

## Effects of Ambient Temperature

# Association of summer temperatures and acute kidney injury in South Korea: a case-crossover study

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## Abstract

**Background:** Due to climate change, days with high temperatures are becoming more frequent. Although the effect of high temperature on the kidneys has been reported in research from Central and South America, Oceania, North America and Europe, evidence from Asia is still lacking. This study aimed to examine the association between short-term exposure to high temperatures and acute kidney injury (AKI) in a nationwide study in South Korea.

**Methods:** We used representative sampling data from the 2002–2015 National Health Insurance Service–National Sample Cohort in South Korea to link the daily mean temperatures and AKI cases that occurred in the summer. We used a bidirectional case-crossover study design with 0–7 lag days before the emergency room visit for AKI. In addition, we stratified the data into six income levels to identify the susceptible population.

**Results:** A total of 1706 participants were included in this study. The odds ratio (OR) per 1°C increase at 0 lag days was 1.051, and the ORs per 1°C increase at a lag of 2 days were both 1.076. The association between exposure to high temperatures and AKI was slightly greater in the low-income group (OR = 1.088; 95% CI: 1.049–1.128) than in the high-income group (OR = 1.065; 95% CI: 1.026–1.105).

**Conclusions:** In our study, a relationship between exposure to high temperatures and AKI was observed. Precautions should be taken at elevated temperatures to minimize the risk of negative health effects.

**Key words:** Temperature, acute kidney injury, case-crossover study

**Key Messages**

- As global warming worsens, exposure to high temperatures, an environmental risk factor, is emerging as an important issue.
- Evidence for the effects of high temperatures on kidney disease is still lacking.
- A relationship between exposure to high temperatures and acute kidney injury was observed.
- This association between exposure to high temperatures and acute kidney injury was greater in the low-income group than in the high-income group.

**Introduction**

As global warming worsens, exposure to high temperatures, an environmental risk factor, is emerging as an important issue.<sup>1,2</sup> Since approximately 1750, greenhouse gases produced by human activities have accelerated global warming, and the changes to the climate caused by global warming are becoming more severe in both frequency and intensity.<sup>3,4</sup> Managing the health effects of high temperatures during exacerbated global warming is an important challenge.<sup>5</sup>

The health effects of high temperatures have been reported in various diseases.<sup>6</sup> Previous studies have mainly focused on cardiovascular and respiratory diseases.<sup>7–9</sup> However, starting in Central and South America from approximately 2000, problems with kidney disease due to high temperatures have also been reported.<sup>10</sup> Kidney disease had a high global prevalence of 9.1% in 2017, and it causes complications such as stroke, heart disease, diabetes and infection and is becoming an important health problem worldwide, leading to increased medical expenses.<sup>11,12</sup> The effect of high temperatures on the kidneys, which was first investigated in Central and South America, has been reported in other regions as well, including Oceania and North America and more recently in Europe.<sup>13,14</sup> Several studies have demonstrated an association between high temperature or heat waves and acute kidney injury (AKI). For example, Gronlund *et al.*<sup>15</sup> analysed data collected on the impact of high temperature and heat waves (temperature greater than or equal to the 95th percentile for at least 2 consecutive days) in people older than 65 during 1992–2006 from 114 cities in the USA. The results showed that high temperature and heat wave increase the number of admissions due to kidney disorders to 4.3% and 14.2%, respectively. Recently, Liu *et al.*<sup>14</sup> reviewed 91 studies, 82 of which met the inclusion criteria for their meta-analysis. The findings revealed that a 1°C increase in the temperature resulted in a 1.2% increase in the risk of AKI. The effects of sex and age are mainly discussed as effect modifiers,<sup>16,17</sup> although studies on variables such as the socioeconomic status (SES) are lacking.

