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Letter to the Editor

Air Pollution and Subarachnoid Hemorrhage Mortality: A Stronger Association in Women than in Men

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Dear Sir:

Subarachnoid hemorrhage (SAH) is a type of stroke caused primarily by the rupture of intracranial aneurysms. Although it has been actively investigated whether air pollution increases the risk of stroke, less attention has been paid to the specific relationship between air pollution and the risk of SAH.[1,2] Growing epidemiological evidence suggests that air pollution and medical conditions are associated differently in men and women, with women having a stronger association.[3,4] Because the female sex is considered a risk factor for aneurysm formation, SAH occurrence, and mortality,[5] we hypothesized that sex-specific differential effects of air pollution would be prominent in women during the disease process of SAH. Thus, we aimed to examine sex differences in the association between air pollutant concentrations and mortality from SAH through a nationwide ecological study.

The study protocol was approved and the requirement for informed consent was waived by the Institutional Review Board committee of Asan Medical Center (No. 2020-0851). The Korean Statistical Information Service (KOSIS) microdata system was used to obtain national mortality data between 2001 and 2018. The number of deaths from SAH was ascertained using the Korean Standard Classification of Diseases code I60. The data were provided per *Si-Gun-Gu*, which is comparable to the county system in the United States. The mortality rates were age-adjusted per 100,000 to the standard populations as of July 2010 in South Korea using a previously reported method.[6] Potential confounding factors such as population density, education rate, smoking rate, obesity rate as of the 2010 census, the prevalence of hypertension among the population (aged ≥30 years) (2008 to 2018), and gross regional domestic product *per capita* as of 2011 were also obtained from the KOSIS database for each district.

Air pollution data, including carbon monoxide (CO), nitrogen dioxide (NO_2), sulfur dioxide (SO_2), and particulate matter 10 μm or less in diameter (PM_{10}) concentrations, from 332 measurement stations nationwide were obtained from the National Ambient Air Quality Monitoring Information System (http://www.airkorea.or.kr/index). The average of each pollutant per district was estimated using inverse-distance-weighted interpolation of nearby measurement stations from the longitudes and latitudes of administrative authority offices. The daily average ambient temperature, relative humidity, and pressure were obtained from the Korean Meteorological Administration database.

Between 2011 and 2018, 36,808 deaths were reported due to SAH, while the population of South Korea was 49,879,812 in the middle of the study period (2010) (Table 1). The spatial distributions of the air pollutant concentrations and age-adjusted mortality rates during the study period are shown in Figure 1. The NO_2, CO, and PM_{10} concentrations were high in the metropolitan area surrounding Seoul. The CO concentrations were also high in the central region of South Korea, which has many

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Table 1. Characteristics of the study districts

Characteristic	Male	Female
Mortality		
Total number of deaths by SAH	13,672	23,136
Age-adjusted SAH mortality rate (per 100,000)*	2.7 (2.3–3.1)	4.4 (4.0–5.0)
Air pollutants		
Carbon monoxide (ppb)†	554 (476–624)	
Nitrogen dioxide (ppb)	20.1 (14.6–26.8)	
Sulfate dioxide (ppb)	4.89 (4.15–5.56)	
PM_{10} (μg/m^3)	50.2 (46.1–55.5)	
Meteorological factors		
Ambient temperature (°C)	12.7 (12.3–13.7)	
Relative humidity (%)	66.2 (63.6–68.2)	
Ambient pressure (hPa)	1,008 (1,006–1,011)	
Socio-economic and behavioral factors		
Population density (/km^2)	361 (109–6042)	
Smoking rate (%)‡	25.1 (23.5–26.8)	
Obesity rate (%)§	22.4 (20.9–24.4)	
Higher-education rate (%)‖	39.9 (29.1–48.6)	29.1 (16.5–36.7)
GRDP *per capita* (million won)¶	22.9 (16.7–29.0)	

Values are presented as number or median (interquartile range). From 2001 to 2018, the population in 249 South Korean administrative districts, *Si-Gun-Gu*, were studied. Korean population, as of 2010 (i.e., in the middle of the study period) was 49,879,812.
SAH, subarachnoid hemorrhage; GRDP, gross regional domestic product.
*Annual raw mortality rates throughout the study period were adjusted for each district's age distribution as per the standard Korean population in 2005; †Air pollution data from 2001 to 2018 were accessed from the Air Korea database in daily mean concentrations according to the positions of the monitoring stations; ‡Rate of current smokers adjusted by the age of the national standard population in 2010; §Rate of the population with body mass index >25 kg/m^2 adjusted for the age of the national standard population in 2010; ‖Rate of >15-year-old population with equal to or higher than a college education in 2010; ¶Gross regional domestic product *per capita* in 2010.

cement factories. SO_2 concentrations were similar across the country, except for Ulsan and Yeosu, which consume a large amount of ship oil because of their proximity to shipyards and the petrochemical industry.

