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Increased risk of sudden sensorineural hearing loss in asthma: A longitudinal follow-up study using a national sample cohort

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Increased risk of sudden sensorineural hearing loss in asthma: A longitudinal follow-up study using a national sample cohort

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Running head: Asthma and otitis media

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Abstract

Objectives: This study investigated the risk of sudden sensorineural hearing loss (SSNHL) in asthma patients.

Design: A longitudinal follow-up study

Setting: The 2002 – 2013 Korean National Health Insurance Service-Health Screening Cohort was used.

Participants and Interventions: The asthma patients were 1:1 matched with the control group for age, sex, income, and region of residence, and the occurrence of SSNHL was followed.

Primary and secondary outcome measures: The stratified Cox proportional hazard model was used. Age, sex, income, and region of residence were stratified, and Charlson comorbidity index scores, obesity, smoking, alcohol consumption, and atopic dermatitis histories were adjusted. Subgroup analysis was performed according to age, sex, obesity, smoking, and alcohol consumption.

Results: The results showed that 1.0% (877/ 90,564) of the asthma group and 0.8% (706/90,564) of the control group exhibited SSNHL ($P < 0.001$). The asthma group demonstrated a higher hazard ratio (HR) for SSNHL than the control group (adjusted HR = 1.23, 95% CI = 1.11 – 1.36, $P < 0.001$). According to age and sex, the female subgroup showed elevated HRs for SSNHL in asthma patients. Both the nonsmoker and current smoker groups demonstrated higher HRs for SSNHL in asthma patients than in controls. According to alcohol consumption or obesity, the < 1 times a week alcohol consumption group and normal weight and severe obesity groups showed higher HRs for SSNHL in asthma patients than in the controls.

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Conclusions: Adult asthma patients had a higher risk of SSNHL than the control participants matched for demographic and socioeconomic factors.

Key words: Hearing loss; Asthma; Risk factors; Cohort studies; Epidemiology

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Strengths and limitations of this study

- This study demonstrated that the risk of developing SSNHL was 1.23 times higher in adult asthma patients than in the control group matched for demographic and socioeconomic factors.
- This association was independent of comorbidities such as allergies and lifestyle factors of obesity, alcohol consumption, and smoking.
- The duration and severity of asthma were heterogeneous, and pulmonary function test results were absent.

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Competing interest: None declared.

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Introduction

Asthma is one of the most common airway disorders, and it is characterized by airway hyperresponsiveness and relapsing airway symptoms of wheezing and sputum [1]. The prevalence of asthma was estimated to be approximately 4.2% (95% confidence intervals [CI] = 3.1 – 5.6) in the ≥ 20-year-old population in East Asia [2]. Asthma has several endotypes encompassing heterogeneous phenotypes with different etiologies [3 4]. Genetic susceptibility, host factors, and environmental factors were suggested to cause asthma [5]. For host factors, in addition to allergic sensitization, obesity was reported to increase the risk of asthma [6]. For environmental factors, pollen, other aeroallergens, and smoking could elevate the risk of asthma [7]. These contributing factors result in airway inflammation and alter airway tone and reactivity, which evoke asthmatic symptoms [3]. A growing number of researchers, not only those investigating airway pathophysiology, have proposed systemic or extrapulmonary manifestations of inflammation in asthma patients [8]. For instance, asthma was suggested to be associated with cardiovascular and cerebrovascular disorders [9 10].

Similarly, the pathophysiology of asthma could also implicate sensorineural hearing loss. The cochlea is an organ that is vulnerable to inflammation or ischemic insertion, which could result in hearing loss [11]. Owing to the blood supply requirements for the extensive collateral microvasculature [12], chronic hypoxia conditions can deteriorate cochlear function [11]. In addition, inner ear inflammation and immune dysfunction can impact sensorineural hearing loss [13]. Among these sensorineural hearing loss cases, the sudden onset of sensorineural hearing loss across 3 continuous frequencies within 3 days for 30 dB HL is defined as sudden sensorineural hearing loss (SSNHL) [14]. The incidence of SSNHL was estimated to be approximately 5 – 20 per 100,000 persons/year worldwide [15]. The pathophysiology of SSNHL is largely unknown and multifactorial. Approximately 71.0 –

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87.4% of SSNHL occurred without any organic causes [16 17]. Less than 10% of SSNHL patients had brain tumors invading the internal auditory canal and causing inner ear anomaly [16]. Inner ear pathophysiology related to inflammation, immune system dysfunction, and vascular causes were suggested as contributing factors for SSNHL [17]. Based on a shared pathophysiologic mechanism, a number of previous studies reported an increased risk of cardiovascular and cerebrovascular disorders in SSNHL patients [18]. Asthma also shares common pathophysiologies with SSNHL, namely, inflammation and immune system dysfunction. Therefore, there may be a relationship between asthma and SSNHL.

