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Impact of CKD and COPD co-existence on mortality, vascular dementia, and Alzheimer's dementia; a comparative cohort study

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Title: Impact of CKD and COPD Co-Existence on Mortality, Vascular Dementia, and Alzheimer's Dementia. A Comparative Cohort Study

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ABSTRACT

Background

Chronic kidney disease (CKD) and chronic obstructive pulmonary disease (COPD) are common conditions associated with increased risks of mortality and cognitive impairment. However, the association between COPD and dementia outcomes in patients with CKD remains incompletely understood.

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Methods

We conducted a retrospective observational cohort study using the TriNetX Global Collaborative Network, including patients aged 18–80 years with CKD stages 3–5, excluding those with prior dialysis, transplantation, dementia, or mild cognitive impairment before cohort entry. Two cohorts were identified: CKD with COPD, defined using classical ICD-10 COPD codes (J41–J44), and CKD without COPD. A secondary sensitivity analysis used a broader respiratory disease definition including asthma, bronchiectasis, and other chronic respiratory conditions. Cohorts were propensity score matched (1:1) for demographic characteristics, comorbidities, smoking exposure, and laboratory parameters. Outcomes included all-cause mortality, non-Alzheimer's dementia, and Alzheimer's disease, assessed over a maximum follow-up of 5 years using Kaplan–Meier and Cox proportional hazards analyses.

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Results

Two cohorts were identified: CKD with COPD (n = 270 566) and CKD without COPD (n = 821 399). After propensity score matching, 234 317 patients remained in each cohort. CKD with COPD was associated with a higher observed risk of mortality compared with CKD alone (18.5% vs 14.5%; HR 1.17; 95% CI 1.16–1.19; $p < 0.001$). The composite outcome of non-Alzheimer's dementia was also more frequent in the CKD with COPD cohort (4.6% vs 3.9%; HR 1.07; 95% CI 1.04–1.10; $p < 0.001$). No significant association was observed for vascular dementia alone or mild cognitive impairment alone. Alzheimer's disease incidence was low in both cohorts, and lower observed hazards were identified in the COPD cohort (HR 0.85; 95% CI 0.80–0.91; $p = 0.002$), although these findings should be interpreted cautiously given the relatively short follow-up and higher competing mortality in the COPD cohort.

Conclusions

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Among patients with CKD, coexisting COPD was associated with higher observed risks of mortality and non-Alzheimer's dementia during follow-up. Further longitudinal studies with longer follow-up and competing-risk methodology are warranted.

Keywords: Chronic kidney disease, Chronic Obstructive Pulmonary Disease, Mortality, Dementia, TriNetX

BACKGROUND

Cognitive function plays a fundamental role in an individual's health. (1) Its decline often evolves progressively, passing from a state of normality to a state of mild cognitive impairment, which can be reversible, to irreversible dementia. (2) Cognitive decline significantly impacts a person's life, gradually diminishing their independence and dignity. Vascular dementia (VaD) is the second most common form of dementia after Alzheimer's disease (AD), accounting for about 20% of all dementia cases. (3) The risk of developing dementia increases with age, (4) affecting approximately 6% of individuals aged 75–79 years, 18.3% of those aged 85–89 years, and 41.1% of those over 95 years. (5) By 2050, over 152.8 million people are expected to be living with dementia, a figure that reflects the ageing global population. (6)

Chronic kidney disease (CKD), as defined by a low glomerular filtration rate (GFR) and/or elevated albuminuria, affects ~10-15% of adults globally.(7) Among significant adverse outcomes related to CKD, cardiovascular disease (CVD) is one of the most important and is the leading cause of death in this population. (8) CKD has been associated with an increased risk of cognitive decline, (9–12) and VaD is more common in people with CKD than in the general population. (13) Patients with CKD are notably more susceptible to small vessel cerebrovascular disease, which could significantly contribute to the onset of VaD. (14)

Chronic obstructive pulmonary disease (COPD) is a chronic, progressive lung and airway disease marked by bronchial obstruction that cannot be fully reversed with bronchodilators. (15) COPD poses a considerable disease burden, with the World Health Organization estimating that by 2050, approximately 600 million patients globally will be affected by

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COPD. (16) A key characteristic of COPD is that comorbidities significantly affect the individual's prognosis. The most common of these include CVD, metabolic disorders and cancer. The causes of COPD are multifactorial: alongside age-related comorbidities and smoking, which serves as a shared risk factor, systemic inflammation originating from the lungs is also crucial. (15) Many studies have highlighted the fact that suffering from COPD can increase VaD risk. (17–21) Various mechanisms have been proposed to elucidate the association between COPD and elevated rates of cognitive impairment. These mechanisms include oxidative stress, tissue hypoxemia, a sedentary lifestyle and a systemic inflammatory response. (22,23)

Shared risk factors link the coexistence of CKD and COPD, yet there is limited understanding of how this connection affects cognitive decline. This study aims to explore the impact of these two common chronic diseases, which have overlapping risk factors, on the development of dementia.

METHODS

Database description

We conducted a retrospective observational cohort study on CKD patients (stages 3 to 5) according to the KDIGO classification. (24) Data for this study were accessed through the TriNetX platform's Global Collaborative Network (GCN) and analyzed using the built-in query builder. (25)

TriNetX is an international research network consolidating anonymised electronic medical records (EMRs) from over 150 healthcare institutions worldwide. These institutions include academic medical centres, specialised hospitals, physician groups, and community hospitals, collectively called Healthcare Organisations (HCOs). The data encompasses insured and uninsured patients, covering various geographic areas, age ranges, and socioeconomic levels. TriNetX continuously collects information directly from EMR systems, providing a wide array of data for analysis. All data collection, processing, and transmission complied with relevant data protection regulations governing the contributing HCOs. This includes full adherence to the EU Data Protection Law Regulation 2016/679, the General Data

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Protection Regulation, and the U.S. Health Insurance Portability and Accountability Act. Diagnoses were coded using the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM), while procedures were identified through the ICD-10-PCS system or the Current Procedural Terminology. Laboratory results were identified via the Logical Observation Identifiers Names and Codes. The requirement for informed consent was waived as the data was fully anonymised.

