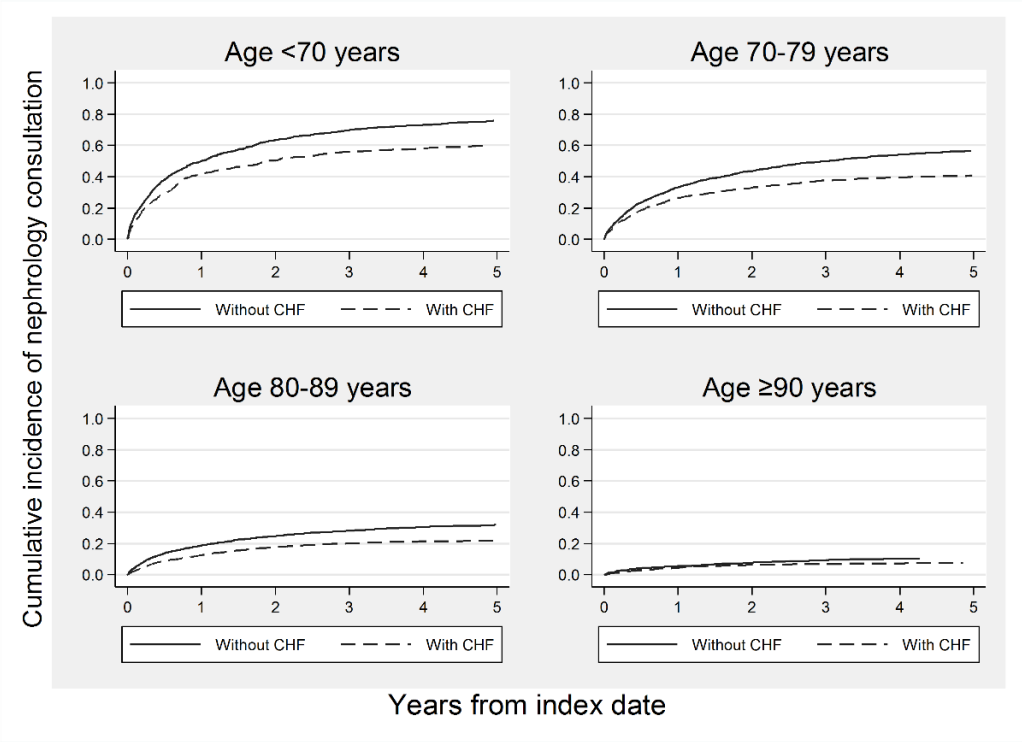
ACEI/ARBs=angiotensin-converting enzyme inhibitor or angiotensin receptor blockers; eGFR=estimated glomerular filtration rate; NSAIDs=nonsteroidal anti-inflammatory drugs; TIA=transient ischemic attack.

