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Communications Medicine

https://doi.org/10.1038/s43856-026-01460-6

Article in Press

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Received: 5 August 2024

Accepted: 12 February 2026

Cite this article as: Zhang, Y., Ghahramani, N., Chinchilli, V.M. *et al.* The risk of kidney disease increases following SARS-CoV-2 infection compared to influenza. *Commun Med* (2026). https://doi.org/10.1038/s43856-026-01460-6

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The risk of kidney disease increases following SARS-CoV-2 infection compared to influenza

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Abstract Word Count: 270

Number of Tables: 3

Number of Figures: 5

Supplementary documents: 2 tables, 4 figures and 1 note

References: 58

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Abstract

Background: Although case reports and observational studies suggest COVID-19 increases the risk of kidney diseases, real-world evidence comparing it with influenza is limited. Our study aims to assess the association between COVID-19 infections and subsequent kidney diseases, using influenza as a positive control and incorporating a negative control to establish clearer associations.

Methods: A large retrospective cohort study with strata matching was conducted using the MarketScan database with records from Jan. 2020 to Dec. 2021. We used the ICD-10 codes to identify individuals and build three cohorts: (1) COVID-19 group, (2) Positive control group: Influenza but no COVID-19, and (3) Negative control group: no COVID-19 / Influenza. The outcomes were acute kidney injury (AKI), chronic kidney disease (CKD), end-stage renal disease (ESRD), and glomerular diseases. Multivariable stratified Cox proportional hazards regression analyses were performed.

Results: The study includes 939,241 individuals with COVID-19, 1,878,482 individuals in the negative control group, and 199,071 individuals with influenza. COVID-19 is significantly associated with increased risks of AKI (adjusted hazards ratio, aHR: 2.74; 95% CI, 2.61-2.87), CKD (aHR: 1.38, 1.32-1.45), ESRD (aHR: 3.22, 2.67-3.88), and glomerular diseases (aHR:1.28, 1.09-1.50), while influenza has no impact on CKD, ESRD, and glomerular diseases. Time-specific analyses indicate that COVID-19 has stronger effects on AKI in the short term but has stable long-term effects on CKD.

Conclusions: In this large real-world study of working-age, commercially insured adults in the United States, COVID-19 infection is associated with a 2.3-fold risk of developing AKI, a 1.4-fold risk of CKD, and a 4.7-fold risk of ESRD compared to influenza. Greater attention to kidney diseases post-COVID-19 is essential to prevent future adverse health outcomes.

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Plain Language Summary:

COVID-19, caused by the SARS-CoV-2 virus, has been linked to multiple organ complications, with emerging evidence suggesting effects on kidney diseases. However, it is unclear how the risk of kidney disease after COVID-19 compares with influenza, another common viral infection. In this study, we analyzed commercial health insurance data from over three million working-age adults in the United States to compare individuals with COVID-19, those with influenza, and those with neither infection. We found that individuals who had COVID-19 were more likely to develop kidney problems, including short-term injury and long-term chronic disease. These findings suggest that COVID-19 may have a stronger impact on kidney diseases than influenza, highlighting the need for greater attention and monitoring of kidney function after COVID-19 infection.

Keywords: COVID-19; Influenza; Chronic Kidney Disease; Acute Kidney Injury; Real-world Evidence

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Introduction

Coronavirus disease 2019 (COVID-19) has been reported to be associated with multiple short-term and long-term conditions following exposure[1–6]. Kidney diseases, including short-term conditions like acute kidney injury (AKI) and long-term conditions like chronic kidney disease (CKD) and glomerular diseases, have attracted significant research attention, particularly regarding the long-term and short-term effects of COVID-19[7–10]. In addition to studying the effects of COVID-19 compared to non-infected individuals, there is increasing interest in comparing the impact of COVID-19 to influenza, one of the most common viral respiratory illnesses in the US[11]. Studies showed that COVID-19 is associated with higher risks of mortality and several comorbidities, including cardiovascular diseases, mental health disorders, and neurologic diseases, compared to influenza[12–14]. Therefore, a better understanding of the effects of COVID-19, in comparison to influenza, on short-term and long-term kidney diseases is needed to provide more comprehensive information to the public.

Current studies assessing the associations between COVID-19 and kidney diseases have primarily focused on specific populations, such as U.S. veterans or hospitalized patients, or often lack comparisons with influenza[7,13,15–19]. To the best of our knowledge, there is no study that has investigated the association among COVID-19, positive controls (influenza only), and negative controls (neither COVID-19 nor influenza infections) and the risk of kidney diseases using a large real-world database among general population. In our study, we include over 3 million working-age, commercially insured individuals from national real-world datasets (MarketScan) in the United States. Additionally, we compare the effects of COVID-19 to both positive control group and negative control group regarding the risks of AKI, CKD, end-stage renal disease (ESRD), and glomerular diseases. We hypothesize that individuals with COVID-19 infections have higher risks of kidney diseases compared to both positive and negative control groups, in both the short term and long term.

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Methods

Data Source

This retrospective cohort study utilized data from Merative™ MarketScan® Commercial Database (hereafter referred to as MarketScan), ranging from January 2019 to December 2021. MarketScan is one of the largest and most comprehensive longitudinal claims databases available for healthcare research, encompassing data on over 275 million unique de-identified patients[20]. This database includes health insurance claims across various types of care (e.g., inpatient, outpatient, pharmacy, and other claims), as well as enrollment data from large employers and health plans across all 50 U.S. states and the District of Columbia. The longitudinal tracking of detailed patient-level healthcare claims information provides comprehensive data, including demographic characteristics such as age, sex, diagnoses, procedures, and medications[21].

The included individuals had continuous enrollment for one year prior to, and 90 days following, the index dates. Data from 2020 and 2021 were primarily used for analytical purposes, while one year before the index dates was utilized to define baseline covariates.

The protocol of this study was reviewed and received a determination of non-human subjects' research by the Penn State Institutional Review Board.

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Cohort Derivation and Assessment of Exposure

Individuals with COVID-19 and without influenza, aged between 18 to 64 years, were identified from 1 January 2020 to 31 December 2021, using the International Classification of Diseases, 10th Revision (ICD-10) (*Supplementary Table 1*). The date of the first COVID-19 diagnosis was defined as the individual's index date (*Supplementary Figure 1*). Two control groups were also established: (1) Positive control group: This group consisted of individuals with influenza, identified using ICD-10 code (*Supplementary Table 1*), but no COVID-19 diagnosis histories. The recorded first diagnosis dates served as the index dates; (2) Negative control group: This group included individuals without any history of

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COVID-19 or influenza diagnoses, and pseudo random index dates were assigned between 1 January 2020 and 31 December 2021.

After excluding individuals with a history of kidney diseases at the study baseline, the COVID-19 group and the negative control group were matched at a maximum ratio of 1:2 across 1,536 strata. These strata were defined by year of birth (ranging from 1956 to 2003), sex (male or female), region (northeast, north-central, south, and west), and index date periods. Matching by index date periods aimed to control for the effects of temporal variations in COVID-19[22]. The periods were defined based on the dominant SARS-CoV-2 variants as follows: (1) January to June 2020: only Alpha (B1.1.7); (2) July to December 2020: Alpha (B1.1.7), Beta (B.1.351) and Gamma (P.1); (3) January to June 2021: Beta (B.1.351) and Delta (B.1.617.2); (4) July to December 2021: Delta (B.1.617.2)[23].

Strata that did not achieve the exact 1:2 ratio between the COVID-19 group and the negative control group were excluded, resulting in 1,469 strata being included in the final analysis. Individuals with influenza were directly assigned to these existing 1,469 strata (*Figure 1*).

Assessment of Outcomes

The new onset of kidney diseases was assessed during the follow-up period, defined as the time between kidney disease onset and the index date. The analysis was censored at the occurrence of kidney disease or at the end of the study, defined as discontinuation of health insurance coverage or 31 December 2021, whichever came first. Kidney diseases were identified using ICD-10 codes, with all kidney diseases and subgroups, including AKI, CKD, and ESRD (including dialysis and kidney transplant). Glomerular disease was also identified for the exploratory analysis (*Supplementary Table 1*).

