Check for updates

*Pharmacoepidemiology and Drug Safety*

WILEY

ORIGINAL ARTICLE OPEN ACCESS

# Association Between Influenza Vaccination and Acute Kidney Injury Among the Elderly: A Self-Controlled Case Series

Haerin Cho[1] | Eunsun Lim[1] | Hee-Jin Kim[1] | Na-Young Jeong[1] | Nam-Kyong Choi[1,2]

[1]Department of Health Convergence, Ewha Womans University, Seoul, Republic of Korea | [2]Department of Health Convergence, Graduate School of Industrial Pharmaceutical Science, Ewha Womans University, Seoul, Republic of Korea

**Correspondence:** Nam-Kyong Choi (nchoi@ewha.ac.kr)

**Received:** 26 February 2024 | **Revised:** 12 August 2024 | **Accepted:** 15 August 2024

**Funding:** This research was supported by grants from the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI) funded by the Ministry of Health & Welfare, Republic of Korea (Government-wide R&D Fund project for infectious disease research, HG18C0067).

**Keywords:** acute kidney injury | influenza vaccines | safety | self-controlled case series | vaccination

## ABSTRACT

**Background:** Several cases of renal complications, including acute kidney injury (AKI), after influenza vaccination have been reported, but the association remains unproven. We evaluated the association between influenza vaccination and AKI occurrence among the Korean elderly in the 2018–2019 and 2019–2020 seasons.

**Methods:** We used a large database combining vaccination registration data from the Korea Disease Control and Prevention Agency and claims data from the National Health Insurance Service. The study subjects were patients hospitalized with AKI for the first-time following vaccination among those who received one influenza vaccine in the 2018–2019 or 2019–2020 season. Only those aged 65 or older at the date of vaccination were included. We performed a self-controlled case series study, designating the risk period as 1 to 28 days post-vaccination and the observation period as each influenza season. The adjusted incidence rate ratio (aIRR) was calculated by adjusting for nephrotoxic drug use and influenza infection that may influence AKI occurrence using a conditional Poisson regression model.

**Results:** A total of 16 713 and 16 272 AKI events were identified during the 2018–2019 and 2019–2020 seasons, respectively. The aIRR for AKI was 0.83 (95% confidence interval [CI] = 0.79–0.87) in the 2018–2019 season. The aIRR for the 2019–2020 influenza season was similar to the 2018–2019 season (aIRR = 0.86; 95% CI = 0.82–0.90).

**Conclusions:** Influenza vaccination is associated with a lower risk of AKI in the elderly over 65. This evidence supports the recommendation of annual influenza vaccination for the elderly. Further studies are needed to determine the biological mechanisms linking the influenza vaccine and AKI.

## 1 | Introduction

Influenza is a respiratory infectious disease occurring globally, causing seasonal epidemics among people of all ages. Among those who were infected by the influenza virus, the elderly are particularly vulnerable to severe sequelae and mortality [1]. The Advisory Committee on Immunization Practices recommends annual influenza vaccination for the elderly [2]. The government of Korea has been providing free influenza vaccines for the elderly aged 65 and above through the National Immunization Program (NIP) since 1997. Additionally, in 2015, the vaccination centers were extended from public health centers to include private medical institutions. The influenza vaccination rate among the elderly aged 65 or older in Korea is over 80% every season [3].

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

© 2024 The Author(s). *Pharmacoepidemiology and Drug Safety* published by John Wiley & Sons Ltd.

**Summary**

- The study identified the association between influenza vaccination and acute kidney injury among the elderly using a self-controlled case series.
- In the 2018–2019 and 2019–2020 influenza seasons, the influenza vaccine was found to be associated with a lower risk of acute kidney injury among elderly aged 65 and older.
- As the strains recommended for annual vaccination change and could affect the risk of AKI differently each season, further studies are needed in seasons with different recommended virus strains than those included in this study.

Acute kidney injury (AKI) is strongly related to age. As individuals age, the kidney changes progressively in both structure and function. Comorbidities that accrue with age, such as renovascular disease and congestive heart failure might demand procedures, medications, or surgeries that function as kidney stressors and nephrotoxins [4]. The elderly with severe AKI have a lower quality of life than those without AKI [5]. In addition, elderly individuals with AKI are at significantly increased risk for chronic kidney disease or end-stage renal disease [6]. AKI has substantial global public health effects because of its poor morbidity and mortality [7].

Since the introduction of the H1N1 influenza vaccine in 2009, the issue of AKI after influenza vaccination has been raised. Several case reports of AKI following influenza vaccination have been documented [8–10]. However, few studies have confirmed the association between influenza vaccination and AKI, and evidence to prove causality between renal effects and influenza vaccination at the population level remains insufficient. Given the significant burden of influenza and AKI on older people in Korea and the importance of influenza vaccination in preventing influenza-related complications, it is necessary to establish the safety of influenza vaccination in this population. Thus, we investigate whether influenza vaccination is associated with AKI among Korean elderly during the 2018–2019 and 2019–2020 influenza seasons.

## 2 | Methods

### 2.1 | Data Source

The data source for this study was vaccination registration data from the Korea Disease Control and Prevention Agency (KDCA) linked with the claims data from the National Health Insurance Service (NHIS). The process of linking this data involves the KDCA delivering data on influenza vaccine recipients to the NHIS, along with resident registration numbers to link with NHI claim data. The NHIS links the influenza vaccination registration data received from the KDCA with the NHI claim data using the resident registration number. Subsequently, the NHIS removes the patient's resident registration number from the linked data, assigns a randomized serial number as the patient ID, and provides the final linked data to the researcher. We used linked data from January 1, 2017, to December 31, 2020. The KDCA collects and merges vaccination data of the NIP electronically in accordance with the Infectious Disease Control and Prevention Act (Article 33–4) [11]. This registration database contains the demographic details of the NIP recipients and vaccination information including vaccination dates and types of vaccine. The National Health Insurance (NHI) claims database in Korea provides comprehensive insurance claim records, including claims for medical service and prescription drugs, for most of the Korean population [12].

The NIP includes 18 essential vaccines for children, such as Bacillus Calmette–Guérin (BCG), hepatitis B (HepB), measles mumps rubella (MMR), diphtheria-tetanus-acellular pertussis (DTaP), inactivated polio-vaccine (IPV), and influenza. It also provides influenza vaccines for high-risk groups, HPV vaccines for female adolescents, and pneumococcal vaccines for the elderly. Inactivated influenza vaccines are administered free of charge once per season to children under 13, pregnant women, and the elderly aged 65 and older [13].

