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Associations of cold exposure with hospital admission and mortality due to acute kidney injury: A nationwide time-series study in Korea

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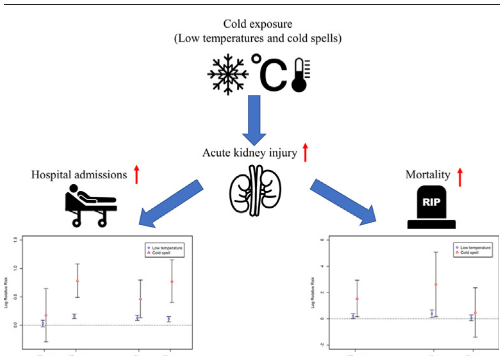
HIGHLIGHTS

- Low temperatures were associated with hospital admission due to acute kidney injury.
- Cold spells were associated with hospital admission due to acute kidney injury.
- Cold spells were also associated with mortality due to acute kidney injury.
- These associations were stronger among individuals aged ≥65 years.

GRAPHICAL ABSTRACT



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ABSTRACT

Background: Emerging evidence supports an association between heat exposure and acute kidney injury (AKI). However, there is a paucity of studies on the association between cold exposure and AKI.
Objective: We aimed to investigate the associations of cold exposure with hospital admission and mortality due to AKI and to explore whether these associations were influenced by age and sex.
Methods: Information on daily counts of hospital admission and mortality due to AKI in 16 regions of Korea during the cold seasons (2010–2019) was obtained from the National Health Insurance Service (a single national insurer providing universal health coverage) and Statistics Korea. Daily mean temperature and relative humidity were calculated from hourly data obtained from 94 monitoring systems operated by the Korean Meteorological Administration. Associations of low temperatures (<10th percentile of daily mean temperature) and cold spells (≥2 consecutive days with <5th percentile of daily mean temperature) up to 21 days with AKI were estimated using quasi-Poisson regression models adjusted for potential confounders (e.g., relative humidity and air pollutants) with distributed lag models and univariate meta-regression models.

Abbreviations: ICD-10, International Classification of Diseases, 10th revision; NHIS, National Health Insurance Service; PM_{10}, particulate matter with an aerodynamic diameter of ≤10 μm; NO_2, nitrogen dioxide; $PM_{2.5}$, particulate matter with an aerodynamic diameter of ≤2.5 μm; df, degrees of freedom; eCI, empirical confidence interval; RR, relative risk; CI, confidence interval.

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Results: Low temperatures were associated with hospital admission due to AKI [relative risk (RR) = 1.12, 95 % confidence interval (CI): 1.09, 1.16]. Cold spells were associated with hospital admission (RR = 1.87, 95 % CI: 1.46, 2.39) and mortality due to AKI (RR = 4.84, 95 % CI: 1.30, 17.98). These associations were stronger among individuals aged ≥65 years than among those aged <65 years.
Conclusion: Our results underscore the need for the general population, particularly the elderly, physicians, and other healthcare providers to be more vigilant to cold exposure, given the risk of AKI. Government agencies need to develop specific strategies for the prevention and early detection of cold exposure-related AKI.

1. Introduction

Acute kidney injury (AKI) is a complex clinical syndrome defined as an abrupt decline in renal function with symptoms varying from increased serum creatinine levels to anuria (Bagga et al., 2007). AKI has been reported for 10–15 % of hospitalized patients in a study conducted in the United States (Al-Jaghbeer et al., 2018) and ≥50 % of intensive care unit patients in a multicenter international study (Hoste et al., 2015). A previous systematic review reported that the mortality rate of AKI was 24 % in adults and 14 % in children worldwide (Susantitaphong et al., 2013). Because of its high prevalence and severe clinical prognosis, AKI is considered a global public health concern (Lameire et al., 2013).

Extreme ages (i.e., very old and very young ages), pre-existing proteinuria, comorbid diseases (e.g., diabetes mellitus, cardiovascular diseases, and chronic kidney disease), use of substances associated with nephrotoxicity (e.g., medicines and contrast media), major surgery, sepsis, and fluid overload have been identified as risk factors for AKI (Rewa and Bagshaw, 2014). Emerging evidence supports an association between high ambient temperatures (i.e., heat) and AKI. For example, heat exposure has been associated with a higher risk of emergency department visits and hospital admission owing to AKI in Australia and Korea (Kim et al., 2018a; Kim et al., 2019; Lim et al., 2018; Xu et al., 2020). These associations may be predominantly attributed to heat-related dehydration and volume depletion, that can lead to hemodynamically mediated AKI (Knowlton et al., 2009; Lim et al., 2018).

Because climate change may increase the frequency and intensity of low-temperature events, especially in the mid-latitudes, (Cohen et al., 2018; Kim et al., 2018a, 2018b; Zhang et al., 2016) and the aging of world populations may lead to increased susceptibility to cold exposure (Chen et al., 2019; Lee et al., 2018), it is urgent to investigate the potential association between cold exposure and AKI. However, there is a paucity of studies on the association between cold exposure and AKI, and the results are inconsistent. Some studies have identified an association (Kim et al., 2018a; Mohammad et al., 2021), whereas other studies reported no association (Kim et al., 2019; Lim et al., 2018).

Therefore, we sought to investigate associations of cold exposure with hospital admission and mortality due to AKI using nationwide time-series data of the Republic of Korea. Further, we explored whether these associations were modified by age and sex to identify populations that were vulnerable to cold exposure. Because global climate change results in increased temperature variability (McMichael et al., 2006) and AKI is associated with substantial complications and poor clinical outcomes (Negi et al., 2018), this study puts forth important public health implications.