Assessment of Potential Covariates

Demographic data on age, sex, and US regional location were extracted directly from MarketScan datasets. Individuals' comorbidities were assessed by the Elixhauser Comorbidity Index within one year prior to the index dates, utilizing ICD-10 codes[24,25]. The six most

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prevalent conditions, which are potentially related to kidney disease, COVID-19, or influenza, include cardiovascular disease (CVD, including congestive heart failure, cardiac arrhythmia, valvular disease, pulmonary circulation disorders, peripheral vascular disorders, and hypertension)[26–28], diabetes[29,30], obesity[31,32], chronic pulmonary disease[33,34], liver diseases[35,36], and depression[37,38] (*Supplementary Table 1*). In addition, we examined the usage history of seven specific medications – angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers (ACEI/ARBs), statins, diuretics, calcium channel blockers (CCB), nonsteroidal anti-inflammatory drugs (NSAIDs), proton pump inhibitors (PPIs), and beta-blockers – within the year preceding the index dates. These medications have been identified as potential risk factors for kidney disease[7,17,39,40]. Drinking and smoking histories within 1 year before the index dates were also assessed based on ICD-10 codes and current procedural terminology (CPT) codes (*Supplementary Table 1*).

Statistical Analysis

Age-adjusted demographic and clinical characteristics were summarized across the COVID-19 group, negative control group, and positive control group, with mean (SD) values for continuous variables, and number and percentage for categorical variables, which were presented after stratum matching. The incidence densities of AKI, CKD, and ESRD were then calculated per 1,000 person-years for the three groups. Additionally, cumulative incidence figures were presented to illustrate the trends of AKI, CKD, and ESRD incidence over the follow-up weeks across the three groups. Given the potential non-proportionality of hazards (*Supplementary Figure 2*), we applied stratified Cox proportional hazards regression models, initially stratified by stratum-match ID, to evaluate overall kidney diseases and the subgroups of CKD, AKI, and ESRD. Subsequently, multivariable stratified Cox proportional hazards regression models were performed, incorporating stratum-match ID, six comorbidities, seven drug use histories, drinking histories, and smoking histories. The corresponding mathematical equations are

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provided in *Supplementary Note 1*. Given the reported complex combination effects between COVID-19 and each of diabetes[41], CVD[42], and chronic pulmonary disease[43], interaction effects were assessed separately using the −2 × log likelihood ratio while controlling for the baseline covariates.

We conducted eight sensitivity analyses to test the robustness of our results, to address the possibility of residual confounding, and to address issue related disenrollment: (1) All individuals from the 1536 strata were included in the analysis to address concerns regarding the exclusion of individuals without an exact 1:2 matching ratio. (2) Individuals without CVD, chronic pulmonary disease, diabetes, obesity, liver diseases, or depression before index dates were included to address the concern of residual confounding introduced from comorbidities. (3) Individuals who did not use ACEI/ARBs, statins, diuretics, CCB, NSAIDs, PPI, and beta-blockers were included, to address potential residual confounding from medications. (4) Propensity score strata were constructed using a logistic regression model with the covariates from the full model to balance baseline data between the COVID-19 group and the negative control group. Stratified Cox proportional hazards regression models were then conducted using the propensity score strata ID. (5) Individuals with index dates from January to June 2020 were included to address concerns regarding the unbalanced distribution of individuals in the influenza group. (6) Individual from the COVID-19, Influenza, and negative control groups were stratum-matched in a 1:1:1 ratio. (7) Because some participants were censored at disenrollment, we assessed cumulative incidence of disenrollment across the three groups and observed differential patterns (Supplementary Figure 3). To address potential bias from disenrollment, we performed a sensitivity analysis restricted to individuals continuously enrolled through 12/31/2021. (8) We included individuals with pre-existing kidney disease and adjusted for this variable in the regression model to assess the effect of COVID-19 and influenza on ESRD.

We conducted an exploratory analysis to assess the risk of COVID-19 and influenza on glomerular diseases. The same multivariable stratified Cox proportional hazards regression models were applied as the primary analysis.

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Another exploratory analysis was performed to compare the effects of COVID-19 and influenza on AKI and CKD over 180, 360, and 540 days to assess effect trends with follow-up days. The same multivariable stratified Cox proportional hazards regression models used in the primary analysis were applied to these situations. Meanwhile, sensitivity analyses were included to estimate the time-varying effects of COVID-19 and Influenza compared to negative control group, using the Cox non-proportional hazards model with R package of "surtvep"[44]. ESRD and glomerular diseases were not included due to the limited number of incident cases during each follow-up period.

The final exploratory analysis was conducted to directly compare the hazards between COVID-19 and influenza, using influenza as the reference. We also conducted a subgroup analysis among individuals hospitalized with COVID-19 or influenza. Hospitalizations with COVID-19 or Influenza were identified using ICD-10 codes, based on the primary admission reason as well as up to four additional recorded diagnoses.

Data were analyzed in SAS software version 9.4 (SAS Institute, Cary, North Carolina) and R software version 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria) using a two-tailed α level of 0.05. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for cohort studies[45].

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Results

Study Population and Demographics

Our study included a total of 3,016,794 individuals, with a median follow-up time of 324 days (interquartile range: 186 to 429 days), divided into three groups: the COVID-19 group (n = 939,241; mean [SD] age 41.3 [13.1] years; 47.3% male), the negative control group (n = 1,878,482; mean [SD] age 41.3 [13.1] years; 47.3% male), and the influenza group (n = 199,071; mean [SD] age 39.7 [12.8] years; 43.1% male). After stratum matching, the COVID-19 and negative control groups showed identical distributions of age, sex, region, and index year. The influenza group showed a similar distribution to the negative control group regarding demographic information, except for the index year, with 92.8% of cases occurring between January and June 2020. To address potential biases introduced by the inconsistent distribution of index years, we conducted sensitivity analyses. Overall, the COVID-19 and influenza groups demonstrated a higher prevalence of comorbidities and medication use than the negative control group (*Table 1*).

Incidence of Kidney Diseases

COVID-19 group showed the highest incidence density in AKI (8.93 cases per 1000 PY, 95% CI (8.73, 9.14)), CKD (6.36 cases per 1000 PY, 95% CI (6.19, 6.54)), and ESRD (0.64 cases per 1000 PY, 95% CI (0.58, 0.69)), compared to negative control and influenza groups (*Figure 2*). In the cumulative incidence plots, COVID-19 group consistently exhibited the significantly highest cumulative incidence for AKI, CKD, and ESRD throughout the entire follow-up period. (*Figure 3*).

Primary Analysis

Stratified Cox proportional hazards regression models, adjusted for (1) match ID only and (2) match ID along with other baseline covariates, presented consistent results for the adjusted hazard ratios (aHR) for COVID-19 and influenza, using the negative control as the reference. Moreover, COVID-19 exhibited higher hazard ratios than influenza for both overall kidney diseases and subgroups of CKD, AKI, and

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ESRD. Specifically, after adjusting for baseline covariates, COVID-19 significantly increased risks of any kidney diseases (aHR, 1.93; 95% CI, 1.87 – 2.00), CKD (aHR, 1.38; 95% CI, 1.32 – 1.45), AKI (aHR, 2.74; 95% CI, 2.61 – 2.87), and ESRD (aHR, 3.22; 95% CI, 2.67 – 3.88). In contrast, influenza significantly but slightly increased the risks of any kidney disease when compared to negative control (aHR, 1.10; 95% CI, 1.01–1.19) and AKI (aHR, 1.24; 95% CI, 1.11–1.38), but had non-significant effects on incident CKD (aHR, 1.03; 95% CI, 0.92–1.14) and ESRD (aHR, 0.84; 95% CI, 0.55–1.29) (*Table 2*).

Interaction effects of COVID-19 with diabetes, CVD, and chronic pulmonary diseases were tested and none were statistically significant (all $p > 0.05$) (*Supplementary Table 2*). The results of sensitivity analyses in eight different scenarios are consistent with the conclusions drawn from our primary analysis (*Table 3*).

Exploratory Analyses

For the exploratory analysis of glomerular disease, there are 561 cases in COVID-19 group (0.69 cases per 1000 person-year), 864 cases in negative control group (0.51 cases per 1000 person-year), and 184 cases in influenza group (0.62 cases per 1000 person-year). Compared to the negative control group, after adjusting for baseline covariates, COVID-19 was associated with increased risk of glomerular disease (aHR 1.28, 95% CI 1.09–1.50), but influenza did not significantly elevate the risk (aHR 1.24, 95% CI 0.95–1.62).

