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Preclinical evidence shows that activation of the cholinergic anti-inflammatory pathway (CAP) may have direct and indirect beneficial effects on the kidney. Cholinesterase inhibitors (ChEIs) are specific Alzheimer's dementia (AD) therapies that block the action of cholinesterases and activate CAP. Here, we explored a plausible effect of ChEIs on slowing kidney function decline by comparing the risk of CKD progression among patients with newly diagnosed AD that initiated ChEI or not within 90 days. Using complete information of routine serum creatinine tests, we evaluated changes in estimated glomerular filtration rate (eGFR) and defined the outcome of chronic kidney disease (CKD) progression as the composite of an eGFR decline of over 30%, initiation of dialysis/transplant or death attributed to CKD. A secondary outcome was death. Inverse probability of treatment-weighted Cox regression was used to estimate hazard ratios. Among 11, 898 patients, 6,803 started on ChEIs and 5,095 did not. Mean age was 80 years (64% women) and the mean eGFR was 68 ml/min/1.73m^2. During a median 3.0 years of follow-up, and compared to non-use, ChEI use was associated with 18% lower risk of CKD progression (1,231 events, adjusted hazard ratio 0.82; 95% confidence interval 0.71-0.96) and a 21% lower risk of death (0.79; 0.72-0.86). Results were consistent across subgroups, ChEI subclasses and after accounting for competing risks. Thus, in patients with AD undergoing routine care, use of ChEI (vs no-use) was associated with lower risk of CKD progression.

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Inflammation is a common and prognostically unfavorable manifestation of several noncommunicable chronic diseases such as hypertension, type 2 diabetes, heart failure, rheumatoid arthritis, inflammatory bowel disease, and chronic kidney disease (CKD).[1] Recent insights in neuroimmunology propose a role for vagal neuromodulation in the management of these diseases[2,3] that center on the cholinergic anti-inflammatory pathway (CAP), a vagal neuroimmune circuit that regulates the homeostatic balance of inflammatory activity responses to cell damage and pathogens.[4–6]

CKD, defined as persistent and irreversible degradation of kidney function, is a common condition (8%–16% population prevalence)[7] that often develops with autonomic dysfunction coupled with a state of systemic chronic inflammation.[8] Such derangements have been associated with poor prognosis, especially in persons with end-stage kidney disease.[8–10] Emerging evidence suggests that CAP can be a target for CKD. Animal studies demonstrate that activation of CAP leads to the release of acetylcholine, which in turn exerts direct renoprotective effects on the kidney.[11–15] Indirect mechanisms by which CAP activation may favorably affect kidney function include reduction in inflammatory mediators[16,17] as well as regulation of heart rate and blood pressure via parasympathetic (vagal nerve) stimulation.[5,18,19]

Cholinesterase inhibitors (ChEIs), namely donepezil, galantamine, and rivastigmine, are approved pharmacological therapies with the potential to offset cognitive decline in persons with Alzheimer's dementia (AD).[20–22] ChEIs inhibit the acetylcholine-degrading enzyme acetylcholinesterase, leading to increasing levels and duration of action of acetylcholine in the synapses of both central and peripheral nervous systems.[23] It is possible that the effects of ChEIs extend beyond the cholinergic system in the brain,[4] and observational studies have indeed associated the use of ChEIs in

patients with AD with a lower risk of myocardial infarction, stroke, and death.[24–26]

To explore the plausibility of CAP activation in modulating kidney damage, we conducted an observational study comparing CKD progression rates among individuals with incident AD diagnosis who were initiated on ChEIs or not.

METHODS

Data sources

This study includes patients with an incident diagnosis of dementia registered in the Swedish Registry for cognitive disease/dementia (SveDem: www.ucr.uu.se/svedem/), a web-based registry established in 2007 with the aim to characterize and follow all patients with dementia in Sweden. The variables include patient demographics, Mini-Mental State Examination (MMSE) scores, the type of dementia disorder, and treatment.[27] For this study, SveDem was merged with the Stockholm Creatinine Measurements (SCREAM) project, a repository of laboratory analyses performed in connection to health care in residents from the Stockholm region between 2006 and 2018, thus providing laboratory measurements information during follow-up.[28] The merged data were linked with other regional and national administrative databases for complete information on health care utilization, dispensed drugs, validated kidney replacement therapy endpoints (dialysis or transplant), and follow-up for death, with virtually no loss to follow-up.

Study design and study population

We created a cohort study with landmark design to compare the risk of CKD progression among patients starting ChEI treatment or not within 3 months after an incident diagnosis of dementia. To that end, we identified all patients receiving an incident diagnosis of AD or mixed AD dementia registered by the date of diagnosis in SveDem and residing in the Stockholm region between January 1, 2007, and December 31, 2018. We included patients with a record of serum or plasma creatinine taken in connection with an outpatient health care encounter at the time of the dementia diagnosis date or within 1 year prior. We excluded patients undergoing kidney replacement therapy (maintenance dialysis or with a history of kidney transplantation) or with ongoing ChEI medication at the time of the dementia diagnosis date (prevalent users), as well as those with missing MMSE scores at the time of dementia diagnosis, because in Sweden the indication for ChEI prescription is mild to moderate AD and we wanted to confirm that the indication existed.

The index date of the study was set 3 months after the incident dementia diagnosis, a clinically reasonable time at which ChEI therapy was initiated or not. The ChEI therapy was defined through filled dispensations at Swedish pharmacies via the National Prescribed Drug Registry (NPDR). As shown in Supplementary Figure S1, >90% of all patients starting ChEIs in our cohort did so within the first 3 months. With this definition, 374 patients who died and 610 patients who ended the follow-up within the first 3 months after dementia diagnosis were excluded. After applying inclusion and exclusion criteria, a total of 11,898 patients with an incident AD or mixed AD composed the study population.