Nevertheless, evidence of the effects of high temperatures on kidney disease in Asia is still required,<sup>18,19</sup> especially in South Korea, where only populations in major cities have been studied.<sup>20,21</sup> Therefore, the purpose of this study was to examine the relationship between high temperatures and AKI using a representative sample of a national population-based investigation in South Korea. In addition, the study attempted to identify the high-risk group through stratification analysis. This hypothesized that a high temperature increases the risk of AKI in the general population in South Korea and that there are differences in the age, sex, co-existing diseases and socioeconomic subgroups.

**Methods****Data collection**

We used the National Health Insurance Service–National Sample Cohort (NHIS-NSC) from South Korea.<sup>22</sup> In South Korea, the National Health Insurance System was implemented in 1963, and it covered most of the citizens residing within the territory of Korea.<sup>23</sup> The National Health Insurance System provides benefits for medical use and stores information on medical use and prescriptions. However, it is difficult to use these data because of the large amount of data stored. In addition, there is the issue of personal information protection; therefore, the NHIS-NSC was established for research and policy development. In 2002, 1 025 340 people, 2.2% of the South Korean population, were selected using stratified sampling based on sex, age, insurance premium and region. This sample constitutes a representative population-based cohort, and follow-up was conducted unless the participant was disqualified due to death or immigration. The representativeness of the data has been presented elsewhere.<sup>22</sup>

**Exposure, outcomes, and other variables**

To define cases, we used diagnostic code N17 (acute kidney injury; outcome variable) from the International

Classification of Diseases-10 (ICD-10) for hospitalizations during summer.<sup>20,24</sup> Since South Korea is located in the northern hemisphere, summer was defined as including the months of June, July and August. However, to strictly define true acute disease and exclude regular inpatients, a case was defined as hospitalization following emergency room admission.<sup>21</sup>

For climate data, we used the 2002–2015 Automated Synoptic Observing System (ASOS) data from the Korea Meteorological Administration (KMA), which is observational data collected regularly from 102 weather monitoring stations. Among the ASOS data, daily mean ambient temperature (°C) was used as the exposure variable. Additionally, the relative humidity (%) in the ASOS data and daily mean concentration of particulate matter with a diameter of 10 microns or less (PM<sub>10</sub>) obtained from the Korean National Institute of Environmental Research (NIER) were used as adjusted variables; 614 air pollution monitoring stations were installed and operated by the Korean Ministry of Environment (KME), and air pollution data were provided by NIER in the KME. We defined each participant's exposure (temperature, relative humidity and PM<sub>10</sub>) based on the closest monitoring data and city-level average values using the participant's address.

The effect modification by sex, age, household income level and co-existing diseases was identified in stratified analysis. Co-existing diseases included hypertension, diabetes mellitus (DM) and chronic kidney disease (CKD). Hypertension was defined as 'one or more claims per year per ICD-10 code I10 or I11 and one claim per year for antihypertensive prescriptions'.<sup>25</sup> DM was defined as 'one or more claims per year per ICD-10 code E10-E14 and one claim per year for antidiabetic prescriptions'.<sup>25</sup> CKD was defined as 'one or more claims per year per ICD-10 code N18-N19, I12-13, E102, E112, E132, or E142'.<sup>26</sup>

### Study design and statistical analysis

We used a bidirectional case-crossover design to evaluate the effect of short-term exposure to high temperature on the risk of AKI. The case-crossover design is a variant of the case-control study and is mainly used in environmental epidemiological studies to evaluate the effect when the outcome is acute and exposure is transient.<sup>27</sup> The case day (baseline) was defined as the day of the emergency room visit, and the days 1 week before and after the emergency room visit day and the days 2 weeks before and after the emergency room visit day were defined as control days. Therefore, the case and control days were compared in a 1:4 ratio. Each individual served as their own control, and all time-invariant confounders were automatically controlled.<sup>28</sup> The relative humidity was adjusted purely to

evaluate the effect of temperature.<sup>29</sup> In addition, the effect of particulate matter on the kidneys has been reported, and adjustment for PM<sub>10</sub> was also performed.<sup>30,31</sup>

Additionally, a non-linear relationship between temperature and AKI was identified. For the non-linear relationship, we used the penalized spline curve as the smoothing technique from the conditional logistic model. Since most health effects of temperature in many studies showed low latency, the lag effect was analysed for up to 7 days before the emergency room visit for AKI.<sup>32,33</sup> To select the best-fit model according to the linearity and lag effect, we selected the model with the lowest Akaike information criterion (AIC) value.<sup>34</sup> Additionally, we estimated the delayed effects of temperature on AKI using the following moving-average lag structures.