This study aimed to evaluate the risk of SSNHL in asthmatic adults. To the best of our knowledge, no prior study has investigated the association between SSNHL and asthma. When PubMed and EMBASE databases were searched for the keywords "asthma" AND "sudden hearing loss", no articles were retrieved until July 1, 2019. To minimize possible confounding effects, comorbidities and lifestyle factors associated with asthma were adjusted in this study. Moreover, SSNHL was confined to idiopathic cases by excluding cases of brain tumor, inner ear anomaly, and head injury.

Materials and Methods

Study Population and Data Collection

The Ethics Committee of Hallym University (2017-I102) approved the use of these data. Written informed consent was waived by the institutional review board.

This national cohort study relied on data from the Korean National Health Insurance Service-Health Screening Cohort (NHIS-HEALS). A detailed description of these data was provided in our previously published study [19].

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Participant Selection

Of the 514,866 cases with 497,931,549 medical claim codes, we included participants who were diagnosed with asthma (ICD-10: J45) or status asthmaticus (J46) from 2002 through 2013 (n = 110,601) as reported in previous studies [20 21]. We excluded participants who had a history of brain tumor (C70-C72, n = 262), otitis media (n = 18,286), or previous history of a head injury (n = 1,075). Among them, we excluded participants who had a previous history of SSNHL (n = 411). The participants were followed through December 31, 2013. SSNHL was diagnosed according to ICD-10 codes (H912), the audiometry exam (claim codes: E6931-E6937, F6341-F6348) and steroid treatment [22].

The asthma group was matched 1:1 with participants (control group) who were not diagnosed with asthma from 2002 through 2013. From the total population (n = 404,265), the control group was selected. Among them, we excluded participants who had a history of brain tumor (n = 844), otitis media (n = 42,700), or inner ear anomaly (n = 18). Matching was performed for age, sex, income, and region of residence.

To prevent selection bias when enrolling the matched participants, the control participants were sorted using a random number order and then selected from top to bottom. We set the index date as the date of the diagnosis of asthma. It was assumed that the matched control participants were involved at the same time as the asthma participants (index date). Therefore, the control patients who died before the index date or who had a history of SSNHL before the index date were replaced. Participants with a history of SSNHL before the index date were excluded from the asthma group (n = 411). All asthma patients were matched with a control participant. The mean follow-up time from the index date to the last follow-up date (December 31, 2013) or the date of death was similar in both the asthma group (87.28 months, standard deviation [SD] =40.56) and control group (87.02 months, SD =40.78).

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Finally, 1:1 matching resulted in the inclusion of 90,564 asthma patients and 90,564 control participants (Fig. 1).

Variables

Age, sex, income, and region of residence were defined as reported previous studies [21 23]. Brain tumor histories were included according to ICD-10 codes (C70-C72). Inner ear anomaly histories were included according to ICD-10 codes of Q16. Head injury histories were included according to ICD-10 codes of S00-S09 with claim codes of brain CT (HA 401-HA 472).

For tobacco smoking, patients were categorized according to their current smoking status (nonsmoker and former/current smoker). For alcohol consumption, patients were categorized according to frequency (< 1 time a week and ≥ 1 time a week). For obesity, patients were categorized as having a BMI (body mass index, kg/m^2) of < 18.5 (underweight), ≥ 18.5 to < 23 (normal), ≥ 23 to < 25 (overweight), ≥ 25 to < 30 (obese I), and ≥ 30 (obese II) following WPRO 2000 [24]. The Charlson comorbidity index (CCI) was used for 16 comorbidities, excluding pulmonary disease as a continuous variable (0 [no comorbidity] through 28 [multiple comorbidities]) [25]. Atopic dermatitis was defined according to the ICD-10 code of L20.

Statistical Analyses

Chi-square tests were used to compare the general characteristics between the asthma and control groups.