Study design

Objective

This is an etiologic study, as per PICO framework, aiming to verify if patients with CKD stages 3 to 5 with a previous diagnosis of COPD have different risks of death and dementia compared with patients with CKD stages 3 to 5 without a COPD diagnosis.

Patient populations

We conducted our study on two cohorts of patients aged between 18 and 80 years, all with CKD stages 3-5, who had never been on dialysis or undergone any transplant and had no history of mild cognitive impairment (G31.84), vascular dementia (F01), dementia in other diseases (F02), unspecified dementia (F03), or Alzheimer's disease (G30) before the diagnosis of CKD. These exclusions were applied before cohort entry to ensure that dementia outcomes represented incident post-index events during follow-up.

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Patients with an estimated GFR < 10 ml/min from the latest blood tests were excluded (as a surrogate marker for end-stage renal disease in individuals who have opted not to undergo dialysis). Cohort 1 (CKD with COPD) included patients with a diagnosis of chronic bronchitis (J41, J42), emphysema (J43), or other chronic obstructive pulmonary disease (J44) before the diagnosis of CKD stage 3–5. Cohort 2 (CKD without COPD) included patients who had never received a COPD diagnosis. This subgroup was analysed and stratified by patient age at index (<65 vs ≥65 years) to explore potential effect modification. The same outcomes and analytical methods were applied within each subgroup.

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To assess the robustness of the findings and address potential diagnostic heterogeneity, a secondary sensitivity analysis was performed using a broader respiratory disease definition that additionally included asthma (J45), bronchiectasis (J47), chronic respiratory conditions due to chemicals, gases, fumes, and vapours (J68.4, J68.8, J68.9), congenital bronchiectasis (Q33.4), and chronic bronchitis not otherwise specified (J40).

The index date for each patient was the day the patient was first diagnosed with CKD stage 3, 4, or 5, which was defined when each patient entered the analysis. The TriNetX platform (www.live.trinetx.com) generated the report on 13 January 2025. We included events that occurred up to 20 years ago. Patients whose diagnosis occurred more than 20 years ago were excluded.

Pre-specified outcome

Outcome measures were captured within a 5-year window after the diagnosis of CKD. Primary outcome measures were (in brackets the ICD-10-CM):

I. Deceased or ill-defined and unknown cause of mortality (R99)
II. Dementias of vascular origin and forms not attributed to Alzheimer's disease (VaD):
    a. Vascular dementia (F01); or
    b. Dementia in other diseases classified elsewhere (F02); or
    c. Unspecified dementia (F03); or
    d. Mild cognitive impairment of uncertain or unknown etiology (G31.84)
III. Alzheimer's disease (G30).

Covariates and propensity score matching (PSM)

To reduce the effect of confounders, we applied PSM using the TriNetX built-in algorithm, which is based on 1:1 nearest-neighbour matching with a calliper of 0.1 pooled SD. The two cohorts of patients were propensity score matched for the following characteristics that were chosen based on known risk factors for mortality and dementia in CKD and COPD patients: age at index, sex, ethnicity, low socioeconomic circumstances, hypertensive diseases, heart failure, atrial fibrillation and flutter, ischemic heart diseases, diseases of arteries, arterioles and capillaries, cerebrovascular diseases, pulmonary heart disease and diseases of

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pulmonary circulation, disorders of lipoprotein metabolism, diabetes mellitus, nicotine dependence, neoplasms. We also matched for haemoglobin [g/dl], serum albumin [g/dl], cholesterol [g/dl], haemoglobin A1c [%], and glomerular filtration rate based on the CKD-EPI formula [ml/min]. The choice of matching parameters was based on the risk factors for death, CVD, and dementia. (26)

Laboratory values were defined at baseline as the closest available measurements to the index date. Continuous variables were included in the propensity score model as continuous variables without categorisation. Covariate balance after matching was assessed using standardised mean differences, with values <0.1 indicating adequate balance. Distribution of key variables was also examined to ensure appropriate overlap between cohorts. (27)

Patients were followed for up to 5 years from the index date. Follow-up duration varied across individuals depending on data availability. Patients were censored at the time of outcome occurrence, death, last recorded healthcare encounter, or end of the study period. Survival analyses were conducted using Kaplan–Meier estimates and Cox proportional hazards models, which account for variable follow-up through right-censoring. Formal competing-risk analyses were not available within the TriNetX platform. Dementia hazard ratios (HR) derived from Cox proportional hazards models should therefore be interpreted cautiously, given the substantially higher mortality observed in the COPD cohort.

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Statistical analysis

All data processing was conducted using the TriNetX built-in algorithms. Numerical baseline characteristics are presented as mean and Standard Deviation (SD). Categorical characteristics are presented as the number of patients and percentage of the cohort. The p-value was calculated with a t-test for continuous variables and Fisher's exact test for categorical variables. We compared the outcomes 5 years after the index event (diagnosis of CKD) with Risk Ratio, Odds Ratio, and a risk comparison expressed as a p-value, using the Compare Outcomes Analytic and Survival tools integrated into TriNetX. Risks and HR with 95% confidence intervals (CI) are presented. Patients with dementia or mild cognitive impairment diagnosed before the CKD index date were excluded during cohort construction.