Subgroup analyses by sex, age, co-existing diseases (hypertension, DM, and CKD) and household income level were performed to determine the sensitivity of each group according to the effect of the temperature on the basis of the day when the lag effect was greatest. As a sensitivity analysis, the same analysis was performed using the heat index, which is the apparent temperature, instead of the ambient temperature. We used the regression equation of Rothfus to calculate the heat index<sup>35</sup> (Part I in the [Supplementary Material](#), available as [Supplementary data](#) at *IJE* online). Case-crossover is similar to matched case-control, so a conditional logistic regression model was used.<sup>36</sup> Statistical analysis was conducted using SAS software 9.4 and R software version 3.1.0 with the survival package.<sup>37</sup>

### Results

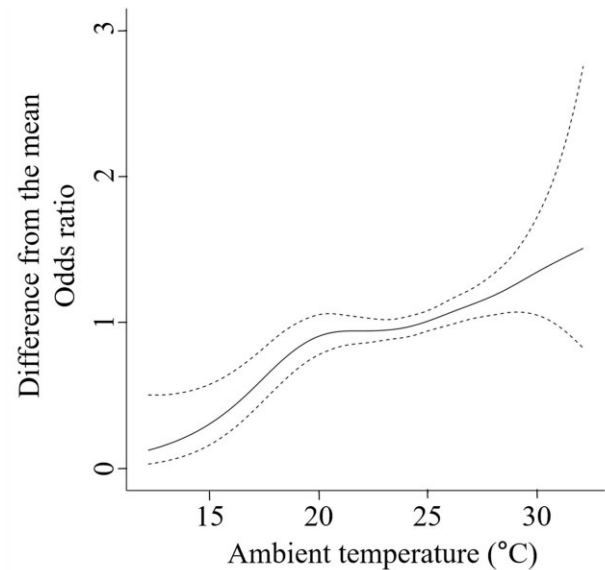
There were 6719 participants, limited to those diagnosed with AKI in 2002–15. Finally, 1706 participants were included after identifying cases that occurred in summer ([Supplementary Table S1](#), available as [Supplementary data](#) at *IJE* online). [Table 1](#) presents the characteristics of the participants. Overall, there were more male and 60.73% of the participants were aged 65 years. Regarding the co-existing diseases, hypertension was present in 71.92% of the participants, DM in 55.33% and CKD in 37.1%. [Supplementary Table S2](#), available as [Supplementary data](#) at *IJE* online, shows the descriptive statistics for environmental variables during the study period. The ambient temperature was 23.68°C (SD, ±2.23) and the heat index was 24.20 (SD, ±3.91).

[Figure 1](#) shows the non-linear relationship between ambient temperature and AKI incidence risk. In general, the risk of AKI increased with increasing temperature. These results were similar to those for the heat index ([Supplementary Figure S1](#), available as [Supplementary data](#) at *IJE* online). Additionally, we compared the AIC values between the

**Table 1** Characteristics of participants included in the final analysis

		Cases, n (%)
Total		1706 (100.00)
Gender	Male	955 (55.98)
	Female	751 (44.02)
Age	<65 years	670 (39.27)
	≥65 years	1036 (60.73)
Past history	Hypertension	1227 (71.92)
	DM	944 (55.33)
	CKD	633 (37.10)
Income level	Medical aid beneficiaries (lowest)	210 (12.31)
	1st quintile	227 (13.31)
	2nd quintile	207 (12.13)
	3rd quintile	244 (14.30)
	4th quintile	331 (19.40)
	5th quintile (highest)	469 (27.49)

DM, diabetes mellitus; CKD, chronic kidney disease.