2. Material and methods

2.1. Study population and definition of AKI

Information on daily counts of hospital admission with the principal diagnosis of AKI [International Classification of Diseases, 10th revision (ICD-10) code N17] for the 16 regions of Korea (Table S1; Fig. S1) was obtained from the National Health Insurance Service (NHIS), a single national insurer providing universal health coverage (Kwon, 2009). This study considered community-acquired and hospital-acquired AKI as cases because individual-level data, such as hospital admission due to underlying diseases, were unavailable. Hospital visits with the same diagnosis within 1 week of prior visits were considered to be caused by continuous episodes and were excluded from further analyses. Information on daily counts of mortality with AKI as the cause of death (ICD-10 code N17) for the same 16 regions of Korea (Table S1; Fig. S1) was obtained from Statistics Korea.

These claims and mortality data included daily counts of cases among the total population and populations stratified by age (<65 years and ≥ 65 years) and sex between January 1, 2010 and December 31, 2019. The Institutional Review Board of Ajou University Hospital reviewed and approved the study protocol (AJIRB-MED-EXP-22-223). This study was performed in accordance with the Declaration of Helsinki. The need for written informed consent was waived because of the use of de-identified count data.

2.2. Meteorological factors and air pollutants

Hourly temperature (°C) and relative humidity (%) data were obtained from 94 automated synoptic observing systems out of the 102 systems operated by the Korean Meteorological Administration. We excluded data from five systems with substantial missing values (>50 %) and three systems that were located on remote islands and mountains. To estimate region-specific daily temperature and relative humidity, we first aggregated daily data from hourly data in each system and then averaged the daily data of all systems in each region.

Hourly concentrations of particulate matter with an aerodynamic diameter of ≤10 μm (PM_{10}) and nitrogen dioxide (NO_2) were obtained from 318 monitoring sites of the National Ambient Air Monitoring Information System. Similarly, we estimated region-specific daily air pollution levels by calculating daily data from hourly data in each monitoring site and averaging the daily data of all monitoring sites in each region. We did not consider particulate matter with an aerodynamic diameter of ≤2.5 μm ($PM_{2.5}$) in the present study because the national data for $PM_{2.5}$ levels have only been available since 2016.

2.3. Analytical models

We restricted our analyses to cold seasons (i.e., November to March) and applied a two-stage analytical strategy to evaluate the associations of cold exposure with hospital admission and mortality due to AKI. We analyzed region-specific estimates in the first stage and then pooled the values to estimate national values in the second stage.

In the first stage, we constructed generalized linear models with a quasi-Poisson distribution combined with distributed lag models in each region (Gasparrini, 2011). Distributed lag models were used to capture the lagged effects of low ambient temperatures. We used two cold exposure variables in our analyses: a low temperature, defined as the region-specific 10th percentile of daily mean temperature (distributed lag non-linear models, using the 90th percentile as a reference), and a cold spell, defined as ≥2 consecutive days with a daily mean temperature lower than the region-specific 5th percentile (distributed lag linear models). We defined the 90th percentile of daily mean temperature as a reference to obtain stable results not affected by extreme values. The percentiles were calculated from daily mean temperatures during the cold seasons. This definition of a cold spell was similar to that used in previous studies conducted in East Asia (Chen et al., 2019; Kim et al., 2022; Ma et al., 2021). We considered cold spells because their effects have been suggested to differ from the effects of low temperatures alone (Lee et al., 2018; Sartini et al., 2016).

The exposure-response associations for daily mean temperature and relative humidity were modeled with a natural cubic spline with three degrees of freedom (df) and two knots placed equally in the exposure spaces. The exposure-response association for cold spells was modeled with a linear function. The lag-response associations for lag days up to 21 days were modeled with a natural cubic spline with three df and one knot placed equally in the log scale. We considered lag days up to 21 days because previous studies have reported that cold exposure effects last for similar periods (Chen et al., 2019; Liu et al., 2021; Ma et al., 2021). Furthermore, our preliminary analyses for lag-specific associations using the distributed lag models generally supported the choice of a lag period of 21 days as well (Fig. S2; Fig. S3).

The first-stage analytical models can be expressed as in the following equation:

$$\begin{aligned}\log\left[E(\mathrm{Outcome}_t)\right] = {} & \beta_0 + \beta_1 CB_{t,l}(\mathrm{Exposuret}) + \beta_2 CB_{t,l}(\mathrm{Humidityt}) \\ & + \beta_3 DOW_t + \beta_4 \mathrm{Holiday}_t + \beta_5 \mathrm{Season}_t \\ & + \beta_6 NS(\mathrm{Seasonality}_t, df = 3) + \beta_7 PM_{10t} + \beta_8 NO_{2t} \\ & + \beta_9 ARI_t,\end{aligned}$$

where $CB_{t,l}(\mathrm{Exposure}_t)$ and $CB_{t,l}(\mathrm{Humidity}_t)$ are cross-basis matrix terms of exposure (low temperature or cold spell) and relative humidity on day t with lag l (21 days), respectively. Dow_t, $Holiday_t$, and $Season_t$ are categorical variables for day of week, public holidays, and seasons (January–March 2010, November 2010–March 2011, …, and November–December 2019) on day t, respectively. NS($Seasonality_t$, df = 3) is a natural cubic spline term of the number of days from November 1 to day t each season. $Season_t$ and NS($Seasonality_t$, df = 3) were adjusted to control the long-term trend. PM_{10t} and NO_{2t} are continuous variables for PM_{10} and NO_2 concentrations on day t, respectively. ARI_t is a categorical variable for acute respiratory infection epidemics [days with ≥95th percentile of hospital admission due to acute respiratory infections (ICD-10 code J00–J06); categorical variable] on day t.