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The Kaplan-Meier Analysis was used to estimate the probability of the outcome at daily temporal resolution. Patients were removed from the analysis (censored) after the last entry in their records. Log-Rank test, HR, and the test for Proportionality assumptions were performed. Statistical significance was defined as p-value < 0.05.

Subgroup and sensitivity analyses were considered exploratory and hypothesis-generating. No formal correction for multiplicity was applied, and these findings should therefore be interpreted cautiously.

Details of the software used to run the analyses

The TriNetX platform is a customized solution designed for use in clinical research. The underlying technology is proprietary (TriNetX LLC, US) and is protected by trade secrets. The statistical methods and software packages used to generate statistical analyses include the following: Java 11.0.16 (featuring Apache Commons Math 3.6.1), R 4.0.2 (with Hmisc1-1 and Survival 3.2-3), and Python 3.7 (incorporating lifelines 0.22.4, matplotlib 3.5.1, numpy 1.21.5, pandas 1.3.5, scipy 1.7.3, and statsmodels 0.13.2).

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RESULTS

Participant selection:

CKD with COPD: a total of 173 HCOs were queried, and 140 providers responded with data. Using the primary COPD definition restricted to ICD-10 codes J41–J44, the final cohort included 267 028 patients who met the query criteria.

CKD without COPD: a total of 142 HCOs were queried, and 121 providers responded with data. The final cohort included 990 794 patients who met the query criteria. Figure 1 shows the cohorts' construction.

Demographic and Clinical Characteristics Before PSM

Before PSM, significant differences were observed between the CKD with COPD and CKD without COPD cohorts across demographic characteristics, comorbidities, and laboratory parameters, as shown in Table 1. The CKD with COPD cohort was older and had a higher prevalence of cardiovascular comorbidities, smoking exposure, and metabolic disorders. The p-values and standard differences confirmed these significant imbalances between the

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groups, underscoring the necessity of PSM to ensure comparability and reduce the influence of confounding variables.

After PSM, the two cohorts, CKD with COPD (n = 234 317) and CKD without COPD (n = 234 317), were well balanced across baseline demographic, clinical, and laboratory characteristics. Covariate balance after matching was achieved across all variables, with standardised mean differences <0.1 (Table 2).

Follow-Up Time

Following propensity score matching, the mean follow-up time was 1 254 days (3.43 years; SD 621 days) in the CKD with COPD cohort and 1 132 days (3.10 years; SD 641 days) in the CKD without COPD cohort, with median follow-up of 1 491 and 1 197 days, respectively. Differences in follow-up between cohorts were accounted for using time-to-event methods with censoring.

Mortality Outcome

In the CKD with COPD cohort, 43 241 patients (18.5%) died during follow-up, compared with 33 875 patients (14.5%) in the CKD without COPD cohort. This corresponded to a higher mortality risk in the COPD cohort (HR 1.17; 95% CI 1.16–1.19; p < 0.001).

Non-Alzheimer's Dementia Outcome

The composite outcome of non-Alzheimer's dementia, defined as vascular dementia (F01), dementia in other diseases classified elsewhere (F02), unspecified dementia (F03), and mild cognitive impairment (G31.84), was more frequent in the CKD with COPD cohort, occurring in 10 766 patients (4.6%) compared with 9 101 patients (3.9%) in the CKD without COPD cohort (HR 1.07; 95% CI 1.04–1.10; p < 0.001).

Subtype analyses showed no significant association for vascular dementia alone (F01) (HR 0.97; 95% CI 0.91–1.04; p = 0.43) or mild cognitive impairment (G31.84) (HR 1.03; 95% CI

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0.98–1.08; p = 0.26). However, a modest increase was observed for the combined outcome of non-vascular dementia or mild cognitive impairment, defined as dementia in other diseases classified elsewhere (F02), unspecified dementia (F03), and mild cognitive impairment (G31.84) (HR 1.08; 95% CI 1.04–1.11; p < 0.001).

Alzheimer's Disease Outcome

Alzheimer's disease (G30) incidence was low in both cohorts. A lower observed hazard of Alzheimer's disease was identified in the CKD with COPD cohort (HR 0.85; 95% CI 0.80–0.91; p = 0.002). Given the relatively short follow-up and substantially higher mortality in the COPD cohort, this finding should be interpreted cautiously, as competing mortality and survivor bias may have influenced risk estimates.

Sensitivity analysis

A secondary sensitivity analysis using the broader respiratory disease definition, including asthma, bronchiectasis, and other chronic respiratory conditions, showed directionally consistent findings for mortality (Figure 2) and dementia outcomes, supporting the robustness of the primary analysis despite broader exposure classification (Figure 3)

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Subgroup analysis by age (<65 vs ≥65 years) revealed distinct patterns. In patients aged <65 years, COPD was associated with increased risks of mortality (HR 1.10; 95% CI 1.07–1.13) and non-Alzheimer's dementia (HR 1.27; 95% CI 1.17–1.38), while no significant association was observed for Alzheimer's disease (HR 1.04; 95% CI 0.80–1.36). In contrast, in patients aged ≥65 years, no significant association with mortality was observed (HR 0.99; 95% CI 0.98–1.01), and lower hazard ratios were identified for non-Alzheimer's dementia (HR 0.86; 95% CI 0.84–0.89) and Alzheimer's disease (HR 0.70; 95% CI 0.65–0.75). These findings should be interpreted cautiously, as competing mortality and survivor bias may have influenced risk estimates in older patients. Full results are presented in Table 3.