**Figure 1** Non-linear relationship between the ambient temperature (°C) in the summer and the risk of acute kidney injury in South Korea

linear and non-linear models. We used the linear model, which exhibited lower AIC values than the non-linear model, as the main analysis for both exposure variables (Supplementary Table S3, available as Supplementary data at *IJE* online). Table 2 exhibits the effects of the ambient temperature and heat index on the risk of AKI in summer at a 0 lag days. Both the ambient temperature and heat index were associated with an increased risk of AKI. Figure 2

shows the effects of ambient temperatures, and Supplementary Figure S2 (available as Supplementary data at *IJE* online) shows the effects of the heat index on AKI incidence risk in summer with days of lag. In both Figure 2 and Supplementary Figure S2,, the peak risk is shown at 2 lag days. Furthermore, the AIC values according to the lag days were compared. Both the daily mean temperature and heat index exhibited the lowest AIC value at a lag of 2 days, so we chose the linear model at a lag of 2 days for the main analysis (Supplementary Table S3).

Table 3 exhibits the results of the stratified analysis regarding the effects of the temperature on AKI at a lag of 2 days. The female group (adjusted OR per 1°C increase, 1.096; 95% CI: 1.055–1.139) had a higher risk of AKI in high temperature conditions than the male group (adjusted OR per 1°C increase, 1.059; 95% CI: 1.023–1.097). The association of the older group (age ≥65 years) was slightly stronger than that of the younger group (age <65 years). The group with co-existing diseases had relatively higher risks of temperature-dependent AKI than the group without co-existing disease. However, the *P*-value for the interaction terms between subgroups was 0.218–0.725. The results of the stratified analysis according to the heat index were also similar (Supplementary Table S4, available as Supplementary data at *IJE* online).

When household income level was divided into low income (medical aid beneficiaries and National Health Insurance Premium 0–50%) and high income (National Health Insurance Premium 50–100%), the risk of AKI according to temperature and heat index was relatively higher in the low-income group than in the high-income group (Table 3, Supplementary Table S4). When household income level was divided into six groups (medical aid beneficiaries and National Health Insurance Premium levels 0–20%, 20–40%, 40–60%, 60–80% and 80–100%), the risk of AKI tended to decrease with temperature as income increased, with a relationship (*P* for trend = 0.0565) (Figure 3), whereas there was no clear trend in the reduction of the risk of AKI according to the heat index with an increased income (*P* for trend = 0.3193) (Supplementary Figure S3, available as Supplementary data at *IJE* online). Additionally, Supplementary Table S5 (available as Supplementary data at *IJE* online) demonstrates the delayed effects of the temperature on AKI using the following moving-average lag structures. The fitting lag structures for both the ambient temperature and heat index for the AKI were lags of 0–7 days.

**Discussion**

We identified an increase in the AKI incidence risk in the South Korean population according to the increase in

**Table 2** Effects of the ambient temperature and heat index on acute kidney injury in summer at a lag of 0 days

Exposure variable	Crude OR <sup>a</sup> (95% CI)	Adjusted OR <sup>b</sup> (95% CI)
Ambient temperature (°C)	1.046 (1.021–1.071)	1.051 (1.025–1.079) <sup>b</sup>
Heat index	1.030 (1.012–1.047)	1.027 (1.010–1.045) <sup>c</sup>

<sup>a</sup>The odds ratio (OR) was calculated using conditional logistic regression analysis. The associations are estimated as the ORs with 95% confidence intervals per 1°C increase in temperature.  
<sup>b</sup>The adjusted OR was calculated after adjusting for the average humidity and PM<sub>10</sub>. The associations are estimated as the ORs with 95% confidence intervals per 1°C increase in temperature.  
<sup>c</sup>The adjusted OR was calculated after adjusting for PM<sub>10</sub>. The associations are estimated as the ORs with 95% confidence intervals per 1°C increase in temperature.