### 2.2 | Study Population

Individuals aged 65 or older at the time of vaccination were included in the study. We identified incident cases of AKI hospitalized during the 2018–2019 and 2019–2020 influenza seasons, spanning from September 1, 2018, to April 30, 2019, and from September 1, 2019, to April 30, 2020. For each subject, the date of AKI diagnosis was defined as the first hospitalization date with AKI diagnosis code (N17) during the study period [14, 15]. Subjects included those who received at least one influenza vaccine in the 2018–2019 or 2019–2020 influenza season. Patients with a history of kidney disease, including AKI, kidney transplantation, and dialysis, from the start of available data on January 1, 2017, until the date of AKI diagnosis, were excluded.

### 2.3 | Study Design and Statistical Analysis

Given the over 80% influenza vaccination rate among those over 65 in Korea, sociodemographic and underlying disease differences may exist between vaccinated and unvaccinated groups. The self-controlled case series (SCCS) method was used to assess associations between influenza vaccination and AKI. The SCCS design evaluates the association between transient exposures and acute events using data only from cases that experienced both the exposure and outcome of interest within the observation period. Using the SCCS design, we controlled for time-invariant confounders, such as gender, genetic factors, and baseline health status. The following assumptions are required to use the SCCS design [16]. First, the events should be independently recurrent. To satisfy this assumption, we analyzed only the first AKI event within the observation period. Second, the event should not influence subsequent exposure. To minimize confounding from the healthy vaccine effect, we excluded the 14 days immediately before vaccination from the control period. The 14 days immediately before vaccination were considered as a separate period, and the AKI incidence rate during this period was compared to that of the control period. Third, the event should not affect the end of the observation period. Since



10991557, 2024, 9, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.70006 by Ewha Womans University Library, Wiley Online Library on [16/01/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

mortality rates among elderly AKI patients in Korea have been steadily decreasing, and we included all AKI patients regardless of severity, cases that died within the observation period were censored.

We defined the day of influenza vaccination as day 0. The risk period was from days 1 to 28 following vaccination, as this was the period with the highest risk considered by several case reports [8, 17]. A pre-vaccination period of 14 days was treated as a pre-exposure period in the analysis to allow for delayed vaccination due to AKI. For each individual, the observation period was restricted to the 2018–2019 and 2019–2020 influenza seasons (Figure 1a). The analysis adjusted for the duration of nephrotoxic drug use and periods of influenza infection, which may impact AKI development, by incorporating them as time-varying covariates in a conditional Poisson regression model. The use of nephrotoxic drug was defined as the prescription period of nephrotoxic drug recorded in NHIS claims data. We referenced several previous studies [18–20] reporting drugs that may affect renal function to create the final list of nephrotoxic drugs, as listed in Table S1. The prescription of nephrotoxic drugs was identified using Anatomical Therapeutic Chemical (ATC) codes. Influenza infection was identified using ICD-10 codes J10 (Influenza due to identified seasonal influenza virus) and J11 (Influenza, virus not identified). We defined the influenza infection period as extending from the infection date to 28 days thereafter.

We estimated the incidence rate ratio (IRR) and 95% confidence interval (95% CI) of AKI in various risk periods following influenza vaccination. The IRR of AKI associated with influenza vaccination was estimated by fitting a conditional Poisson regression model [21]. IRR is calculated by comparing the rate of events in the at-risk periods after the transient exposure, known as the risk periods, with the rate during all other periods of observation, which are defined as control periods.

The study conducted sensitivity analysis with extended observation period to span from 1 September, 2018 to 30 April, 2020 (Figure 1b). We conducted an additional sensitivity analysis applying the risk periods of varying lengths, ranging from 1 to 7, 14, or 42 days following vaccination. Considering that severe AKI symptoms requiring hospitalization often take several days to manifest, we conducted an additional sensitivity analysis by dividing the risk period into 1–7 days and 8–28 days. Subgroup analyses were stratified by sex, insurance type, region of vaccination, a history of diabetes mellitus (DM), and Charlson comorbidity index (CCI) score. All covariates were identified from NHIS claims data as of the vaccination date. Diabetes was defined using ICD-10 codes: type 1 diabetes (E10), type 2 diabetes (E11), and other/unspecified diabetes (E13, E14). Diabetes status and CCI score were based on diagnoses made within 365 days prior to vaccination. All analyses were conducted using SAS enterprise guide version 7.1 (SAS Inc., Cary, NC, USA).

## 2.4 | Ethics Approval

This study was approved by the Institutional Review Boards of Ewha Womans University (ewha-202209-0022-01) and obtained an exemption from obtaining informed consent since it relied on linked databases that contained de-identified

