



Comparison of the Incidence of Sudden Sensorineural Hearing Loss in Northern Taiwan and Southern Taiwan (2000–2015)

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Background: The aim of the study is to compare the incidence of sudden sensorineural hearing loss (SSNHL) in Northern and Southern Taiwan, areas with different levels of air pollution. **Methods:** This was a retrospective, cross-sectional, 15-year nationwide study of SSNHL diagnoses between 2000 and 2015 in Taiwan National Health Insurance Research Database. **Results:** In total, 12,497 patients were included, 5584 in Northern Taiwan and 2532 in Southern Taiwan. In Northern and Southern Taiwan, the mean patients' age was 50.94 ± 16.62 and 50.70 ± 15.86 years, respectively; males (53.56% vs. 53.48%) were more frequently diagnosed than females (46.44% vs. 46.52%). The crude incidence was 41.13/100,000 and 49.45/100,000 in Northern and Southern Taiwan. The increasing trend was significantly higher in Southern than in Northern Taiwan. The maximal difference between Northern and Southern Taiwan, 44.31 versus 77.01/100,000 people/year, occurred in 2012. Mean particulate matter (PM_{2.5}) annual concentration steadily decreased from 25.5 $\mu\text{g}/\text{m}^3$ in 2010 to 19.20 $\mu\text{g}/\text{m}^3$ in 2015 in Northern Taiwan, 37.10 $\mu\text{g}/\text{m}^3$ in 2010 to 26.50 $\mu\text{g}/\text{m}^3$ in 2015 in Southern Taiwan, Tainan City area, and 38.20 $\mu\text{g}/\text{m}^3$ in 2010 to 25.10 $\mu\text{g}/\text{m}^3$ in 2015 in Southern Taiwan, Kaohsiung City area. Cumulative PM_{2.5} exposure (PM_{2.5}-year) from 2000 to 2015 was $441.1 \mu\text{g}/\text{m}^3 \times \text{year}$ in Northern Taiwan, $563.3 \mu\text{g}/\text{m}^3 \times \text{year}$ in Southern Taiwan – Tainan City area, and $684.3 \mu\text{g}/\text{m}^3 \times \text{year}$ in Southern Taiwan – Kaohsiung City area. **Conclusion:** SSNHL incidence increased from 2000 to 2015 and was higher in Southern than in Northern Taiwan. Cumulative PM_{2.5} exposure was higher in Southern than in Northern Taiwan. The relationship between cumulative PM_{2.5} exposure and SSNHL pathogenesis needs further investigation.

Key words: Air pollution, particulate matter, sudden sensorineural hearing loss

INTRODUCTION

Sudden sensorineural hearing loss (SSNHL) is an emergent otologic condition that requires urgent evaluation and treatment.¹ The most widely accepted diagnostic criteria include hearing loss that is sensorineural in nature,¹ of at least 30 decibels (dB) over at least three consecutive test frequencies, and that occurs within a 72-h period.¹

Hearing loss can be caused by damage to any portion of the peripheral and central auditory systems. SSNHL is an enigmatic entity with an obscure pathophysiology. Although a variety of identifiable factors - including neoplastic, infectious, autoimmune, neurologic, otologic, metabolic, cardiac, and vascular diseases; a hypercoagulable state; drugs; and trauma - can lead to SSNHL,¹ most cases are idiopathic.¹ An underlying cause is identified in only 10%–15% of

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cases.² Environmental noise, toxins, diet, smoking, alcohol consumption, low serum folate levels, and metabolic syndrome have been associated with idiopathic SSNHL.³

Taiwan's National Health Insurance (NHI) Program, a single-payer payment system in which the government is the sole insurer, was launched in March 1995 and covered >99.5% of the 23.74 million Taiwanese citizens in 2014. The NHI maintains a database with high validity and integrity that can be used to investigate the profile and incidence of SSNHL across Taiwan. Our previous 14-year, nationwide analysis of the Taiwan NHI Research Database showed that the annual numbers of patients hospitalized with SSNHL in Taiwan steadily increased from 5.15/100,000 people in 2000 to 13.97/100,000 people in 2013, indicating that the incidence of SSNHL is increasing in Taiwan.⁴

Ambient particulate air pollution is associated with increased all-cause mortality, cardiovascular mortality, and respiratory mortality in more than 600 cities worldwide.⁵ Air pollution not only increases the risk of ischemic heart disease but also increases the risk of SSNHL.⁶ To further explore the differences of the increased incidence of SSNHL in different cities in Taiwan,⁵ this study compared the incidence of SSNHL in Northern Taiwan and Southern Taiwan, two areas with different levels of air pollution.