eFigure 1. Study design

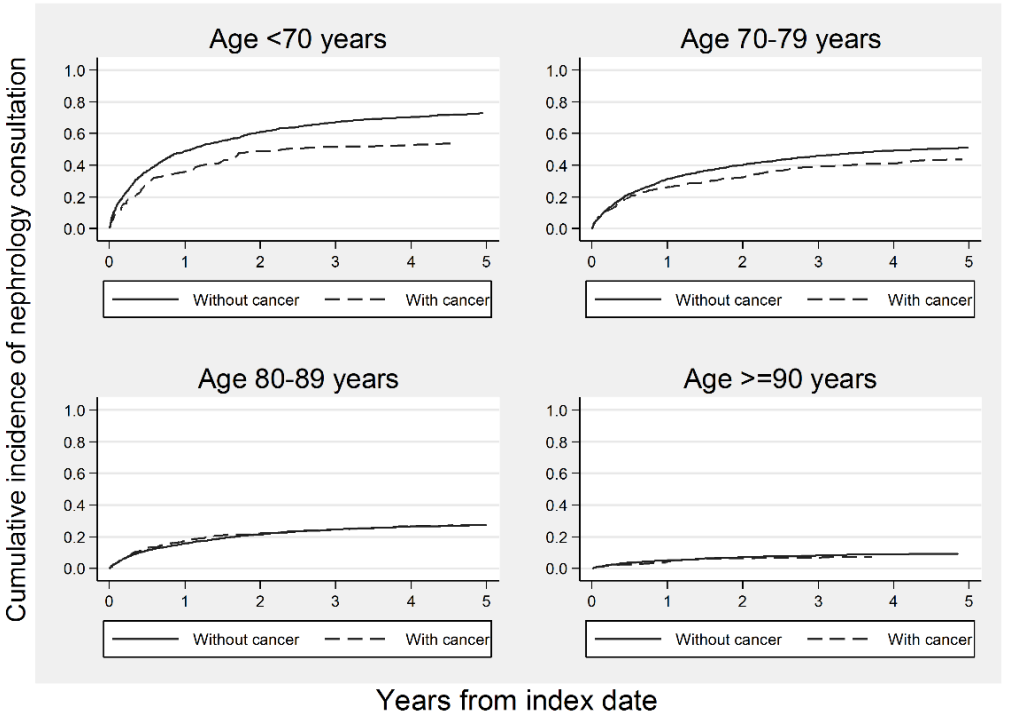


eFigure 2. Probability of nephrology consultation, by key baseline comorbidities and age categories