Stratified Cox proportional hazard models were used to assess hazard ratios (HRs) for SSNHL with respect to asthma. In this analysis, crude (simple) and adjusted models (for CCI

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score, obesity, smoking, alcohol consumption, and atopic dermatitis histories) were used, and 95% CIs were calculated. In these analyses, age, sex, income, and region of residence were stratified. Kaplan-Meier analysis and the Log rank test were used.

For subgroup analyses, we divided the participants by age and sex (<60 years old and ≥60 years old; male and female) to confirm that these relations were reliable according to age and sex. In another subgroup analysis, we analyzed HRs according to smoking status, alcohol consumption status, and obesity because we believe that these lifestyle factors could influence the occurrence of SSNHL.

Two-tailed analyses were conducted, and P values less than 0.05 were considered to indicate significance. The results were statistically analyzed using SPSS version 22.0 (IBM, Armonk, NY, USA) and SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Patients and public involvement statement

This national cohort study used data from the NHIS-HEALS. Detailed descriptions of these data are available in our previous studies[21,22]. No patients were involved in the development of the research question or the design of the study. We have no plan to disseminate the results to the patients. Because the NHIS-HEALS data are based on national health claim codes, release of the data by the researcher is illegal. All data are available from the National Health Insurance Sharing Service (NHISS) database (https://nhiss.nhis.or.kr/).

The NHISS allows all of these data to be used by any researcher who promises to follow the research ethics guidelines, with some associated costs. If one wants to access the data described in this article, one could download them from the website after promising to adhere to the research ethics requirements.

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Results

The duration from the index date to SSNHL (≥ 1 time) was 86.66 months (SD = 40.88) in the asthma group and 86.82 months (SD = 40.67) in the control group. The rates of SSNHL were higher in the asthma group (1.0% [877/90,564]) than in the control group (0.8% [706/90,564], P < 0.001, Table 1). No differences in the general characteristics of the participants (age, sex, income, and region of residence) were found due to the matching procedure (P = 1.000). However, the CCI score was different between the asthma and control groups (P < 0.001), the rate of atopic dermatitis was higher in the asthma group than in the control group (P < 0.001), and the distributions of obesity and alcohol consumption were different between the asthma and control groups (P < 0.001).

The adjusted HR of SSNHL was 1.23 (95% CI = 1.11-1.36) in the asthma group (P < 0.001, Table 2). Kaplan-Meier analysis showed consistent results (Fig. 2). In subgroup analyses according to age and sex, the adjusted HRs were 1.29 (95% CI = 1.08-1.54) in < 60-year-old women and 1.24 (95% CI = 1.01-1.52) in ≥60-year-old women.

According to smoking status, both the nonsmoker and former/current smoker subgroups showed elevated HRs for SSNHL in the asthma group compared to the control group (Table 3). The adjusted HRs were 1.20 (95% CI = 1.08-1.33) in nonsmokers and former smokers and 1.45 (95% CI = 1.09-1.93) in current smokers. According to alcohol consumption, the alcohol consumption subgroup demonstrated increased HR for SSNHL in the asthma group (adjusted HR = 1.24, 95% CI = 1.11 – 1.38). For obesity, the normal weight group and obese I group demonstrated increased HR for SSNHL in the asthma group (adjusted HR = 1.24, 95% CI = 1.05 – 1.48 of normal weight and adjusted HR = 1.35, 95% CI =1.13 – 1.60 for obese I).

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Discussion

The risk of developing SSNHL was 1.23 times higher in adult asthma patients than in the control group matched for demographic and socioeconomic factors. This association was independent of comorbidities such as allergies and lifestyle factors of obesity, alcohol consumption, and smoking. According to sex, the female subgroup demonstrated a higher risk of SSNHL in the asthma patients than in the matched controls. According to lifestyle factors, the participants without lifestyle risk factors, less alcohol consumption and normal BMI showed consistent results for the relationship between asthma and SSNHL. The novelty of this study is that it delineates the risk of SSNHL in asthma patients. A few plausible mechanisms could mediate this risk.