In the exploratory analysis with follow-up periods, both COVID-19 and influenza showed significantly increased risks of AKI across 180, 360, and 540 days. However, COVID-19 (aHR, 4.35; 95% CI, 4.09–4.63) had nearly three times the hazard ratio of influenza (aHR, 1.51; 95% CI, 1.29–1.78) for AKI within the first 180 days after infection. The impact on AKI declined for both COVID-19 (aHR, 2.75; 95% CI, 2.62–2.88) and influenza (aHR, 1.28; 95% CI, 1.14–1.44) by 540 days. Both COVID-19 and influenza showed relatively stable trends in their effects on CKD from 0–180 days to 0–540 days. However, COVID-19 showed significant impact on CKD across all three periods, while influenza remained non-significant (*Figure 4*).

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The results from the time-varying effects analyses were consistent with those obtained from the time interval models (0–180, 0–360, and 0–540 days). For AKI, COVID-19 was associated with an initially high aHR of approximately 4.8, which declined to around 1.8 within the first 100 days and remained significant at approximately 1.5 throughout the follow-up period. In contrast, influenza was associated with a peak aHR of approximately 1.8, which declined and became non-significant after about 300 days. For CKD, COVID-19 was associated with a persistently elevated and significant aHR across the follow-up period, whereas influenza was not significantly associated with CKD for most of the follow-up time (*Supplementary Figure 4*).

Exploratory analysis for the effects of COVID-19 with influenza as the positive control group showed significantly increased risks of AKI (aHR 2.28, 95% CI 2.00–2.60), CKD (aHR 1.39, 95% CI 1.21–1.60), and ESRD (aHR 4.67, 95% CI 2.85–7.66), but a non-significant impact on glomerular diseases (aHR 1.08, 95% CI 0.73–1.60). For subgroup of individuals with hospitalization due to COVID-19 and influenza, COVID-19 group showed increased risks of both AKI (aHR 3.32, 95% CI 1.91–4.73) and CKD (aHR 2.24, 95% CI 1.02–3.21), comparing to influenza group (*Figure 5*).

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Discussion

In this large national retrospective cohort study of 3,016,794 working-age, commercially insured adults in the United States, we found that COVID-19 was associated with significantly higher risks of incident AKI, CKD, ESRD, and glomerular diseases, independent of baseline lifestyle factors and comorbidity conditions. In contrast, influenza was associated with a significant but mild effect on incident AKI and had no significant effects on CKD, ESRD, and glomerular diseases. Furthermore, COVID-19 had stronger effects on AKI within 180 days post-infection but demonstrated stable effects on CKD from 0-180 days to 0-540 days post-infection. Conversely, influenza had relatively stable mild effects on AKI after infection and showed no impact on CKD at any observed intervals. To the best of our knowledge, our study is the first to comprehensively compare the associations of COVID-19 and influenza on AKI, CKD, and ESRD using large national real-world datasets with general population in the United States. Moreover, this study is the first to explore the risk of COVID-19 on glomerular diseases based on real-world evidence.

Our findings are consistent with several previous studies. Bowe et al. conducted a retrospective cohort study using the Veterans Health Administration (VHA) healthcare system data to compare COVID-19 individuals with non-infected individuals from March 1, 2020, to March 15, 2021 (median follow-up days with 172 days). They found that the COVID-19 group had significantly increased risks of AKI (aHR 1.94, 95% CI 1.86 to 2.04) and ESRD (aHR 2.96, 95% CI 2.49 to 3.51)[7]. Similarly, our study reached the same conclusions but reported slightly higher aHR, likely due to the longer follow-up days in our study (median follow-up days with 324 days), and the different study population (91.2% of individuals in VHA are males). Xie et al. compared the risk of COVID-19 to influenza on 91 comorbidities in a retrospective cohort study using VHA data among hospitalized patients with COVID-19 or influenza. They observed higher risks of AKI and CKD in the COVID-19 group compared to the influenza group[13]. Our study extends these conclusions to a broader population, including non-hospitalized and non-veteran individuals. Aklilu et al. conducted a retrospective cohort study using data from England among

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individuals hospitalized with COVID-19 infection. They observed higher hazards of kidney failure compared with the AKI outcomes reported in our study[19]. Similarly, Mahalingasivam et al. also used data from England and confirmed elevated hazards of kidney failure among hospitalized COVID-19 patients compared with our findings[18]. In addition to the diagnosis of kidney failure, Mahalingasivam et al. also reported an association between COVID-19 and an accelerated decline in kidney function, measured by eGFR, particularly after hospitalization, using data from Sweden[46]. These higher hazards observed among hospitalized patients are expected, as hospitalized patients with COVID-19 generally have more severe infections, greater comorbidity burden, and a higher likelihood of progressing to kidney failure. Moreover, several prospective cohort studies with smaller sample sizes have observed increased risks of glomerular diseases (including proteinuria and hematuria) following COVID-19 infections, which are consistent with our exploratory results on glomerular diseases[47,48].

Compared to influenza, COVID-19 has potential pathways leading to kidney diseases. First, Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) enters kidney cells through specific biomechanisms. The virus binds to angiotensin-converting enzyme 2 (ACE2) via its spike (S) protein, which is then cleaved by the Type 2 transmembrane serine protease (TMPRSS2) or other proteases, forming a fusion pore[49]. Renal parenchymal cells, express high levels of ACE2, TMPRSS2, and other proteases, facilitating S protein cleavage and viral entry, making the kidneys susceptible to SARS-CoV-2 infection[9,50]. Moreover, several studies have found SARS-CoV-2 RNA and protein in the kidneys of COVID-19 individuals, which indicates the kidney is a target for SARS-CoV-2[51–53]. In contrast, although some studies have identified pathways for influenza A virus entry into host cells and its potential replication in human kidney cells[54], further evidence is still needed[55]. Secondly, current observational studies have reported higher risks of comorbidities such as CVD and metabolic diseases in COVID-19 individuals compared to influenza[13,14]. These elevated comorbidity risks may also explain the increased incidence of kidney diseases in COVID-19 individuals compared to those with influenza[9,56]. Additionally, our study is the first to compare the effects of COVID-19 to influenza on glomerular diseases using large

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real-world data, providing evidence and valuable information for both mechanism and epidemiological research on glomerular diseases after COVID-19 infections.

Our study highlights several important public health implications if COVID-19 increases the risk of kidney disease. First, individuals diagnosed with COVID-19 may require closer and more prolonged monitoring of kidney function to enable earlier detection and intervention. Second, attention to COVID-19 remains important even in the post-pandemic period, as our findings suggest a greater adverse impact on kidney health compared with seasonal influenza. Third, for nephrology research using data collected during the pandemic, COVID-19 infection should be considered both an essential covariate for adjustment and a potentially important predictor in risk models for kidney disease[10].

Our study has multiple strengths. First, we employed comprehensive epidemiologic study designs to mitigate potential bias and confounding effects. We performed stratum matching to better balance the distribution of demographic characteristics and matched diagnosis dates to reduce bias from virus variants. Additionally, we included both positive and negative control groups to better evaluate the effects of COVID-19. In the negative control groups, we randomly assigned index dates for individuals, systematically excluding person-time before the random index dates, which may lead to a potential overestimation of the hazard ratio. By including influenza as a positive control group, with index dates corresponding to diagnosis dates, we avoided such overestimation when comparing COVID-19 directly with influenza.