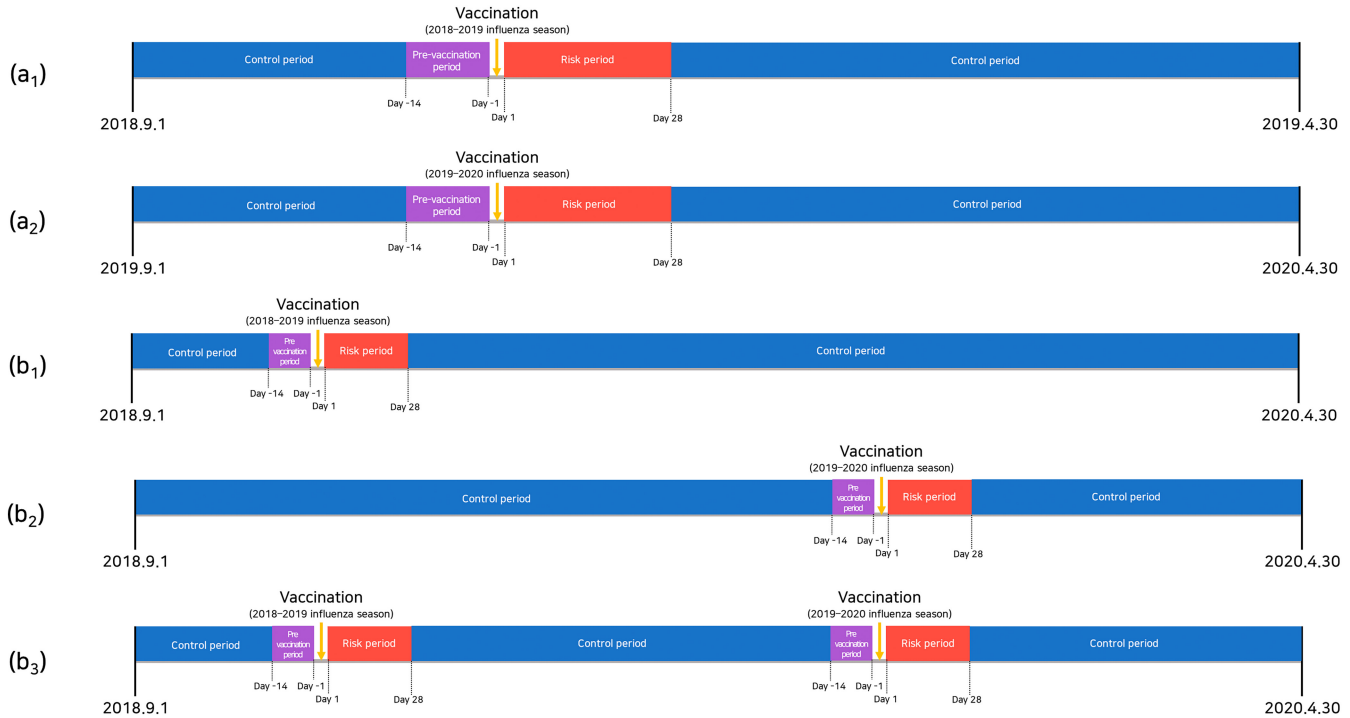



**FIGURE 1** | Overview of the self-controlled case series study design. (a) for primary analysis; (b) for sensitivity analysis; Panel (a1) SCCS with observation period defined 2018–2019 flu season; Panel (a2) SCCS with observation period defined 2019–2020 flu season; Panel (b1) Subjects who were only vaccinated 2018–2019 influenza season during the observation period; Panel (b2) Subjects who were only vaccinated 2019–2020 influenza season during the observation period; Panel (b3) Subjects who were both vaccinated 2018–2019 and 2019–2020 influenza seasons during the observation period.



10991557, 2024, 9, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.70006 by Ewha Womans University Library, Wiley Online Library on [16/01/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

information, preventing the identification of individual patients.

## 3 | Results

In total, we identified 7 222 439 people aged over 65 years who received influenza vaccination in either the 2018–2019 or 2019–2020 influenza season. Of these, 58 023 people were hospitalized for AKI. In SCCS analysis, 16 713 and 16 272 cases were included during the 2018–2019 and 2019–2020 influenza seasons, respectively (Figure 2). The characteristics of these patients are shown in Table 1. In both seasons, the gender distribution was similar and the majority of vaccinations occurred in October.

Risk estimates for AKI following influenza vaccine are shown in Table 2. The crude IRR of AKI for days 1 to 28 after influenza vaccination was 0.79 (95% CI 0.76–0.83) for the 2018–2019 influenza season and 0.84 (95% CI 0.80–0.88) for the 2019–2020 season. When adjusted for the use of nephrotoxic medications and influenza infection, the IRR during the 28 days after influenza vaccination still showed a statistically significant reduction in both seasons (adjusted IRR 0.83, 95% CI 0.79–0.87; adjusted IRR 0.86, 95% CI 0.82–0.90). The adjusted IRR 14 days prior to vaccination was reduced to 0.38 (95% CI 0.35–0.43) for the 2018–2019 influenza season and to 0.31 (95% CI 0.28–0.35) for the 2019–2020 influenza season.

The risk estimates remained unchanged even after extending the observation period to span from September 1, 2018, to April 30, 2020 (adjusted IRR 0.86; 95% CI 0.83–0.89) (Table 3). In both seasons, the risk of AKI was statistically significantly lower during the risk periods of 1–7 days, 8–28 days, 1–14 days, and 1–21 days after influenza vaccination, compared with the control period (Table 4). The subgroup analyses showed similar results to the other findings (Table 5).

## 4 | Discussion

In this study, we evaluated the risk of AKI following influenza vaccination in the 2018–2019 and 2019–2020 seasons in Korea. Using a self-controlled design, we found a reduced risk of AKI in 1–28 days post-vaccination during the 2018–2019 and 2019–2020 influenza seasons. The lower risk persisted across sensitivity analyses and was observed in all subgroups. This finding aligns with a previous nested case–control study in Taiwan, which suggests that influenza vaccination may help prevent AKI in the elderly, showing a statistically significant reduction in risk among vaccinated older individuals [22].

AKI is one of the potential complications of influenza infection. A narrative review of 20 studies found that 33% of patients admitted with influenza A infection developed AKI [23]. Several studies showed that patients with influenza who later developed AKI were typically older and had more comorbidities

