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Effect of Socioeconomic Status and Underlying Disease on the Association between Ambient Temperature and Ischemic Stroke

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Purpose: Inconsistent findings have been reported regarding the effect of ambient temperature on ischemic stroke. Furthermore, little is known about how underlying disease and low socioeconomic status influence the association. We, therefore, investigated the relationship between ambient temperature and emergency department (ED) visits for ischemic stroke, and aimed to identify susceptible populations.

Materials and Methods: Using medical claims data, we identified ED visits for ischemic stroke during 2005–2009 in Seoul, Korea. We conducted piecewise linear regression analyses to find optimum ambient temperature thresholds in summer and winter, and estimated the relative risks (RR) and 95% confidence intervals (CI) per a 1°C increase in temperature above/below the thresholds, adjusting for relative humidity, holidays, day of the week, and air pollutant levels.

Results: There were 63564 ED visits for ischemic stroke. In summer, the risk of ED visits for ischemic stroke was not significant, with the threshold at 26.8°C. However, the RRs were 1.055 (95% CI, 1.006–1.106) above 25.0°C in medical aid beneficiaries and 1.044 (1.007–1.082) above 25.8°C in patients with diabetes. In winter, the risk of ED visits for ischemic stroke significantly increased as the temperature decreased above the threshold at 7.2°C. This inverse association was significant also in patients with hypertension and diabetes mellitus above threshold temperatures.

Conclusion: Ambient temperature increases above a threshold were positively associated with ED visits for ischemic stroke in patients with diabetes and medical aid beneficiaries in summer. In winter, temperature, to a point, and ischemic stroke visits were inversely associated.

Key Words: Temperature, ischemic stroke, cardiovascular diseases, diabetes mellitus

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INTRODUCTION

Globally, stroke is the second leading cause of death, with 6.7 million deaths in 2012.[1] Particularly, over the past two decades, there were a significant increase in the absolute number of cases of ischemic stroke worldwide, from 4 to 7 million cases.[2] Moreover, incidence rate of ischemic stroke exponentially increased after middle age,[2] therefore, its prevention is becoming of more interest due to ageing population.

Conventional risk factors for cardiovascular disease are known to be related to the development of ischemic stroke,

but several environmental factors have also been reported as well. In addition to air pollution,[3] provoked by concerns about health effects of climate change, several studies have investigated the relationships of ambient temperature with ischemic stroke. Null associations between ambient temperature and ischemic stroke were found in winter and summer in Brisbane, Australia.[4] However, lower temperatures in winter were linked to higher risk of ischemic stroke in Incheon, Korea,[5] and inverse relationships between temperature and risk of ischemic stroke were observed during all seasons in Jinan, China,[6] and in Boston in the United States.[7] Besides the inconsistency of the results, little is known about potentially susceptible populations, although identifying high-risk groups is beneficial in the context of primary prevention of ischemic stroke related to cold and hot weather. Furthermore, previous studies have examined the risk for ischemic stroke in the elderly and in patients with cardiovascular diseases,[4,5,7] whereas other underlying diseases such as diabetes mellitus and socioeconomic status have been of little weight in studies on the effect of temperature on health. Heat waves may increase the risk of medical care utilization for diabetes mellitus,[8] and individuals with diabetes may be more vulnerable to morbidity and mortality during heat waves.[9,10] Furthermore, individuals with low socioeconomic status such as medical aid beneficiaries are more likely to be sensitive to heat and cold waves because of poor housing features.[11,12] Meanwhile, previous studies focused on estimating the risk for ischemic stroke per a 1°C change in temperature.[4-7] From a public health perspective, it may be helpful to provide a temperature point where the risk of ischemic stroke significantly increases. This approach may be beneficial for environmental health policy, because extremely hot and cold weather may become more severe and prevalent because of climate change.[13,14]

Thus, the purpose of the present study was to explore threshold temperatures where the risk of temperature-related ischemic stroke significantly changes and to estimate the risks above and below the estimated threshold temperatures. Additionally, this study aimed to identify susceptible populations by including individuals with cardiovascular diseases, diabetes mellitus, and of varying socioeconomic status.