MATERIALS AND METHODS

Data sources

The NHI Research Database (NHIRD) was employed to investigate the incidence of SSNHL over a 15-year period (2000–2015) using data from the Outpatient and Hospitalization Longitudinal Health Insurance Database for patients from different areas of Taiwan. The area defined as Northern Taiwan in this study includes Keelung City, Taipei City, New Taipei City, Taoyuan City, Hsinchu County, and Hsinchu City; the area defined as Southern Taiwan includes Tainan City, Kaohsiung City, and Pingtung County.

Study design and sampled participants

This retrospective cross-sectional study included patients with a diagnosis of SSNHL (International Classification of Diseases, Version 9, Clinical Modification [ICD-9-CM] code: 388.2) between 2000 and 2015. We excluded patients for whom information such as age and sex was missing. A total of 12,497 patients were included.

Outcome variables

Outcome variables were factors related to the occurrence of SSNHL (ICD-9-CM code 388.2). To increase diagnostic precision, the inclusion criteria required patients had received ≥ 3

ambulatory visits or ≥ 1 inpatient visit, and the SSNHL diagnostic code had been assigned by an otolaryngologist. The demographic factors considered included age, comorbidities, season, location, and urbanization. In accordance with criteria established by the NHRI, towns and cities in Taiwan were stratified into four urbanization categories, with 1 indicating the highest level of urbanization and 4 indicating the lowest, based on the population density (persons/km²), percentage of people with a college-level education or higher, percentage of people aged 65 years or older, percentage of agricultural workers in the local population, and number of physicians per 100,000 people.

Exposure measurement

Air quality data are collected via ambient air quality monitoring stations across Taiwan by the Taiwan Environmental Protection Administration. The mean annual particulate matter (PM_{2.5}) concentrations for 2000–2020 were retrieved. However, comprehensive data on PM_{2.5} in Taiwan are not available for 2000–2009. The estimated mean annual PM_{2.5} concentration during 2000–2009 was 30.10 $\mu\text{g}/\text{m}^3$ in Northern Taiwan, 35.97 $\mu\text{g}/\text{m}^3$ in Southern Taiwan, Tainan City area, and 47.80 $\mu\text{g}/\text{m}^3$ in Southern Taiwan, Kaohsiung city area (Environmental Protection Administration, Taiwan).

Ethics statement

This study was conducted in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki). The NHIRD encrypts personal patient information to maintain privacy and provides anonymous identification numbers associated with relevant claim information. None of the analyzed data contain identifiable personal information. Patient consent is not required to access the NHIRD. The history diagnoses are coded according to the ICD-9-CM. The Institutional Review Board of the Tri-Service General Hospital approved this study (TSGHIRB Number: B-110-27). The committee waived the requirement of informed consent.

Statistical analysis

All statistical analyses were performed using SPSS (version 22.0; IBM Corp., Armonk, NY, USA). Categorical and continuous variables were evaluated. The trend test was performed using one sample *t*-tests. The crude incidence was defined as all new cases occurring from 2000 to 2015 divided by the population at risk from 2000 to 2015 (summation of the mid-year population from 2000 to 2015).

RESULTS

Comparison of the incidence of sudden sensorineural hearing loss during 2000–2015 in Northern Taiwan and Southern Taiwan