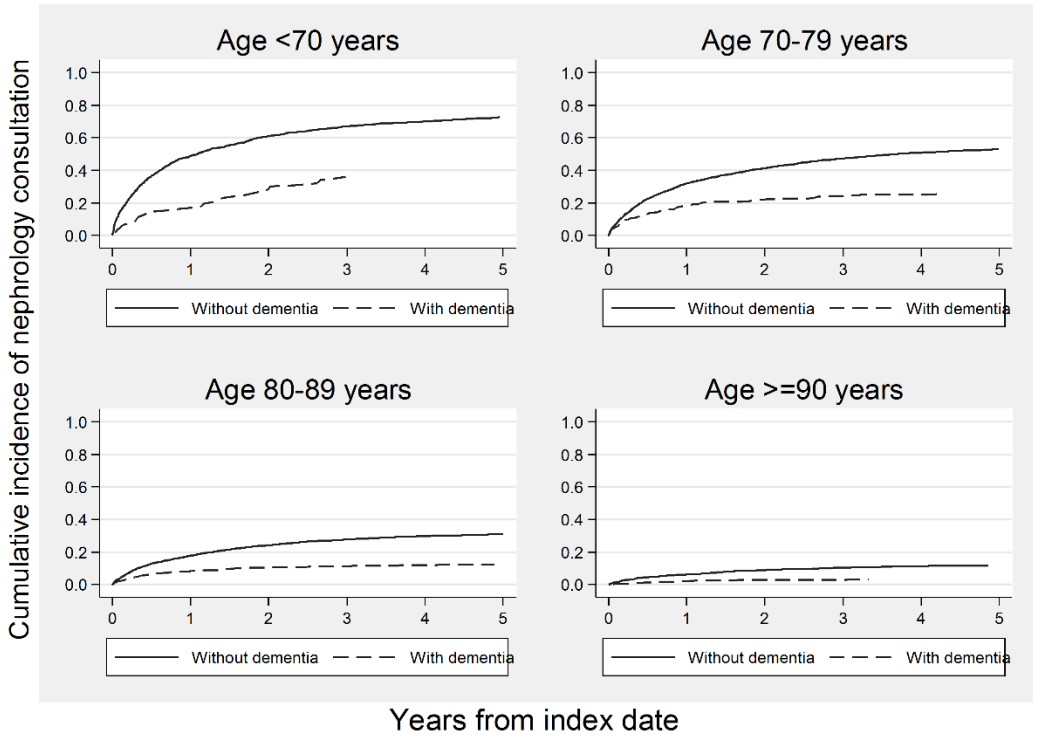
A) Congestive heart failure



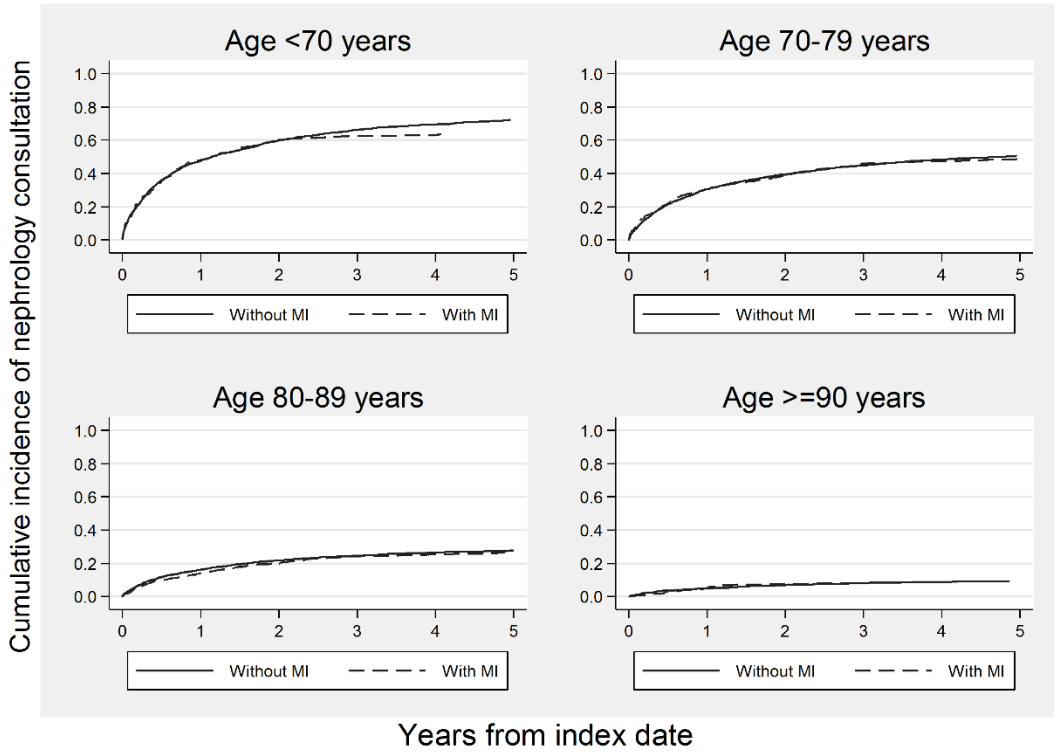
B) Cancer


Age <70 years
Age 70-79 years
Age 80-89 years
Age >=90 years
Cumulative incidence of nephrology consultation
Years from index date
Without cancer
With cancer
0.0
0.2
0.4
0.6
0.8
1.0
0
1
2
3
4
5