Because a single best combination of model parameters could not be determined due to the heterogeneity of analytical models for different exposures, outcomes, and regions, the model specifications were set a priori based on previous studies (Chen et al., 2019; Kim et al., 2022; Ma et al., 2021). The robustness of the results was further assessed in sensitivity analyses using different df and covariate sets.

In the second stage, we pooled the overall cumulative association estimates of 16 regions using univariate meta-regression models (Gasparrini and Armstrong, 2013; Lei et al., 2022) to calculate the national estimates. Potential heterogeneity of the associations between regions was assessed using I^2 statistics, which represents the proportion of association variability explained by a specific heterogeneity factor (i.e., regions), and Cochran's Q-test, which is performed to statistically test the null hypothesis of no heterogeneity in the associations with a heterogeneity factor (i.e., regions).

Alternatively, to control the potential population effects, we constructed generalized linear mixed models (Poisson distribution) with a random effect of 16 regions of the Republic of Korea, combined with the distributed lag non-linear (low temperatures) and linear (cold spells) models. The generalized linear mixed models were adjusted for the same covariate set as the main models.

Further, we performed age- (<65 years and ≥65 years) and sex-stratified analyses based on previous studies that have suggested differences in the association between extreme temperatures and AKI risk by age and sex (Lombardi et al., 2021; Xu et al., 2020). Because mortality due to AKI among individuals aged <65 years was very rare (Table 1), we could not assess the associations between cold exposure and mortality due to AKI among those aged <65 years and have excluded those results. In addition, we excluded Jeju when drawing national estimates for the association between cold spells and mortality due to AKI among men because the regional estimate for Jeju among men could not be calculated. Differences in the associations according to these strata were assessed using the following equation: $\left(\widehat{B1} - \widehat{B2}\right) \pm 1.96\sqrt{\left(\widehat{SE1}\right)^2 + \left(\widehat{SE2}\right)^2}$, where $\widehat{B1}$ and $\widehat{B2}$ are regression coefficients of the associations in each stratum, and $\widehat{SE1}$ and $\widehat{SE2}$ are their standard errors in each stratum.

Finally, we calculated the attributable fractions and numbers of daily mean temperatures below the 90th percentile of the national daily mean temperature during the cold seasons (<11.3 °C), those between the 10th and 90th percentile (−3.5–11.3 °C), and those below the 10th percentile (<−3.5 °C) for hospital admission and mortality due to AKI. Analyses were conducted based on the method developed for distributed lag non-linear model frameworks (Gasparrini and Leone, 2014). Briefly, cold exposure-related excess outcomes were calculated by summing the daily contributions estimated from nation-level data and similar distributed lag non-linear models that were further adjusted for regions. Attributable fractions were calculated by dividing these excess values by corresponding total hospital admissions or mortality due to AKI. We estimated 95 % empirical confidence intervals (eCIs) of attributable numbers and fractions using Monte Carlo simulations.

We performed the following sensitivity analyses. First, we changed the df of exposure-response associations for daily mean temperature and

Table 1
Meteorological factors, air pollution levels, and daily counts of hospital admission and mortality due to acute kidney injury in the Republic of Korea during the cold seasons (November–March), 2010–2019.

	Mean ± SD	Percentiles				
		Min	25th	50th	75th	Max
Meteorological factors						
Ambient temperature (°C)	3.7 ± 5.1	−10.6	0.2	3.7	7.0	19.2
Relative humidity (%)	61.0 ± 12.0	27.9	52.4	60.4	69.0	94.6
Air pollution levels						
PM_{10} (μg/m^3)	53.0 ± 30.6	4.7	34.8	46.3	62.4	568.7
NO_2 (ppb)	36.5 ± 12.8	11.0	26.0	36.0	46.0	80.0
Daily counts of hospital admission due to acute kidney injury						
Total	39.0 ± 16.3	5.0	25.8	35.0	48.0	94.0
<65 years	12.0 ± 5.1	0.0	8.0	11.0	15.0	35.0
≥65 years	26.0 ± 12.4	4.0	17.0	24.0	34.0	70.0
Men	20.5 ± 9.3	1.0	14.0	19.0	26.0	58.0
Women	17.5 ± 8.2	2.0	11.0	16.0	23.0	48.0
Daily counts of mortality due to acute kidney injury						
Total	1.2 ± 1.2	0.0	0.0	1.0	2.0	7.0
<65 years	0.1 ± 0.4	0.0	0.0	0.0	0.0	2.0
≥65 years	1.0 ± 1.1	0.0	0.0	1.0	2.0	6.0
Men	0.5 ± 0.8	0.0	0.0	0.0	1.0	6.0
Women	0.6 ± 0.8	0.0	0.0	0.0	1.0	4.0

Abbreviations: Max, maximum; Min, minimum; NO_2, nitrogen dioxide; PM_{10}, particulate matter with an aerodynamic diameter ≤ 10 μm; ppb, parts per billion; SD, standard deviation.