**Figure 2** Effects of the ambient temperature in the summer on acute kidney injury by the number of lag days

temperature, which was also confirmed in the non-linear graph. The highest risk for AKI was observed at a lag of 2 days in our study. With the exception of some studies that used a broad definition of kidney disease,<sup>38,39</sup> the relationship between temperature and kidney disease in most studies showed a increase in risk, and the same results were found in a meta-analysis.<sup>13,14</sup>

This analysis adds to past evidence highlighting the impact of high temperatures on AKI. The study conducted in the USA by Fletcher *et al.*<sup>40</sup> had a design very similar to the design of this study, and the results are also similar. They studied the association between summer temperatures and the admissions due to kidney disorders in New York during the months of July and August between 1991 and 2004. The results suggest a 9% increase in the OR for hospitalizations due to AKI for every 2.78°C increase in the mean ambient temperature. More recently, Wen *et al.*<sup>41</sup> investigated the risk and attributive burden of hospitalization for kidney disease related to ambient temperature using daily hospitalization data from 1816 cities in Brazil between 2000 and 2015. The results demonstrate that for every 1°C increase in the average daily temperature, the risk of hospitalization for kidney disease increases by 0.9% for 0–7 days at the national level. The association between the temperature and kidney disease was greatest at 0 lag day,

but it was maintained at 1–2 days of lag. The risk was more pronounced in women and in individuals older than 80 years. Although it could be difficult to compare the results of this study with those of other studies, due to the differences in the study population and methods, results similar to ours have been found. A recent review and meta-analysis of epidemiological evidence demonstrated that for every 1°C increase in the temperature, there is a 1% increase in the risk of kidney-related morbidity.<sup>14</sup>

The effects of high temperature on the kidneys are known to be mainly related to dehydration. High temperature exposure induces dehydration,<sup>42</sup> which leads to the loss of body fluid and decreased renal blood flow. This in turn results in ischaemic conditions due to renal hypoperfusion.<sup>43</sup> Dehydration can also lead to electrolyte imbalance and activate regulatory mechanisms, causing the impairment of renal function.<sup>44,45</sup> The effect of high temperature is usually known to be acute<sup>46</sup>; similar to previous studies,<sup>40,47</sup> this study showed the highest risk for AKI in the short period after high temperature exposure.

The stratification analysis showed that there were differences in the effect size between stratified groups. In this study, the risk of AKI incidence due to high temperature was relatively higher in the female group than in the male group, and higher in the older group (≥65 years) than in