According to the data retrieved for January 1, 2000, to December 31, 2015, a total of 12,497 patients with SSNHL fulfilled the eligibility criteria: 5584 patients from Northern Taiwan and 2532 from Southern Taiwan [Figure 1]. The crude incidence of SSNHL from 2000 to 2015 was 41.13/100,000 people/year in Northern Taiwan and 49.45/100,000 people/year in Southern Taiwan. The annual incidence steadily increased from 27.91/100,000 people in 2001 to 44.73/100,000 people in 2015 in Northern Taiwan. The annual incidence rate also increased from 29.71/100,000 people in 2001 to 55.04/100,000 people in 2015 in Southern Taiwan [Table 1 and Figure 2]. One sample *t*-test revealed that the trend toward an increase in the incidence of SSNHL was significantly higher in Southern Taiwan than in Northern Taiwan ($P < 0.001$). The maximal difference in the incidence of SSNHL between these areas was observed in 2012, with 44.31/100,000 people per year in Northern Taiwan versus 77.01/100,000 people/year in Southern Taiwan. The lowest incidence observed in Northern Taiwan was 27.91/100,000 people in 2001, and the peak incidence in Northern Taiwan was 47.25/100,000 people in 2010 followed by 46.61/100,000 people in 2009. Unfortunately, the incidence in Northern Taiwan remained above 40.00/100,000 during 2011–2015. In contrast, the peak incidence in Southern Taiwan was 77.01/100,000 people in 2012, followed by 69.59/100,000 people in 2013 and 60.9/100,000 people in 2014. The incidence of SSNHL obviously decreased from 2012 to 2015 in Southern Taiwan but was still higher than the rate in Northern Taiwan (44.73 vs. 55.04/100,000 in 2015).

Comparison of the average PM2.5 concentration during 2000–2020 in Northern Taiwan and Southern Taiwan

Comprehensive data on PM2.5 are not available for the period from 2000 to 2009 in Taiwan. However, the estimated mean annual PM2.5 concentration during 2000–2009 was 30.10 $\mu\text{g}/\text{m}^3$ in Northern Taiwan, 35.97 $\mu\text{g}/\text{m}^3$ in Southern Taiwan, Tainan City area, and 47.80 $\mu\text{g}/\text{m}^3$ in Southern Taiwan, Kaohsiung City area. The mean annual PM2.5 concentration steadily decreased from 25.5 $\mu\text{g}/\text{m}^3$ in 2010 to 19.20 $\mu\text{g}/\text{m}^3$ in 2015 and 12.70 $\mu\text{g}/\text{m}^3$ in 2020 in Northern Taiwan. The mean annual PM2.5 concentration also decreased from 37.10 $\mu\text{g}/\text{m}^3$ in 2010 to 26.50 $\mu\text{g}/\text{m}^3$ in 2015 and 18.40 $\mu\text{g}/\text{m}^3$ in 2000 in Southern Taiwan, Tainan City area, as well as decreased from 38.20 $\mu\text{g}/\text{m}^3$ in 2010 to 25.10 $\mu\text{g}/\text{m}^3$ in

2015 and 18.80 $\mu\text{g}/\text{m}^3$ in 2000 in Southern Taiwan, Kaohsiung City area [Figure 3].

Comparison of cumulative to PM2.5 exposure (PM2.5-year) during 2000–2015 in Northern Taiwan and Southern Taiwan

PM2.5-year was used as an index to investigate the cumulative effects of exposure to PM2.5 over many years. The year 2000 was defined the 1st year; the mean PM2.5-year levels in 2000 were 30.10 $\mu\text{g}/\text{m}^3 \times \text{year}$ in Northern Taiwan, 35.97 $\mu\text{g}/\text{m}^3 \times \text{year}$ in Southern Taiwan, Tainan City area, and 47.80 $\mu\text{g}/\text{m}^3 \times \text{year}$ in Southern Taiwan, Kaohsiung City area. The PM2.5-year value increased from 326.5 $\mu\text{g}/\text{m}^3 \times \text{year}$ in 2010 to 441.1 $\mu\text{g}/\text{m}^3 \times \text{year}$ in 2015 in Northern Taiwan, 396.8 in 2010 to 563.5 $\mu\text{g}/\text{m}^3 \times \text{year}$ in 2015 in Southern Taiwan, Tainan City area, and 516.2 $\mu\text{g}/\text{m}^3 \times \text{year}$ in 2010 to 684.3 $\mu\text{g}/\text{m}^3 \times \text{year}$ in 2015 in Southern Taiwan, Kaohsiung City area [Figures 4 and 5].