MATERIALS AND METHODS

Study subjects

The study subjects were patients who visited the emergency department (ED) for ischemic stroke during 2005–2009 in Seoul, the Republic of Korea, identified from health insurance claims data. Multiple ED visits of an individual were regarded as separate cases. The data were obtained from the Health Insurance Review and Assessment Service, and included encrypted individual codes, age, gender, national health insurance type (national health insurance or medical aid beneficiaries), date of the visit, and diagnosis code based on the 10th version of the International Classification of Disease (ICD-10). We defined those with underlying disease as those with corresponding medical care utilization (≥3 outpatient visits or ≥1 admission) in the three years prior to the ED visit for ischemic stroke (ICD-10: I63–I66). Individuals with pre-existing cardiometabolic illnesses may be at a higher risk for ischemic stroke;[15] hence, underlying diseases considered in this study were cardiovascular disease [cerebrovascular disease (ICD-10: I60–I69), ischemic heart disease (ICD-10: I20–I25), hypertensive disease (ICD-10: I10–I15)], and diabetes mellitus (ICD-10: E10–E14). The present study was approved by the Institutional Review Board at Yonsei University Health System (IRB No. 4-2014-0471). Given the nature of the study design and data source, the Institutional Review Board waived the requirement for informed written consent.

Data on meteorology and air pollution

We acquired meteorological data from the Korea Meteorological Administration. These data included daily average, maximum and minimum temperature, and relative humidity, measured at one station in Seoul. Air pollution data were provided by the Ministry of Environment, and we calculated daily mean values of particulate matter with a diameter <10 μm (PM_{10}) and ozone (O_3), by averaging the 24-hour levels from 27 monitoring stations in Seoul.

Statistical analysis

Our analyses were restricted to those aged ≥40 years because ischemic stroke cases are rare in young adults (n=1912, 3.0% of cases in the database). To estimate optimum threshold temperatures and the risk of ED visits for ischemic stroke related to temperature, we applied a method used in a previous study on ambient temperature and heat-related illnesses,[16] with the HEAT package (https://cran.r-project.org/web/packages/HEAT/HEAT.pdf) in R version 3.2.3. First, we plotted the relationship between daily average temperature and the number of ED visits for ischemic stroke on the same day. Analyses were conducted for all seasons (January to December) and each four seasons (spring, March to May; summer, June to August; fall, September to November; winter: December to February). We found the relationship varying in direction at a point in summer and winter (Fig. 1). Second, to find optimum temperature thresholds in summer and winter, piecewise linear regression analyses were conducted. A piecewise linear regression model is useful when a regression coefficient is varied from a certain point, which is called a threshold, below and above.[17] Piecewise linear regression analyses allowed us to explore the points where a regression coefficient varies, identifying the model with the optimum point based on the smallest Akaike's information criterion value (i.e., the highest goodness of fit). Finally, above and below the thresholds shown by the piecewise linear regression model, we estimated the relative risks (RR) and 95% confidence intervals (CI) per a 1°C increase in temperature using