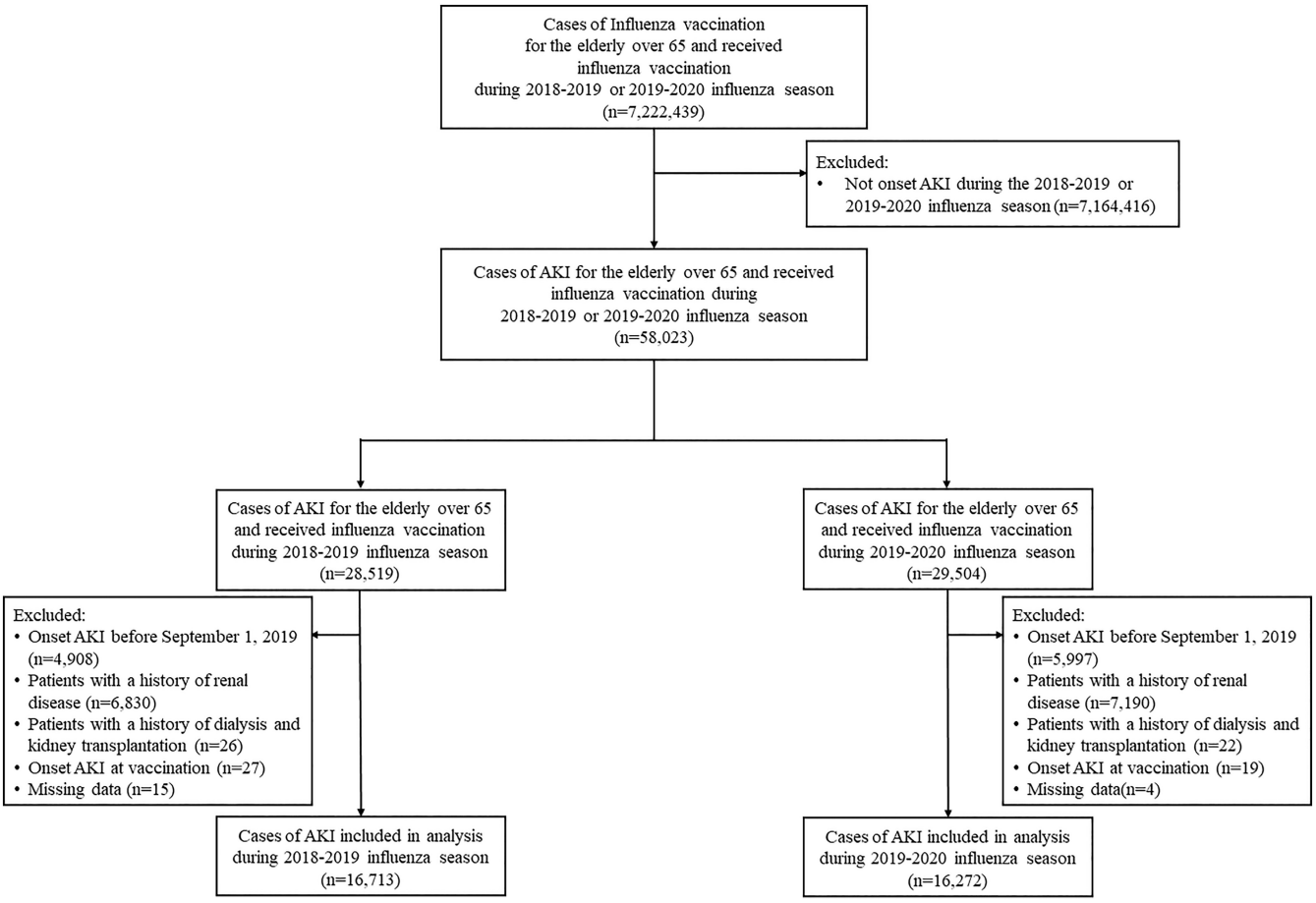



**FIGURE 2** | Flow chart of the study.



10991557, 2024, 9, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.70006 by Ewha Womans University Library, Wiley Online Library on [16/01/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

**TABLE 1** | Characteristics of the study population.

| Characteristics | 2018–2019 influenza season | | 2019–2020 influenza season | |
|---|---|---|---|---|
| | *N* | (%) | *N* | (%) |
| Total | 16 713 | (100.0) | 16 272 | (100.0) |
| Age | | | | |
| 65–74 | 4279 | (25.6) | 4058 | (24.9) |
| 75–84 | 8427 | (50.4) | 8051 | (49.5) |
| ≥85 | 4007 | (24.0) | 4163 | (25.6) |
| Sex | | | | |
| Male | 8050 | (48.2) | 7713 | (47.4) |
| Female | 8663 | (51.8) | 8559 | (52.6) |
| Months of vaccination | | | | |
| September | 52 | (0.3) | 22 | (0.1) |
| October 1st–15th | 12 885 | (77.1) | 3700 | (22.7) |
| October 16th–31st | 3085 | (18.5) | 10 862 | (66.8) |
| November–March | 691 | (4.1) | 1688 | (10.4) |
| Insurance type | | | | |
| Health insurance | 14 796 | (88.5) | 14 407 | (88.5) |
| Medical aid | 1917 | (11.5) | 1865 | (11.5) |
| Type of organization | | | | |
| General hospital | 1274 | (7.6) | 1222 | (7.5) |
| Hospital | 1309 | (7.8) | 1213 | (7.5) |
| Long-term care hospital | 1696 | (10.2) | 1749 | (10.7) |
| Clinic | 10 406 | (62.3) | 10 420 | (64.0) |
| Public health institution | 2019 | (12.0) | 1659 | (10.2) |
| Others[a] | 9 | (0.1) | 9 | (0.1) |
| Region | | | | |
| Metropolis[b] | 6188 | (37.0) | 6051 | (37.2) |
| Provinces | 10 525 | (63.0) | 10 221 | (62.8) |
| CCI | | | | |
| CCI < 5 | 6496 | (38.9) | 6113 | (37.6) |
| CCI ≥ 5 | 10 217 | (61.1) | 10 159 | (62.4) |

Abbreviation: CCI, Charlson comorbidity index.
[a]Includes dental clinic, dental hospital, and Korean oriental medicine clinic.
[b]Includes Seoul, Busan, Daegu, Incheon, Gwangju, Daejeon, Ulsan, and Sejong.

[24, 25]. Another study found that severe pneumonia from influenza increased AKI and mortality risks, with mortality significantly associated with older age, high pneumonia severity index scores, and nephrotoxic drug use [26]. We adjusted or stratified these AKI risk factors by considering influenza infection, the use of nephrotoxic drugs, and CCI score, and found that the risk of AKI was lower after influenza vaccination. The underlying biological mechanisms for this potential reduction of AKI risk remain elusive in the current body of literature. We aim to put forth several plausible explanations regarding how influenza vaccines reduce AKI risk, based on the findings of this study and existing literature. One explanation is that the influenza vaccination provides a protective effect against hospitalization and influenza-related complications, such as pneumonia, sepsis, and dehydration, which are known risk factors for AKI [27–30]. Most AKI cases occurred among those who were primarily admitted with the diagnosis of circulatory diseases (25.4%) and infections (16.4%) [31]. Additionally, influenza vaccination shortens hospital stays in the elderly [32]. The comprehensive analysis of previous



10991557, 2024, 9, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.70006 by Ewha Womans University Library, Wiley Online Library on [16/01/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