This study has some limitations. The MarketScan dataset is a claims dataset with insured individuals aged between 18 and 64 years. Our findings may not be generalized to elderly or pediatric populations, individuals without health insurance, and those covered by Medicare or Medicaid[57], where severe COVID-19 and influenza are more common. Additionally, beginning in 2016, the MarketScan data omitted inpatient discharge status, including death. Although we censored patients at the time of health insurance discontinuation, this does not necessarily indicate death. Therefore, our study could not account for the competing risk of death. Furthermore, we observed differential disenrollment across the three

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groups: individuals with influenza were more likely to disenroll by the end of follow-up, followed by those with COVID-19, compared with the negative control group. This differential disenrollment may introduce informative censoring, potentially biasing the observed kidney outcomes downward in the influenza and COVID-19 groups. However, our sensitivity analysis remains consistent with primary results, which confirmed the robustness of our findings. Moreover, MarketScan does not provide information on race or lab test results, preventing us from adjusting for potential unmeasured confounding by race and baseline creatinine or eGFR levels. Also, our data did not include information on medication dose or duration prior to baseline, which limited our ability to adjust for these factors. Furthermore, our study had a median follow-up time of 324 days (interquartile range: 186 to 429 days), which may not capture the full pattern of chronic outcomes, such as CKD and ESRD, after COVID-19 infection. Additionally, because the study period coincided with the height of the pandemic, misclassification of influenza may have occurred. However, we were unable to use pre-pandemic influenza cases as a positive control due to the lack of data prior to 2019. In addition, some individuals in the COVID-19 group may have had uncoded influenza prior to their COVID-19 infection, as influenza testing was less common in the community compared with COVID-19 testing. Lastly, we acknowledge the potential information bias in the diagnosis of kidney diseases, particularly mild CKD. The incidence of kidney diseases may be underestimated due to limited access to healthcare services, especially for negative control groups, as restricted healthcare access can result in undiagnosed cases[58]. Information bias may also have affected the measurement of covariates such as smoking and drinking, which are often under-recorded or uncoded in ICD-10 diagnosis system.

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Conclusions

In this large national retrospective cohort study of working-age, commercially insured adults in the United States, COVID-19 is associated with higher risks of AKI, CKD, and ESRD compared with influenza. The risk of AKI is highest shortly after infection, while the increased risk of CKD persists over

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longer follow-up. These findings indicate that COVID-19 has a stronger and more sustained impact on kidney diseases than influenza and highlight the need for greater attention to kidney outcomes following COVID-19 infection.

Data Availability: Data are available from third-party partners Merative™ MarketScan® Commercial Database. Source data for Figure 2, Figure 4, and Figure 5 are provided in the Supplementary Data files, with figure numbers used as worksheet names.

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Acknowledgments:

This project is supported by Artificial Intelligence and Biomedical Informatics Pilot Funding, Penn State College of Medicine. The authors have no conflicts of interest to disclose.

Authors' contributions: Designed research (project conception, development of overall research plan): YZ, DMB, NG, and VMC. Data extraction and study oversight: YZ, DMB. Analyzed data: YZ, and DMB. Performed statistical analysis: YZ. Wrote the first draft of the manuscript: YZ. Review and editing: YZ, NG, VMC, and DMB. All authors have read and approved the final manuscript. This study is part of the YZ's doctoral dissertation research project with the Penn State College of Medicine, United States of America.

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Table 1 Age-adjusted demographic and clinical characteristics stratified by COVID-19 and Influenza status after stratum matching

	COVID-19 (N= 939,241)	Negative Control (N=1,878,482)	Influenza (Positive Control) (N= 199,071)
Age*, mean (SD)	41.3 (13.1)	41.3 (13.1)	39.7 (12.8)
Sex			
Male	443,991 (47.3%)	887,983 (47.3%)	85,874 (43.1%)
Region			
Northeast	150,159 (16.0%)	300,319 (16.0%)	38,352 (19.3%)
North Central	185,136 (19.7%)	370,272 (19.7%)	35,684 (17.9%)
South	485,969 (51.7%)	971,938 (51.7%)	106,190 (53.3%)
West	117,977 (12.6%)	235,954 (12.6%)	18,845 (9.5%)
Index Year			
Jan. - June 2020	88,924 (9.5%)	177,847 (9.5%)	184,764 (92.8%)
July - Dec. 2020	367,195 (39.1%)	734,390 (39.1%)	5,977 (3.0%)
Jan. - June 2021	303,434 (32.3%)	606,867 (32.3%)	6,134 (3.1%)
July - Dec. 2021	179,689 (19.1%)	359,377 (19.1%)	2,196 (1.1%)
Comorbidities			
Cardiovascular Disease, Yes (%)	247,914 (26.4%)	395,381 (21.0%)	49,401 (24.8%)
Chronic Pulmonary Disease, Yes (%)	75,568 (8.0%)	105,710 (5.6%)	20,351 (10.2%)
Diabetes, Yes (%)	90,520 (9.6%)	125,514 (6.7%)	16,067 (8.1%)
Obesity, Yes (%)	134,615 (14.3%)	189,611 (10.1%)	26,266 (13.2%)
Liver disease, Yes (%)	27,509 (2.9%)	38,772 (2.1%)	5,498 (2.8%)
Depression, Yes (%)	112,614 (12.0%)	193,466 (10.3%)	26,197 (13.2%)
Smoking, Yes (%)	48,003 (5.1%)	86,104 (4.6%)	13,531 (6.8%)
Drinking, Yes (%)	9,418 (1.0%)	17,083 (0.9%)	2,119 (1.1%)
Medications			
ACEI/ARBs, Yes (%)	143,810 (15.3%)	251,743 (13.4%)	27,256 (13.7%)
Beta-blockers, Yes (%)	39,876 (4.2%)	70,416 (3.7%)	8,059 (4.0%)
CCB, Yes (%)	62,494 (6.7%)	108,784 (5.8%)	11,815 (5.9%)
Diuretics, Yes (%)	102,904 (11.0%)	173,600 (9.2%)	19,974 (10.0%)
NSAID, Yes (%)	153,588 (16.4%)	238,015 (12.7%)	34,283 (17.2%)
PPIs, Yes (%)	98,615 (10.5%)	142,827 (7.6%)	20,572 (10.3%)
Statins, Yes (%)	123,213 (13.1%)	227,654 (12.1%)	23,673 (11.9%)

* Value is not age-adjusted; Binary and Categorical variables are standardized to the age distribution of the study population;
Values of Categorical variables may not sum to 100% due to rounding.
Abbreviation:
ACEI/ARBs: angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers
CCB: calcium channel blockers
NSAID: nonsteroidal anti-inflammatory drugs
PPIs: proton pump inhibitors

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Table 2. Stratified Cox proportional hazards models HR (95% CI) for the association between COVID, Influenza, and kidney diseases

Models	Diseases	Negative Control	COVID-19	Influenza
Model 1	Any Kidney Diseases	Reference	2.08 (2.02, 2.13)	1.17 (1.10, 1.24)
	Chronic Kidney Disease	Reference	1.54 (1.48, 1.60)	1.09 (1.01, 1.17)
	Acute Kidney Injury	Reference	2.87 (2.77, 2.97)	1.30 (1.20, 1.40)
	End Stage Renal Disease	Reference	3.66 (3.18, 4.23)	0.99 (0.73, 1.33)
Model 2	Any Kidney Diseases	Reference	1.93 (1.87, 2.00)	1.10 (1.01, 1.19)
	Chronic Kidney Disease	Reference	1.38 (1.32, 1.45)	1.03 (0.92, 1.14)
	Acute Kidney Injury	Reference	2.74 (2.61, 2.87)	1.24 (1.11, 1.38)
	End Stage Renal Disease	Reference	3.22 (2.67, 3.88)	0.84 (0.55, 1.29)

Model 1: Stratified with match ID
Model 2: Stratified with match ID, 6 comorbidities (cardiovascular disease, chronic pulmonary disease, diabetes, obesity, liver diseases, depression), 7 drug use histories (angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers (ACEI/ARBs), statins, diuretics, calcium channel blockers (CCB), nonsteroidal anti-inflammatory drugs (NSAIDs), proton pump inhibitors (PPIs), and beta-blockers), drink histories, and smoking histories.

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Table 3. Sensitivity analysis for the association between COVID, Influenza, and kidney diseases: (1) all strata; (2) exclude individuals who had any comorbidities; (3) exclude individuals who had any medications; (4) stratified with propensity score strata; (5) only include individuals who were diagnosed during Jan. to June 2020; (6) Three groups with 1:1:1 exact matching; (7) only include individuals with continuous enrollment through 12/31/2021; (8) include individuals with pre-existing kidney diseases.