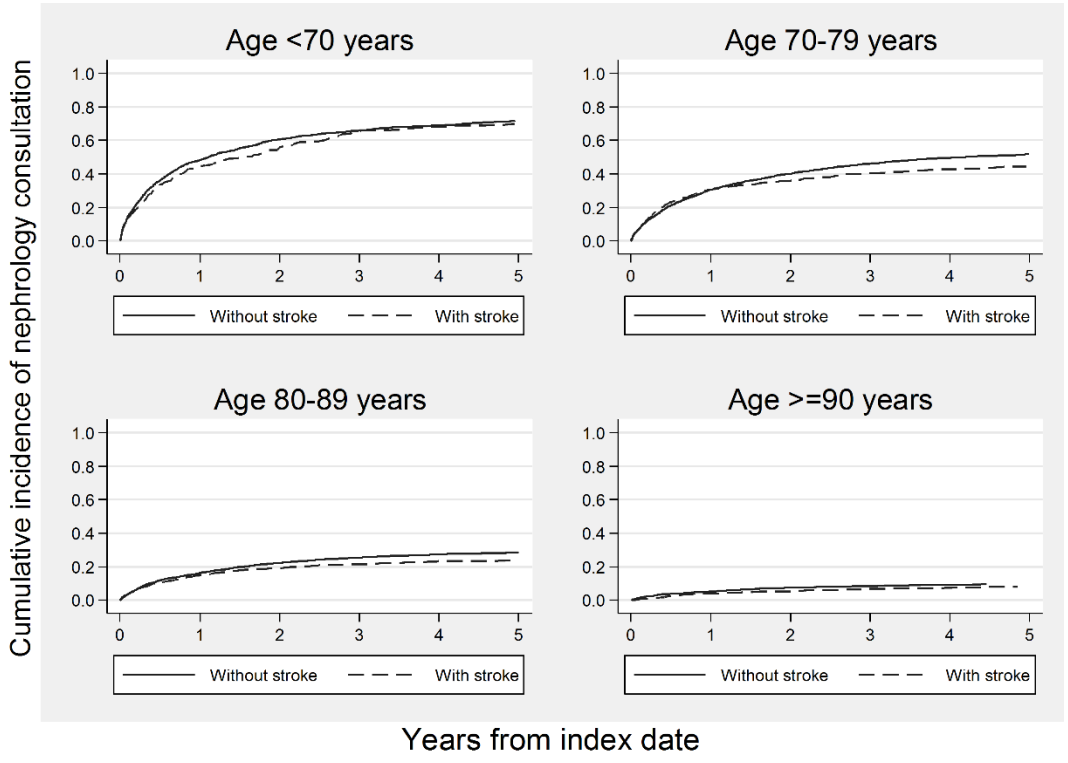
C) Dementia



D) Myocardial infarction

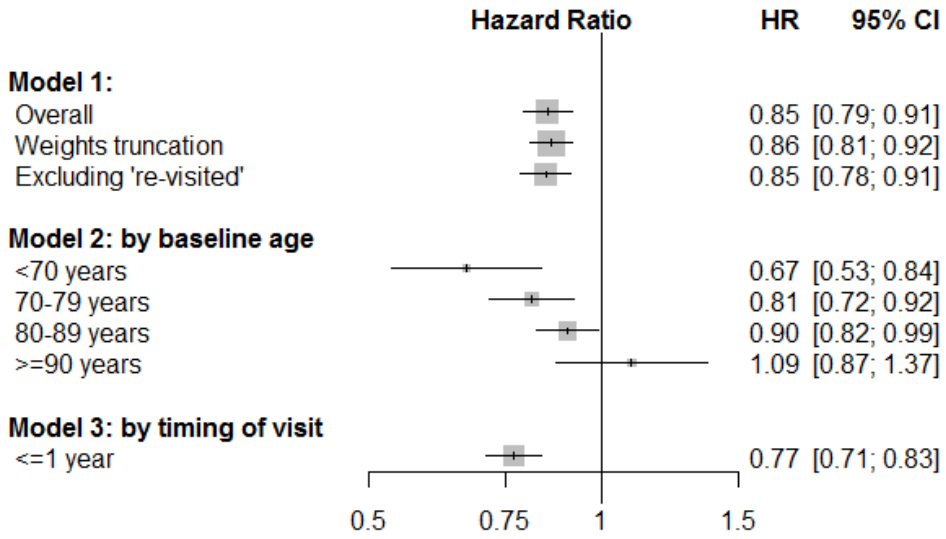


E) Stroke



CHF=Congestive heart failure; MI=myocardial infarction.
Note: The presence of cancer was defined as the presence of lymphoma, metastatic cancer, or non-metastatic cancer.