**TABLE 2** | Association between influenza vaccination and acute kidney injury.

| Risk period (days) | Number of cases | Person-year | Incidence rate[a] | IRR (95% CI) | Adjusted[b] IRR (95% CI) |
|---|---|---|---|---|---|
| 2018–2019 influenza season | | | | | |
| Control period | 14502 | 7925.86 | 1.83 | 1.00 (ref) | 1.00 (ref) |
| Pre-vaccination interval: 1–14 days | 365 | 640.39 | 0.57 | 0.31 (0.28–0.35) | 0.38 (0.35–0.43) |
| Post vaccination interval: 1–28 days | 1846 | 1271.26 | 1.45 | 0.79 (0.76–0.83) | 0.83 (0.79–0.87) |
| 2019–2020 influenza season | | | | | |
| Control period | 14080 | 7815.55 | 1.80 | 1.00 (ref) | 1.00 (ref) |
| Pre-vaccination interval: 1–14 days | 318 | 623.67 | 0.51 | 0.28 (0.25–0.32) | 0.31 (0.28–0.35) |
| Post vaccination interval: 1–28 days | 1874 | 1238.48 | 1.51 | 0.84 (0.80–0.88) | 0.86 (0.82–0.90) |

Abbreviations: CI, confidence interval; IRR, incidence rate ratio.
[a]Incidence of AKI per 100000 person-year.
[b]Adjusted for drug-related kidney injury and influenza infection.

**TABLE 3** | Sensitivity analyses: Defined the observation period as between September 1, 2018, and April 30, 2020.

| Risk period (days) | Number of cases | Person-year | Incidence rate[a] | IRR (95% CI) | Adjusted[b] IRR (95% CI) |
|---|---|---|---|---|---|
| Control period | 45603 | 61073.60 | 0.75 | 1.00 (ref) | 1.00 (ref) |
| Pre-vaccination interval: 1–14 days | 686 | 3039.59 | 0.23 | 0.30 (0.28–0.33) | 0.35 (0.33–0.38) |
| Post vaccination interval: 1–28 days | 3745 | 6052.35 | 0.62 | 0.83 (0.80–0.86) | 0.86 (0.83–0.89) |

Abbreviations: CI, confidence interval; IRR, incidence rate ratio.
[a]Incidence of AKI per 100000 person-year.
[b]Adjusted for drug-related kidney injury and influenza infection.

research show that influenza vaccination has the potential to reduce hospitalization rates and incidence rates of influenza-related complications in the elderly, which in turn may reduce the risk of AKI. Another rationale is that the influenza vaccine's cardioprotective effects can decrease the risk of kidney disease. A recent meta-analysis study revealed that influenza vaccines are associated with a reduced risk of major adverse cardiovascular events, cardiovascular mortality, and myocardial infarction [33], which are linked to declining kidney function and kidney disease [34]. Therefore, influenza vaccines may have contributed to reducing the incidence of kidney disease by decreasing the risk of cardiovascular disease. If the influenza vaccine prevented influenza infection and reduced the risk of AKI, the control period may have included the legacy effect of vaccine. This study did not consider the legacy effect in the analysis; however, if it had been accounted for, the risk of AKI might have been further reduced.

One of the key assumptions of the SCCS design applied in this study is that events should not affect subsequent exposure. To avoid violating this assumption, we excluded the 14 days immediately before influenza vaccination from the control period and analyzed it as a separate risk interval. The results showed a significantly lower risk of AKI in this period compared to the control period. This finding suggests that elderly individuals may delay vaccination if they experience health issues prior to vaccination, indicating a healthy vaccine effect. By excluding this period from the control interval, we mitigated this bias; however, residual bias may exist if patients delayed their vaccination for extended periods. Since AKI requiring hospitalization may have a delay from symptom onset to hospitalization, further studies extending the pre-vaccination period are needed.

The type of influenza vaccine provided free of charge to the elderly through Korea's NIP is the inactivated influenza vaccine. Each year, the World Health Organization predicts prevalent influenza viruses and announces recommended vaccines for the season. The virus strains for the 2018–2019 and 2019–2020 seasons differed in two out of four types. However, our study found that the risk of AKI was low in both seasons, suggesting that the protective effect of the influenza vaccine against AKI may be due to the prevention of influenza infection itself. Nonetheless, as the recommended virus strains were not



10991557, 2024, 9, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.70006 by Ewha Womans University Library, Wiley Online Library on [16/01/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

**TABLE 4** | Sensitivity analyses: Defined the risk period as 1–7 days, 8–28 days, 1–14 days, 1–42 days following vaccination.

| | Number of cases | Person-year | Incidence rate[a] | IRR (95% CI) | Adjusted[b] IRR (95% CI) |
|---|---|---|---|---|---|
| 2018–2019 influenza season | | | | | |
| Control period | 14 502 | 7925.86 | 1.83 | 1.00 (ref) | 1.00 (ref) |
| Pre-vaccination interval: 1–14 days | 365 | 640.39 | 0.57 | 0.31 (0.28–0.35) | 0.38 (0.35–0.43) |
| Post vaccination interval: 1–7 days | 405 | 319.93 | 1.27 | 0.70 (0.64–0.78) | 0.77 (0.70–0.85) |
| Post vaccination interval: 8–28 days | 1441 | 951.33 | 1.51 | 0.83 (0.75–0.90) | 0.84 (0.77–0.92) |
| Control period | 15 123 | 8558.45 | 1.81 | 1.00 (ref) | 1.00 (ref) |
| Pre-vaccination interval: 1–14 days | 365 | 640.39 | 0.57 | 0.32 (0.28–0.35) | 0.39 (0.35–0.43) |
| Post vaccination interval: 1–14 days | 888 | 638.67 | 1.39 | 0.77 (0.72–0.82) | 0.83 (0.78–0.89) |
| Control period | 13 568 | 7301.68 | 1.86 | 1.00 (ref) | 1.00 (ref) |
| Pre-vaccination interval: 1–14 days | 365 | 640.39 | 0.57 | 0.31 (0.28–0.34) | 0.38 (0.34–0.42) |
| Post vaccination interval: 1–42 days | 2780 | 638.67 | 1.39 | 0.79 (0.76–0.86) | 0.80 (0.77–0.84) |
| 2019–2020 influenza season | | | | | |
| Control period | 14 080 | 7815.55 | 1.80 | 1.00 (ref) | 1.00 (ref) |
| Pre-vaccination interval: 1–14 days | 318 | 623.67 | 0.51 | 0.28 (0.25–0.32) | 0.31 (0.28–0.35) |
| Post vaccination interval: 1–7 days | 385 | 311.57 | 1.24 | 0.69 (0.62–0.76) | 0.73 (0.66–0.80) |
| Post vaccination interval: 8–28 days | 1489 | 926.89 | 1.61 | 0.89 (0.82–0.97) | 0.90 (0.82–0.98) |
| Control period | 15 090 | 8431.87 | 1.79 | 1.00 (ref) | 1.00 (ref) |
| Pre-vaccination interval: 1–14 days | 318 | 623.67 | 0.51 | 0.28 (0.25–0.32) | 0.31 (0.28–0.35) |
| Post vaccination interval: 1–14 days | 864 | 622.16 | 1.39 | 0.78 (0.72–0.83) | 0.81 (0.76–0.87) |
| Control period | 12 998 | 7209.31 | 1.80 | 1.00 (ref) | 1.00 (ref) |
| Pre-vaccination interval: 1–14 days | 318 | 623.67 | 0.51 | 0.28 (0.25–0.32) | 0.31 (0.28–0.34) |
| Post vaccination interval: 1–42 days | 2956 | 622.16 | 1.60 | 0.89 (0.85–0.92) | 0.90 (0.87–0.94) |