relative humidity from 3 to 4 and 5 to confirm that the results were insensitive to specific analytical models. Second, we conducted analyses that were not adjusted for air pollution levels (i.e., PM_{10} and NO_2 concentrations). Air pollution levels were included as covariates in the main models because they are closely related to meteorological factors and may decrease renal function and increase the risk of chronic kidney disease (Bowe et al., 2018; Mehta et al., 2016). However, because air pollution levels were not controlled for in some previous studies (Lim et al., 2018; Lombardi et al., 2021), we constructed analytical models that were not adjusted for air pollution levels to enable comparison of the current results with those of previous studies. Third, we restricted the regions to seven metropolitan cities (Seoul, Busan, Daegu, Incheon, Gwangju, Daejeon, and Ulsan) with relatively small areas to decrease measurement errors of exposure due to areas that were too large (Table S1). Fourth, we excluded Jeju in sex-stratified analyses of the association between cold spells and mortality due to AKI among both men and women in order to increase the comparability.

The analyses were performed using R version 4.1.1, with "dlnm," "dplyr," "FluMoDL," "forestplot," "mvmeta," and "splines" packages.

3. Results

The mean ambient temperature and relative humidity during the cold seasons were 3.7 °C (standard deviation, 5.1 °C) and 61.0 % (12.0 %), respectively (Fig. 1). The mean daily counts of hospital admission due to AKI were 39.0 (16.3) among the total population, 12.0 (5.1) among individuals aged <65 years, 26.0 (12.4) among those aged ≥65 years, 20.5 (9.3) among men, and 17.5 (8.2) among women. The mean daily counts of mortality due to AKI were 1.2 (1.2) among the total population, 0.1 (0.4) among individuals aged <65 years, 1.0 (1.1) among those aged ≥65 years, 0.5 (0.8) among men, and 0.6 (0.8) among women (Table 1; Fig. 2).

Low temperatures (10th percentile of daily mean temperature) were associated with a higher risk of hospital admission due to AKI [relative risk (RR) = 1.12, 95 % confidence interval (CI): 1.09, 1.16] compared to the 90th percentile of the daily mean temperature. The association was stronger between cold spells and hospital admission due to AKI (RR = 1.87, 95 % CI: 1.46, 2.39) (Table 2; Table S2). Cold spells were also associated with a higher risk of mortality due to AKI, with a point estimate for the association of 4.84 (95 % CI: 1.30, 17.98) (Table 2; Table S3).

We found consistent results from the generalized linear mixed models combined with the distributed lag non-linear and linear models. Low temperatures (10th percentile of national daily mean temperature, −3.5 °C) were associated with a higher risk of hospital admission due to AKI (RR = 1.12, 95 % CI: 1.09, 1.16) compared to the 90th percentile of the national daily mean temperature (11.3 °C), while the association with mortality due to AKI had a wider CI (RR = 1.11, 95 % CI: 0.94, 1.31) (Fig. 3). Cold spells were associated with a higher risk of hospital admission (RR = 1.72, 95 % CI: 1.05, 2.18) and mortality due to AKI (RR = 5.73, 95 % CI: 1.75, 18.73).