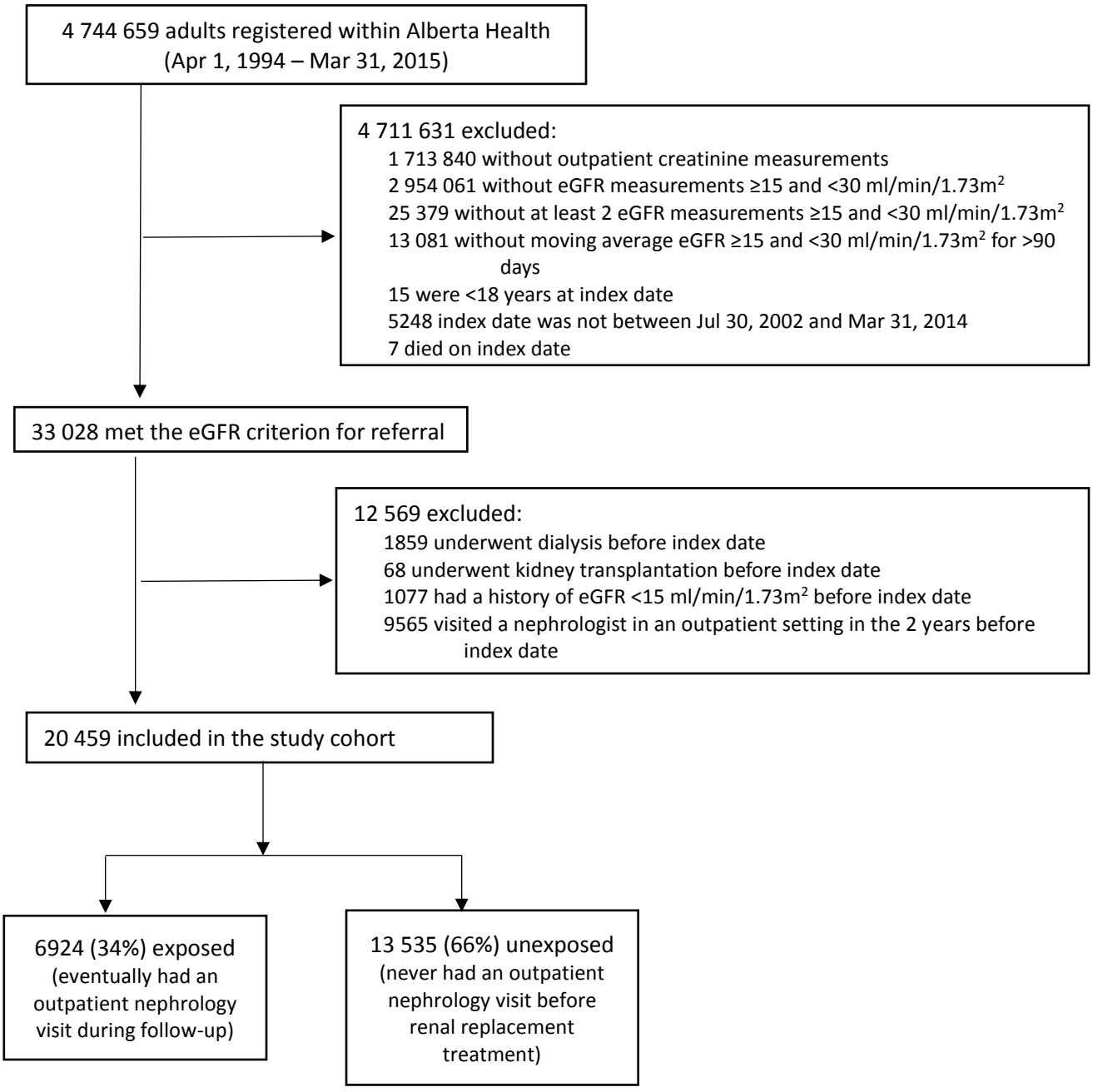
eFigure 3. Sensitivity analyses of association between nephrology consultation and mortality



Note: For the covariates controlled for, see the eMethods in the appendix
Model 1: marginal structural Cox models
Model 2: a marginal structural Cox model tested whether the association between nephrology consultation and mortality differed by age categories
Model 3: a sequential Cox model for the first four mini-trials, with propensity score matching within each mini-trial.

Sensitivity Analysis: Impact of less stringent eligibility criteria (moving average eGFR)

eFigure 4. Derivation of study cohort



Appendix to: Liu P, Quinn RR, Karim ME, et al. Nephrology consultation and mortality in people with stage 4 chronic kidney disease: a population-based study. *CMAJ* 2019. doi: 10.1503/cmaj.181372.