Abbreviations: CI, confidence interval; IRR, incidence rate ratio.
[a]Incidence of AKI per 100 000 person-year.
[b]Adjusted for drug-related kidney injury and influenza infection.

entirely different during the study period, further studies are needed for seasons with completely different recommended virus strains.

To our knowledge, this is the first population-based study that investigates the association between influenza vaccines and the risk of hospitalization due to AKI among the elderly in Korea. As it employees the data encompassing the entire population, it adequately represents the elderly demographic in Korea and its findings can be generally applied. We minimized selection bias by comparing each person before and after vaccination and adjusted for time-invariant confounders using the SCCS design.



10991557, 2024, 9, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.70006 by Ewha Womans University Library, Wiley Online Library on [16/01/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

**TABLE 5** | Incidence rate ratio for acute kidney injury following influenza vaccination by sex, insurance type, region, with or without diabetes mellitus, and Charlson comorbidity index.

| | 2018–2019 influenza season | | | | 2019–2020 influenza season | | | |
|---|---|---|---|---|---|---|---|---|
| | Number of cases | Person-year | Incidence rate[a] | Adjusted[b] IRR (95% CI) | Number of cases | Person-year | Incidence rate[a] | Adjusted[b] IRR (95% CI) |
| Sex | | | | | | | | |
| Male | 875 | 612.59 | 1.43 | 0.82 (0.76–0.88) | 889 | 586.68 | 1.52 | 0.85 (0.80–0.91) |
| Female | 971 | 658.67 | 1.47 | 0.84 (0.78–0.89) | 985 | 651.79 | 1.51 | 0.86 (0.81–0.92) |
| Insurance type | | | | | | | | |
| Health insurance | 1615 | 1125.76 | 1.43 | 0.82 (0.78–0.87) | 1657 | 1096.61 | 1.51 | 0.86 (0.82–0.90) |
| Medical aid | 231 | 145.50 | 1.59 | 0.86 (0.75–0.99) | 217 | 141.86 | 1.53 | 0.85 (0.74–0.98) |
| Region | | | | | | | | |
| Metropolis | 672 | 471.18 | 1.43 | 0.81 (0.75–0.88) | 668 | 460.77 | 1.45 | 0.81 (0.75–0.88) |
| Provinces | 1174 | 800.08 | 1.47 | 0.84 (0.79–0.89) | 1206 | 777.70 | 1.55 | 0.88 (0.83–0.94) |
| Diabetes mellitus | | | | | | | | |
| Yes | 1003 | 721.02 | 1.39 | 0.79 (0.74–0.84) | 1076 | 713.51 | 1.51 | 0.85 (0.80–0.91) |
| No | 843 | 550.24 | 1.53 | 0.87 (0.81–0.94) | 798 | 524.96 | 1.52 | 0.86 (0.80–0.93) |
| CCI | | | | | | | | |
| CCI < 5 | 746 | 493.44 | 1.51 | 0.86 (0.80–0.93) | 715 | 465.17 | 1.54 | 0.88 (0.81–0.95) |
| CCI ≥ 5 | 1100 | 777.82 | 1.41 | 0.81 (0.76–0.86) | 1159 | 773.31 | 1.50 | 0.85 (0.80–0.90) |

[a]Incidence of AKI per 100 000 person-year.
[b]Adjusted for drug-related kidney injury and influenza infection.



10991557, 2024, 9, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.70006 by Ewha Womans University Library, Wiley Online Library on [16/01/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

The risk of AKI related to influenza vaccination was estimated for each season, taking into account the recommended composition of influenza virus vaccines annually. In addition, we extended the observation period to evaluate the vaccine's association with AKI among the elderly who received the vaccines for two consecutive seasons. The sensitivity analysis where we applied diverse risk periods, consistently showed a significant reduction in AKI risk across all intervals, confirming the robustness of our findings. With 80.7% influenza vaccination rate among the elderly over 65 as of 2022, Korea stands at the top among the Organization for Economic Co-operation and Development (OECD) countries [35], highlighting the importance of confirming the vaccine's safety profile. This research provides a reassuring message about consistent administration of the influenza vaccine in the elderly.

However, the study has its own limitations. First, AKI diagnosis was identified using hospital admission and diagnosis codes due to the lack of laboratory data like serum creatinine measurement and estimated glomerular filtration rate in claims data. We also could not identify the AKI severity stage for our study population. However, a validation study comparing discharge diagnoses in the claims database with medical records revealed an overall positive predictive value of 83.4% [36]. Previous studies using insurance claims data in Korea have also utilized hospitalization and diagnosis codes to define cases of AKI [37–39]. Second, our study may have been affected by bacterial or viral infections. The 2019–2020 influenza season of this study coincided with the early outbreak of Coronavirus disease (COVID-19) for approximately 3 months. Since COVID-19 data is managed as a separate database by the KDCA, we could not identify COVID-19 infection because this data was not linked to the database we used. However, given that COVID-19 had just emerged at the time, its impact on this study would have been minimal. Third, hospitalization due to AKI in the elderly can lead to death. This study censored patients who died within the observation period. However, according to previous study [38], the mortality rate due to AKI among the Korean elderly is steadily decreasing. Additionally, a study in Japan using the SCCS design to evaluate the association between drugs and AKI found no difference in results, whether or not deaths due to AKI were considered [40]. Nevertheless, further research using a modified SCCS design that accounts for deaths due to AKI is necessary.