Exposure

The study exposure was initiation of ChEI therapy with donepezil, rivastigmine, or galantamine within 3 months of the dementia diagnosis versus no initiation within 3 months. We also collected information on the doses of each dispensation of ChEIs over the initial 3-month period.

Our primary analysis used an intention-to-treat design and assumed study exposures to be constant until end of follow up.

Covariates

Study covariates included sociodemographics, laboratory values, comorbidities, and ongoing medications. Sociodemographics were age, sex, body weight at time of dementia diagnosis, highest-attained education, and calendar year. The highest-educational attainment for each participant was obtained by linkage with the government-run Longitudinal Integrated Database for Health Insurance and Labor Market Studies (LISA) registry[29] and categorized as compulsory school, secondary school, and university education. Laboratory values were albuminuria and estimated glomerular filtration rate (eGFR) measured in outpatient care during the year prior to the index date. The presence of CKD was defined as having an eGFR <60 ml/min per 1.73 m^2 according to the Kidney Disease: Improving Global Outcomes (KDIGO) classification.[30] The presence and severity of albuminuria was determined through extraction of all tests of dipstick albuminuria/proteinuria, urinary albumin to creatinine ratio, and albuminuria excretion rates and by categorization into KDIGO categories A1 to A3.[31] We did not consider measurements in connection with a hospital stay, because they could be influenced by the condition the person was hospitalized for and therefore may not reflect stable kidney function.

Covariates related to the characterization of dementia included type of dementia diagnosis (AD or mixed AD); MMSE score at the time of the dementia diagnosis; whether the diagnosing unit was a memory clinic or primary care; whether the patient was living alone, in their own home, or in a nursing home; and whether a dementia basic workup (clock test, blood test, MMSE test, and computed tomography/ magnetic resonance imaging) had been performed. Comorbidities were ascertained by *International Classification of Diseases, Tenth Revision* (ICD-10) codes prior to the index date and included hypertension, diabetes, congestive heart failure, myocardial infarction, peripheral vascular disease, cerebrovascular disease, chronic obstructive pulmonary disease, rheumatic disease, peptic ulcer disease, cancer, stroke, atrial fibrillation, liver disease, alcohol abuse, fracture, and depression. Ongoing medications were ascertained by Anatomical Therapeutic Chemical (ATC) codes according to the presence of filled pharmacy prescriptions within the 6 months prior to the index date. Medications registered were angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, β-blockers, calcium channel blocker, diuretics, lipid-lowering agents, acetylsalicylic acid, nonsteroidal anti-inflammatory drugs, antithrombotics, anxiolytics, hypnotics, antipsychotics, antidepressants, and memantine. Covariate definitions are further detailed in Supplementary Table S1.

Outcomes

The primary outcome was the composite of a sustained eGFR decline of >30% from the index date,[32] initiation of kidney replacement therapy (maintenance dialysis or kidney transplantation, ascertained by linkage to the Swedish Renal Registry), or death attributed to kidney disease (as main cause of death, ICD-10 codes N18-N19). To reduce outcome misclassification bias due to intrinsic eGFR variability, we used a linear interpolation method to ascertain a sustained >30% decline in eGFR as follows: for each individual, a linear regression line was fitted through all outpatient eGFR measurements; to be considered a sustained >30% decline in eGFR, the linear

regression slope needed to be negative; and the >30% decline threshold needed to be crossed before the last measurement. The time to event was then defined as the moment in which the linear regression line crossed the >30% decline threshold.[33] The secondary outcome was all-cause death, taken as a positive control outcome where a previous clinical trial reported a direct benefit.[34] Patients were followed from index date until the occurrence of event, migration from the region, death, or the end of follow-up (December 31, 2018), whichever happened first.

Statistical analyses

Continuous variables are presented as mean with SD or median with interquartile range, depending on the distribution. Categorical variables are presented as percentages. Study covariates had no missing data except for attained education, body weight, and baseline albuminuria, which were missing in 2%, 7%, and 59% of patients, respectively. We used multiple imputation by chained equations to impute 5 complete data sets with complete baseline information. The propensity score and effect estimates were estimated separately in each imputed data set and then pooled using Rubin's rule.

We then used inverse probability of treatment weighting to adjust for confounding by indication.[35] We estimated the probability of initiating ChEI treatment as a function of all study covariates mentioned previously. Patients in the ChEI group were weighted by 1/PS and in the non-ChEI group by 1/(1 − PS); PS denotes the propensity score. Weights were stabilized by adding the marginal probability of the received treatment to the numerator of the weights. Standardized mean differences were calculated to evaluate the balance of covariates between study groups before and after weighting, using a standardized mean difference >0.1 as the threshold for meaningful imbalance.[36] We estimated crude incidence rates per 1000 person-years. Cox proportional-hazards models were used to estimate hazard ratios. Confidence intervals were obtained by robust variance estimation.[37] Using all subsequent eGFR tests, we graphically represented the change in eGFR as a function of time between treatment groups by using a weighted mixed effects repeated measures model that included treatment, date of the eGFR measurement (time), and their interaction term as fixed effects, with patient as a random effect.

We evaluated the association between initiation dose and study outcomes. To that end, we created a subcohort of patients of ChEI users who dispensed ≥2 ChEI packages within the first 3 months from a dementia diagnosis. The date of the last dispensation in this time period was the cohort's index date, at which point we derived study covariates. The defined daily dosages (DDD) are the assumed average maintenance dose per day for a drug used for its main indications in adults and are specific to each ATC code. The value of DDD is founded by the World Health Organization International Working Group for Drug Statistics Methodology and is an established approach for quantification of drug utilization and exposure (https://www.whocc.no/atc_ ddd_index/). We defined the initiation dose as the DDD for each ATC dispensed, multiplied by the number of pills contained in the package and milligrams of active principle by pill, and divided by the number of days it took to collect the last ChEI dispensation. This estimated the number of DDD consumed per day normalized by the potency of each ChEI subclass. We modeled ChEI doses as a continuous exposure for increasing doses in a cubic spline with each outcome.