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DISCUSSION

Before matching, the CKD with COPD group exhibited a higher prevalence of hypertensive diseases, diabetes, ischemic heart disease, heart failure, and cerebrovascular disease. Additionally, nicotine dependence was more prevalent, consistent with the well-established association between COPD and smoking. This group also had an increased incidence of neoplasms, likely linked to elevated smoking rates. These findings align with existing literature and meet expected patterns (28).

After PSM, both cohorts had identical numbers of patients and similar baseline characteristics, ensuring a robust comparison of outcomes. Despite this, significant differences in clinical outcomes were observed, suggesting that COPD is independently associated with adverse outcomes in patients with CKD.

Patients with CKD and COPD were associated with a 17% higher hazard of mortality within approximately 3 years compared to their CKD counterparts without COPD. This relative increase is clinically meaningful given the already elevated baseline mortality risk in CKD. COPD was associated with an absolute mortality risk increase of 4.0%, corresponding to approximately one excess death per 25 CKD patients with COPD over 5 years of follow-up. These findings highlight the potential importance of optimising management strategies in patients with coexisting CKD and COPD.

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Several mechanisms may underlie this association. COPD is associated with systemic inflammation, oxidative stress, and increased cardiovascular risk. Anaemia in CKD may further exacerbate tissue hypoxia, increasing cardiac workload through compensatory mechanisms such as elevated cardiac output. In addition, volume expansion and acid–base disturbances may contribute to cardiovascular stress. These mechanisms are proposed as potential contributors rather than definitive causal pathways. Increased susceptibility to infections may also contribute to the higher mortality observed in this population (29,30).

The cognitive findings of this study deserve careful consideration. Patients with CKD and COPD demonstrated a 7% higher observed hazard of the composite non-Alzheimer's

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dementia outcome compared with matched CKD patients without COPD. Importantly, this association was identified within a population already recognised to be at elevated vascular and neurocognitive risk, suggesting that COPD may contribute additional systemic burden in vulnerable CKD patients.

The subtype analyses provide further insight into the potential nature of this association. No significant increase was observed for vascular dementia alone or for mild cognitive impairment alone. However, a modest but significant increase persisted for the broader composite of non-vascular dementia and cognitive impairment. These findings may reflect the heterogeneous and multifactorial nature of cognitive dysfunction in CKD and COPD populations, where overlapping vascular, inflammatory, hypoxic, metabolic, and frailty-related mechanisms likely interact rather than producing a single dominant dementia phenotype.

From a clinical perspective, even relatively small increases in cognitive risk may be highly relevant in CKD populations. Cognitive impairment in patients with CKD is associated with reduced treatment adherence, impaired decision-making capacity, increased frailty, higher hospitalisation rates, and poorer suitability for dialysis and transplantation pathways. COPD may therefore act as a marker identifying a subgroup of CKD patients with greater systemic vulnerability and increased risk of adverse cognitive and functional outcomes.

The present findings also highlight the importance of improving recognition and assessment of cognitive impairment in patients with CKD and COPD. Dementia and milder cognitive disorders remain substantially underdiagnosed in routine nephrology practice despite their major implications for medication adherence, self-management, shared decision-making, and long-term care planning. Greater collaboration between renal and respiratory specialists may therefore be important when managing patients with coexisting CKD and COPD, particularly in older or multimorbid populations.

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Biologically, several mechanisms may plausibly contribute to the observed associations (31–33). Chronic systemic inflammation, endothelial dysfunction, oxidative stress, intermittent hypoxaemia, microvascular disease, and recurrent infection have all been implicated in both COPD and CKD and may contribute to accelerated cerebrovascular and neurodegenerative injury (19,34–36). However, given the observational design, competing mortality, modest effect sizes, and lack of granular cognitive phenotyping, these findings should be interpreted as hypothesis-generating rather than definitive evidence of causal pathways.

Age-stratified analyses demonstrated differing patterns across groups. In younger patients (<65 years), COPD was associated with increased risks of mortality and non-Alzheimer's dementia, consistent with the primary findings. In contrast, in older patients (≥65 years), no significant association with mortality was observed, and lower hazard ratios were identified for dementia outcomes. These findings likely reflect survivor bias and competing mortality rather than a true protective association. Patients with more severe cardiopulmonary disease may experience earlier death, thereby reducing the likelihood of surviving long enough to receive a dementia diagnosis. As mortality was substantially higher in the COPD cohort, dementia estimates derived from standard Cox proportional hazards models should be interpreted cautiously, since death may preclude subsequent recognition of cognitive decline. Formal competing-risk approaches such as Fine–Gray modelling were not available within the TriNetX platform; therefore, dementia-related hazard ratios should be considered exploratory associations rather than definitive estimates of cumulative dementia incidence. This is an important observation, as it highlights the potential for misleading risk estimates in populations with high competing mortality. The relatively limited follow-up and higher mortality in the COPD cohort may reduce the opportunity to observe long-term outcomes such as dementia. Consequently, the observed associations may represent conservative estimates of the true effect.

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The findings relating to AD require particularly cautious interpretation. Although lower observed hazards of AD were identified in the COPD cohort, these results should not be interpreted as suggesting a protective effect of COPD against neurodegeneration. Several methodological and biological factors may explain this observation.

First, the mean follow-up duration of approximately 3 years is relatively short for the development and clinical recognition of AD, which typically evolves over prolonged periods before diagnosis becomes clinically apparent. Patients with CKD and COPD also demonstrated substantially higher mortality, increasing the likelihood that many individuals died before sufficient cognitive decline could be recognised and formally coded within the EHR. Consequently, competing mortality and survivor bias may have substantially influenced AD estimates in this cohort.