The allergic response in asthma patients could impact the elevated risk of SSNHL. Previous studies have demonstrated the etiologic role of allergy for SSNHL [13 26 27]. A few case reports have described SSNHL following IgE-mediated inflammatory responses [26 27]. In a cross-sectional study, patients in the adult asthma group showed higher serum IgE levels than the age-matched control group ($P < 0.001$) [13]. An allergy history was reported in 61.9% of asthma patients, which was higher than that reported in the control group (21.8%) [13]. The histamine and the degranulated mediators of mast cells could induce the vasodilation of inner ear vessels, impeding lymphatic circulation in the inner ear [28]. Circulating immune complexes could also occlude the strial capillaries and induce cochlear ischemia [29]. In addition, an allergic response could evoke inflammatory cascades via lymphocytes and macrophages of the inner ear, leading to inflammation and dysfunction of the inner ear [30].

In addition to an allergic response, other inflammatory mechanisms in asthma patients could induce inner ear inflammation and result in SSNHL. Only approximately 50% of asthma patients had Th2-high responses, while others had Th2-low cytokine profiles with

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neutrophilia and systemic inflammation [31]. This systemic inflammation might be linked to extrapulmonary disorders, including cardiovascular and metabolic diseases [6 10]. For instance, asthma patients with obesity demonstrated high levels of serum C-reactive protein, representing a systemic inflammatory response [32]. Similarly, these inflammatory conditions could influence inner ear inflammation and SSNHL.

The recurrent hypoxic conditions in asthma patients could act as an insult to the cochlear blood supply and cause SSNHL. Several previous studies have reported auditory dysfunction in patients with chronic lung disease [33-35]. The transient evoked otoacoustic emission (TEOAE), which primarily originates from outer hair cells, was found to be decreased in children with chronic lung disease compared to age- and sex-matched controls [33]. These results implied that outer hair cell functions were impaired following chronic exposure to hypoxia. Another case-control study demonstrated elevated hearing thresholds in pure tone audiometry and delayed interpeak latencies in the auditory brainstem response (ABR) in chronic obstructive lung disease patients [34]. Because the ABR records the evoked auditory response from multiple auditory brainstem nuclei, the abnormality in ABR implied the involvement of retrocochlear dysfunction as well as cochlear OHC dysfunction following hypoxic conditions. Because asthma is a pulmonary disorder with reversible airway obstruction, the impact of hypoxia might be less than that of other chronic lung diseases. However, the accumulated effects of recurrent hypoxic attack could result in cochlear dysfunction. Indeed, a previous study reported elevated hearing thresholds at high frequencies (10 – 20 kHz) in asthma patients [35]. The high frequencies are tonotopically allocated to the basal turn of the cochlea, which is susceptible to hypoxic injuries [36].

This study used a large, representative population cohort, which provided adequate statistical power. The large number of participants in the cohorts permitted the unbiased

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selection of control groups matched for both demographic and socioeconomic factors. In addition, comorbid conditions were adjusted using CCI. Lifestyle factors such as obesity, alcohol consumption, and smoking were also adjusted and analyzed using subgroups. The diagnoses of asthma and SSNHL were based on objective criteria according to ICD-10 codes and medication histories. However, this study had a few limitations, which should be noted. The duration and severity of asthma were heterogeneous, and pulmonary function test results were absent. Similarly, the degree and prognosis of hearing loss in SSNHL were not considered.

Conclusions

Asthma was associated with an increased risk of SSNHL in the adult asthma population compared to controls matched for demographic and socioeconomic factors.

Author contributions

HGC designed the study; CM, and HGC analyzed the data; SYK and CHL drafted and revised the paper; all authors approved the final version of the manuscript.

Data sharing statement

Release of the data by the researcher is illegal. All data are available from the National Health Insurance Sharing Service (NHISS) database (https://nhiss.nhis.or.kr/).

The NHISS allows all of these data to be used by any researcher who promises to follow the research ethics guidelines, with some associated costs. If one wants to access the data of this article, one can download them from the website after promising to adhere to the research ethics requirements.