DISCUSSION

In this study, the crude incidence of SSNHL from 2000 to 2015 was 41.13/100,000 people/year in Northern Taiwan and 49.45/100,000 people/year in Southern Taiwan. In contrast, a previous study in Taiwan that only included hospitalized patients showed that the crude incidence was 9.76/100,000 people/year during 2000–2013 and the annual incidence steadily increased from 5.15/100,000 people in 2000 to 13.97/100,000 people in 2013.⁴ These discrepancies are due to the use of different inclusion criteria, as we included hospitalized patients as well as patients who attended at least

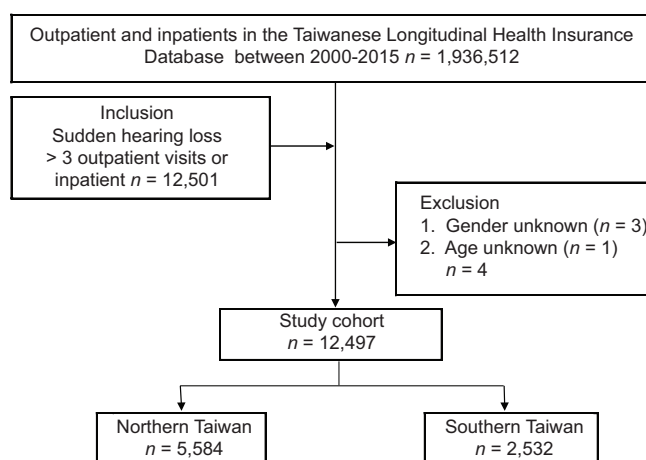


Figure 1: Flowchart of selection of the cohort or patients with sudden sensorineural hearing loss from the National Health Insurance Research Database in Taiwan. Northern Taiwan: Keelung City, Taipei City, New Taipei City, Taoyuan City, Hsinchu County, Hsinchu City. Southern Taiwan: Tainan City, Kaohsiung City, Pingtung County

Table 1: Demographic characteristics of the patients with sudden hearing loss (International Classification of Diseases-9-Clinical Modification 388.2) from Northern Taiwan and Sothern Taiwan (2000–2015)

	Northern Taiwan, <i>n</i> (%)	Southern Taiwan, <i>n</i> (%)	<i>P</i>
Overall	5584 (44.68)	2532 (20.26)	
Gender			
Male	2991 (53.56)	1354 (53.48)	0.910
Female	2593 (46.44)	1178 (46.52)	
Age (years)	50.94±16.62	50.70±15.86	<0.001
Age group (years)			
<5	8 (0.14)	1 (0.04)	<0.001
5-14	84 (1.50)	43 (1.70)	
15-24	322 (5.77)	153 (6.04)	
25-44	1527 (27.35)	621 (24.53)	
45-64	2472 (44.27)	1250 (49.37)	
≥65	1171 (20.97)	464 (18.33)	
CCI	0.23±0.70	0.26±0.71	0.340
Season			
Spring (March–May)	1422 (25.47)	646 (25.51)	0.797
Summer (June–August)	1341 (24.02)	659 (26.03)	
Autumn (September–November)	1493 (26.74)	668 (26.38)	
Winter (December–February)	1328 (23.78)	559 (22.08)	
Urbanization			
1 (highest)	2687 (48.12)	1201 (47.43)	<0.001
2	2733 (48.94)	1061 (41.90)	
3	50 (0.90)	62 (2.45)	
4 (lowest)	114 (2.04)	208 (8.21)	
Level of care			
Hospital center	3286 (58.85)	1422 (56.16)	<0.001
Regional hospital	2145 (38.41)	874 (34.52)	
Local hospital	153 (2.74)	236 (9.32)	

P: Chi-square test/Fisher's exact test of categorical variables and one-way ANOVA with Scheffe *post hoc* test for continuous variables, Northern Taiwan: Keelung City, Taipei City, New Taipei City, Taoyuan City, Hsinchu County, Hsinchu City, Southern Taiwan: Tainan City, Kaohsiung City, Pingtung County. CCI=Charlson comorbidity index

three outpatient department visits in this study. The incidence of SSNHL observed in this study appears to be higher than that of a nationwide survey in the United States, which reported an incidence of 27/100,000 people from 2006 to 2007.⁷ Interestingly, the peak SSNHL incidence was observed among 45–60-year-olds during 2000–2015 in Taiwan; in contrast, in the USA, the peak incidence occurred among patients aged 65 years and older.⁷ The average age of patients with SSNHL has increased in Japan: The average respective ages of female and male patients were 39.9 ± 14.9 and 40.5 ± 15.8 years between July 1973 and June 1974; 44.0 ± 15.4 and 46.2 ± 15.4 years in 1987; and 49.3 ± 15.8 and 48.8 ± 16.2 years in 1993.⁸ The changes in the peak incidence of SSNHL in Taiwan cannot

solely be explained by an aging society; thus, other factors may contribute to the younger age of development of SSNHL in the Taiwanese population.