Second, AD diagnoses in routine clinical practice are often delayed, under-recognised, or incompletely coded, particularly in patients with multiple chronic illnesses and high healthcare utilisation. In complex multimorbid populations such as CKD and COPD, cognitive symptoms may be attributed to frailty, vascular disease, metabolic disturbance, depression, or delirium rather than prompting formal neurodegenerative assessment. This may further reduce sensitivity for AD detection within retrospective EHR-based datasets.

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These findings underscore the importance of considering cognitive outcomes in patients with CKD, particularly those with coexisting COPD, and highlight the need for comprehensive management of modifiable risk factors such as hypertension, diabetes, and smoking. To our knowledge, this is the first study demonstrating an association between COPD and increased risks of mortality and non-Alzheimer's dementia in patients with CKD.

Limitations

This study has several limitations. Its retrospective observational design allows assessment of associations but does not establish causality. The analyses relied on the accuracy and

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completeness of EHR coding, although TriNetX applies standardised data quality procedures (37). Important indicators of CKD and COPD severity, including proteinuria, lung function parameters (e.g., FEV1), GOLD classification, oxygen therapy, and exacerbation burden, were not consistently available. Although laboratory markers and comorbidities were included as surrogate measures of disease burden, residual confounding remains possible.

The relatively short mean follow-up duration (approximately 3 years) may have limited detection of slowly progressive outcomes such as AD. Higher mortality in the COPD cohort may additionally have acted as a competing risk, reducing opportunities for subsequent dementia diagnosis and potentially influencing hazard ratio estimates. Dementia diagnoses were based on ICD coding, baseline cognitive assessments were unavailable, and cause-of-death data were not accessible within the platform.

Some cardiovascular variables included in the propensity score matching strategy, including ischaemic heart disease and cerebrovascular disease, may partially lie on the causal pathway between COPD and adverse outcomes. Matching on these potential intermediates may therefore have attenuated observed associations. In addition, treatment-level data were not available in sufficient detail to adjust for therapies such as bronchodilators, bicarbonate supplementation, or non-invasive ventilation, leaving the possibility of confounding by indication.

Despite these limitations, the large multicentre matched cohort design provides valuable real-world data on the association between COPD, mortality, and cognitive outcomes in patients with CKD.

CONCLUSION

Individuals with CKD and COPD are at increased risk of mortality and vascular dementia compared with patients with CKD alone, highlighting the compounded burden of these

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coexisting conditions. These findings underscore the importance of integrated, multidisciplinary care strategies that address both cardiopulmonary and cognitive health. In addition, COPD should be considered a potential confounding factor when evaluating dementia risk in patients with CKD, as its presence may influence vascular, inflammatory, and hypoxia-related pathways contributing to cognitive impairment. Early identification and targeted management of modifiable risk factors, including cardiovascular disease and smoking, may help improve outcomes in this high-risk population. From a clinical perspective, recognising the increased vulnerability of these patients is essential when considering long-term management decisions, including renal replacement therapy and transplantation. Furthermore, commonly used treatments in CKD, such as bicarbonate supplementation for metabolic acidosis, may interact with compensatory mechanisms in patients with COPD; however, the clinical implications of these interactions remain uncertain and warrant further investigation. Finally, these findings provide a foundation for future research exploring the complex interactions between renal and pulmonary disease and their impact on cognitive outcomes.

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List of abbreviations

AD: Alzheimer's disease

CI: confidence interval

CKD: chronic kidney disease

COPD: chronic obstructive pulmonary disease

CVD: cardiovascular disease

EMRs: electronics medical records

GCN: global collaborative network

HCOs: health care organisations

HR: hazard ratio

ICD 10 – CM: International Classification of Diseases, Tenth Revision, Clinical Modification

PSM: propensity score matching

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SD: standard deviation

VaD: vascular dementia

Declarations

Ethics Approval and Consent to Participate: This analysis is a non-interventional, retrospective study utilising data obtained from TriNetX, LLC (“TriNetX”) and conducted in accordance with ethical guidelines aligned with the Declaration of Helsinki, the International Conference on Harmonization, and Good Clinical Practice. TriNetX is a global federated health research network providing access to EMRs from HCOs worldwide. Research studies utilising TriNetX do not require ethical approval as part of a federated network. Participating HCOs' identities to each dataset are kept confidential, adhering to ethical norms and regulatory frameworks that prevent data re-identification. The TriNetX platform uses only aggregated counts and statistical summaries of deidentified information. No Protected Health Information or personal data is accessible to platform users. All data collection, processing, and transmission comply with applicable Data Protection laws for the contributing HCOs, including the EU Data Protection Law Regulation 2016/679, the General Data Protection Regulation regarding the protection of individuals in relation to personal data processing, and the Health Insurance Portability and Accountability Act (HIPAA), the US federal law protecting the privacy and security of healthcare data. Individual personal data does not leave the HCO. TriNetX is ISO/IEC 27001: 2022 certified and maintains a robust IT security program to protect personal and healthcare data.

This retrospective study is exempt from informed consent. The data reviewed constitutes a secondary analysis of existing data and does not involve intervention or interaction with human subjects, and it is deidentified per the deidentification standard defined in Section § 164. 514 (a) of the HIPAA Privacy Rule. The process of deidentifying the data is validated through a formal determination by a qualified expert as outlined in Section § 164. 514 (b)(1) of the HIPAA Privacy Rule, with this determination refreshed in December 2020. Consequently, the study was deemed exempt from Institutional Review Board (IRB) oversight and did not necessitate patient consent.