In a multivariable analysis of the association between air pollutants and SAH mortality, only SO_2 concentration showed a significant association across all populations; a district with a higher interquartile range (IQR) SO_2 concentration (1.41 ppb) had a 1.04 (95% confidence interval [CI], 1.01 to 1.07) higher SAH mortality rate (Figure 2). When examined separately by sex, significant positive associations between NO_2, SO_2, and PM_{10} concentrations and female SAH mortality were identified, whereas all air pollutants exhibited null associations with male SAH mortality. A district with a higher IQR concentration of NO_2 (12.2 ppb), SO_2 (1.41 ppb), and PM_{10} (9.4 μg/m^3) had 1.06 (IQR, 1.02 to 1.10), 1.06 (IQR, 1.03 to 1.10), and 1.05 (IQR, 1.01 to 1.09) fold higher mortality rates from SAH in females, respectively.

These findings suggest a close relationship between air pollution and SAH mortality, particularly in female patients. There are a few studies that have focused on the risk of SAH and have reported inconsistent results.[1,2,7] One study found an association in the short-term,[2] but other studies reported null associations[1,7] between SAH mortality and air pollution in terms of months. The current study has the advantage of being based on data collected over the longest period on the largest scale in a nationwide manner. Moreover, for the first time, it was shown that the detrimental effects of air pollution on SAH may be more pronounced in women.

There are several possible mechanisms by which air pollution and brain hemorrhage are linked.[2] Air pollutants may cause direct ischemic damage to blood vessels or endothelial dysfunction, leading to vessel rupture. These may also trigger vasoconstriction and autonomic dysfunction, resulting in altered cardiovascular homeostasis. Moreover, the coughing caused by air pollution may increase intracranial pressure, which may lead to the rupture of vulnerable aneurysms. However, the prominent effect of air pollution on SAH mortality in women requires further investigation. Women are more likely to develop an intracranial aneurysm than men, and if they do, they tend to have

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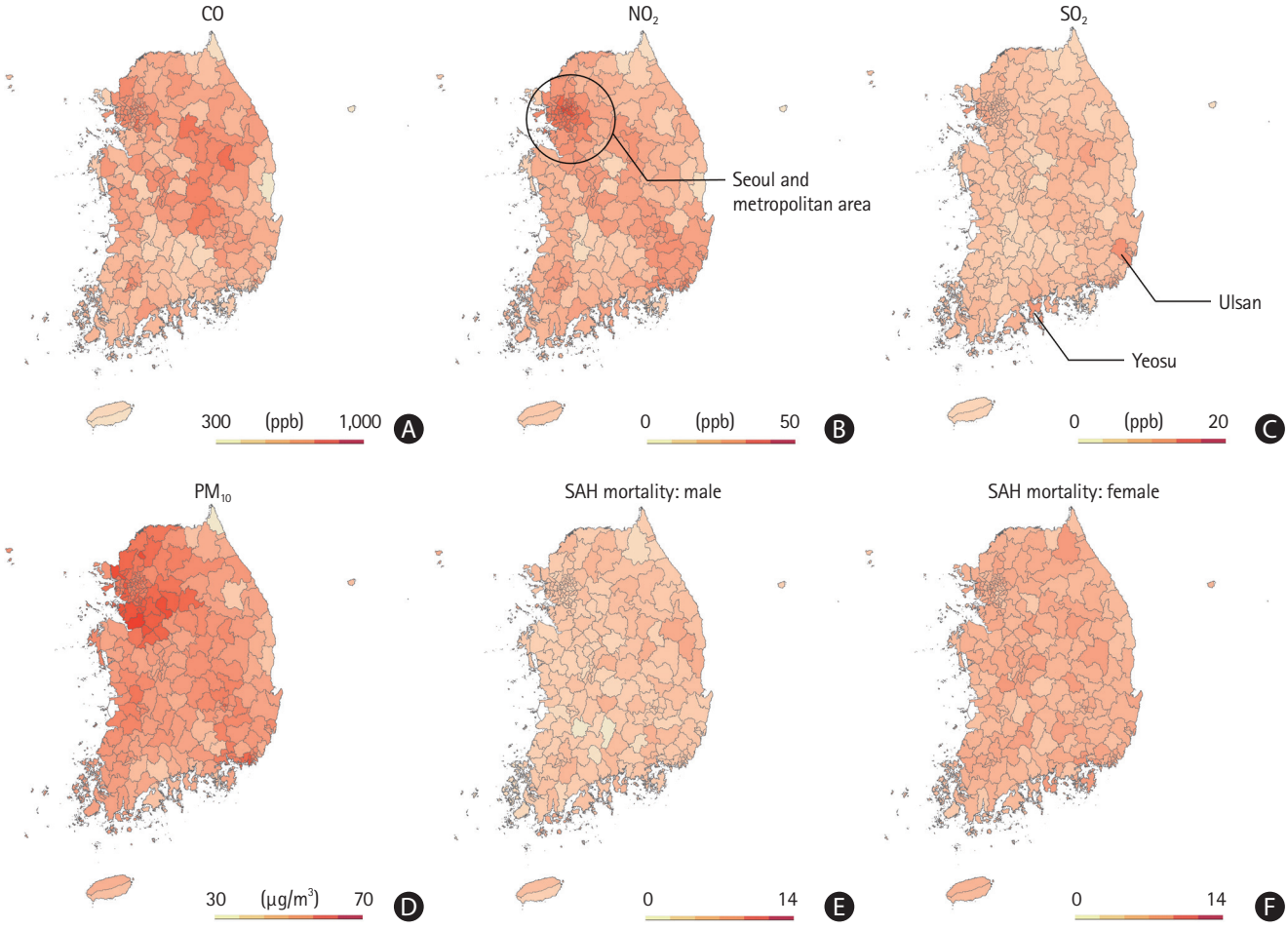