Subgroup analyses were performed to test for potential effect modification of age (≥85 vs. <85 years), sex, eGFR (≥60 vs. <60 ml/min per 1.73 m^2), MMSE (<20 vs. ≥20 scores), and type of dementia (AD vs. mixed AD) with adjustment for the variables defined herein. We also evaluated consistency of effect across ChEI types (vs. nonuse) at therapy start (donepezil, galantamine, or rivastigmine) with multivariable adjustment through Cox proportional-hazards model.

In addition, we conducted various sensitivity analyses to test the robustness of our results: (i) because some patients initiated ChEIs after 90 days from the incident dementia diagnosis, we evaluated the impact of this misclassification on our effect estimates by censoring at the time of ChEIs start, thereby estimating an as-treated effect; (ii) we performed a competing risk analysis, for this approach, death from any cause other than kidney disease was considered as a competing event for our primary outcome; weighted cumulative incidence curves were used to plot the cumulative incidences of study outcomes between study groups after competing risk analysis; (iii) we calculated an E-value to investigate the minimum strength of association that an unmeasured confounder would need to have with both treatment and outcome, with all measured covariates adjusted, to fully explain away the observed association;[38] (iv) to investigate potential differential outcome ascertainment due to differences in the frequency of serum creatinine testing between the ChEI and non-ChEI arms, we evaluated the number of serum creatinine tests during follow-up with Poisson regression in the unweighted population; (v) we repeated our main analysis in a 1:1 PS matched cohort; and (vi) we repeated our main analysis in the subcohort of patients where baseline albuminuria was available (that is, without multiple imputation).

All analyses were performed using R (version 3.4.3 software, The R Project for Statistical Computing) and Stata (version 17.0, StataCorp).

RESULTS

Patient characteristics

We included a total of 11,898 individuals with incident AD dementia between January 1, 2007, and December 31, 2018. Of these, 6,803 individuals started on ChEIs within 90 days (48% with donepezil, 32% galantamine, and 20% rivastigmine), and 5,095 did not (patient selection flow chart in Figure 1). Baseline characteristics before and after weighting are reported in Table 1 and Supplementary Figure S2, and they were well-balanced after weighting. Compared with nonusers, ChEI users tended to be younger (79 vs. 83 years), with slightly better kidney function (70 vs. 66 ml/min per 1.73 m^2), higher MMSE score (22 vs. 20 points), and less proportion of patients in nursing home care (4% vs. 7%). ChEI users had in general a higher education level, a lower prevalence of comorbidities, and less use of concomitant medication than nonusers did.

Use of ChEI and the risk of CKD progression

During a median follow-up time of 3.0 (interquartile range [IQR]: 1.3–4.5; range 0.1–11) years, corresponding to 37,586 person-years, 659 CKD progression events occurred among ChEI users and 572 among nonusers, corresponding to incidence rates of 27 (95% confidence interval [CI]: 25–29) and 43 (95% CI: 39–46) per 1000 person-years, respectively (Table 2). Compared with nonuse, ChEI use was associated

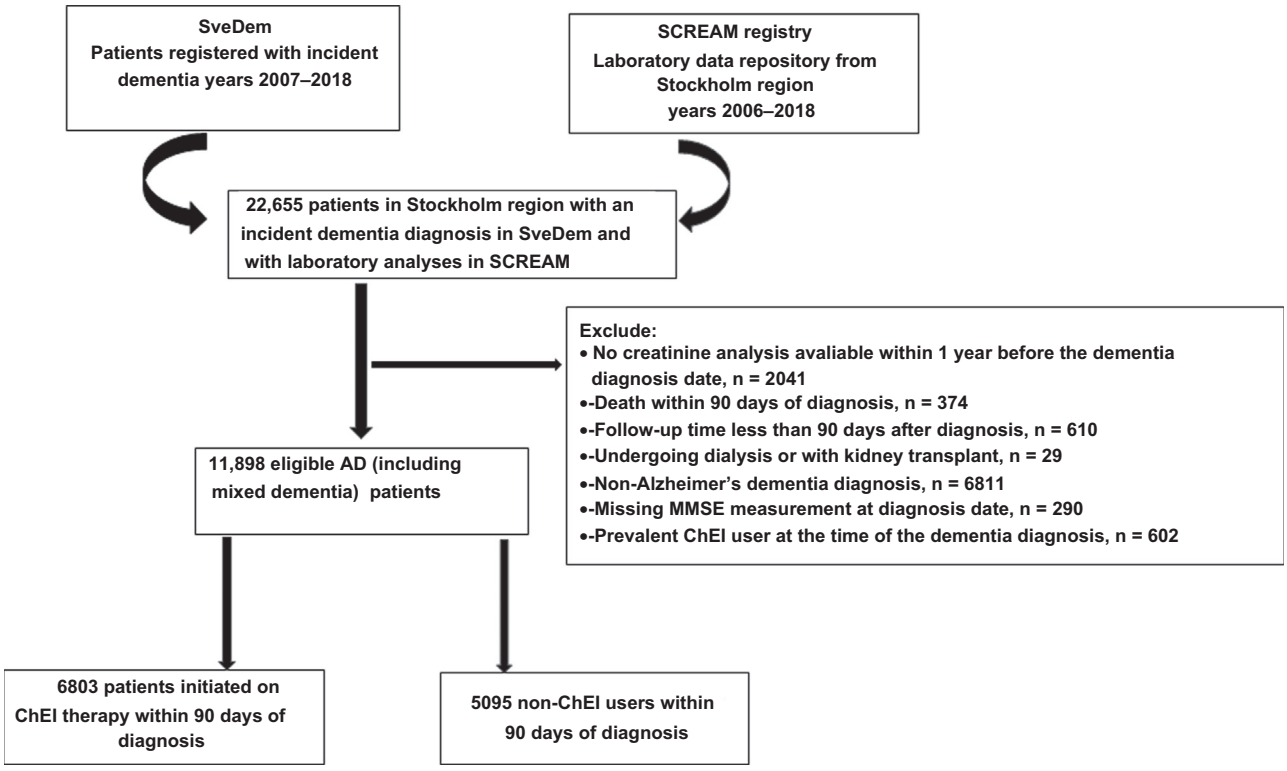

Figure 1 | Flowchart of patient inclusion into the study. AD, Alzheimer's dementia; ChEIs, cholinesterase inhibitors; MMSE, Mini-Mental State Examination; SCREAM, Stockholm Creatinine Measurements project; SveDem, Swedish Dementia Registry.