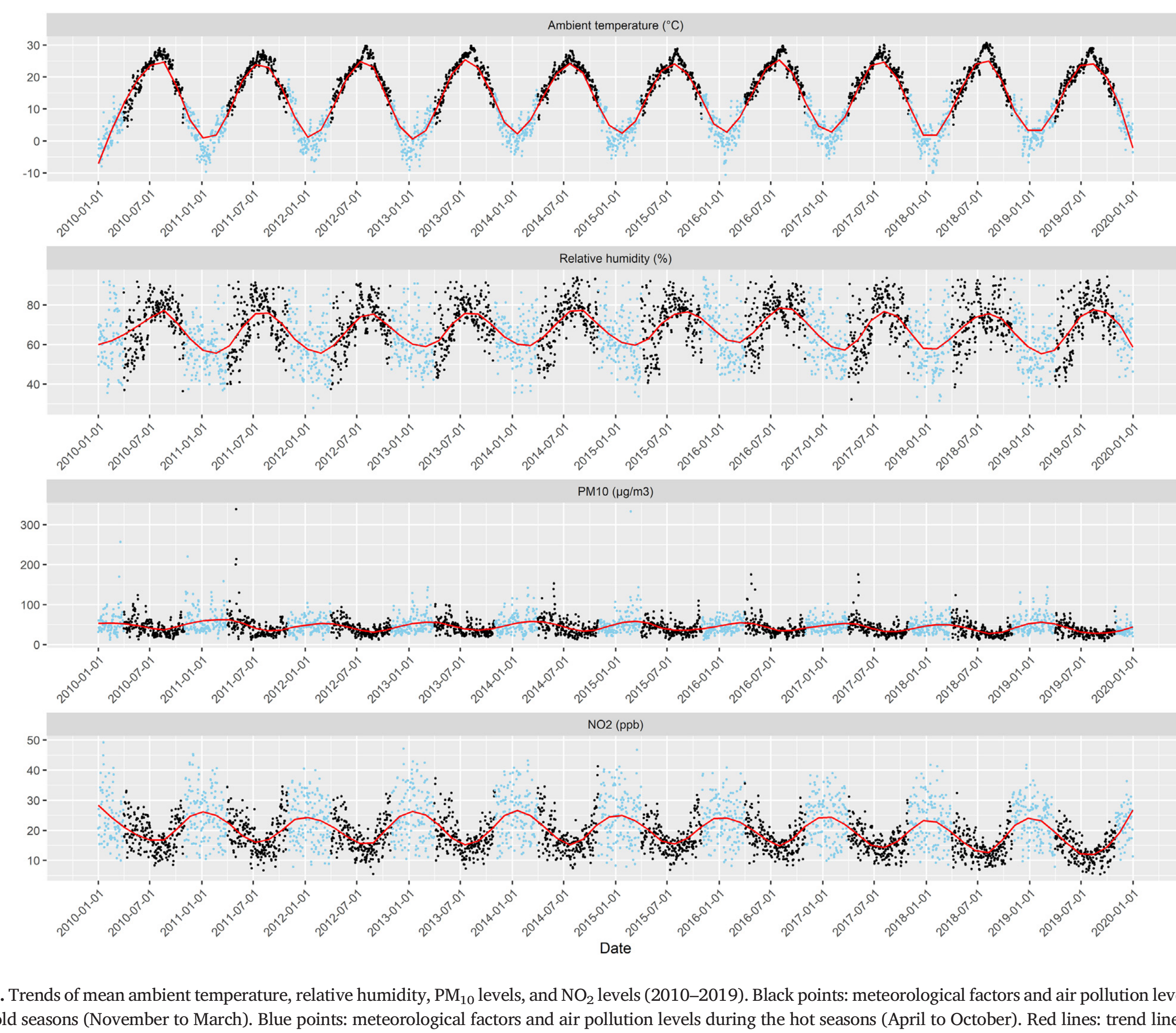

Fig. 1. Trends of mean ambient temperature, relative humidity, PM_{10} levels, and NO_2 levels (2010–2019). Black points: meteorological factors and air pollution levels during the cold seasons (November to March). Blue points: meteorological factors and air pollution levels during the hot seasons (April to October). Red lines: trend lines.

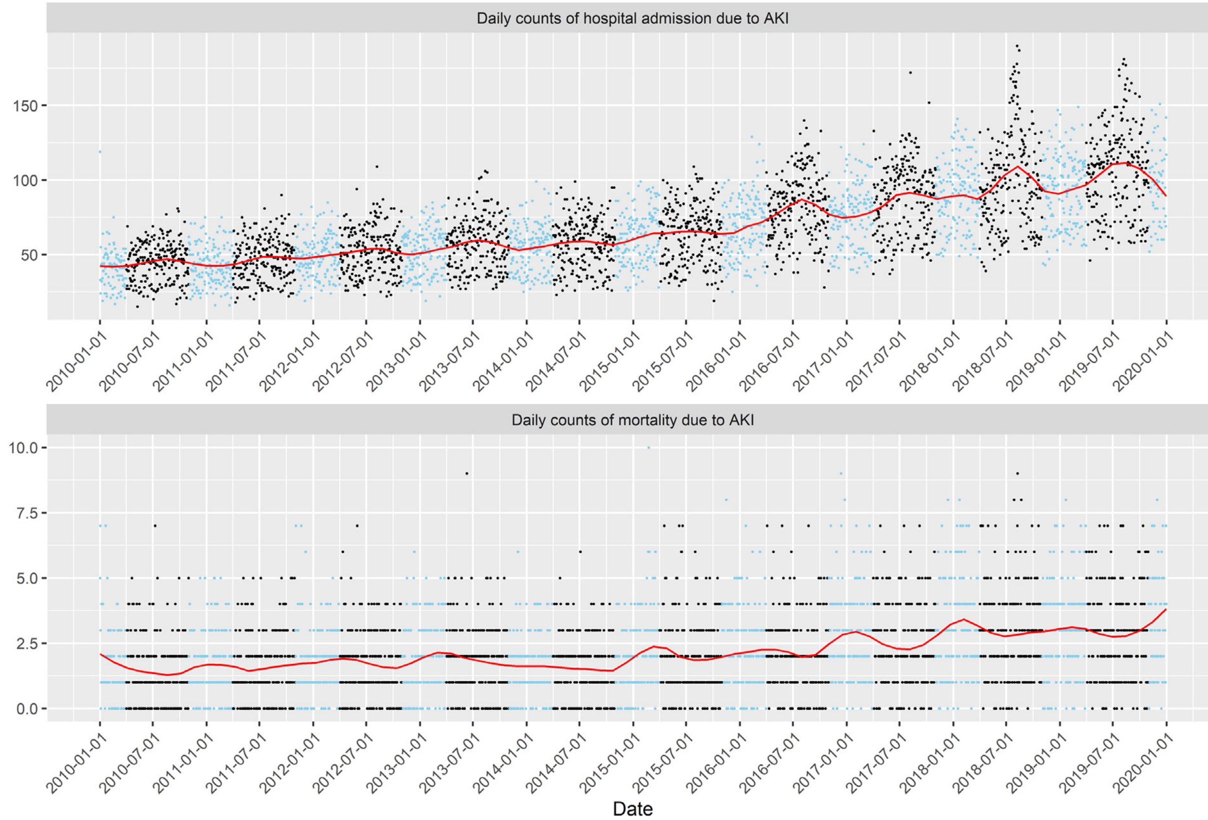

Fig. 2. Trends of mean counts of hospital admission and mortality due to acute kidney injury (2010–2019). Abbreviation: AKI, acute kidney injury. Black points: mean counts of hospital admission and mortality due to AKI during the cold seasons (November to March). Blue points: mean counts of hospital admission and mortality due to AKI during the hot seasons (April to October). Red lines: trend lines.