Various potential causes have been suggested for SSNHL, but no definitive causes have been confirmed. Although we observed a trend toward higher numbers of cases of SSNHL in autumn, the incidence rates were not significantly different between seasons in Taiwan over the period from 2000 to 2015 in this study. Similarly, a previous study reported no significant relationship between the monthly SSNHL incidence rates and the weather conditions in Taiwan between 1998 and 2002.⁹ There was no proven link between meteorological conditions, such as temperature, humidity, or atmospheric pressure, and the incidence

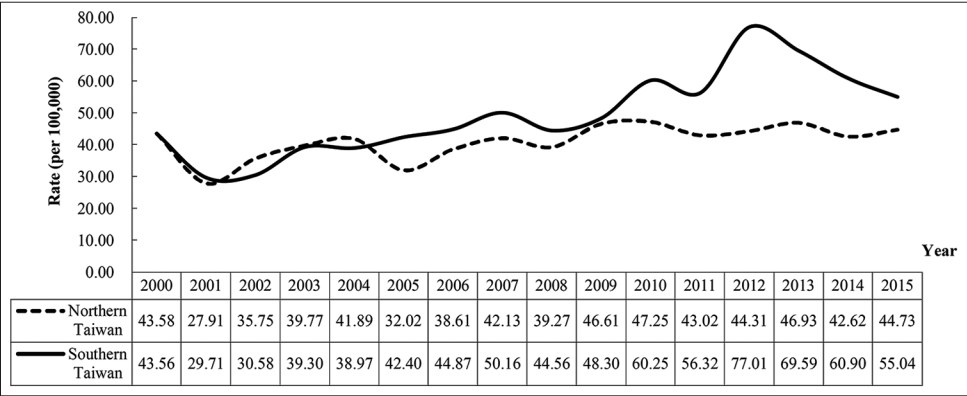


Figure 2: Crude incidence of sudden sensorineural hearing loss from 2000 to 2015 in Northern Taiwan and Southern Taiwan. Northern Taiwan: Keelung City, Taipei City, New Taipei City, Taoyuan City, Hsinchu County, Hsinchu City. Southern Taiwan: Tainan City, Kaohsiung City, Pingtung County

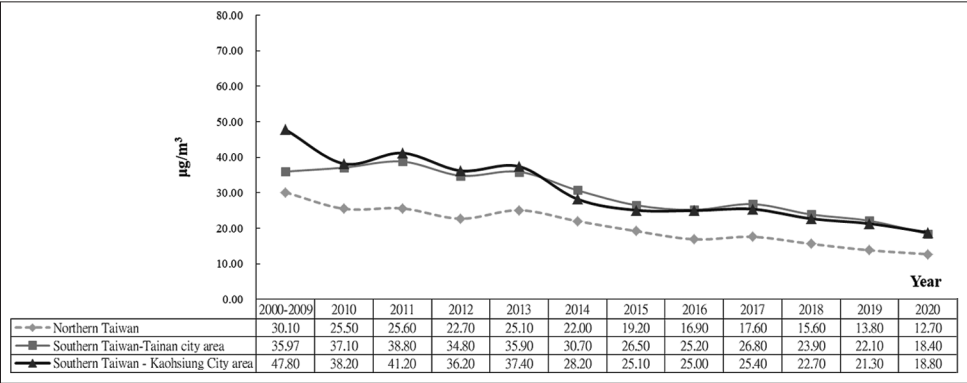


Figure 3: Average concentrations of PM2.5 during 2000–2020 in Northern Taiwan and Southern Taiwan