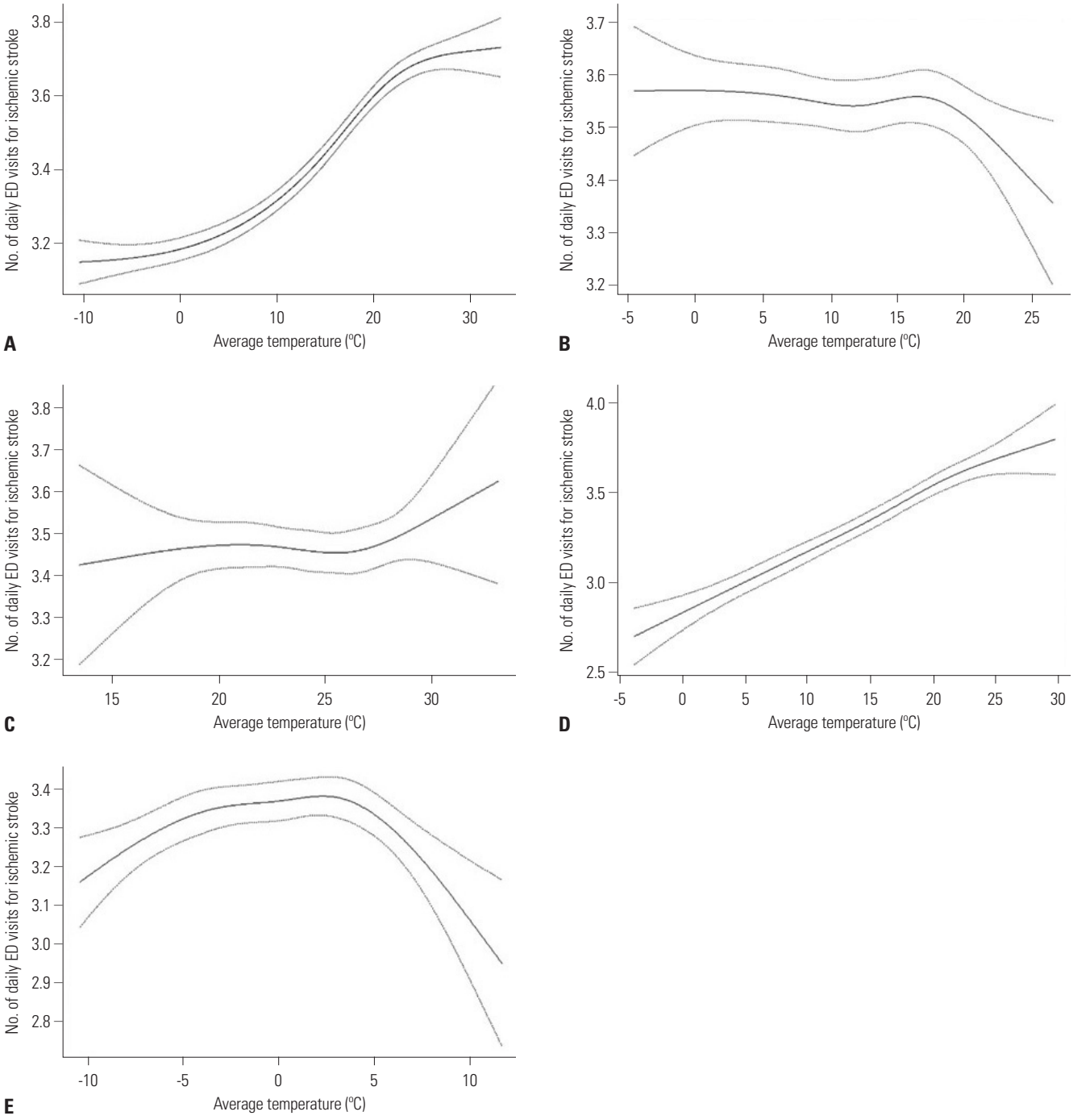

Fig. 1. Relationship of average temperature to daily number of ED visits for ischemic stroke in Seoul, Republic of Korea. (A) All seasons, (B) spring, (C) summer, (D) fall, and (E) winter. ED, emergency department.

generalized linear models with Poisson link, adjusting for relative humidity,[18] holidays, day of the week, and air pollutants. Among air pollutants, PM_{10} and O_3 were selected according to pre-existing evidence on the association with ischemic stroke.[3] Using the same statistical model, subgroup analyses for summer and winter were conducted in relation to age and gender group, national health insurance type, and underlying disease, respectively. Age and gender group consisted of the middle-aged (40–64 year-old) and the elderly (≥65 year-old) men and women.

RESULTS

The overall mean temperature was 12.87°C (standard deviation, 10.16°C) and the mean relative humidity was 60.81% (14.67%) in 2005–2009 in Seoul (Table 1). In summer, the average temperature was 24.23°C and the maximum was 30.10°C. In winter, the average temperature was -0.21°C and the minimum was -11.57°C.

The total number of ED visits for ischemic stroke during

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Table 1. Distribution of Ambient Temperature and Relative Humidity in 2005–2009 in Seoul, Republic of Korea

	Mean	SD	Minimum	Maximum	25%	50%	75%
All seasons							
Temperature (°C)	12.87	10.161	-11.57	30.10	4.16	14.51	21.89
Relative humidity (%)	60.81	14.673	19.42	96.00	49.79	61.60	71.33
Spring							
Temperature (°C)	12.15	6.128	-4.99	24.13	7.73	12.54	17.23
Relative humidity (%)	55.35	14.838	19.42	93.33	44.71	54.60	74.96
Summer							
Temperature (°C)	24.23	2.648	14.94	30.10	22.56	24.43	26.14
Relative humidity (%)	71.61	11.57	24.00	96.00	65.21	71.73	79.42
Fall							
Temperature (°C)	15.09	16.123	-4.23	26.95	10.02	16.11	20.80
Relative humidity (%)	62.25	11.919	25.29	90.79	53.38	62.83	70.92
Winter							
Temperature (°C)	-0.21	4.330	-11.57	10.63	-3.31	0.19	3.13
Relative humidity (%)	53.92	13.015	27.00	93.38	43.42	52.63	62.83

SD, standard deviation.