with a 18% lower risk of CKD progression (adjusted hazard ratio [aHR]: 0.82; 95% CI: 0.71–0.96). The weighted cumulative incidence curves are shown in Figure 2, which showed an early separation that was sustained throughout follow-up.

A lower risk of CKD progression compared to nonuse was observed for all ChEI subtypes (Supplementary Table S2), with consistent estimates for donepezil (aHR: 0.68; 95% CI: 0.57–0.80), galantamine (aHR: 0.85; 95% CI: 0.72–0.99), and rivastigmine (aHR: 0.86; 95% CI: 0.71–1.05).

We used 74,656 subsequent routine outpatient measurements of eGFR to compute the slopes of eGFR decline in both treatment groups. The median number of eGFR tests per patient was 5 (IQR: 3–9). Overall, the average annual reduction of eGFR was 1.39 (95% CI: 1.46–1.32) ml/min per 1.73 m^2 per year (Supplementary Table S3). Graphically, there was no difference between groups at baseline −0.10 (95% CI −0.44 to 0.24) ml/min per 1.73 m2. During observation, the slope of eGFR decline was slightly flatter in the ChEI group compared with in the nonuser group, with a predicted difference of mean eGFR decline of 0.12 (95% CI: 0.04–0.21) ml/min per 1.73 m2 per year (or 8.6% reduction in the annual eGFR decline) favoring ChEI users (Supplementary Figure S3).

The majority of patients (59%) initiated treatment with the standard daily dose of ChEIs, 22% with half the standard daily dose, and 19% with more than the standard daily dose. Their characteristics are shown in Supplementary Table S4 and Supplementary Figure S4. Supplementary Figure S5A shows the association between initial ChEI dose and the risk of CKD progression. Compared with the lowest dose, higher treatment dosages were not different in their risk of CKD progression; however, CIs were broad and HRs were numerically lower, with a magnitude of approximately 0.85 throughout the range of dosages evaluated.

Use of ChEIs and the risk of death

During a median 3.0 (IQR: 1.4–4.8; range 0.1–11) years of follow-up, corresponding to 39,513 person-years, 5,691 patients (48%) died. Users of ChEIs had lower mortality rates (119; 95% CI: 114–123)/1000 person-years) than nonusers (190; 95% CI: 182–197)/1000 person-years) did. Compared with nonuse, use of ChEI was associated with a 21% lower risk of death (HR: 0.79; 95% CI: 0.72–0.86) (Table 2 and Figure 2), which was similarly attributed to all ChEI subtypes (Supplementary Table S2). Supplementary Figure S5B shows the association between initial ChEI dose and the risk of death. Compared with the lowest dose, higher treatment dosages were associated with lower risk of death.

Subgroup and sensitivity analyses

We observed a significant interaction between patients with eGFR below and above 60 ml/min per 1.73 m^2 (P interaction = 0.02), indicating that use of ChEIs was more strongly associated with CKD progression in people with low baseline eGFR (eGFR <60 ml/min per 1.73 m^2). For other subgroups (age, sex, MMSE score, and dementia

Table 1 | Baseline characteristics overall and stratified by ChEI treatment status within 3 months from an incident diagnosis of AD, before and after weighting

		Before IPTW			After IPTW		
Characteristics	Overall	ChEI	Non-ChEI	Standardized mean difference[a]	ChEI	Non-ChEI	Standardized mean difference[a]
Dementia diagnosis, %							
AD	47	53	40	−0.269	46	47	
Mixed AD	53	47	60		54	53	0.032
Age, y, mean ± SD	80 ± 7	79 ± 7	83 ± 7	−0.502	80 ± 7	81 ± 7	−0.014
Age category, %				−0.469			−0.013
<70 yr	8	11	4		4	4	
70–79 yr	33	38	26		28	29	
80–89 yr	50	46	57		58	58	
≥90 yr	9	5	13		10	9	
Women, %	64	65	62	0.062	63	64	−0.008
Body weight, kg, mean ± SD	67 ± 14	67 ± 14	66 ± 14	−0.007	66 ± 14	66 ± 14	−0.002
Body weight category, %				0.055			0.014
<50 kg	8	8	10		9	9	
50–59 kg	23	24	25		25	25	
60–69 kg	26	29	28		28	28	
70–79 kg	20	22	22		22	22	
80–89 kg	10	11	11		11	10	
≥90 kg	5	6	5		5	5	
Missing	7						
Highest attained education, %				0.110			0.008
Compulsory education	32	31	35		36	35	
Secondary	40	42	40		40	41	
College/university	26	28	24		24	24	
Missing	2						
Albuminuria category, %				−0.122			0.006
A1	31	79	74		75	76	
A2	8	18	21		21	20	
A3	2	3	4		4	4	
Missing	59						
eGFR, ml/min per 1.73 m^2, mean ± SD	68 ± 16	70 ± 15	66 ± 16	0.265	68 ± 15	68 ± 15	0.003
eGFR category, %				0.245			0.006
≥90 ml/min per 1.73 m^2	2	7	4		4	4	
60–89 ml/min per 1.73 m^2	28	68	61		63	63	
30–59 ml/min per 1.73 m^2	65	24	32		31	31	
<30 ml/min per 1.73 m^2	5	1	3		2	2	
MMSE score, mean ± SD	21 ± 5	22 ± 5	20 ± 5	0.391	21 ± 5	21 ± 5	0.006
MMSE category, %				0.366			0.008
≥25 points	29	34	22		23	23	
20–24 points	39	40	37		40	40	
10–19 points	30	24	37		34	34	
0–9 points	2	2	4		3	3	
Memory clinics visit, %	100	100	99	0.029	100	99	0.018
Living alone, %	51	48	55	−0.152	51	51	0.003
Nursing home care, %	5	4	7	−0.137	5	5	0.012
Basic workups, %							
Clock test	93	94	92	0.096	93	93	0.006
Blood test	97	97	98	−0.033	98	97	0.006
MMSE test	100	100	100	0.001	100	100	0.000
CT/MRI	97	97	0.98	−0.075	98	97	0.020
Comorbidities, %							
Hypertension	69	65	74	−0.204	69	69	−0.002
Diabetes mellitus	16	15	16	−0.038	17	16	0.027
Congestive heart failure	10	8	14	−0.220	11	11	0.008
Myocardial infarction	6	5	7	−0.110	6	6	−0.001
Peripheral vascular disease	4	3	5	−0.072	5	4	0.036
Cerebrovascular disease	12	01	14	−0.102	12	12	−0.016
Chronic obstructive pulmonary disease	10	9	11	−0.089	11	10	0.015
Rheumatic disease	5	5	5	−0.034	5	5	−0.013
Peptic ulcer disease	2	1	2	−0.053	2	2	0.006