eTable 4. Characteristics of participants at study entry

Characteristics	Exposed* (n=6924)	Unexposed* (n=13 535)
Demographics		
Age, years, mean (SD)	75.2 (10.8)	83.6 (8.9)
median (IQR)	77.1 (69.5−82.8)	84.8 (79.2−89.6)
18−44	117 (1.7%)	33 (0.2%)
45−69	998 (14.4%)	486 (3.6%)
70−79	3204 (46.3%)	3219 (23.8%)
80−89	2331 (33.7%)	6696 (49.5%)
≥90	274 (4.0%)	3101 (22.9%)
Men	3104 (44.8%)	4744 (35.0%)
First Nations	170 (2.5%)	143 (1.1%)
Rural residence	1093 (15.8%)	2238 (16.5%)
Health system factors		
Period of study entry		
2002−2004	1617 (23.4%)	3116 (23.0%)
2005−2009	2930 (42.3%)	5421 (40.1%)
2010−2014	2377 (34.3%)	4998 (36.9%)
Primary care network attachment	3389 (48.9%)	7188 (53.1%)
Renal factors		
Index eGFR, ml/min/1.73m^2, median (IQR)	27.1 (24.3−28.7)	27.4 (25.0−28.9)
25−29	4829 (69.7%)	10 127 (74.8%)
20−24	1637 (23.6%)	2743 (20.3%)
15−19	458 (6.6%)	665 (4.9%)
Disease duration, days, median (IQR)	140 (106−228)	154 (108−264)
91−180	4471 (64.6%)	7913 (58.5%)
181−365	1665 (24.0%)	3711 (27.4%)
366−730	627 (9.1%)	1487 (11.0%)
>730	161 (2.3%)	424 (3.1%)
eGFR trajectory, ml/min/1.73m^2/year		
Improve >5	1589 (22.9%)	3623 (26.8%)
Improve or decline ≤5	2467 (35.6%)	5059 (37.4%)
Decline >5 to ≤10	967 (14.0%)	1537 (11.4%)
Decline >10	1901 (27.5%)	3316 (24.5%)
Prior eGFR, ml/min/1.73m^2		
≥60	13 (0.2%)	38 (0.3%)
≥30 to <60	1432 (20.7%)	3202 (23.7%)
≥15 to <30	171 (2.5%)	367 (2.7%)
Unmeasured	5308 (76.7%)	9928 (73.4%)
Albuminuria		
Normal or mild	3426 (49.5%)	7990 (59.0%)
Moderate	1559 (22.5%)	2522 (18.6%)
Severe	1842 (26.6%)	1654 (12.2%)
Unmeasured	97 (1.4%)	1369 (10.1%)
Outpatient nephrology visit >2 years before study entry	967 (14.0%)	1041 (7.7%)

Appendix to: Liu P, Quinn RR, Karim ME, et al. Nephrology consultation and mortality in people with stage 4 chronic kidney disease: a population-based study. *CMAJ* 2019. doi: 10.1503/cmaj.181372.

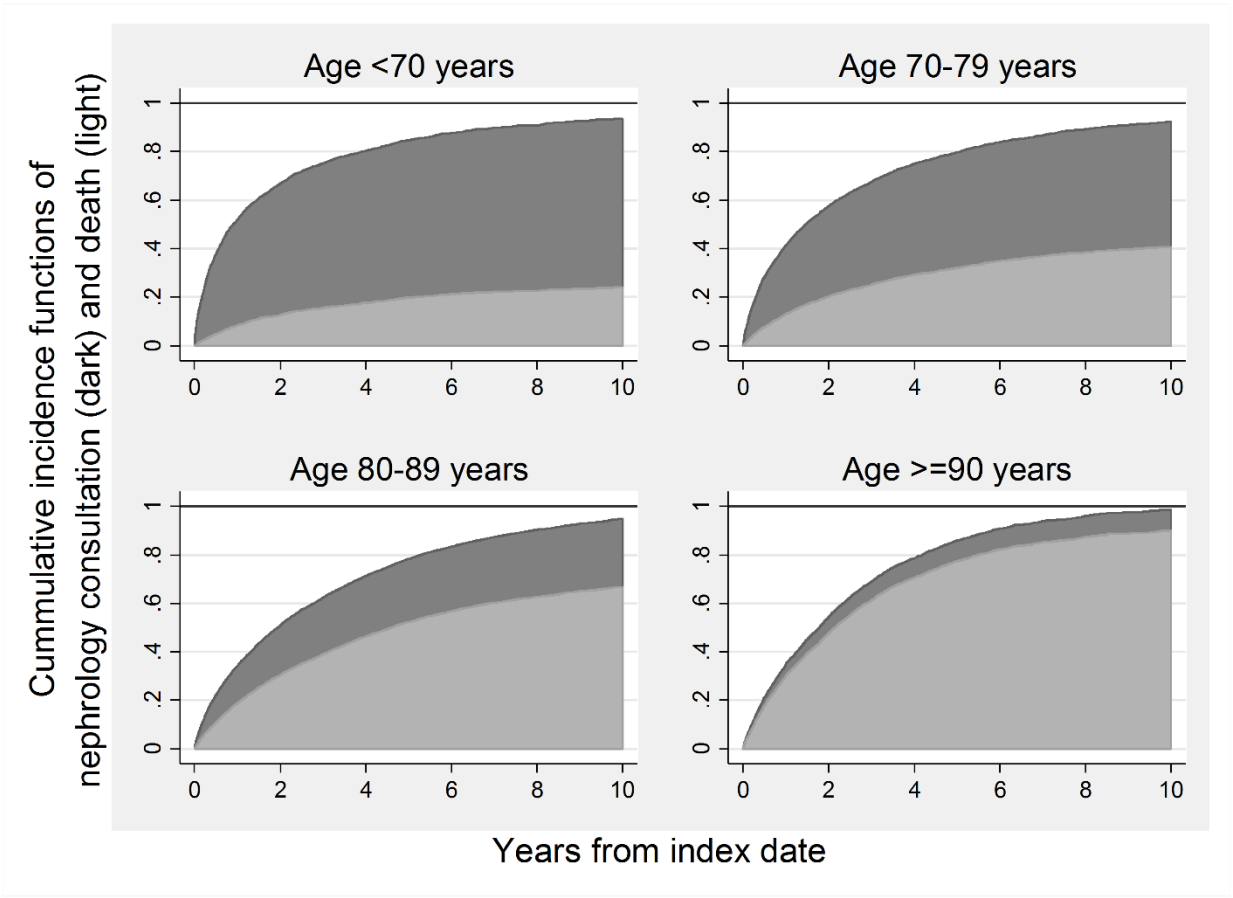
eTable 4. Characteristics of participants at study entry (Continued)