Table 2. Characteristics of Emergency Department Visits for Ischemic Stroke in 2005–2009 in Seoul, Republic of Korea (n=63564)

Variable	n (%)
Age and gender group	
40–64 year-old men	15585 (24.52)
40–64 year-old women	9057 (14.25)
≥65 year-old men	18160 (28.57)
≥65 year-old women	20762 (32.66)
National health insurance type	
National health insurance	57616 (90.64)
Medical aid beneficiaries	5948 (9.36)
Underlying disease	
Cerebrovascular disease (I60–I69)	16327 (25.69)
Ischemic heart disease (I20–I25)	11796 (18.56)
Hypertensive disease (I10–I15)	26442 (41.60)
Diabetes mellitus (E10–E14)	18473 (29.06)
Season	
Spring	17412 (27.39)
Summer	16889 (26.57)
Fall	14852 (22.67)
Winter	14411 (22.67)

2005–2009 in Seoul was 63564. Men accounted for 33745 (53.1%) of these visits and women for 29819 (46.9%) (Table 2). Those aged ≥65 years and medical aid beneficiaries accounted for 61.2% (n=38922) and 9.4% (n=5948) of visits, respectively. Underlying diseases were present in 16327 (25.7%) patients for stroke, 11796 (18.6%) for ischemic heart disease, 26442 (41.6%) for hypertension, and 18473 (29.1%) for diabetes mellitus. In summer, 16889 (26.6%) ischemic stroke ED visits were observed, with 14411 (22.7%) in winter.

In all seasons, the risk of ED visits for ischemic stroke rose with a temperature increased (Fig. 1). In summer, the risk of ED visits for ischemic stroke was related to temperature increases above the threshold temperature of 26.8°C, but this was not statistically significant (Table 3). The threshold temperature for medical aid beneficiaries was 25.0°C, and the risk significantly increased by 5.5% per 1°C increase (95% CI, 0.6%–10.6%) above this threshold. Patients with ischemic heart disease had a significantly higher risk of ED visits for ischemic stroke in ambient temperatures ≥28.0°C (RR per 1°C increase, 1.179, 95% CI, 1.028–1.352). Patients with diabetes were also at high risk of ED visits for ischemic stroke above the ambient temperature threshold of 25.8°C (RR per 1°C increase, 1.044; 95% CI, 1.007–1.082).

In winter, the threshold temperature of ED visits for ischemic stroke was 7.2°C (Table 4). The risk of ischemic stroke decreased significantly as the temperature rose (RR per 1°C increase, 0.773; 95% CI, 0.700–0.852). The risk of ED visits for ischemic stroke significantly declined with temperature increases above the threshold at 0.8°C in the elderly women (RR per 1°C increase, 0.966; 95% CI, 0.948–0.984) and at 0.6°C among medical aid beneficiaries (0.968; 0.938–0.999). In hypertensive patients, the risk of ischemic stroke visits dropped as temperatures rose above 8.2°C (RR per 1°C increase, 0.618; 95% CI, 0.453–0.842). Among patients with diabetes, the risk declined with temperature increases above 7.4°C (0.643; 0.501–0.824).

DISCUSSION

Using piecewise linear regression, we identified ambient temperature thresholds at which the risk of ED visits for ischemic stroke increased, and analyzed their differences among subgroups. In summer, no significant associations were found among the total study population, but significantly higher risks were observed above threshold temperatures in medical aid

Table 3. Threshold Temperatures and RRs of Emergency Department Visits for Ischemic Stroke in Relation to a 1°C Increase of Ambient Temperature in Summer

Characteristic	Threshold temperature (°C)*	RR (95% CI)
Total		
	<26.8	0.998 (0.990–1.005)
	≥26.8	1.026 (0.995–1.057)
Age and gender group		
40–64 year-old men	<17.6	0.770 (0.648–0.915)
	≥17.6	1.011 (0.998–1.024)
40–64 year-old women	<27.0	0.984 (0.965–1.003)
	≥27.0	1.085 (0.994–1.184)
≥65 year-old men	<17.4	0.822 (0.683–0.988)
	≥17.4	1.005 (0.993–1.017)
≥65 year-old women	<26.8	0.998 (0.990–1.005)
	≥26.8	1.026 (0.995–1.057)
Health insurance type		
National health insurance	<26.8	0.999 (0.991–1.007)
	≥26.8	1.018 (0.986–1.052)
Medical aid beneficiaries	<25.0	0.977 (0.947–1.007)
	≥25.0	1.055 (1.006–1.106)
Underlying disease		
Cerebrovascular disease	<28.8	0.999 (0.985–1.011)
	≥28.8	1.193 (0.924–1.540)
Ischemic heart disease	<28.0	1.002 (0.987–1.018)
	≥28.0	1.179 (1.028–1.352)
Hypertensive disease	<15.4	3.085 (0.736–12.923)
	≥15.4	1.008 (0.998–1.018)
Diabetes mellitus	<25.8	0.998 (0.982–1.014)
	≥25.8	1.044 (1.007–1.082)