(Continued on following page)

Table 1 | (Continued) **Baseline characteristics overall and stratified by ChEI treatment status within 3 months from an incident diagnosis of AD, before and after weighting**

		Before IPTW			After IPTW		
Characteristics	Overall	ChEI	Non-ChEI	Standardized mean difference[a]	ChEI	Non-ChEI	Standardized mean difference[a]
Cancer (≤3 yr prior)	14	13	15	−0.047	14	14	−0.011
Stroke	8	7	10	−0.090	8	9	−0.018
Atrial fibrillation	17	13	22	−0.252	17	17	0.002
Liver disease	1	1	1	−0.014	1	1	0.001
Alcohol abuse	2	2	2	−0.015	2	2	−0.009
Fracture (≤1 yr prior)	15	14	17	−0.078	16	16	0.021
Depression	15	16	14	0.058	15	15	0.000
Medication use, %							
ACEi/ARBs	37	36	39	−0.079	38	38	0.010
β-blocking agents	35	31	40	−0.205	36	35	0.011
Calcium channel blockers	21	21	22	−0.031	21	22	−0.007
Diuretics	23	20	28	−0.173	24	24	0.004
Lipid modifying agents	29	29	29	0.009	30	29	0.029
ASA	32	31	34	−0.075	33	33	0.002
NSAIDs	7	8	5	0.101	7	6	0.018
Antithrombotic agents	46	42	51	−0.184	46	46	0.001
Anxiolytics	13	12	14	−0.038	13	13	0.004
Hypnotics	22	22	24	−0.050	24	23	0.028
Antipsychotics	5	4	6	−0.079	5	5	0.031
Antidepressants	25	25	25	−0.016	25	25	−0.009
Memantine	6	0	13	−0.521	7	6	0.039
Calendar year, %				−0.211			0.004
2007	1	1	1		1	1	
2008	5	6	4		4	5	
2009	8	10	7		8	8	
2010	9	9	8		9	9	
2011	9	10	8		9	9	
2012	8	8	8		8	8	
2013	9	8	9		9	9	
2014	10	10	10		10	10	
2015	11	10	11		11	11	
2016	11	10	12		11	10	
2017	11	11	13		12	12	
2018	8	7	9		8	8	
Propensity score, mean	0.57	0.66	0.46	0.989	0.56	0.56	−0.032

ACEi, angiotensin-converting enzyme inhibitor; AD, Alzheimer's dementia; ARB, angiotensin receptor blocker; ASA, acetylsalicylic acid; ChEI, acetylcholinesterase inhibitor; CT, computed tomography; eGFR, estimated glomerular filtration rate; IPTW, inverse probability of treatment weighting; MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging; NSAID, nonsteroidal anti-inflammatory drug.

[a]Standardized difference is calculated by dividing the mean by the standard deviation of the difference between treated and untreated groups. Standardized difference >0.1 indicates covariate imbalance.

Multiple imputation was performed for body weight, attained education, and albuminuria prior to calculating the propensity score.

type) there was no suggestion of heterogeneity (Figure 3 and Supplementary Table S5). After censoring 464 non-users who initiated ChEIs during follow-up, we observed similar results to our main analysis (Supplementary Tables S6–S8). Similar associations were also observed when accounting for death as a competing risk (Supplementary Tables S9 and S10). *E* values for the kidney composite outcome and death were 1.56 and 1.63, respectively, for the point estimates and 1.25 and 1.60, respectively, for the upper confidence limit (Supplementary Table S11). By comparing with the HR of other confounders in the model (Supplementary Table S12), we interpreted the risk of unmeasured confounding to be moderate. We observed a similar rate of creatinine testing between both study groups during follow-up (Supplementary Table S13). We observed similar results to our main analysis in a 1:1 PS-matched cohort (Supplementary Tables S14 and S15) or in the subcohort with information on albuminuria available at baseline (Supplementary Tables S16 and S17).