**Table 3** Effects of the temperature on acute kidney injury at a lag of 2 days

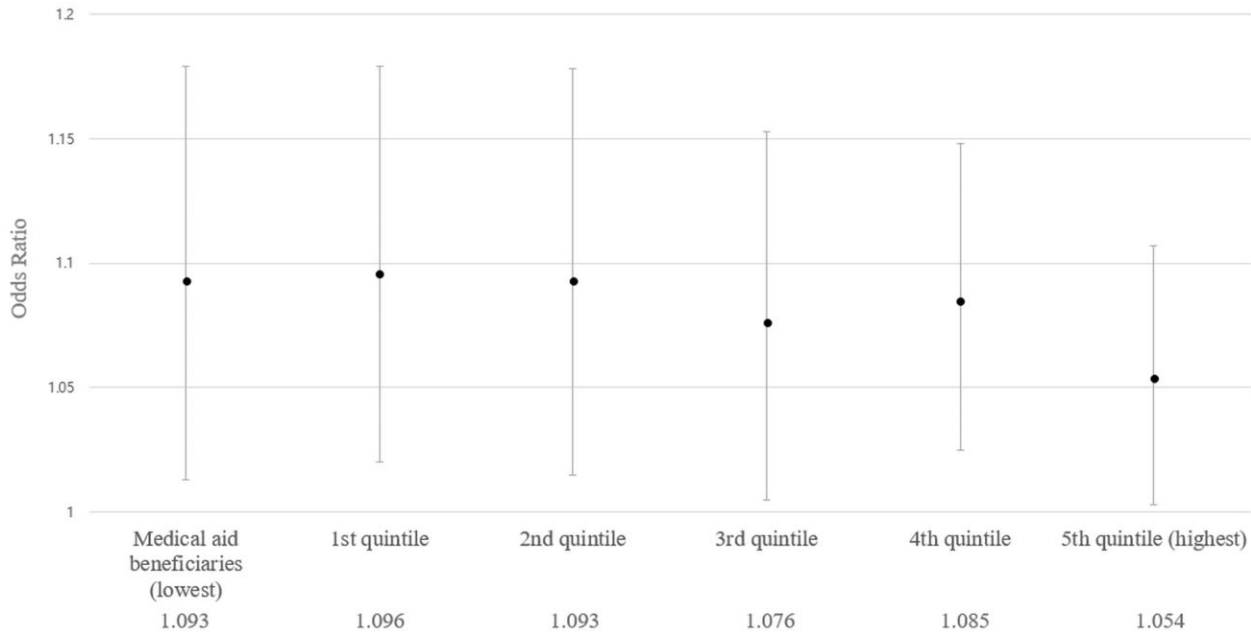
	Crude OR <sup>a</sup> (95% CI)	Adjusted OR <sup>b</sup> (95% CI)	P-value for interaction
Overall	1.069 (1.044–1.095)	1.076 (1.048–1.104)	
Sex			
Male	1.051 (1.018–1.086)	1.059 (1.023–1.097)	0.219
Female	1.091 (1.053–1.131)	1.096 (1.055–1.139)	
Age group			
<65	1.059 (1.020–1.099)	1.060 (1.018–1.104)	0.507
≥65	1.076 (1.044–1.110)	1.086 (1.051–1.123)	
Hypertension			
Yes	1.068 (1.038–1.098)	1.077 (1.044–1.110)	0.591
No	1.073 (1.026–1.123)	1.075 (1.024–1.129)	
DM			
Yes	1.074 (1.040–1.110)	1.086 (1.048–1.124)	0.618
No	1.063 (1.026–1.102)	1.064 (1.025–1.106)	
CKD			
Yes	1.077 (1.035–1.121)	1.079 (1.034–1.127)	0.725
No	1.065 (1.034–1.097)	1.073 (1.040–1.109)	
Income (quantile) <sup>c</sup>			
Low income	1.079 (1.043–1.115)	1.088 (1.049–1.128)	0.473
High income	1.062 (1.026–1.099)	1.065 (1.026–1.105)	

DW, diabetes mellitus; CKD, chronic kidney disease.

<sup>a</sup>The odds ratio (OR) was calculated using conditional logistic regression analysis. The associations are estimated as the ORs with 95% confidence intervals per 1°C increase in temperature.

<sup>b</sup>The adjusted OR was calculated after adjusting for the average humidity and PM<sub>10</sub> (particulate matter with a diameter of 10 microns or less). The associations are estimated as the ORs with 95% confidence intervals per 1°C increase in temperature.

<sup>c</sup>Low income: medical aid beneficiaries + National Health Insurance Premium 0–50%; high income: National Health Insurance Premium 50–100%.



**Figure 3** Effects of the ambient temperature on acute kidney injury in the summer by income level at 2 days of lag

the younger group (<65 years). In previous studies, this was found to be inconsistent according to the method of defining the subgroups, type of kidney disease and method of defining the disease.<sup>21,48</sup> In addition, there is no clear

mechanism to explain the differences according to sex and age group.<sup>14</sup> However, given that women have on average lower total body water per body mass than men, the loss of the same percent body mass between sexes can



potentially place a greater physiological burden on women.<sup>49</sup> Older people may be vulnerable to heat due to compromised thermoregulation during heat stress<sup>50</sup> and many co-existing diseases.<sup>15</sup> Our study found that the risk of temperature-dependent AKI was high in patients with co-existing diseases such as hypertension, DM and CKD. This explains in part why the older group is more vulnerable to heat exposure-related AKI.<sup>51</sup>