RR, relative risk; CI, confidence interval.
*Piecewise linear regression analyses were used to find optimum temperature thresholds, adjusting for relative humidity, holidays, day of week, PM_{10}, and O_3.

Table 4. Threshold Temperatures and RRs of Emergency Department Visits for Ischemic Stroke in Relation to a 1°C Increase of Ambient Temperature in Winter

Characteristic	Threshold temperature (°C)*	RR (95% CI)
Total		
	<7.2	1.006 (1.001–1.010)
	≥7.2	0.773 (0.700–0.852)
Age and gender group		
40–64 year-old men	<7.2	1.002 (0.993–1.011)
	≥7.2	0.774 (0.630–0.951)
40–64 year-old women	<7.4	1.002 (0.990–1.014)
	≥7.4	0.612 (0.421–0.890)
≥65 year-old men	<0.8	1.021 (1.007–1.035)
	≥0.8	0.983 (0.965–1.002)
≥65 year-old women	<1.0	1.025 (1.013–1.038)
	≥1.0	0.966 (0.948–0.984)
Health insurance type		
National health insurance	<7.2	1.005 (1.000–1.009)
	≥7.2	0.753 (0.676–0.838)
Medical aid beneficiaries	<0.6	1.050 (1.024–1.077)
	≥0.6	0.968 (0.938–0.999)
Underlying disease		
Cerebrovascular disease	<7.4	0.996 (0.987–1.004)
	≥7.4	0.779 (0.628–0.966)
Ischemic heart disease	<0.8	1.004 (0.987–1.021)
	≥0.8	0.967 (0.944–0.991)
Hypertensive disease	<8.2	0.999 (0.993–1.006)
	≥8.2	0.618 (0.453–0.842)
Diabetes mellitus	<7.4	1.008 (0.999–1.016)
	≥7.4	0.643 (0.501–0.824)

RR, relative risk; CI, confidence interval.
*Piecewise linear regression analyses were used to find optimum temperature thresholds, adjusting for relative humidity, holidays, day of week, PM_{10}, and O_3.

beneficiaries and in patients with ischemic heart disease and diabetes. In particular, medical aid beneficiaries were affected by temperature increases above 25.0°C, the lowest meaningful threshold temperature in summer. In winter, the risk of ED visits for ischemic stroke increased as temperature decreased to a certain level. Below that level, however, the risk rather declined as temperature decreased. This prominent trend was present in all subgroups. The temperature thresholds for patients with hypertension and diabetes were similar to those of the total study population, but the magnitude of risk was remarkably greater.

Earlier studies have shown null associations[4,5] or inverse relationships between ischemic stroke morbidity and temperature[5-7] in summer. In the present study, we also found no association between them for the total study population in summer, which is consistent with an Australian study.[4] However, as the temperature rose above a certain level, the risk of ED visits for ischemic stroke increased significantly in medical aid beneficiaries and in patients with ischemic heart disease and diabetes. This indicates that individuals with low socioeconomic status, ischemic heart disease, and diabetes may be susceptible to ischemic stroke if they are exposed to high enough temperatures. Considering the increasing number of days with extremely hot weather due to climate change,[19] the effects of ambient temperature on ischemic stroke might become apparent in the general population and be amplified in susceptible groups.

Previous studies have shown an inverse relationship between temperature and ischemic stroke in winter,[5-7] whereas we found an inverted V-shape. The inconsistency may be due to the fact that we used a piecewise linear regression model. We observed an increased risk of ischemic stroke due to a temperature decrease, as previous studies have suggested, but only to a certain temperature; however, below that temperature, a decreased risk of ischemic stroke related to a decrease in temperature showed borderline significance for the total

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study population. Our present study suggests that there is an inverse association between temperature and ischemic stroke in winter, but there is a temperature threshold at which the association changes to a null or weak positive one. It is quite possible that individuals are more likely to avoid cold exposure by reducing outdoor activities at below a certain temperature threshold.