Characteristics	Exposed* (n=6924)	Unexposed* (n=13 535)
Comorbidities		
Alcohol misuse	249 (3.6%)	438 (3.2%)
Atrial fibrillation	1494 (21.6%)	4416 (32.6%)
Cancer, lymphoma	77 (1.1%)	228 (1.7%)
Cancer, metastatic	137 (2.0%)	520 (3.8%)
Cancer, non-metastatic (breast, cervical, colorectal, lung, prostate)	575 (8.3%)	1376 (10.2%)
Congestive heart failure	2292 (33.1%)	6664 (49.2%)
Chronic pain	521 (7.5%)	1041 (7.7%)
Chronic pulmonary disease	2191 (31.6%)	5207 (38.5%)
Cirrhosis	57 (0.8%)	110 (0.8%)
Dementia	390 (5.6%)	3028 (22.4%)
Depression	719 (10.4%)	1871 (13.8%)
Diabetes	3440 (49.7%)	5118 (37.8%)
Hypertension	6361 (91.9%)	12,389 (91.5%)
Myocardial infarction	841 (12.1%)	1863 (13.8%)
Peripheral vascular disease	538 (7.8%)	968 (7.2%)
Stroke or TIA	1573 (22.7%)	4135 (30.6%)
Long-term care	486 (7.0%)	3200 (23.6%)
Days of hospital stay within 1 year before study entry		
0	4375 (63.2%)	7447 (55.0%)
1−7	904 (13.1%)	1794 (13.3%)
8−14	569 (8.2%)	1131 (8.4%)
15−28	497 (7.2%)	1194 (8.8%)
>28	579 (8.4%)	1969 (14.5%)
Drugs dispensed		
ACEI or ARBs		
No	1181 (17.1%)	3822 (28.2%)
Yes	5301 (76.6%)	9525 (70.4%)
Data missing	442 (6.4%)	188 (1.4%)
Statins		
No	3151 (45.5%)	8523 (63.0%)
Yes	3263 (47.1%)	4780 (35.3%)
Data missing	510 (7.4%)	232 (1.7%)
NSAIDs		
No	4745 (68.5%)	10449 (77.2%)
Yes	1586 (22.9%)	2832 (20.9%)
Data missing	593 (8.6%)	254 (1.9%)

ACEI/ARBs=angiotensin-converting enzyme inhibitor or angiotensin receptor blockers; eGFR=estimated glomerular filtration rate; IQR=inter quartile range; NSAIDs=nonsteroidal anti-inflammatory drugs; SD=standard deviation; TIA=transient ischemic attack. Values are number (%), otherwise stated.