Figure 1. Spatial distributions of the concentrations of (A) carbon monoxide, (B) nitrogen dioxide, (C) sulfur dioxide, and (D) particulate matter of size ≤10 μm, the mortality rates from subarachnoid hemorrhage (SAH) in the (E) males, and (F) females.

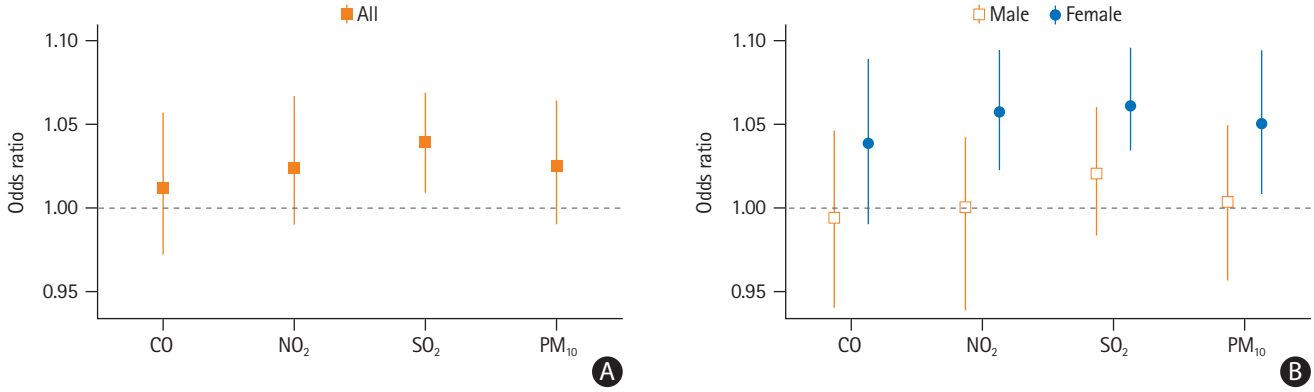

Figure 2. Odds ratios and 95% confidence intervals of estimated associations between age-adjusted subarachnoid hemorrhage mortality rate and air pollutants' concentrations in (A) both the sexes and (B) male and females with multivariable beta-regression models controlling for population density, higher education rate, smoking rate, obesity rate, gross regional domestic production *per capita*, ambient temperature, humidity, and pressure per interquartile range change of air pollutant concentrations (carbon monoxide [CO] 148 ppb; nitrogen dioxide [NO_2] 12.2 ppb; sulfur dioxide [SO_2] 1.41 ppb; particulate matter 10 μm or less in diameter [PM_{10}] 9.4 μg/m^3) in males and females in 249 South Korean administrative districts between 2001 and 2018.

multiple aneurysms.[5] In addition, women have higher overall mortality after the advent of SAH.[5] Meanwhile, women are known to be more vulnerable to air pollutants due to lower rates of smoking exposure than due to usual, smaller airways[8] with higher reactivity,[9] and higher particulate matter deposition.[10] Therefore, women's vulnerability to air pollution may

have maximized their susceptibility to SAH mortality.

This study had several limitations. This study had an ecological design; thus, it should be used primarily to generate a hypothesis. With the current study design, interactions with sex could not be evaluated to determine the effect of air pollution on SAH mortality. Moreover, the generalizability is limited because of the lack of subject-level data for potential confounding factors. In this case, the unit of analysis is the district, not the patient. Finally, we were unable to assess the cumulative effect of air pollution and the long exposure lag period in this study. Further research is needed to consider the effect of air pollutants on SAH mortality according to various exposure durations and lag analyses. Nevertheless, our results suggest that the effects of air pollution on the disease process and outcome of intracranial aneurysms may differ by sex, which warrants future studies.

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