The association between low temperatures and hospital admission due to AKI was stronger among individuals aged ≥65 years (RR = 1.17, 95 % CI: 1.13, 1.21) than among those aged <65 years (RR = 1.03, 95 % CI: 0.97, 1.09) (*p*-value for difference = 0.01). The association was similar between men (RR = 1.14, 95 % CI: 1.09, 1.19) and women (RR = 1.11, 95 % CI: 1.06, 1.16) (*p*-value for difference = 0.46). The association between cold spells and hospital admission due to AKI was also stronger among individuals aged ≥65 years (RR = 2.19, 95 % CI: 1.63, 2.93) than among those aged <65 years (RR = 1.19, 95 % CI: 0.74, 1.91) (*p*-value for difference = 0.03). The association was not significantly different between men and women (*p*-value for difference = 0.22), although the point estimate for the association was larger among women (RR = 2.17, 95 % CI: 1.49, 3.16) than among men (RR = 1.59, 95 % CI: 1.14, 2.22) (Fig. S4; Table S4). The associations of low temperatures and cold spells with mortality due to AKI were not significantly different between men and women (*p*-values for difference = 0.08 and 0.18 for low temperatures and cold spells, respectively), although the point estimates for the associations were larger among men (RR = 1.47, 95 % CI: 1.11, 1.95 for low temperatures; RR = 13.81, 95 % CI: 1.17, 162.99 for cold spells) than among women (RR = 1.07, 95 % CI: 0.86, 1.33 for low temperatures; RR = 1.62, 95 % CI: 0.25, 10.74 for cold spells) (Fig. S5; Table S5).

Table 2

Associations[a] of cold exposure with hospital admission and mortality due to acute kidney injury in the Republic of Korea during the cold seasons (November–March), 2010–2019.

	Relative risk	95 % CI
Hospital admission due to acute kidney injury		
Low temperature[b]	1.12	1.09, 1.16
Cold spell[c]	1.87	1.46, 2.39
Mortality due to acute kidney injury		
Low temperature[b]	1.18	0.99, 1.41
Cold spell[c]	4.84	1.30, 17.98

Abbreviation: CI, confidence interval.

[a] Overall cumulative associations up to 21 days estimated using quasi-Poisson regression models adjusted for relative humidity, days of the week, public holidays, seasons, days of the season, PM_{10} concentrations, NO_2 concentrations, and acute respiratory infection epidemics.

[b] Defined as the region-specific 10th percentile of daily mean temperature in the distributed lag non-linear models.

[c] Defined as ≥2 consecutive days with a daily mean temperature lower than the region-specific 5th percentile in the distributed lag linear models.

The attributable fractions of daily mean temperatures <11.3 °C, −3.5–11.3 °C, and <−3.5 °C for hospital admission due to AKI were 6.7 % (95 % eCI: 4.8 %, 8.5 %), 5.4 % (3.7 %, 7.3 %), and 1.3 % (0.9 %, 1.7 %), respectively. The corresponding attributable numbers were 6581.9 (4629.8, 8294.2), 5310.3 (3606.3, 7059.7), and 1271.6 (865.6, 1643.8), respectively. The attributable fractions of daily mean temperatures <11.3 °C, −3.5–11.3 °C, and <−3.5 °C for mortality due to AKI were 5.2 % (−6.3 %, 15.7 %), 2.7 % (−8.1 %, 11.9 %), and 2.5 % (0.9 %, 4.1 %), respectively. The corresponding attributable numbers were 179.4 (−212.6, 530.0), 92.2 (−244.6, 385.9), and 87.2 (23.6, 136.4), respectively (Table S6).

We observed robust results in the sensitivity analysis in which the df of the exposure-response associations for daily mean temperature and relative humidity were changed from 3 to 4 and 5 (Table S7). The analyses that were not adjusted for air pollution levels revealed similar results (Table S8). The analyses restricted to seven metropolitan cities presented consistent associations, while the precision of the associations was slightly lower (Table S9). The results were similar when Jeju was excluded from sex-stratified analyses of the association between cold spells and mortality due to AKI among both men and women (Table S10).