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Consent for publication: not applicable

Availability of data and materials: All data is presented in the manuscript and/or supporting information. The data that supports the findings of this study are available from TriNetX, LLC, but third-party restrictions apply to their availability. The data were used under license for this study with restrictions that prevent redistribution or public availability. However, for accredited researchers, the TriNetX data is available for licensing at TriNetX, LLC. Data access may require a data-sharing agreement and may incur fees. Additionally, the platform offers real-time data, ensuring that displayed patient records are continuously updated to reflect the latest diagnoses, procedures, medications, and more. To clarify, the authors specify time frames and provide a network description to illuminate which data set was used. The data generated and/or analysed during the current study are available from the corresponding author upon request.

Competing interests: L.M., R.C., G.B., and P.C. declare no competing interests. F.R. is on an advisory board for Alnylam. R.D. received grants from NIHR, Alzheimer's Society, and Lilly, consulting fees and honoraria from Lilly, and is on an advisory board for Otsuka. J.T. received consulting fees from AstraZeneca and the Royal College of GPs, honoraria from AstraZeneca and Bayer, support for attending meetings from Bayer, and consulting fees from Boehringer Ingelheim. S.S. received a grant from Kidney Research UK. P.K. received grants from Vifor, Astellas, Pharmacosmos, and Unicyte; consulting fees and honoraria from Vifor, AstraZeneca, Pfizer, Pharmacosmos, Napp, GSK, Novartis, and Bayer; consulting fees from AstraZeneca, Vifor, Unicyte, UCB, and Otsuka; and support for attending meetings from Pharmacosmos, Vifor, and Medice. G.H. and F.Ru. are employed by TriNetX Europe NV. The research was conducted without any commercial or financial relationships that could be perceived as a potential conflict of interest. All authors read and approved the final manuscript.

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Authors' contributions, according to Contributor Roles Taxonomy:

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LM: conceptualisation, methodology, formal analysis, investigation, data curation, writing the original draft, reviewing and editing and visualisation.

FR: writing original draft, writing review and editing

JT: review and editing

RC: Validation

FRu: resources, validation

GH: validation, visualisation

GB: resources, review and editing

PC: Software

SS: review and editing

RD: writing- review and editing, supervision, project administration

PK: writing- review and editing, supervision, project administration

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Figure 1 Cohorts' construction:

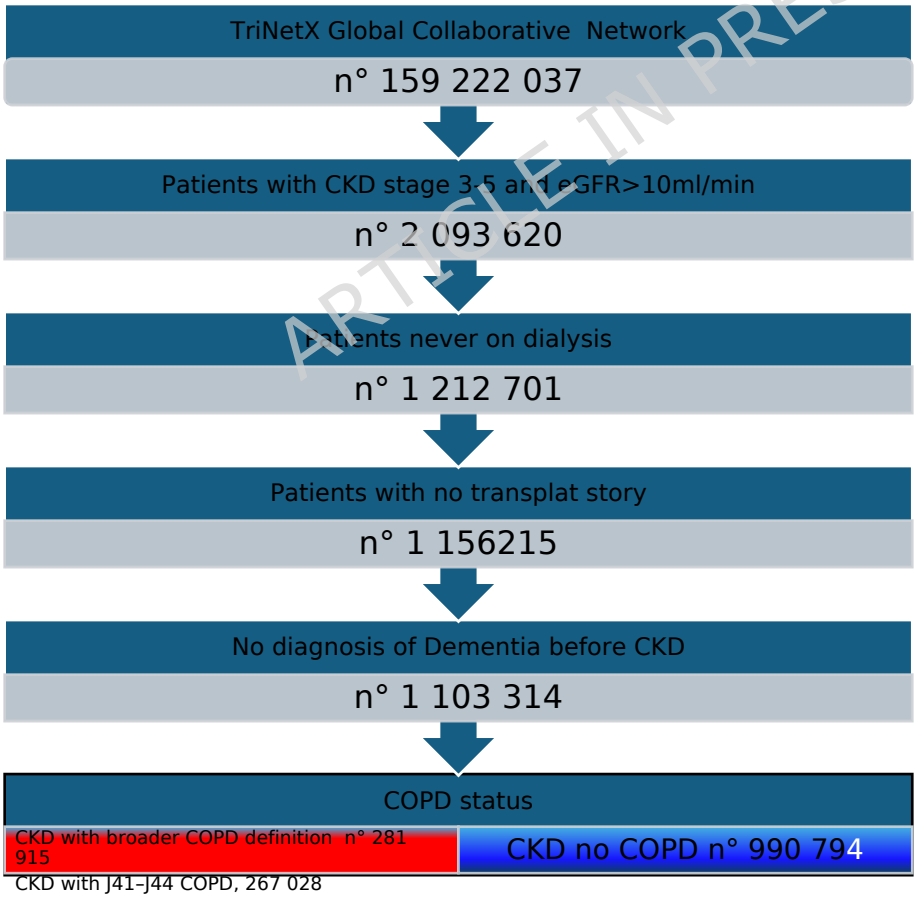

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Table 1. Baseline demographic, clinical, and laboratory characteristics before propensity score matching