Models	Diseases	Negative Control	COVID-19	Influenza
Situation 1*	Any kidney diseases	Reference	1.95 (1.88, 2.01)	1.11 (1.02, 1.20)
	Chronic Kidney Disease	Reference	1.38 (1.32, 1.45)	1.03 (0.92, 1.14)
	Acute Kidney Injury	Reference	2.74 (2.62, 2.87)	1.24 (1.11, 1.38)
	End Stage Renal Disease	Reference	3.23 (2.68, 3.88)	0.84 (0.55, 1.30)
Situation 2†	Any kidney diseases	Reference	2.19 (2.08, 2.31)	1.14 (1.01, 1.29)
	Chronic Kidney Disease	Reference	1.51 (1.40, 1.63)	1.04 (0.88, 1.23)
	Acute Kidney Injury	Reference	2.93 (2.74, 3.14)	1.22 (1.04, 1.43)
	End Stage Renal Disease	Reference	3.13 (2.42, 4.04)	0.77 (0.41, 1.45)
Situation 3‡	Any kidney diseases	Reference	2.13 (2.02, 2.24)	1.18 (1.05, 1.31)
	Chronic Kidney Disease	Reference	1.53 (1.42, 1.64)	1.07 (0.92, 1.24)
	Acute Kidney Injury	Reference	2.79 (2.61, 2.98)	1.29 (1.11, 1.49)
	End Stage Renal Disease	Reference	3.07 (2.42, 3.90)	0.62 (0.36, 1.08)
Situation 4§	Any kidney diseases	Reference	1.81 (1.76, 1.86)	1.13 (1.06, 1.21)
	Chronic Kidney Disease	Reference	1.35 (1.30, 1.40)	1.05 (0.97, 1.14)
	Acute Kidney Injury	Reference	2.50 (2.41, 2.59)	1.32 (1.20, 1.44)
	End Stage Renal Disease	Reference	3.22 (2.78, 3.71)	1.06 (0.75, 1.50)
Situation 5**	Any kidney diseases	Reference	2.28 (2.07, 2.51)	1.11 (1.01, 1.22)
	Chronic Kidney Disease	Reference	1.54 (1.35, 1.76)	1.02 (0.91, 1.15)
	Acute Kidney Injury	Reference	3.51 (3.09, 4.00)	1.30 (1.14, 1.48)
	End Stage Renal Disease	Reference	4.73 (3.06, 7.32)	1.05 (0.63, 1.74)
Situation 6††	Any kidney diseases	Reference	2.19 (1.72, 2.80)	1.27 (0.98, 1.64)
	Chronic Kidney Disease	Reference	1.46 (1.04, 2.05)	0.94 (0.69, 1.21)
	Acute Kidney Injury	Reference	3.69 (2.63, 5.18)	1.95 (1.37, 2.79)
	End Stage Renal Disease	Reference	NA‡‡	NA‡‡
Situation 7§§	Any kidney diseases	Reference	1.87 (1.80, 1.94)	1.12 (1.01, 1.22)
	Chronic Kidney Disease	Reference	1.34 (1.27, 1.41)	1.03 (0.92, 1.17)
	Acute Kidney Injury	Reference	2.68 (2.54, 2.82)	1.23 (1.08, 1.41)
	End Stage Renal Disease	Reference	2.93 (2.35, 3.66)	0.82 (0.44, 1.53)
Situation 8***	End Stage Renal Disease	Reference	4.12 (3.66, 4.54)	2.03 (1.45, 2.63)

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*Situation 1, with 1536 strata and a total of 3,206,270 individuals. Models stratified with match ID, 6 comorbidities (cardiovascular disease, chronic pulmonary disease, diabetes, obesity, liver diseases, depression), 7 drug use histories (angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers (ACEI/ARBs), statins, diuretics, calcium channel blockers (CCB), nonsteroidal anti-inflammatory drugs (NSAIDs), proton pump inhibitors (PPIs), and beta-blockers), proton pump inhibitors (PPIs), insulin, beta-blockers, and other hypertension drugs), drink histories, and smoking histories.

†Situation 2, 1,802,333 individuals who did not have cardiovascular disease, chronic pulmonary disease, diabetes, obesity, liver diseases, or depression before index dates. Models stratified with match ID, 7 drug use histories, drink histories, and smoking histories.

‡Situation 3, 1,886,101 individuals who did not have any medication histories of angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers (ACEI/ARBs), statins, diuretics, calcium channel blockers (CCB), nonsteroidal anti-inflammatory drugs (NSAIDs), proton pump inhibitors (PPIs), and beta-blockers. Models stratified with match ID, 6 comorbidities, drinking and smoking histories.

§Situation 4, a total of 20 built propensity score strata were built based on age, sex, region, year of index date, 6 comorbidities, 7 drug use histories, drink histories, and smoking histories. Models were stratified with propensity score strata number.

**Situation 5, individuals with index year on Jan. - June 2020, including 88,756 individuals in the COVID-19 group, 177,512 individuals in the negative control group, and 185,932 individuals in the Influenza group. Models stratified with stratum, 6 comorbidities, 7 drug use histories, drink histories, and smoking histories.

††Situation 6, the COVID-19, Influenza, and negative control groups were stratum-matched in a 1:1:1 ratio, resulting in 28,977 individuals per group and a total of 86,931 individuals. Models stratified with match ID, 7 drug use histories, drink histories, and smoking histories.

‡‡Not applicable (NA) due to small sample size of end stage renal diseases cases in each group: COVID-19 group (37 cases / 28,977); Negative control group (5 cases / 28,977); Influenza group (10 cases / 28,977).

§§Situation 7, individuals with continuous enrollment through 12/31/2021 were included, with 793,608 individuals in the COVID-19 group, 1,653,446 individuals in the negative control group, 128,040 individuals in the influenza group. Models stratified with age, sex, index year, 6 comorbidities, 7 drug use histories, drink histories, and smoking histories.

***Situation 8, individuals with pre-existing kidney diseases were included, with 966,933 individuals in the COVID-19 group, 1,930,221 individuals in the negative control group, 202,232 individuals in the influenza group. Models stratified with age, sex, index year, pre-existing kidney diseases, 6 comorbidities, 7 drug use histories, drink histories, and smoking histories.

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Figure 1: Participant Selection Flow Diagram for COVID-19, Positive Control, and Negative Control Groups from the MarketScan Dataset

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Figure 2: Incidence density (cases per 1000 person-years, 95% confidence interval) of (1) Acute Kidney Injury (2) Chronic Kidney Disease (3) End Stage Renal Diseases across COVID-19 (N = 939,241), Influenza (N = 199,071), and Negative Control groups (N = 1,878,482

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Figure 3: Cumulative Incidence of (1) Acute Kidney Injury (2) Chronic Kidney Disease (3) End Stage Renal Diseases across COVID-19, Influenza, and Negative Control Groups

Figure 4: Exploratory Analysis of (1) Acute Kidney Injury and (2) Chronic Kidney Disease Risks Associated with COVID-19 (N = 939,241) and Influenza (N = 199,071) Compared to Negative Control Across Three Time Intervals: 0–180, 0–360, and 0–540 Days (Adjusted Hazard Ratios, 95% Confidence Interval).

Adjusted Hazard Ratios were estimated using multivariable stratified Cox proportional hazards regression models were performed, incorporating stratum-match ID, six comorbidities, seven drug use histories, drinking histories, and smoking histories.

Figure 5: Exploratory Analysis of COVID-19 Impacts on Kidney Diseases Using Influenza as the Reference Group (Adjusted Hazard Ratios, 95% Confidence Interval)

Sample size for all individuals: COVID-19 group (N = 939,241); Influenza group (N=199,071);
Sample size for individuals with Hospitalization: COVID-19 group (N = 28,089); Influenza group (N=1,193);
For individuals with hospitalization, ESRD and GD are not included due to limited event during follow-up.
Abbreviation: AKI: Acute Kidney Injury CKD: Chronic Kidney Disease ESRD: End Stage Renal Disease GD: Glomerular Disease

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Ed Summary

Zhang et al. utilized a large real-world dataset from more than three million adults in the United States to compare the incident of kidney disease risks following COVID-19 and influenza infections. The study found that COVID-19 is associated with a higher risk of acute kidney injury, chronic kidney disease, and end stage renal disease than influenza.

Peer review information: *Communications Medicine* thanks Mami Ishida and the other, anonymous, reviewer(s) for their contribution to the peer review of this work.