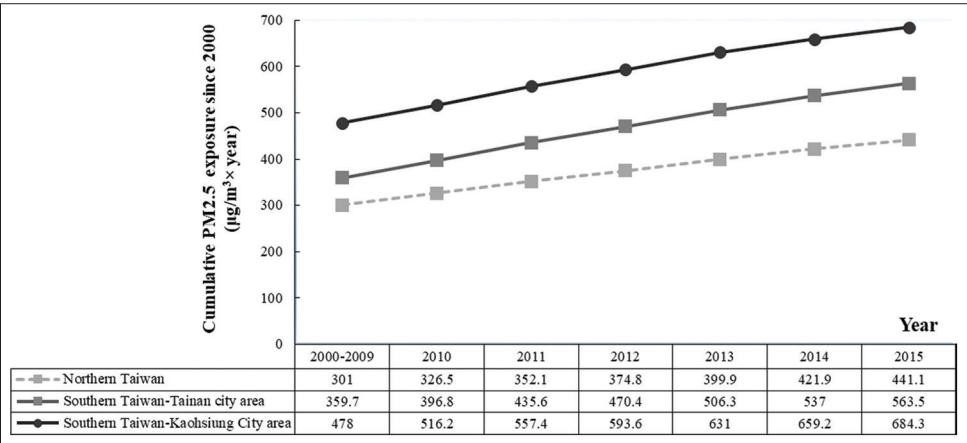


Figure 4: Cumulative exposure to PM2.5 (PM2.5-year) during 2000–2015 in Northern Taiwan and Southern Taiwan

of SSNHL in Northwestern Greece.¹⁰ The rates of SSNHL were also independent of weather parameters in Germany¹¹ and New York.¹² However, in a study conducted in Busan, Korea, the mean wind speed, maximum wind speed, and daily atmospheric pressure range were weakly positively associated with the numbers of SSNHL patients.¹³ Moreover, a weak relationship

between the daily numbers of patients diagnosed with SSNHL and PM levels was observed in the same study.¹³

Associations between air pollution and SSNHL are increasingly being reported. Many patients have a history of upper respiratory tract infections before the onset of SSNHL.¹⁴ However, vaccination programs have decreased the prevalence

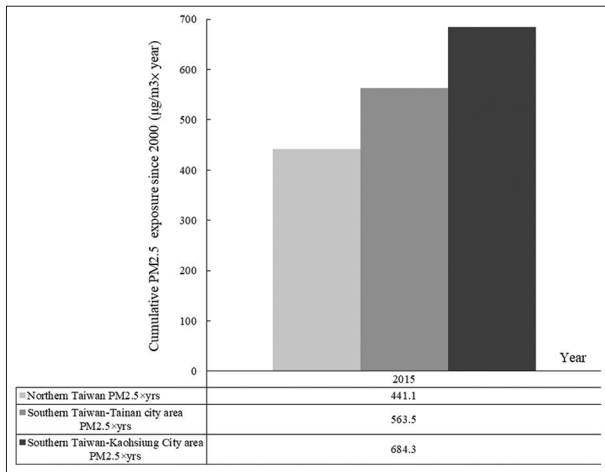


Figure 5: Cumulative PM2.5 exposure in 2015 (from 2000 to 2015) in Northern Taiwan and Southern Taiwan

of infectious diseases.¹⁴ Studies have suggested that air pollution may contribute to the severity of the coronavirus disease 2019 (COVID-19) pandemic. Exposure to air pollution leads to a decreased immune response, which may facilitate viral infection and replication.¹⁵ In addition, chronic exposure to air pollutants delays or complicates the recovery of patients with COVID-19.¹⁶ Moreover, the incidence of SSNHL increased during the COVID-19 pandemic.¹⁷

Vascular issues, such as atherosclerosis, thrombosis, and vasospasm, may be another possible cause of SSNHL.¹ A 5-year follow-up study conducted in Taiwan from 1998 to 2003 reported the hazard of stroke was 1.64 times greater for patients with SSNHL.¹⁸ Ambient air pollution due to PM2.5 is the leading environmental risk factor for atherosclerotic cardiovascular disease, such as stroke and myocardial infarction.¹⁹ Epidemiological studies in humans suggest that the association between PM2.5 levels and the risk of atherosclerotic cardiovascular disease exists at levels well below the air quality guidelines in North America and Europe.¹⁹ PM exposure was also associated with microvascular changes, and each 10-µg/m³ increase in PM10 was associated with a 0.93-µm decrease in central retinal arteriolar equivalent in healthy adults.²⁰ Moreover, each doubling in recent exposure to PM2.5 was associated with a 0.51-fold narrowing of the retinal arteriolar caliber in healthy 8–12-year-olds.²¹ Thus, we hypothesize that interactions between air pollution, viral infection, and microvascular circulatory problems are involved in the development of SSNHL.