DISCUSSION

There is growing evidence of a link between kidney disease and mild cognitive decline or dementia.[39–42] This observational study explores the possibility that ChEIs, drugs offsetting cognitive decline,[20–22] could potentially reduce the speed of kidney function loss through activation of the CAP system. We observed that compared with no initiation, initiation of ChEI therapy within 90 days from AD diagnosis was associated with a 18% lower risk of CKD progression. Results were consistent across subgroups and across ChEI subclasses. The results proved robust to a range of sensitivity analyses including accounting for the competing risk of death. We are not aware of other studies evaluating the

Table 2 | Number of events, incidence rates, and adjusted HRs for the association between ChEI initiation and study outcomes

Outcomes	Patients (n)	Events (n)	Person-time (yr)	Incidence rate per 1000 person-years (95% CI)[a]	HR (95% CI)[b]
CKD progression					
Nonusers	5095	572	13,378	42.76 (39.39–46.41)	Ref
ChEI users	6803	659	24,208	27.22 (25.22–29.38)	0.82 (0.71–0.96)
All-cause death					
Nonusers	5095	2678	14,120	189.66 (182.61–196.98)	Ref
ChEI users	6803	3013	25,393	118.66 (114.49–122.97)	0.79 (0.72–0.86)
Single components of the primary outcome					
Sustained eGFR decline >30%					
Nonusers	5095	472	13,378	35.28 (32.24–38.61)	Ref
ChEI users	6803	586	24,208	24.21 (22.32–26.25)	0.83 (0.71–0.98)
KRT or kidney-related death					
Nonusers	5095	156	14,119	11.05 (9.44–12.93)	Ref
ChEI users	6803	118	25,393	4.65 (3.88–5.57)	0.68 (0.51–0.89)

Abbreviations: ChEI, cholinesterase inhibitor; eGFR, estimated glomerular filtration rate; HR, hazard ratio; KRT, kidney replacement therapy; Ref, reference.
[a]Incidence rates are presented as number of events per 1,000 patient-years in unweighted cohort.
[b]HR is obtained in inverse probability of treatment weighted cohort adjusting for the variables listed in Table 1.

effect of ChEIs on kidney function, and the observational nature of our analysis renders our findings hypothesis-generating.

The CAP is a regulatory mechanism through which the autonomic nervous system affects the immune response.[4] Autonomic dysfunction with an imbalance between sympathetic and parasympathetic nerve activity is prevalent in a variety of chronic diseases, including CKD.[1] This neural immune-regulatory circuit termed the "inflammatory reflex" is believed to regulate macrophage cytokine release in the spleen via acetylcholine-synthesizing lymphocytes located in the proximity of catecholaminergic nerve endings.[43,44] A series of animal studies have shown that the application of efferent vagus nerve stimulation and brainstem C1 neuron stimulation can reduce kidney damage and protect the kidney from ischemia reperfusion by activating the CAP through the splenic nerve.[11–13,15] In a rat model, activation of the CAP reduced chronic allograft nephropathy without any side effects for the recipient.[16] Another animal study showed that use of selective nicotinic acetylcholine receptor agonist may improve autonomic control, inhibit nuclear factor κB activation, and reduce renal, fibrosis and inflammatory response via CAP activation.[14] In rats with glycerol-induced acute kidney failure, treatment with the ChEI donepezil protected rats from kidney dysfunction in a dose-dependent manner via activation of CAP.[45] In addition, other alternative and/or complementary effects of CAP activation may also explain our findings, such as stimulation of the vagal nerve to regulate heart rate and blood pressure,[46] modulation of vasodilation/constriction mediated through nitric oxide and prostaglandins[47] or kidney perfusion.[48,49]

However, less is known about the effects of CAP activation in humans. In a recent placebo-controlled randomized study of patients with the metabolic syndrome, galantamine 8 mg/d for 4 weeks followed by 16 mg/d for 8 weeks alleviated the inflammatory state, improved insulin resistance, and decreased the low frequency–high frequency ratio of heart rate variability;[50] the latter reflecting improvement in autonomic dysfunction. In a small pilot study of 7 patients with Crohn's disease, 71% of patients achieved clinical remission

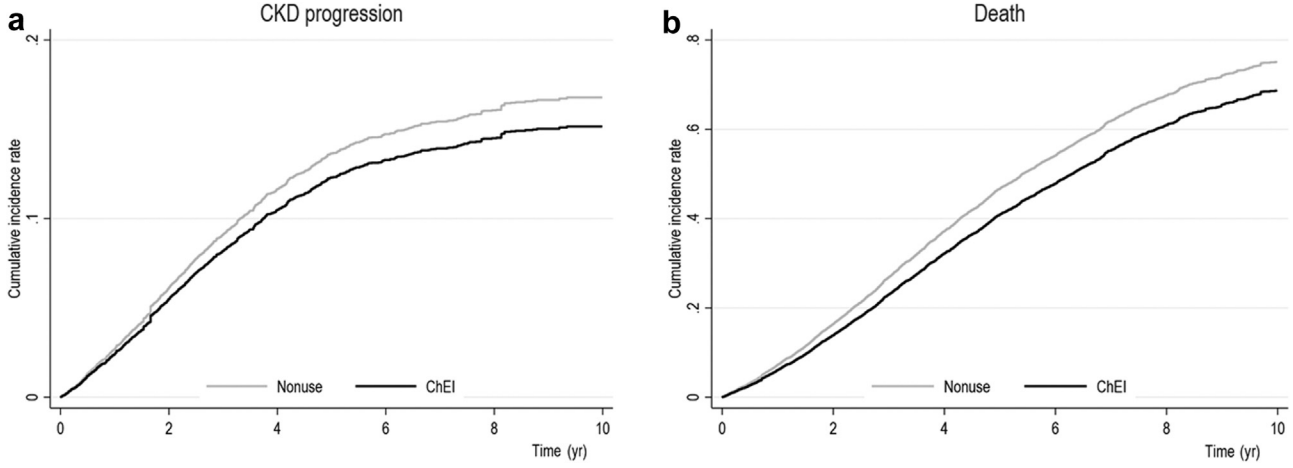

Figure 2 | Weighted cumulative incidence curves of study outcomes (a) chronic kidney disease (CKD) progression or (b) death stratified by initiation of cholinesterase inhibitor (ChEI) therapy.