It is noteworthy in the present study that medical aid beneficiaries and patients with diabetes had an increased risk of ED visits for ischemic stroke, being related to temperature increases from moderately high temperatures of 25.0°C and 25.8°C, respectively. The threshold temperatures were slightly higher than the average temperature (24.2°C) in summer, suggesting that the susceptible populations may be at higher risk of ischemic stroke even in moderately hot weather. Individuals with low socioeconomic status may be sensitive to heatwave impacts because of poor health status,[20] social isolation,[21] and housing features such as poor insulation and no air conditioning.[11] Furthermore, patients with diabetes may be predisposed to hot temperatures induced ischemic stroke through dehydration[22] and high counter-regulatory hormone and glucose levels.[23,24] Therefore, it is imperative for patients with diabetes to maintain hydration and to appropriately control their blood glucose in hot weather to prevent ischemic stroke, potentially induced by high temperatures.

In winter, the elderly and medical aid beneficiaries showed rising risks of ED visits for ischemic stroke as temperature decreases to the temperature thresholds, which were lower than for the total populations. This implies that the elderly and those with low socioeconomic status may be vulnerable to ischemic stroke due to cold even at a temperature that does not increase the risk of the disease in the other subgroups. Older people are more likely to develop ischemic stroke due to augmented blood pressure mediated by their increased central arterial stiffness during cold exposure.[25,26] In terms of low socioeconomic status, the susceptibility to cold-induced ischemic stroke could be linked to several factors including personal behaviors related to cold exposure outdoors,[27] housing conditions leading to indoor cold,[28] and blue-collar jobs.[29] Compared to the total study population, hypertensive patients had a greater risk of ED visits for ischemic stroke as temperature decreased, which was consistent with an earlier study.[5] Cold exposure may facilitate arterial thrombosis by increasing plasma cholesterol and fibrinogen levels.[30] Moreover, sympathetic nervous system activated by cold exposure may lead to increased platelet function.[31] In winter, as in summer, patients with diabetes had a greater risk of ischemic stroke due to cold exposure. It has been previously reported that air temperature is inversely associated with the level of hemoglobin A1C in patients with diabetes,[32] implying that cold exposure might negatively influence blood glucose control, thereby increasing the likelihood of developing ischemic stroke. This highlights the importance of blood glucose control in patients with diabetes, also in cold weather.

To our best knowledge, the present study is the first to suggest that socioeconomic inequalities and vulnerability of patients (such as those with diabetes) influence the relationship between temperature and ischemic stroke. However, potential limitations should be mentioned. First, we identified ischemic stroke, based on diagnosis in the ED, without confirmation by neurologists or imaging studies. Of the total ED visits for ischemic stroke, 73.7% (n=46875) was hospital admission, in which the diagnosis had high specificity[33] and was less biased in estimating risks.[34] In further analysis with hospitalization cases, patterns of the relationship between average temperature and the number of cases remained the same as the ED visits (Supplementay Fig. 1, only online). In summer, the temperature threshold was 25.6°C. The risk of hospitalization for ischemic stroke significantly increased above the threshold (RR per 1°C increase, 1.015; 95% CI, 1.001–1.031), suggesting a more remarkable impact of temperature on ischemic stroke morbidity at a lower temperature compared to the ED case results. In winter, the RRs per 1°C increase were 1.007 (95% CI, 1.002–1.013) below the threshold at 7.2°C, which was the same as the ED case results, and 0.785 (0.702–0.878) above the threshold. However, considering hospitalization as an outcome seems inappropriate in dealing with socioeconomic inequality because it might miss poor patients who could not afford hospital admission. Second, we performed a single-city study, therefore, the results may not be applicable to other geographic areas. Even if we had conducted a multi-city study in Korea, we could not generalize the results because temperature effects may vary with latitude and longitude. Nonetheless, the present study may be worthy of attention, since we focused on socioeconomic inequalities and underlying disease differences in the effect of temperature on ischemic stroke, which has public health implications.

In conclusion, in summer, an increase of temperature above a threshold was positively associated with ED visits for ischemic stroke in medical aid beneficiaries and patients with ischemic heart disease or diabetes, whereas an increase of daily average temperature in winter above a threshold, was inversely associated with ED visits for ischemic stroke with the highest risks observed in patients with hypertension and diabetes.

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