Characteristic	CKD with COPD (n = 267 028)	CKD without COPD (n = 990 794)	Standard Difference
Age at index, mean ± SD	66.7 ± 9.0	65.6 ± 10.5	0.111
Male sex, %	46.8	50.6	0.076
White race, %	69.2	63.2	0.127
Black or African American race, %	17.2	17.7	0.011
Asian race, %	3.4	5.3	0.092
Hispanic or Latino ethnicity, %	2.7	3.8	0.067
Not Hispanic or Latino ethnicity, %	72.8	65.8	0.152
Unknown ethnicity, %	24.6	30.4	0.130
Hypertensive diseases, %	84.7	70.1	0.356
Disorders of lipid metabolism, %	70.1	54.2	0.332
Diabetes mellitus, %	47.1	38.6	0.173
Heart failure, %	31.5	12.3	0.479
Ischemic heart diseases, %	43.0	21.7	0.469
Diseases of arteries, arterioles and capillaries, %	28.0	12.3	0.401
Atrial fibrillation and flutter, %	20.9	10.9	0.276
Cerebrovascular diseases, %	18.5	10.6	0.226
Pulmonary heart disease and diseases of pulmonary circulation, %	13.5	4.3	0.329
Nicotine dependence, %	33.4	7.7	0.670
Neoplasms, %	40.1	29.9	0.215
Socioeconomic and psychosocial risk factors, %	4.8	2.0	0.155
Haemoglobin, g/dL, mean ± SD	12.6 ± 2.2	12.7 ± 2.1	0.070
Albumin, g/dL, mean ± SD	3.9 ± 0.6	4.0 ± 0.6	0.192
eGFR, mL/min/1.73 m², mean ± SD	51.8 ± 15.7	49.9 ± 15.5	0.119
Cholesterol, mg/dL, mean ± SD	168.3 ± 49.1	173.6 ± 49.1	0.108
Haemoglobin A1c, %, mean ± SD	6.7 ± 1.8	6.8 ± 1.8	0.038

Baseline demographic and clinical characteristics of patients with chronic kidney disease (CKD) with and without chronic obstructive pulmonary disease (COPD) prior to propensity score matching. COPD was defined using classical ICD-10 COPD codes (J41–J44). Continuous variables are presented as mean ± standard deviation (SD), and categorical variables as percentages. Standardised differences are provided to quantify the magnitude of imbalance between groups, with values >0.1 indicating meaningful differences. CKD patients with COPD exhibited a higher burden of cardiovascular comorbidities, smoking exposure, and socioeconomic risk factors compared with those without COPD.

Table 2. Baseline demographic, clinical, and laboratory characteristics after propensity score matching

Characteristic	CKD with COPD (n = 234 317)	CKD without COPD (n = 234 317)	Standard Difference
Age at index, mean ± SD	66.7 ± 9.1	66.6 ± 9.5	0.007
Male sex, %	47.1	48.3	0.024
White race, %	68.3	68.4	0.002

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Black or African American race, %	17.3	17.4	0.002
Asian race, %	3.8	3.9	0.007
Hispanic or Latino ethnicity, %	2.8	2.6	0.014
Not Hispanic or Latino ethnicity, %	71.6	72.1	0.011
Unknown ethnicity, %	25.6	25.3	0.007
Hypertensive diseases, %	83.2	84.4	0.033
Disorders of lipid metabolism, %	67.8	68.8	0.021
Diabetes mellitus, %	46.0	46.8	0.016
Heart failure, %	26.8	27.2	0.008
Ischemic heart diseases, %	38.3	39.2	0.018
Diseases of arteries, arterioles and capillaries, %	23.8	24.1	0.005
Atrial fibrillation and flutter, %	18.9	19.2	0.007
Cerebrovascular diseases, %	16.5	16.6	0.004
Pulmonary heart disease and diseases of pulmonary circulation, %	10.8	10.5	0.007
Nicotine dependence, %	25.7	25.0	0.017
Neoplasms, %	38.4	38.2	0.004
Socioeconomic and psychosocial risk factors, %	4.0	3.9	0.006
Haemoglobin, g/dL, mean ± SD	12.6 ± 2.1	12.6 ± 2.2	0.002
Albumin, g/dL, mean ± SD	3.9 ± 0.6	3.9 ± 0.6	0.066
eGFR, mL/min/1.73 m², mean ± SD	51.7 ± 15.5	50.2 ± 15.7	0.099
Cholesterol, mg/dL, mean ± SD	169.8 ± 48.9	169.4 ± 50.5	0.006
Haemoglobin A1c, %, mean ± SD	6.7 ± 1.8	6.8 ± 1.8	0.048

Baseline demographic and clinical characteristics of patients with chronic kidney disease (CKD) with and without chronic obstructive pulmonary disease (COPD) after propensity score matching. COPD was defined using classical ICD-10 COPD codes (J41–J44). Continuous variables are presented as mean ± standard deviation (SD), and categorical variables as percentages. Standardised differences are reported to assess covariate balance, with values <0.1 indicating adequate balance between cohorts. After matching, all baseline characteristics were well balanced, supporting the validity of subsequent comparative analyses.

Figure 2: Kaplan–Meier survival probability in patients with CKD with and without COPD

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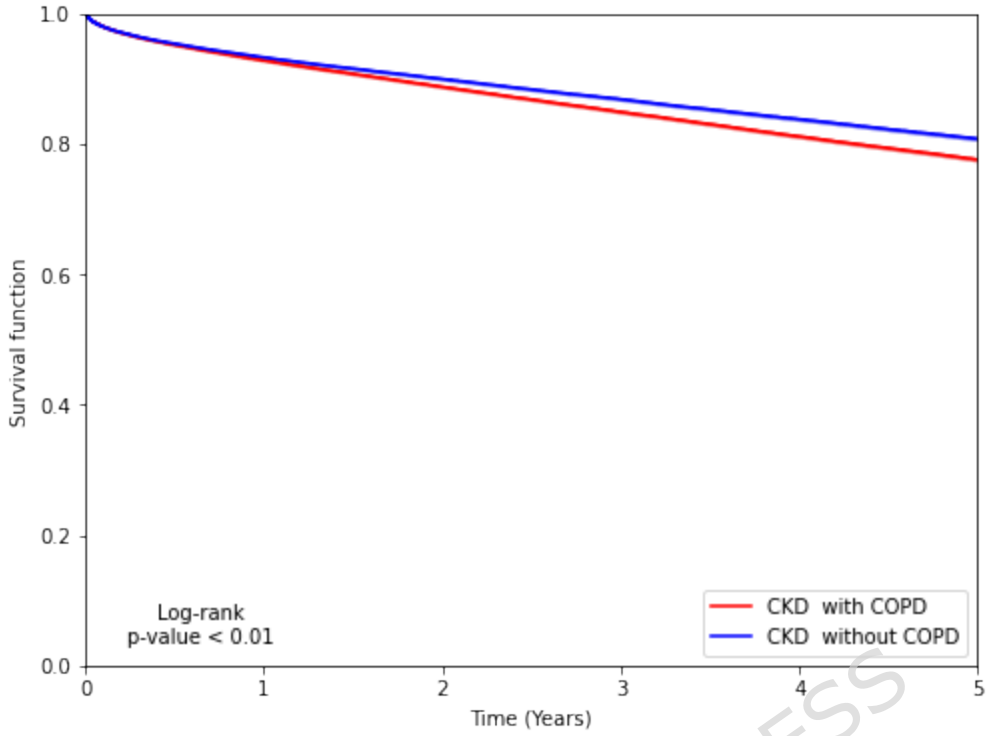