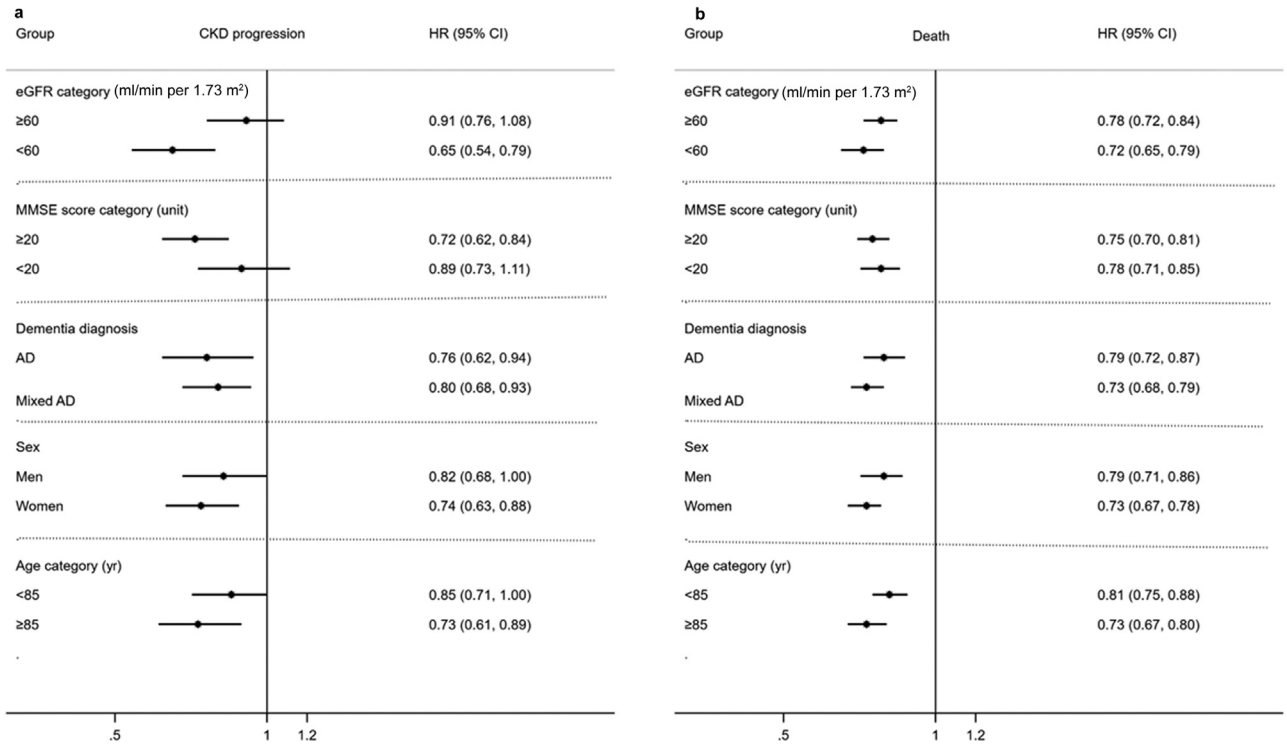

Figure 3 | Association between cholinesterase inhibitor (ChEI) use and the risk of (a) chronic kidney disease (CKD) progression or (b) all-cause death across subgroups. AD, Alzheimer's dementia; CI, confidence interval; eGFR, estimated glomerular filtration rete; HR, hazard ratio; MMSE, Mini-Mental State Examination.

after activation of CAP for 6 months.[51] Another study of 17 patients with rheumatoid arthritis showed that CAP activation inhibits cytokine production and attenuates the severity of disease.[52] Finally, in a noncontrolled pilot study of 12 persons on dialysis, activation of CAP by electrical stimulation of the vagus nerve led to modest nonstatistically significant reductions in inflammatory markers.[5]

In a broader sense, the sympathetic and parasympathetic nervous systems balance governs the autonomic function of major organs such as kidneys as in the classical view of the system. The cross talk between sympathetic and parasympathetic nervous systems is nowadays considered to play a major role in fine-tuning the immune cells and system.[53] Given that parasympathetic nerves are cholinergic, a major part of preganglionic neurons of the sympathetic nervous system are also cholinergic, and about 65% of neurons in the enteric nervous system are cholinergic, it becomes apparent that the therapeutic effects of ChEIs extend beyond the mere stimulation of the central cholinergic system involved in cognitive function.[38,54] Neuropeptide Y, a sympathetic neurotransmitter, has been shown to be associated with CKD progression.[55] Testing circulating neuropeptide Y in patients may be a way to confirm the effect of ChEIs on balance of sympathetic and parasympathetic nervous systems.[56]

Comparing the use of a medication with nonuse may be affected by confounding by indication, and our careful design aimed at minimizing this by restricting our study to a population with an incident validated diagnosis of AD (the sole approved indication for ChEIs) and by a rich weighting of information that may have prompted the use of ChEIs, including body weight, MMSE score, basic dementia workup, or use of other medications such as memantine. We note, however, that the reduction in kidney outcomes is also an "unintended" effect of ChEIs, as these are not an indication for treatment, and unintended effects generally suffer less from confounding by indication than intended effects do.[57,58] Because >90% of all patients starting ChEIs in our cohort did so within the first 3 months, our landmark at day 90 seems appropriate with low risk of exposure misclassification. Furthermore, our sensitivity analysis censoring 430 patients who initiated ChEIs during follow-up did not modify our findings.