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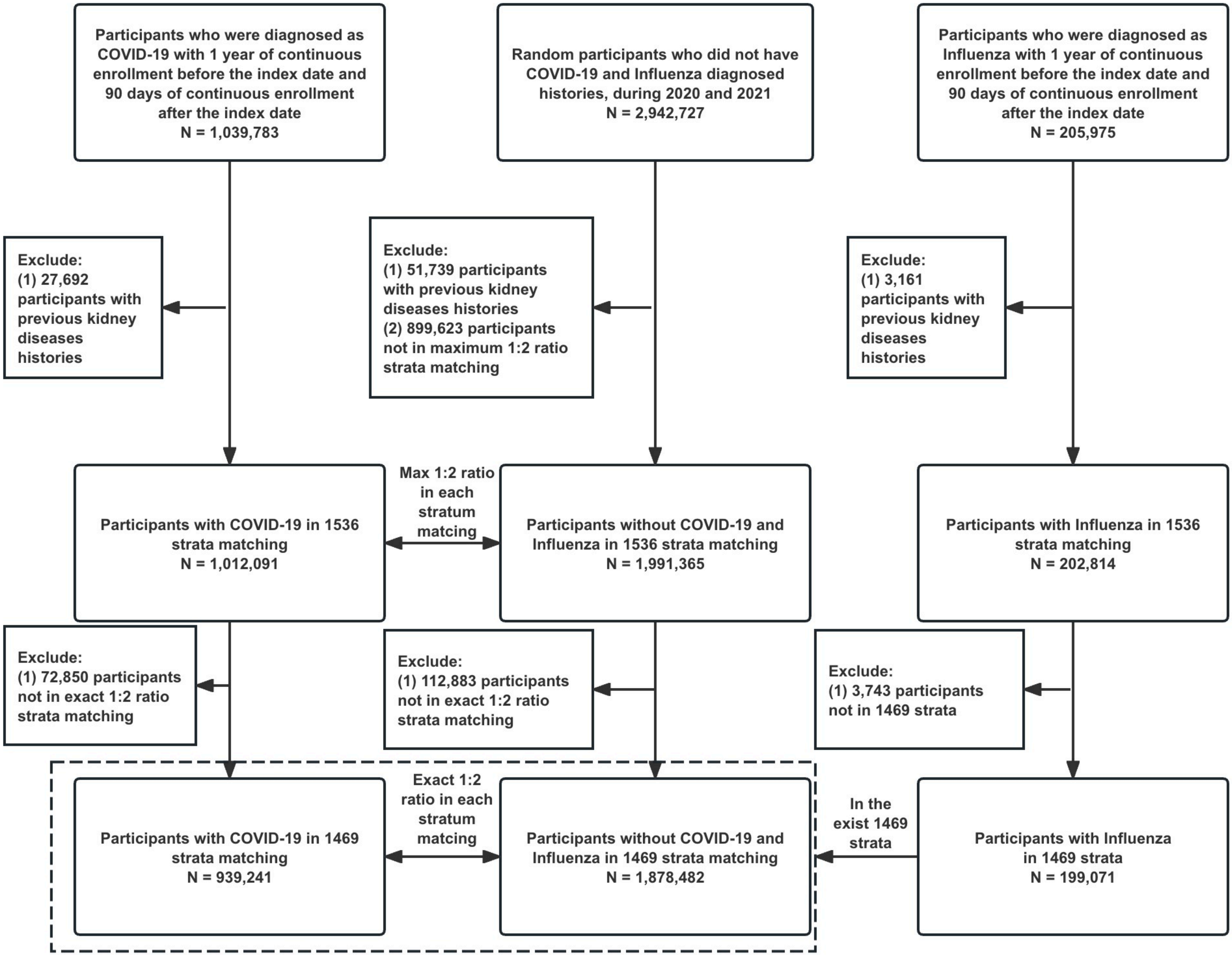
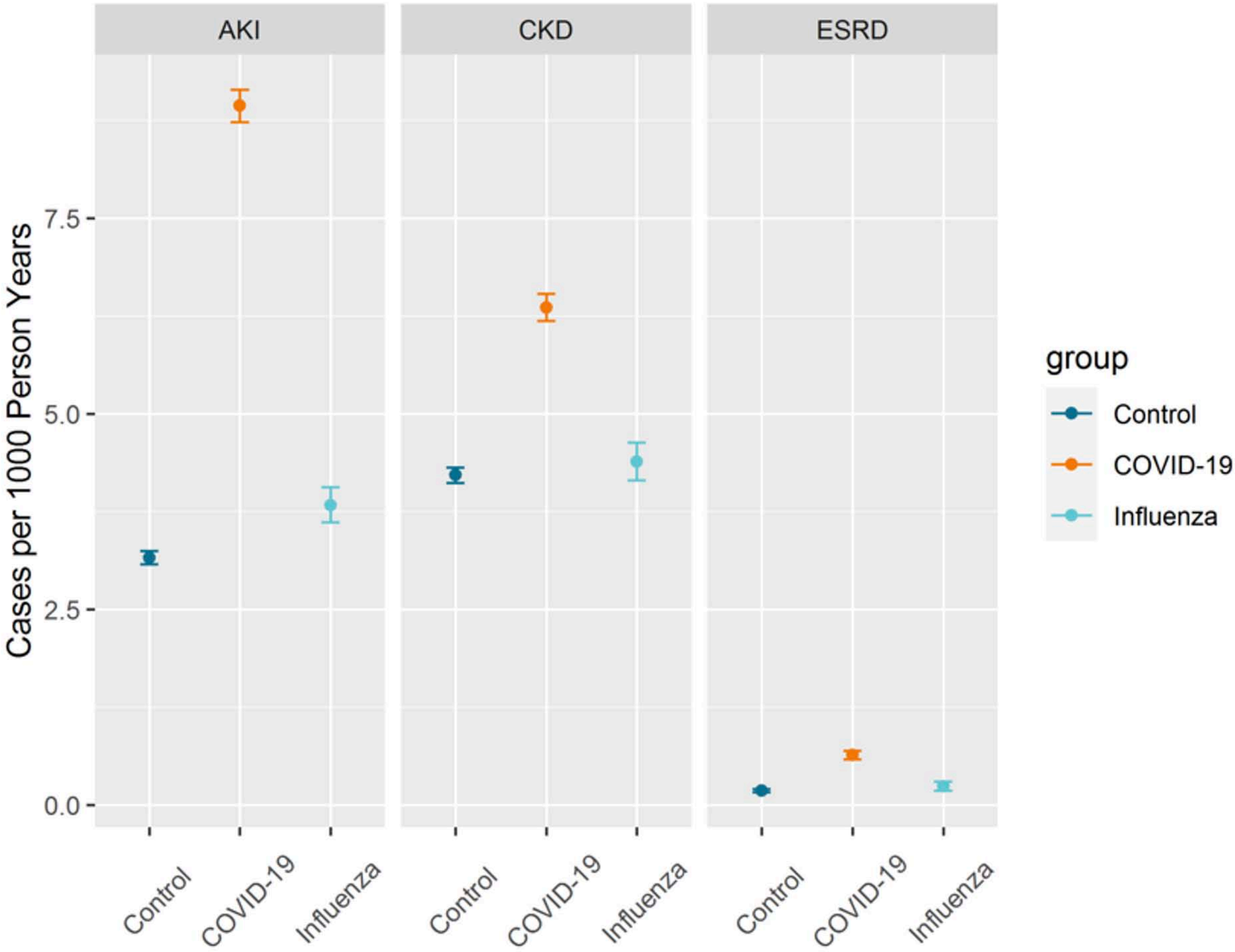
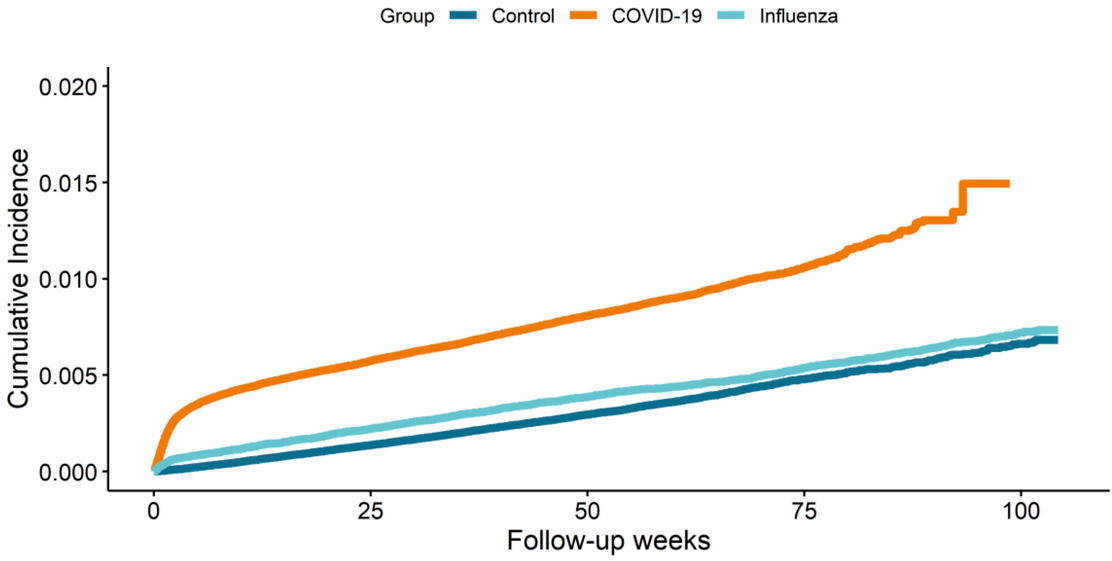