*Exposed: those eventually had an outpatient nephrology visit during follow-up; unexposed: those never had an outpatient nephrology visit before renal replacement treatment.

eFigure 5. Probabilities of nephrology consultation and death by age

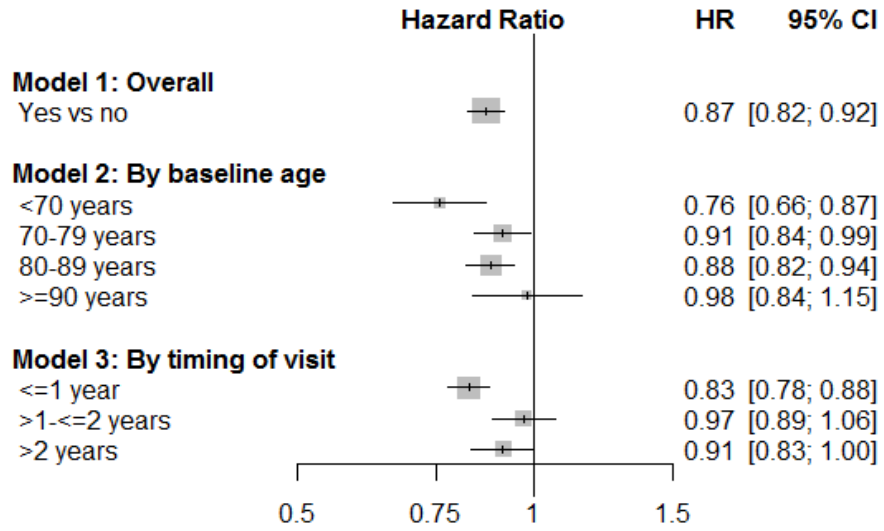


eTable 5. Overall crude mortality by follow-up times

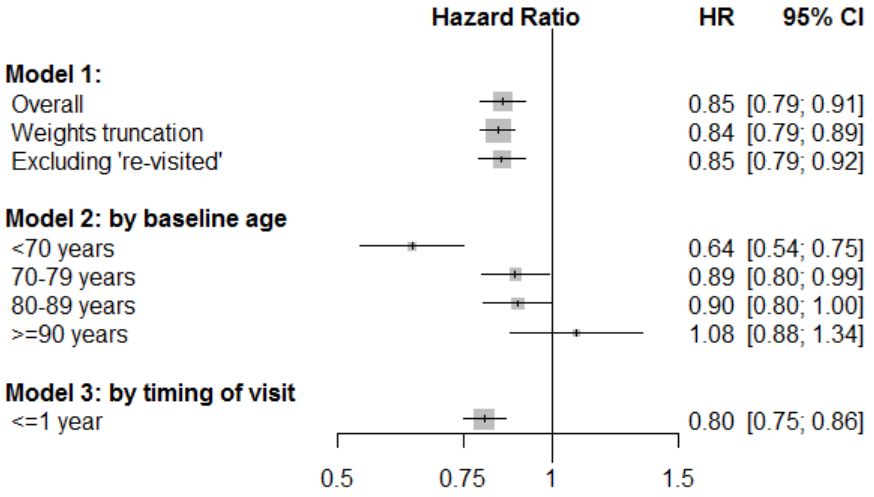
Follow-up time, year	Number of deaths	Person-years	Mortality rate per 100 person-years (95% CI)
(0−1]	4020	18 245	22 (21−23)
(1−2]	2614	14 286	18 (18−19)
(2−3]	1898	10 823	18 (17−18)
(3−4]	1428	8111	18 (17−19)
(4−5]	1117	6048	18 (17−20)
>5	2388	13 170	18 (17−19)
Total	13 465	70 683	19 (19−19)

eFigure 6. Association between nephrology consultation and mortality

Panel A:



Panel B:



Note: For the covariates controlled for, see the eMethods in the appendix.
Panel A: three models were from Sequential Cox modelling

Panel B:
Model 1: marginal structural Cox models
Model 2: a marginal structural Cox model tested whether the association between nephrology consultation and mortality differed by age categories
Model 3: a sequential Cox model for the first four mini-trials, with propensity score matching within each mini-trial.

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