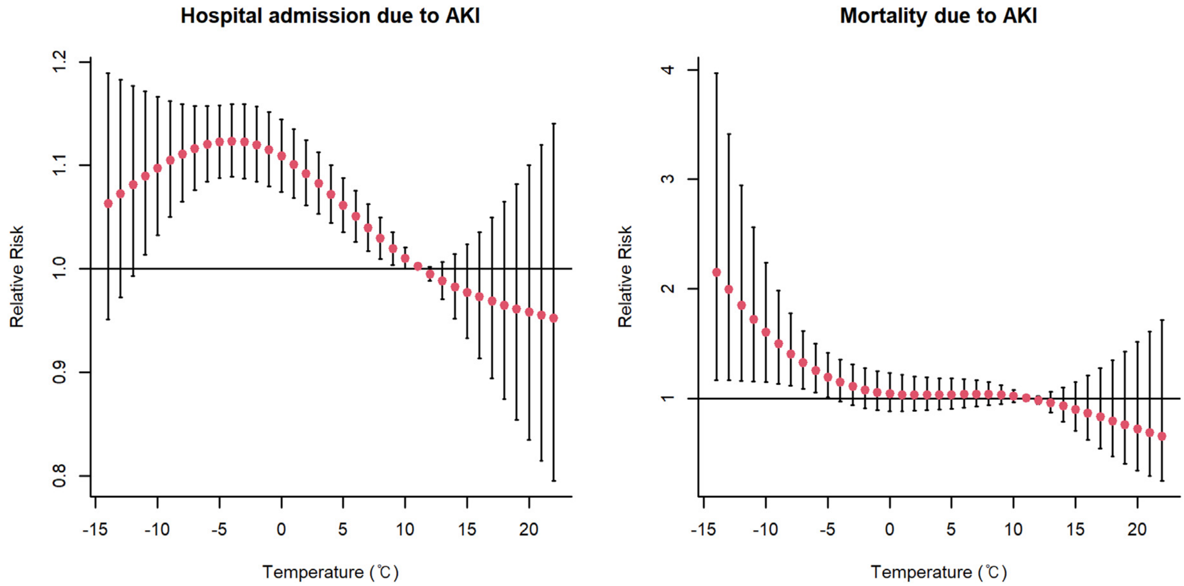

Fig. 3. Concentration-response curves for the associations of low temperatures with hospital admission and mortality due to acute kidney injury. Cumulative associations up to 21 days were estimated from the generalized linear mixed models with a random effect of 16 regions of the Republic of Korea, combined with the distributed lag non-linear models. The analytical models were adjusted for relative humidity, days of the week, public holidays, seasons, days of the season, PM_{10} concentrations, NO_2 concentrations, and acute respiratory infection epidemics.

4. Discussion

In this Korean study conducted during the cold seasons with a mean temperature of 3.7 °C, low temperatures and cold spells were associated with a higher risk of hospital admission due to AKI. Cold spells were also associated with a higher risk of mortality due to AKI. The associations of low temperatures and cold spells with hospital admission due to AKI were stronger among individuals aged ≥65 years than among those aged <65 years. The attributable fractions of daily mean temperatures <11.3 °C, −3.5–11.3 °C, and <−3.5 °C for hospital admission due to AKI were 6.7 %, 5.4 %, and 1.3 %, respectively, and those for mortality due to AKI were 5.2 %, 2.7 %, and 2.5 %, respectively.

Previous studies on the association between cold exposure and AKI have shown inconsistent results. In a time-series study performed in Hong Kong, which has a subtropical climate with a median temperature of 24.7 °C, the risk of hospital admission due to AKI was higher when the daily mean temperature was 8.2 °C than when it was 24.7 °C (RR = 1.72, 95 % CI: 1.44, 2.05) (Mohammad et al., 2021). In another time-series study conducted in 16 regions of Korea, low temperatures with lag days up to 7 days were associated with a higher risk of hospital admission due to AKI (Kim et al., 2018a). However, an association between cold exposure and emergency department visits or hospital admission due to AKI was not observed in a case-crossover study (Kim et al., 2019) and time-series study (Lim et al., 2018), both of which were conducted in a single city (i.e., Seoul) in Korea. The inconsistencies between previous results and the current findings may be due to different analytical strategies (consideration of lag days 0 and 1 in previous studies vs. lag days up to 3 weeks in the present study), study settings (data obtained only from Seoul in previous studies vs. from 16 regions including Seoul in the present study), and model specifications (e.g., adjusted covariate set). A cross-sectional study among older individuals in the United States reported that cold exposure was not associated with two biomarkers of AKI (neutrophil gelatinase-associated lipocalin and adiponectin) (Honda et al., 2019). Because this previous study used biomarkers of AKI, delayed effects of cold exposure were not explored, which may be responsible for the discrepancy in the results.

Clinically severe cases of AKI and mortality from this condition were reported to be more common in winter than in the other seasons in Japan (Iwagami et al., 2018). However, to our knowledge, the present study is the first to explicitly assess the association between cold exposure and mortality due to AKI, which may reflect clinically more severe cases. Considering the potential clinical implications of these findings and the paucity of evidence in this regard, further studies are warranted to confirm this association.

To our knowledge, no study to date has investigated the association between cold spells (rather than just low temperatures) and AKI. The point estimates of the associations for cold spells were 1.7–4.1 times greater than those of the associations for low temperatures among the total population in the present study, suggesting stronger effects of cold spells than those of low temperatures on AKI. These results are plausible because cold spells reportedly exert greater strain on the body's homeostatic systems and may impose greater health effects (Chen et al., 2017; Ma et al., 2021). Further, it is notable that the point estimates of the associations between cold spells and AKI were relatively large (RR = 1.98 and 4.84 for hospital admission and mortality due to AKI, respectively) in the present study. Therefore, we assumed that these associations are less likely to occur due to residual confounding.

The association between cold exposure and AKI can be explained by the following biological mechanisms. Cold exposure may increase urinary voiding and respiratory water losses and decrease fluid intake, leading to dehydration (Kenefick et al., 2004; Lim et al., 2015). Dehydration, in turn, may increase the risk of AKI by imposing ischemic damage caused by reduced renal flow and renal vein thrombosis (Kim et al., 2018a; Lim et al., 2015; Suga et al., 2001). In addition, peripheral vasoconstriction due to cold exposure or frostbite can cause rhabdomyolysis, which is a common cause of AKI accounting for 7–10 % of AKI cases in the United States (Bagley et al., 2007; Mikkelsen and Toft, 2005; Sharp et al., 2004).