## 5 | Conclusions

Our study demonstrated that influenza vaccination was associated with lower risk of AKI in the population over 65, thereby reinforcing confidence in the current practice of administering annual influenza vaccination to the elderly.

### 5.1 | Plain Language Summary

Vaccination stands as the most effective defense against influenza infection. Although there have been several case reports about acute kidney injury (AKI) after influenza vaccination, the association between influenza vaccination and AKI has remained unclear. We assessed the association between influenza vaccination and AKI by comparing the incidence rates during the risk periods (influenced by vaccination) and the control periods (not influenced by vaccination) within each individual. Our study suggests a reduction in the risk of AKI among individuals aged 65 and older following influenza vaccination. This significant finding supports the recommendation for influenza vaccinations among the elderly, a population particularly susceptible to both influenza and AKI. Thus, our results advocate for widespread vaccination efforts to safeguard the well-being of this elderly population.

#### Author Contributions

Research idea and study design: H.C., E.L., H.K., N.C. Data acquisition: N.J. Data analysis/interpretation: H.C., E.L., H.K., N.C. Statistical analysis: H.C. Supervision or mentorship: N.C. Every author provided significant intellectual input in the creation or revision of the manuscript and committed to taking personal responsibility for their respective contributions. They also agree to address and resolve inquiries regarding the accuracy or integrity of any part of the work.

#### Conflicts of Interest

The authors declare no conflicts of interest.

#### Data Availability Statement

This study was conducted utilizing a large database that combined vaccination registration data from the Korea Disease Control and Prevention Agency (KDCA) and the claims data from the National Health Insurance Service (NHIS). We were granted access to data from the KDCA and NHIS during the study period. Due to privacy and ethical considerations, the data are not publicly available. Since all data are kept and managed by KDCA and NHIS, the authors are not authorized to provide related research data to third parties.

#### References

1. J. Smetana, R. Chlibek, J. Shaw, M. Splino, and R. Prymula, "Influenza Vaccination in the Elderly," *Human Vaccines & Immunotherapeutics* 14, no. 3 (2018): 540–549.

2. L. A. Grohskopf, "Prevention and Control of Seasonal Influenza With Vaccines: Recommendations of the Advisory Committee on Immunization Practices—United States, 2023–24 Influenza Season," *MMWR Recommendations and Reports* 72 (2023): 1–25.

3. J. Seo and J. Lim, "The Impact of Free Vaccination Policies Under the Korean Influenza National Immunization Program: Trends in Influenza Vaccination Rates in South Korea From 2010 to 2019," *PLoS One* 17, no. 1 (2022): e0262594.

4. S. G. Coca, "Acute Kidney Injury in Elderly Persons," *American Journal of Kidney Diseases* 56, no. 1 (2010): 122–131.

5. A. Åhlström, M. Tallgren, S. Peltonen, P. Räsänen, and V. Pettilä, "Survival and Quality of Life of Patients Requiring Acute Renal Replacement Therapy," *Intensive Care Medicine* 31 (2005): 1222–1228.

6. A. Ishani, J. L. Xue, J. Himmelfarb, et al., "Acute Kidney Injury Increases Risk of ESRD Among Elderly," *Journal of the American Society of Nephrology* 20, no. 1 (2009): 223–228.

7. M. D. Okusa, G. M. Chertow, D. Portilla, and Acute Kidney Injury Advisory Group of the American Society of Nephrology, "The Nexus of Acute Kidney Injury, Chronic Kidney Disease, and World Kidney Day 2009," *Clinical Journal of the American Society of Nephrology* 4, no. 3 (2009): 520–522.

8. C. Patel and H. H. Shah, "Membranous Nephropathy and Severe Acute Kidney Injury Following Influenza Vaccination," *Saudi Journal of Kidney Diseases and Transplantation* 26, no. 6 (2015): 1289–1293.



10991557, 2024, 9, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.70006 by Ewha Womans University Library, Wiley Online Library on [16/01/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

9. M. Parikh, G. Dolson, V. Ramanathan, and W. Sangsiraprapha, "Novel H1N1-Associated Rhabdomyolysis Leading to Acute Renal Failure," *Clinical Microbiology and Infection* 16, no. 4 (2010): 330–332.

10. B. Norton, S. P. Kon, R. Perera, and R. Hull, "Vaccine: Friend or Foe? Double Seropositive Vasculitis Following Influenza Vaccination," *Oxford Medical Case Reports* 2019, no. 5 (2019): omz031.

11. "Infectious Disease Control and Prevention Act." Korean Law Information Center, Accessed Oct 17, 2022, https://www.law.go.kr/%EB%B2%95%EB%A0%B9/%EA%B0%90%EC%97%BC%EB%B3%91%EC%9D%98%EC%98%88%EB%B0%A9%EB%B0%8F%EA%B4%80%EB%A6%AC%EC%97%90%EA%B4%80%ED%95%9C%EB%B2%95%EB%A5%A0.

12. S. O. Song, C. H. Jung, Y. D. Song, et al., "Background and Data Configuration Process of a Nationwide Population-Based Study Using the Korean National Health Insurance System," *Diabetes & Metabolism Journal* 38, no. 5 (2014): 395–403.

13. Agency KDCaP, "National Immunization Program." Accessed 10 June, 2024, https://nip.kdca.go.kr/irhp/index.jsp.

14. N.-K. Choi, Y. Chang, S.-Y. Jung, et al., "A Population-Based Case-Crossover Study of Polyethylene Glycol Use and Acute Renal Failure Risk in the Elderly," *World Journal of Gastroenterology* 17, no. 5 (2011): 651–656.

15. E. Kim, H. Kim, Y. C. Kim, and J. P. Lee, "Association Between Extreme Temperature and Kidney Disease in South Korea, 2003–2013: Stratified by Sex and Age Groups," *Science of the Total Environment* 642 (2018): 800–808.

16. I. Petersen, I. Douglas, and H. Whitaker, "Self Controlled Case Series Methods: An Alternative to Standard Epidemiological Study Designs," *BMJ* 354 (2016): i4515.