However, our study has limitations. We excluded 374 patients who died within 90 days from AD diagnosis, and their causes of death may be informative. We followed an intention-to treat design, but some patients may have stopped treatment over time. We opted for this approach given that the use of this medication is recommended to be chronic, and the effect of ChEIs on kidney function is not immediate. The progression of kidney disease is a slow process often requiring years to reduce kidney function by 30%. We used a state-of-the-art interpolation method to ascertain chronic declines in kidney function, which is less susceptible to temporary acute declines that may misclassify the outcome when requiring only 1 measurement to pass the threshold. Because the

frequency of creatinine testing was similar between both treatment arms, we believe that findings are unlikely to be explained by differential outcome ascertainment. A mean difference of 0.12 ml/min per 1.73 m^2 per year in the ChEI group compared to the decline of 1.39 ml/min per 1.73 m^2 per year among nonusers may seem small. However, for comparison, we note that the BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) reported a reduction of 0.19 $\pm$ 0.11 ml/min per 1.73 m^2 per year in the empagliflozin group and 1.67 $\pm$ 0.13 ml/min per 1.73 m^2 per year in the placebo group, which during the median 3.1 years of observation, resulted in a 39% reduction in the risk of adverse kidney outcomes.[59] We also observed lower risk of death among ChEI users, in a magnitude similar to what was reported by a previous trial[60] and several observational studies,[24,25,61] a finding that we believe can be considered as a positive control outcome and that offers indirect validity to our kidney outcome estimates. Information of albuminuria was available by indication, which may invalidate our assumption of missing at random for multiple imputation. However, we could observe similar results after weighting for albuminuria in the >4800 individuals where this was available. Our evaluation of dose responses are based on the dosages used at the beginning of treatment. Most patients received standard initiation ChEI dose, and we were probably unpowered to evaluate dosages at the higher end of the treatment spectrum. Furthermore, up-titration is frequent during the first months of prescription, and this analysis should thus be considered largely exploratory. We recognize that we were unpowered to describe risks by ChEI subclasses, and that lack of information on body weight changes over time is a limitation that may bias the accuracy of eGFR during follow-up. Our study, as all observational studies, is potentially affected by residual and unmeasured confounding and should not be used to guide clinical decisions.

To conclude, this study from routine care data suggests that use of ChEIs, compared with nonuse, is associated with a lower risk of CKD progression in patients with incident AD. Further studies are warranted to better elucidate underlying mechanisms and to assess potential pleiotropic effects of ChEIs on kidney function in humans.

DISCLOSURE

BL is affiliated with Baxter Healthcare Corporation. All the other authors declared no competing interests.

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AUTHOR CONTRIBUTIONS

HX, SG-P, ME, and JJC developed the study concept and design. HX and JJC contributed to data analysis. HX and JJC contributed to writing of the report. ME and JJC provided study materials. All authors contributed to data interpretation, critical revision of the report, and final approval. HX, ME, and JJC obtained funding. HX, ME, and JJC take responsibility for all aspects of the report, and all authors take responsibility for their contributions.

SUPPLEMENTARY MATERIAL

Supplementary File (Word)

Figure S1. Proportion of patients initiating cholinesterase inhibitors (ChEIs) during the year after incident dementia diagnosis.

Figure S2. Balance of baseline characteristics before and after weighting.

Figure S3. Mixed model output of estimated glomerular filtration rate (eGFR) trajectories among cholinesterase inhibitor (ChEI) users and nonusers.

Figure S4. Distribution of initiation dosages of ChEIs.

Figure S5. Starting cholinesterase inhibitor (ChEI) dose and risk with (**A**) chronic kidney disease (CKD) progression and (**B**) all-cause death risk using cubic splines.

Table S1. Definition of study covariates.

Table S2. Association between cholinesterase inhibitor (ChEI) subclasses and the risk of study outcomes.

Table S3. Mixed model output of estimated glomerular filtration rate (eGFR) trajectories among cholinesterase inhibitor (ChEI) users and nonusers.

Table S4. Baseline characteristics stratified by initial cholinesterase inhibitor (ChEI) dose among those with at least 2 ChEI dispenses during the 3-month eligibility window (n = 5893)

Table S5. Subgroups exploring interactions with cholinesterase inhibitor (ChEI) use and the risk of study outcomes.

Table S6. Association between cholinesterase inhibitor (ChEI) use and the risk of study outcomes censoring for ChEI initiation during follow-up (as-treated analysis).

Table S7. Association between cholinesterase inhibitor (ChEI) subclasses and the risk of study outcomes censoring for ChEI initiation during follow-up (as-treated analysis).

Table S8. Subgroup analysis between ChEI use and the risk of CKD progression censoring for ChEI initiation during follow-up.

Table S9. Competing risk model for cholinesterase inhibitor (ChEI) use and the risk of chronic kidney disease (CKD) progression or death attributed to nonrenal causes.

Table S10. Competing risk model for cholinesterase inhibitor (ChEI) subclasses and the risk of chronic kidney disease (CKD) progression or death attributed to nonrenal causes.

Table S11. *E* values for study outcomes.

Table S12. Full model of the association between cholinesterase inhibitor (ChEI) initiation and study outcomes.

Table S13. Frequency of creatinine testing during follow-up, overall and within yearly intervals.

Table S14. Sensitivity analysis; 1:1 propensity score–matched cohort. Baseline characteristics stratified by cholinesterase inhibitor (ChEI) treatment status within 3 months from an incident diagnosis of Alzheimer's dementia after matching.

Table S15. Sensitivity analysis; 1:1 propensity score–matched cohort. Number of events, incidence rates, and adjusted hazard ratios for the association between cholinesterase inhibitor (ChEI) initiation and study outcomes.

Table S16. Baseline characteristics stratified by cholinesterase inhibitor (ChEI) treatment status within 3 months from an incident diagnosis of Alzheimer's dementia, before and after weighting in the subcohort with albuminuria information available at baseline (n = 4834).

Table S17. Number of events, incidence rates, and adjusted hazard ratios for the association between cholinesterase inhibitor (ChEI) initiation and study outcomes in the subcohort with albuminuria information available at baseline (n = 4834).

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