We found that the associations between cold exposure and hospital admission due to AKI were stronger among individuals ≥65 years than those aged <65 years. This increased susceptibility to cold exposure of those aged ≥65 years may be due to lower thermoregulatory abilities, renal reserve, adaptation behaviors, and alertness to dehydration among the elderly (Bunker et al., 2016). Meanwhile, excess all-cause mortality related to cold exposure in Switzerland was estimated to be substantially higher among individuals aged ≥80 years (excess rate of 1275 per 100,000) than among those aged 65–79 years (excess rate of 239 per 100,000) and < 65 years (excess rate of 7 per 100,000) (de Schrijver et al., 2022). These results suggest that the association between cold exposure and AKI may be more prominent among the oldest group. However, further stratification of the elderly group by age was impossible due to data limitations in the present study. Because evidence is scarce on the association between cold exposure and AKI in susceptible populations, more efforts are needed to identify susceptible populations, including the oldest group.

The associations of cold exposure with hospital admission and mortality due to AKI were not found to be different appreciably between men and women in the present study. These findings support that sex-related biological pathways might not be involved in the effects of cold exposure on AKI. However, because sex-stratified analyses on the associations between cold exposure and AKI were rarely performed previously and cold-exposure patterns of men and women might differ by culture and region, further studies are needed before concluding the results.

This study has several limitations. First, although the effects of cold exposure on AKI may be stronger among individuals with underlying diseases, such as chronic kidney disease and diabetes mellitus (Chawla et al., 2014; Xu et al., 2019), this could not be assessed in this time-series study using aggregated data. This issue warrants further exploration using individual-level data. Second, repeated cold exposure-related insults may lead to progressively irreversible renal damage (Chawla et al., 2014). However, we were unable to evaluate this possibility, which might have notable clinical implications, in this study with region-level count data. Longitudinal studies that repeatedly measure exposures and outcomes are warranted. Third, ambient temperatures used in this study may not reflect individual cold exposure, given the differences in heating systems and cold weather gears worn by the individuals. This exposure misclassification may be non-differential and bias the results to accepting the null hypothesis. Fourth, information on nephrotoxic drug applications, which can affect the risk of outcome development, could not be incorporated due to the lack of data. However, we assumed that cold exposure would not affect the application of nephrotoxic drugs, which, therefore, would not act as a confounder. Fifth, because this study used secondary claims and mortality data, we could not evaluate the types of AKI (i.e., pre-renal, intrinsic, and post-renal), which may shed light on underlying mechanisms. Sixth, in this study, some scheduled hospital admissions and AKI occurring during hospitalization due to other diseases were considered cases. Because they were not likely to be associated with cold exposure, these misclassifications may have led the results toward the null hypothesis. However, we found consistent results in analyses using mortality due to AKI as an outcome. Seventh, because hospital deaths are likely to be associated with many critical conditions, such as multi-organ failure, it is sometimes difficult to determine a principal cause of death, especially for patients with various underlying diseases. Although we found consistent results in analyses using the claims data, future studies with various individual-level information, such as clinical pathways and underlying diseases, are needed to reduce the concern of outcome misclassification and confirm the results of analyses using only daily counts of mortality data.

Nevertheless, this study also has notable strengths. First, this is one of the first studies on the association between cold exposure and AKI. Among studies exploring this association, this study is the first to consider cold spells as the exposure and mortality due to AKI as the outcome. Second, we used two independent nationwide multi-region data sources (i.e., claims data from the NHIS and mortality data from Statistics Korea), which may increase the reliability and generalizability of the results. In addition, the large sample sizes of these data enabled us to perform stratified analyses by age and sex, although we could not obtain some estimators among individuals aged <65 years due to small outcome counts. Third, we conducted extensive analyses (e.g., analyses using the distributed lag model and univariate meta-regression methodology, analyses stratified by age and sex, and analyses for attributable fractions and numbers) and confirmed the results through various sensitivity analyses.

5. Conclusions

During the cold seasons in Korea, cold exposure was associated with a higher risk of hospital admission and mortality due to AKI, and these associations were stronger among individuals aged ≥65 years than among those aged <65 years. Significant proportions (approximately 5–7 %) of hospital admission and mortality due to AKI during the cold seasons were estimated to be preventable by appropriate protective measures against cold exposure. The results of this study underscore the need for the general population, particularly the elderly, physicians, and other healthcare providers to be more vigilant to cold exposure in consideration of the risk of AKI. Additionally, government agencies need to develop specific strategies for the prevention and early detection of cold exposure-related AKI.

CRediT authorship contribution statement

Kyoung-Nam Kim: Conceptualization, Methodology, Software, Formal analysis, Writing – original draft, Visualization, Project administration, Funding acquisition. **Moon-Kyung Shin:** Conceptualization, Writing – review & editing. **Youn-Hee Lim:** Conceptualization, Methodology, Writing – review & editing. **Sanghyuk Bae:** Conceptualization, Methodology, Writing – review & editing. **Jong-Hun Kim:** Conceptualization, Methodology, Writing – review & editing. **Seung-Sik Hwang:** Conceptualization, Writing – review & editing. **Mi-Ji Kim:** Conceptualization, Writing – review & editing. **Jongmin Oh:** Data curation, Writing – review & editing. **Hyungryul Lim:** Conceptualization, Writing – review & editing. **Jonghyuk Choi:** Conceptualization, Writing – review & editing. **Ho-Jang Kwon:** Conceptualization, Methodology, Writing – review & editing, Supervision.

Data availability

The authors do not have permission to share data.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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