17. A. Kutlucan, I. Gonen, E. Yildizhan, Y. Aydin, T. Sav, and U. Yildirim, "Can Influenza H1N1 Vaccination Lead to the Membranous Glomerulonephritis?" *Indian Journal of Pathology and Microbiology* 55, no. 2 (2012): 239–241.

18. M. Schetz, J. Dasta, S. Goldstein, and T. Golper, "Drug-Induced Acute Kidney Injury," *Current Opinion in Critical Care* 11, no. 6 (2005): 555–565.

19. J. A. Kellum, P. Romagnani, G. Ashuntantang, C. Ronco, A. Zarbock, and H.-J. Anders, "Acute Kidney Injury," *Nature Reviews Disease Primers* 7, no. 1 (2021): 1–17.

20. R. N. Okoro and V. T. Farate, "The Use of Nephrotoxic Drugs in Patients With Chronic Kidney Disease," *International Journal of Clinical Pharmacy* 41 (2019): 767–775.

21. H. J. Whitaker, C. Paddy Farrington, B. Spiessens, and P. Musonda, "Tutorial in Biostatistics: The Self-Controlled Case Series Method," *Statistics in Medicine* 25, no. 10 (2006): 1768–1797.

22. C.-H. Shih, Y.-J. Lee, P.-W. Chao, et al., "Association Between Influenza Vaccination and the Reduced Risk of Acute Kidney Injury Among Older People: A Nested Case-Control Study," *European Journal of Internal Medicine* 54 (2018): 65–69.

23. S. Al Dalbhi, H. A. Alshahrani, A. Almadi, et al., "Prevalence and Mortality Due to Acute Kidney Injuries in Patients With Influenza A (H1N1) Viral Infection: A Systemic Narrative Review," *International Journal of Health Sciences* 13, no. 4 (2019): 56.

24. A. Rodríguez, L. Reyes, J. Monclou, et al., "Relationship Between Acute Kidney Injury and Serum Procalcitonin (PCT) Concentration in Critically Ill Patients With Influenza Infection," *Medicina Intensiva* 42, no. 7 (2018): 399–408.

25. T. Watanabe, "Renal Complications of Seasonal and Pandemic Influenza A Virus Infections," *European Journal of Pediatrics* 172 (2013): 15–22.

26. G. A. Casas-Aparicio, I. León-Rodríguez, R. J. Hernández-Zenteno, et al., "Aggressive Fluid Accumulation Is Associated With Acute Kidney Injury and Mortality in a Cohort of Patients With Severe Pneumonia Caused by Influenza A H1N1 Virus," *PLoS One* 13, no. 2 (2018): e0192592.

27. E. A. Hoste, J. A. Kellum, N. M. Selby, et al., "Global Epidemiology and Outcomes of Acute Kidney Injury," *Nature Reviews Nephrology* 14, no. 10 (2018): 607–625.

28. T. Jefferson, D. Rivetti, A. Rivetti, M. Rudin, C. Di Pietrantonj, and V. Demicheli, "Efficacy and Effectiveness of Influenza Vaccines in Elderly People: A Systematic Review," *Lancet* 366, no. 9492 (2005): 1165–1174.

29. J. Y. Heo, J. Y. Song, J. Y. Noh, et al., "Effects of Influenza Immunization on Pneumonia in the Elderly," *Human Vaccines & Immunotherapeutics* 14, no. 3 (2018): 744–749.

30. J. Ryan, Y. Zoellner, B. Gradl, B. Palache, and J. Medema, "Establishing the Health and Economic Impact of Influenza Vaccination Within the European Union 25 Countries," *Vaccine* 24, no. 47–48 (2006): 6812–6822.

31. H. E. Wang, P. Muntner, G. M. Chertow, and D. G. Warnock, "Acute Kidney Injury and Mortality in Hospitalized Patients," *American Journal of Nephrology* 35, no. 4 (2012): 349–355, https://doi.org/10.1159/000337487.

32. C.-S. Wang, S.-T. Wang, C.-T. Lai, L.-J. Lin, C.-T. Lee, and P. Chou, "Reducing Major Cause-Specific Hospitalization Rates and Shortening Hospital Stays After Influenza Vaccination," *Clinical Infectious Diseases* 39, no. 11 (2004): 1604–1610, https://doi.org/10.1086/425323.

33. V. Jaiswal, S. P. Ang, S. Yaqoob, et al., "Cardioprotective Effects of Influenza Vaccination Among Patients With Established Cardiovascular Disease or at High Cardiovascular Risk: A Systematic Review and Meta-Analysis," *European Journal of Preventive Cardiology* 29, no. 14 (2022): 1881–1892.

34. E. F. Elsayed, H. Tighiouart, J. Griffith, et al., "Cardiovascular Disease and Subsequent Kidney Disease," *Archives of Internal Medicine* 167, no. 11 (2007): 1130–1136.

35. "OECD Health Statistic." Accessed Oct 16, 2022, https://data.oecd.org/healthcare/influenza-vaccination-rates.htm.

36. B. Park, J. Sung, K. Park, S. Seo, and S. Kim, *Report of the Evaluation for Validity of Discharged Diagnoses in Korean Health Insurance Database* (Seoul: Seoul National University, 2003), 19–52.

37. N. Choi, J. Lee, Y. Chang, et al., "Polyethylene Glycol Bowel Preparation Does Not Eliminate the Risk of Acute Renal Failure: A Population-Based Case-Crossover Study," *Endoscopy* 45, no. 3 (2013): 208–213.

38. S. Hwang, H. Park, Y. Kim, et al., "Changes in Acute Kidney Injury Epidemiology in Critically Ill Patients: A Population-Based Cohort Study in Korea," *Annals of Intensive Care* 9 (2019): 1–9.

39. K.-N. Kim, M.-K. Shin, Y.-H. Lim, et al., "Associations of Cold Exposure With Hospital Admission and Mortality due to Acute Kidney Injury: A Nationwide Time-Series Study in Korea," *Science of the Total Environment* 863 (2023): 160960.

40. K. Ikuta, S. Nakagawa, C. Yamawaki, et al., "Use of Proton Pump Inhibitors and Macrolide Antibiotics and Risk of Acute Kidney Injury: A Self-Controlled Case Series Study," *BMC Nephrology* 23, no. 1 (2022): 383.

## Supporting Information

Additional supporting information can be found online in the Supporting Information section.



10991557, 2024, 9, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.70006 by Ewha Womans University Library, Wiley Online Library on [16/01/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License