Patients at risk

Years	0	1	2	3	4	5
CKD with COPD	246423	205580	166445	133626	104747	81265
CKD without COPD	246423	197932	154920	120897	93092	70840

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Kaplan–Meier curves showing cumulative survival probability over a maximum follow-up of 5 years in propensity score–matched cohorts of patients with chronic kidney disease (CKD) with and without chronic obstructive pulmonary disease (COPD). The CKD with COPD cohort (red line) demonstrates lower survival probability compared with the CKD without COPD cohort (blue line). Statistical significance was assessed using the log-rank test ($p < 0.01$).

Numbers at risk at each time point are presented below the figure. Patients were censored at the time of death, last recorded healthcare encounter, or end of the study period.

Figure 3 displays a Forest plot illustrating the risk of death, non-Alzheimer's dementia, and Alzheimer's dementia in the cohort of patients affected by CKD with COPD.

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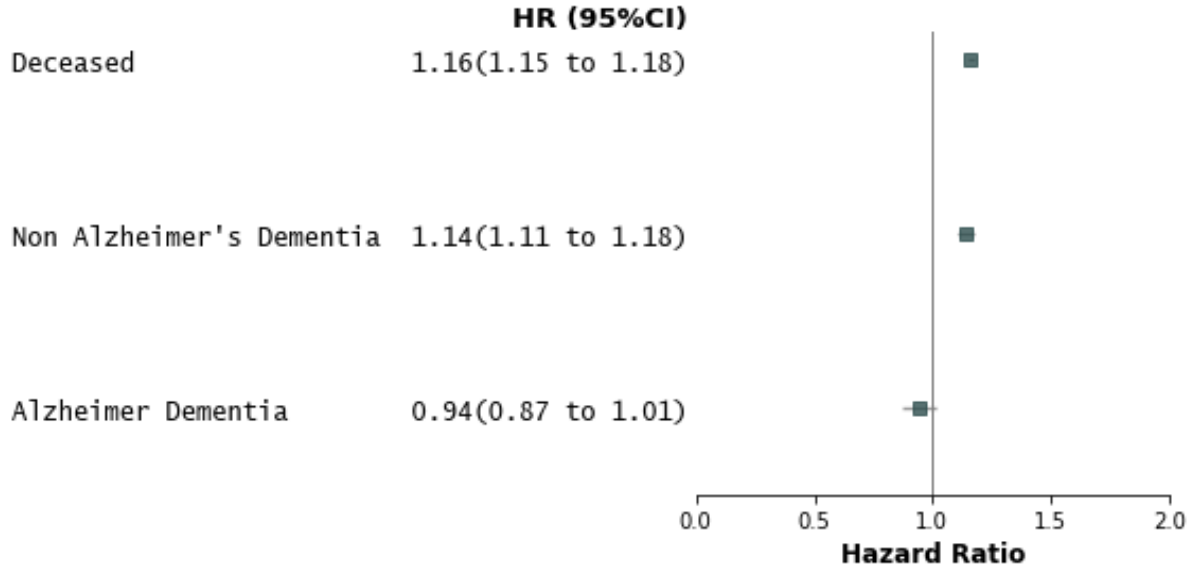

Forest plot displaying hazard ratios (HRs) with 95% confidence intervals (CIs) for all-cause mortality, non-Alzheimer's dementia, and Alzheimer's disease in propensity score–matched cohorts of patients with chronic kidney disease (CKD) with and without chronic obstructive pulmonary disease (COPD). The vertical reference line represents a hazard ratio of 1.0 (no difference between groups). Values greater than 1 indicate higher risk in the CKD with COPD cohort, while values less than 1 indicate lower observed risk.

Table 3. Age-stratified analysis of outcomes in patients with CKD with and without COPD

Outcome	<65 years HR (95% CI)	p-value	≥65 years HR (95% CI)	p-value
All-cause mortality	1.10 (1.07–1.13)	<0.001	0.99 (0.98–1.01)	0.228
Non-Alzheimer's dementia	1.27 (1.17–1.38)	<0.001	0.86 (0.84–0.89)	<0.001
Alzheimer's disease	1.04 (0.80–1.36)	0.142	0.70 (0.65–0.75)	<0.001

Hazard ratios (HRs) were derived from Cox proportional hazards models following propensity score matching. Analyses were stratified by age at index (<65 vs ≥65 years). Results reflect time-to-event analyses over a maximum follow-up of 5 years. Differences across age groups should be interpreted cautiously, as they may be influenced by competing risk and survivor bias, particularly in older patients with higher mortality.