Participants who were diagnosed as COVID-19 with 1 year of continuous enrollment before the index date and 90 days of continuous enrollment after the index date
N = 1,039,783
Random participants who did not have COVID-19 and Influenza diagnosed histories, during 2020 and 2021
N = 2,942,727
Participants who were diagnosed as Influenza with 1 year of continuous enrollment before the index date and 90 days of continuous enrollment after the index date
N = 205,975
Exclude:
(1) 27,692 participants with previous kidney diseases histories
Exclude:
(1) 51,739 participants with previous kidney diseases histories
(2) 899,623 participants not in maximum 1:2 ratio strata matching
Exclude:
(1) 3,161 participants with previous kidney diseases histories
Participants with COVID-19 in 1536 strata matching
N = 1,012,091
Max 1:2 ratio in each stratum matcing
Participants without COVID-19 and Influenza in 1536 strata matching
N = 1,991,365
Participants with Influenza in 1536 strata matching
N = 202,814
Exclude:
(1) 72,850 participants not in exact 1:2 ratio strata matching
Exclude:
(1) 112,883 participants not in exact 1:2 ratio strata matching
Exclude:
(1) 3,743 participants not in 1469 strata
Participants with COVID-19 in 1469 strata matching
N = 939,241
Exact 1:2 ratio in each stratum matcing
Participants without COVID-19 and Influenza in 1469 strata matching
N = 1,878,482
In the exist 1469 strata
Participants with Influenza in 1469 strata
N = 199,071



Cases	**5,324**	**7,235**	**1,137**	**7,100**	**5,162**	**1,302**	**307**	**518**	**71**
PYs	**1,684,992**	**809,829**	**296,841**	**1,683,974**	**811,727**	**296,902**	**1,687,472**	**814,061**	**297,721**

Acute Kidney Injury

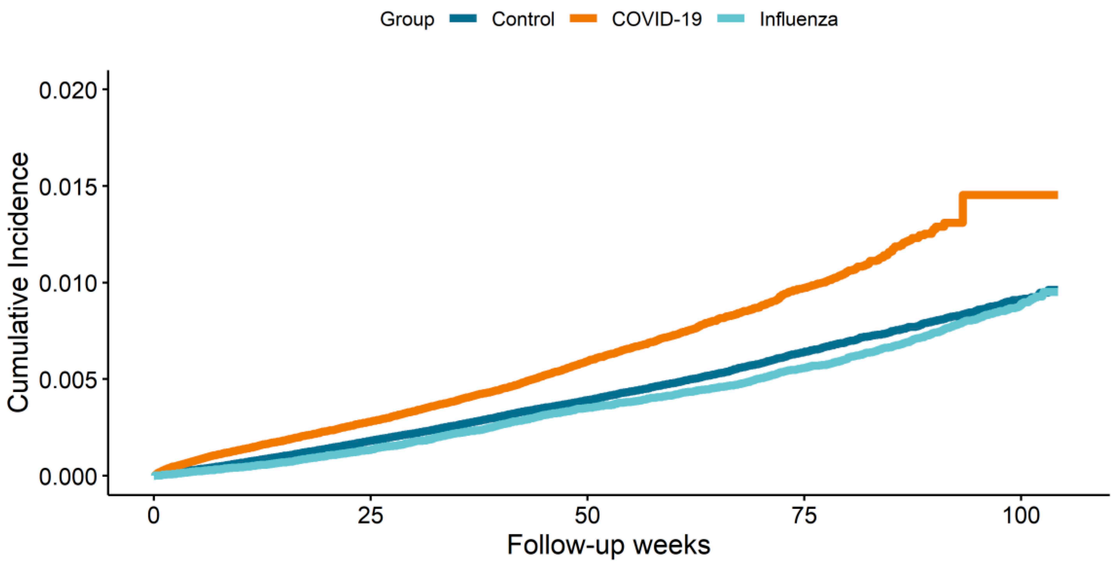


Number at risk

Group	0	25	50	75	100
Control	1878482	1467781	820678	215947	22598
COVID-19	939241	715258	428009	78111	43
Influenza	199071	189332	147370	126314	43230

Follow-up weeks

Chronic Kidney Diseases

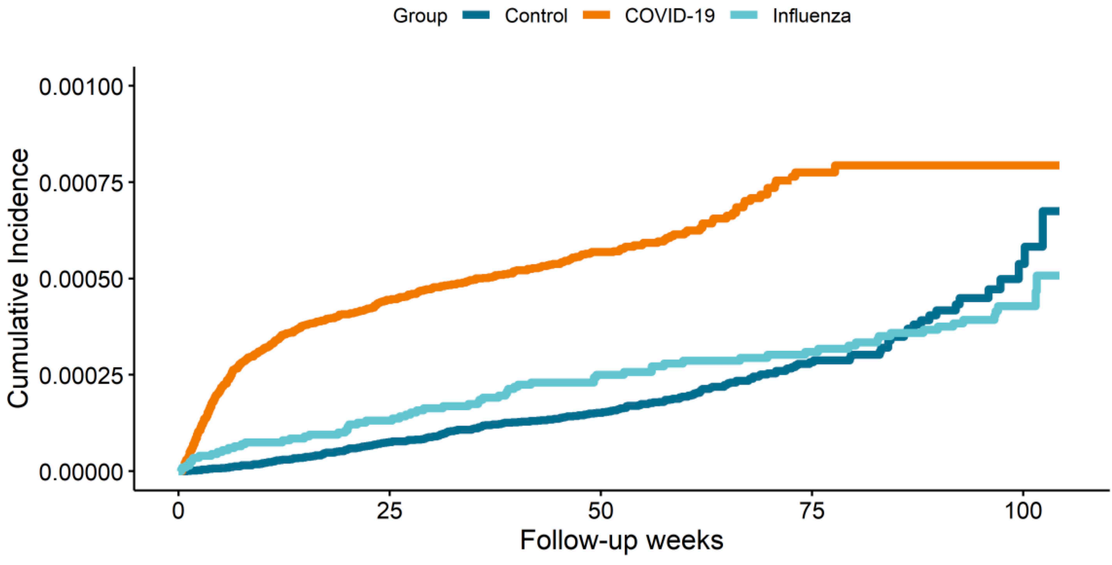


Number at risk

Group	0	25	50	75	100
Control	1878482	1467095	819784	215533	22551
COVID-19	939241	717074	428634	78316	47
Influenza	199071	189495	147404	126267	43180