A 2019 nested case-control study indicated that short-term exposure to NO₂ - but not SO₂, O₃, CO, or PM10 - significantly increased the risk of SSNHL (adjusted odds ratio: 3.12) in Korea.⁶ In another Korean NHI Service-Health Screening Cohort study, both short-term (below 1 year) and

long-term (more than 1 year) exposure to SO₂ (0.01 ppm) was positively related to ischemic heart disease. However, 365 and 730 days of exposure to PM10 (10 µg/m³) - but not short-term exposure (<1 year) - was related to increased risk of ischemic heart disease.²²

There are several ways to assess smoking in epidemiological studies: (1) average number of cigarettes smoked in a time period, (2) cumulative pack-years of smoking, (3) current, past, ever, and never smoking, and (4) cumulative average. The prevalence of chronic obstructive pulmonary disease (COPD) increases with prolonged smoking duration. Moreover, smoking influences the risk of lung disease in a dose-dependent manner. There is no safe smoking intensity threshold for lung disease risk, and even infrequent smokers have an increased risk of future lung disease. Prolonged chronic PM2.5 exposure results in poorer lung function, and long-term PM2.5 exposure exacerbates cigarette smoke-induced changes in COPD.²³ Assessment of 3941 nonsmoking Taiwanese adults recruited to the Taiwan Biobank project between 2008 and 2015 found that exposure to PM2.5 at concentrations >38.98 µg/m³ was associated with increased susceptibility to COPD.²⁴ Moreover, cumulative PM2.5 exposure (median work area PM2.5 concentration multiplied by estimated exposure period) was associated with shorter leukocyte telomere length due to genotoxic oxidative damage caused by metals present in PM2.5.²⁵ A study in Seoul, Korea, conducted during 2002–2013 found that each 10-µg/m³ increment in cumulative average long-term PM2.5 exposure was associated with an increased risk of hemorrhagic stroke (hazard ratio = 1.43), although the annual mean PM2.5 concentration in Seoul decreased from 38.9 µg/m³ in 2002 to 25.1 µg/m³ in 2013.²⁶ Cumulative 1-month PM2.5 exposure has adverse effects on cardiovascular mortality. Importantly, risk assessments based on single-day or 2-day moving average exposures, rather than cumulative exposure, are likely underestimate the effects of air pollution.²⁷ Nevertheless, the association between long-term exposure to air pollution and the development of SSNHL needs further investigation.

Guidelines from the American Academy of Otolaryngology-Head and Neck Surgery suggest that all patients with idiopathic SSNHL should be offered treatment with oral glucocorticoids, with intratympanic glucocorticoids as initial treatment and as salvage therapy.² Hyperbaric oxygen (HBO) therapy for idiopathic SSNHL was approved in 2011 by the Undersea and Hyperbaric Medical Society Board of Directors.²⁸ Routine application of HBO in conjunction with pharmacologic agents is recommended for initial profound SSNHL (>90 dB hearing level).²⁹ HBO therapy may potentially exert antiaging effects, as 60 days of HBO therapy over 90 days increased telomere length and

decreased immunosenescence in blood cells from 35 healthy independently living adults aged 64 and older.³⁰ Unfortunately, HBO therapy is not covered by the Taiwanese NHI system for the treatment of SSNHL.

This study has some limitations. First, the NHIRD lacks information on patient behaviors, physical examinations, severity of hearing loss, possible etiologies and clinical details (noise exposure, tobacco use, alcohol consumption), and treatment details (HBO therapy, treatment response, hearing recovery). Second, the incidence of SSNHL may remain underestimated as some patients may not have attended at least three clinical visits or been hospitalized due to mild hearing loss, delayed diagnosis, unwillingness to be hospitalized, or rapid recovery. Third, this is a retrospective study; thus, bias related to unknown confounders may have affected the results; a well-designed randomized prospective study is necessary to establish a causal relationship between personal cumulative PM2.5 exposure and the risk of SSNHL.

CONCLUSION

SSNHL incidence increased from 2000 to 2015 and was higher in Southern than Northern Taiwan. Cumulative PM2.5 exposure was higher in Southern than in Northern Taiwan. The relationship between cumulative PM2.5 exposure and SSNHL pathogenesis needs further investigation.

Acknowledgments

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Conflicts of interest

There are no conflicts of interest.

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