In this study, lower income groups were at higher risk of AKI incidence according to temperature. When examining the temperature-mortality relationship from 1991 to 1994 in São Paulo, Brazil, there was no difference according to socioeconomic status.<sup>8</sup> However, when looking at the relationship between temperature and hospitalization between 2000 and 2015 in 1814 cities in Brazil, there was a difference according to socioeconomic status.<sup>17</sup> The vulnerability to heat in the low SES group can be explained by increased susceptibility to disease and heat exposure.<sup>17</sup> In the low SES group, the risk of accompanying underlying diseases was relatively high, treatment compliance was low and hygiene conditions were poor, so they may have been more vulnerable to the effects of heat.<sup>52,53</sup> In terms of heat exposure, in working conditions in which it is difficult to avoid exposure to heat, facilities and air conditioners that can reduce exposure to heat should be considered.<sup>54–58</sup> People with low SES tend to be involved in outdoor industries such as agriculture and construction, making it difficult to avoid heat exposure during working hours.<sup>54,55</sup> People with a low SES generally lack the economic capacity to afford air conditioners<sup>56,57</sup> and have fewer amenities to avoid heat, such as shady parks.<sup>56,58</sup>

The strength of this study is that it covered a topic not previously examined in Asia. In addition, by using the case-crossover design, we were able to minimize inter-individual variation and confounding bias, which are difficult to control in environmental studies.<sup>59</sup> However, this study had several limitations. First, the outcome of AKI diagnosis was based on using the ICD-10 code as used in other studies; however, the ICD-10 code cannot identify the actual clinical details, so there may be misdiagnoses.<sup>20</sup> Second, using the ambient air temperature close to participants' residential locations rather than individual measurements can lead to the misclassification of the exposure. In addition, the difference between indoor and outdoor temperatures may affect the association between the temperature and AKI. However, individual measurements are difficult to apply in large-scale studies such as this, so the ambient air temperature at participants' residential locations was used for practicality. Third, in this study, PM<sub>10</sub> was used as a covariate for particulate matter, but PM<sub>2.5</sub> may be more appropriate.<sup>60</sup> However in South Korea, the PM<sub>2.5</sub> measurement started in 2015, so adjustment for the

PM<sub>2.5</sub> could not be performed in this study.<sup>61,62</sup> Analysis using the PM<sub>2.5</sub> should be implemented in future studies. Finally, bias due to intra-individual variation could be minimized with a case-crossover design; however unknown variables, not intra-individual variation, could not be adjusted due to a lack of information.

## Conclusion

In conclusion, the results of this study further support the evidence for the relationship between high temperature exposure and kidney disease; this relationship is relatively stronger among females, elderly individuals, those with co-existing diseases and those with a low SES. This suggests that it is necessary to focus on and manage groups that are more vulnerable to the effects of climate.

## Ethics approval

This study was approved with an exemption of ethical deliberation by the Institutional Review Board of St. Mary's Hospital, The Catholic University of Korea (exemption number: KC20ZISI0387).

## Data availability

The data that are used in this study will be shared on reasonable request to the National Health Insurance Data Sharing Service [<https://nhiss.nhis.or.kr>] and the Korea Meteorological Administration [<http://www.kma.go.kr>].

## Supplementary data

Supplementary data are available at *IJE* online.

## Author contributions

M.Y.K. conceptualized and designed the study. J.A. conducted the data analysis and writing of the original draft of the manuscript. M.Y.K., S.B., B.H.C., J.-P.M, M.Y.P. and Y-H.L. contributed to the statistical analyses and validated the results of the data analysis. All authors participated in the data interpretation, reviewed the initial draft of the manuscript with important intellectual content and approved the final version of the manuscript.

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## Conflict of interest

None declared.

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