Follow-up weeks

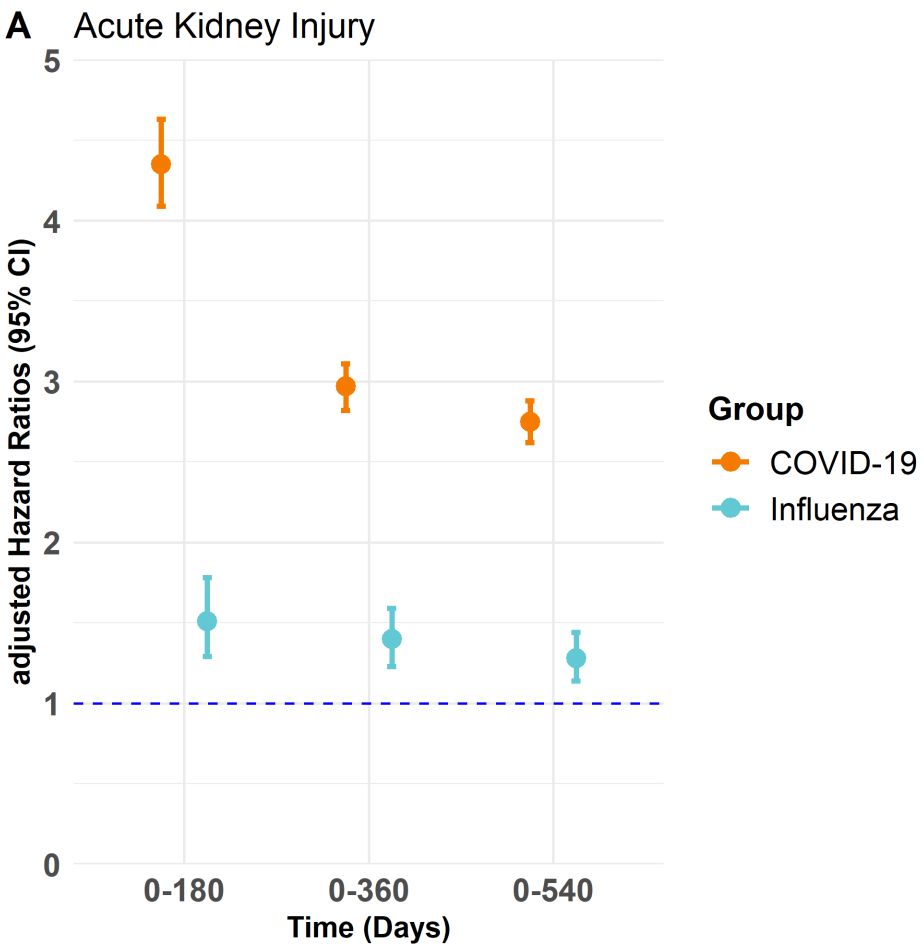
End Stage Renal Disease

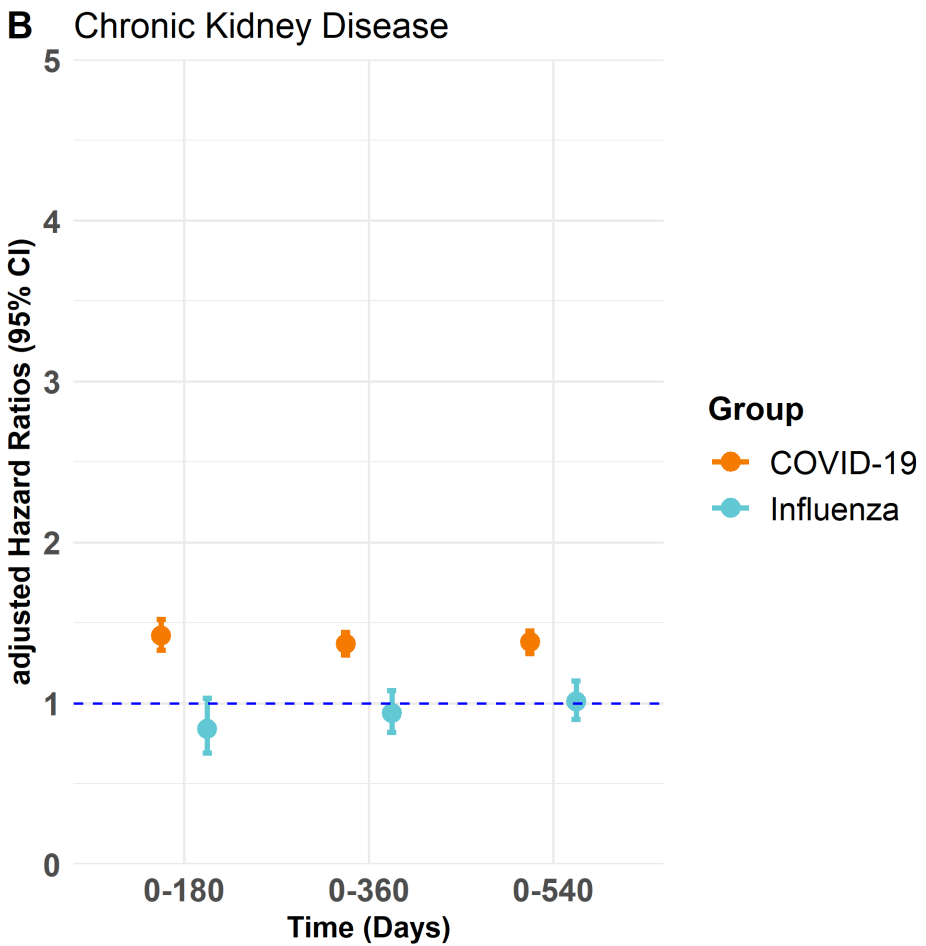


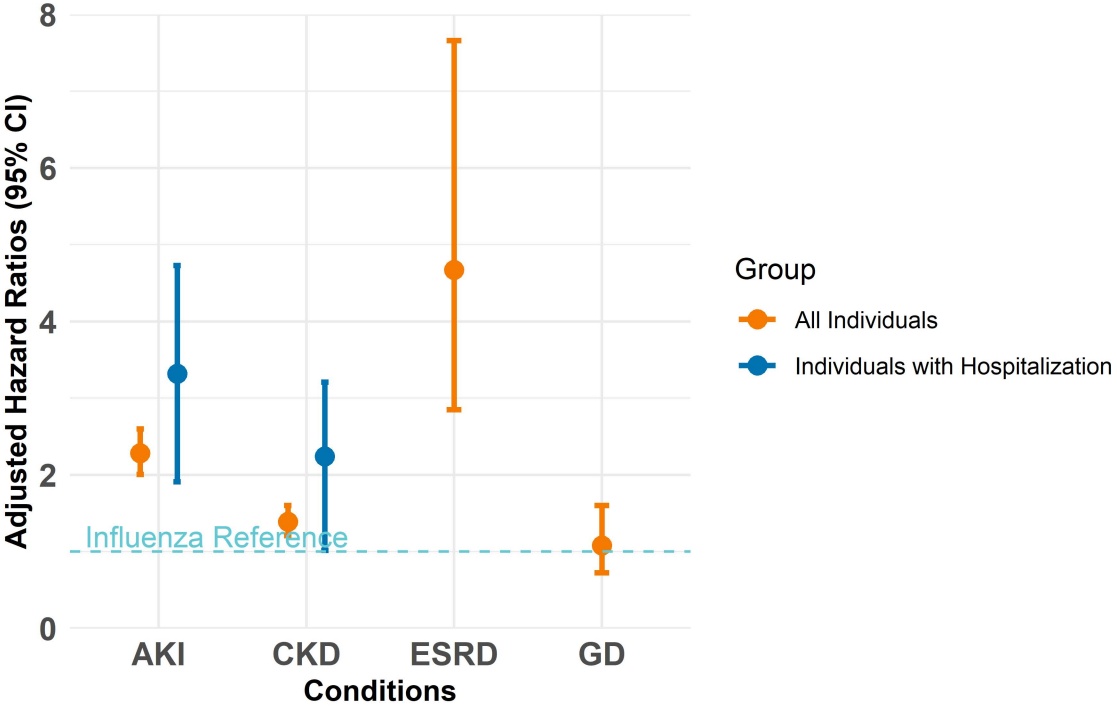
Number at risk

Group	0	25	50	75	100
Control	1878482	1469575	822765	216761	22730
COVID-19	939241	718712	430792	78927	48
Influenza	199071	189708	147850	126874	43492

Follow-up weeks


A
Acute Kidney Injury
adjusted Hazard Ratios (95% CI)
5
4
3
2
1
0
0-180
0-360
0-540
Time (Days)
Group
COVID-19
Influenza


B
Chronic Kidney Disease
adjusted Hazard Ratios (95% CI)
5
4
3
2
1
0
0-180
0-360
0-540
Time (Days)
Group
COVID-19
Influenza


8
6
4
2
0
Adjusted Hazard Ratios (95% CI)
Influenza Reference
AKI
CKD
ESRD
GD
Conditions
Group
All Individuals
Individuals with Hospitalization