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Table 1 General Characteristics of Participants

Characteristics	Total participants		
	Asthma (n, %)	Control group (n, %)	P-value
Age (years old)			1.000
40-44	5,316 (5.9)	5,316 (5.9)	
45-49	11,747 (13.0)	11,747 (13.0)	
50-54	14,272 (15.8)	14,272 (15.8)	
55-59	14,013 (15.5)	14,013 (15.5)	
60-64	14,084 (15.6)	14,084 (15.6)	
65-69	13,553 (15.0)	13,553 (15.0)	
70-74	9,982 (11.)	9,982 (11.)	
75-79	5,552 (6.1)	5,552 (6.1)	
80+	2,045 (2.3)	2,045 (2.3)	
Sex			1.000
Male	40,842 (45.1)	40,842 (45.1)	
Female	49,722 (54.9)	49,722 (54.9)	
Income			1.000
1 (lowest)	15,966 (17.6)	15,966 (17.6)	
2	13,041 (14.4)	13,041 (14.4)	
3	14,266 (15.8)	14,266 (15.8)	
4	18,676 (20.6)	18,676 (20.6)	
5 (highest)	28,615 (31.6)	28,615 (31.6)	
Region of residence			1.000
Urban	38,170 (42.1)	38,170 (42.1)	
Rural	52,394 (57.9)	52,394 (57.9)	
CCI score			<0.001*

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0	89,184 (98.5)	87,800 (96.9)	
1	122 (0.1)	538 (0.6)	
2	180 (0.2)	474 (0.5)	
≥ 3	1,078 (1.2)	1,752 (1.9)	
Atopic dermatitis	10,622 (11.7)	7,324 (8.1)	<0.001*
BMI			<0.001*
< 18.5 (underweight)	2,483 (2.7)	2,456 (2.7)	
≥ 18.5 to < 23 (normal)	30,140 (33.3)	33,446 (36.9)	
≥ 23 to < 25 (overweight)	23,826 (26.3)	24,412 (27.0)	
≥ 25 to < 30 (obese I)	30,706 (33.9)	27,687 (30.6)	
≥ 30 (obese II)	3,409 (3.8)	2,563 (2.8)	
Smoking			0.551
Nonsmoker or past smoker	75,610 (83.5)	75,704 (83.6)	
Current smoker	14,954 (16.5)	14,860 (16.4)	
Drinking alcohol			<0.001*
< 1 time a week	71,773 (79.3)	70,381 (77.7)	
≥ 1 time a week	18,791 (20.7)	20,183 (22.3)	
SSNHL	877 (1.0)	706 (0.8)	<0.001*

SSNHL: sudden sensory neural hearing loss

*Chi-square test. Significance at P < 0.05

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Table 2 Crude and adjusted hazard ratios (95% confidence interval) of asthma for SSNHL according to age and sex

Characteristics	Hazard ratios for SSNHL			
	Crude†	P-value	Adjusted†‡	P-value
Total participants (n = 181,128)				
Asthma	1.24 (1.12-1.37)	<0.001*	1.23 (1.11-1.36)	<0.001*
Control	1.00		1.00	
Age < 60 years old, men (n = 40,166)				
Asthma	1.27 (1.03-1.56)	0.024*	1.22 (0.99-1.51)	0.058
Control	1.00		1.00	
Age < 60 years old, women (n = 50,530)				
Asthma	1.28 (1.08-1.53)	0.006*	1.29 (1.08-1.54)	0.005*
Control	1.00		1.00	
Age ≥ 60 years old, men (n = 41,518)				
Asthma	1.15 (0.93-1.43)	0.187	1.15 (0.93-1.43)	0.195
Control	1.00		1.00	
Age ≥ 60 years old, women (n = 48,914)				
Asthma	1.24 (1.01-1.52)	0.039*	1.24 (1.01-1.52)	0.038*
Control	1.00		1.00	

* Cox-proportional hazard regression model, Significance at P < 0.05

† Stratified model for age, sex, income, and region of residence.

‡ Adjusted model for Charlson Comorbidity Index, obesity (BMI), smoking, alcohol intake, atopic dermatitis histories.

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Table 3 Crude and adjusted hazard ratios (95% confidence interval) of asthma for SSNHL according to smoking, drinking alcohol, and obesity

Characteristics	Hazard ratios for SSNHL			
	Crude	P-value	Adjusted†	P-value
Non or past smoker (n = 151,314)				
Asthma	1.21 (1.09-1.35)	<0.001*	1.20 (1.08-1.33)	0.001*
Control	1.00		1.00	
Current smoker (n = 29,814)				
Asthma	1.47 (1.11-1.95)	0.007*	1.45 (1.09-1.93)	0.010*
Control	1.00		1.00	
Drinking alcohol < 1 time a week (n = 142,154)				
Asthma	1.24 (1.11-1.39)	<0.001*	1.24 (1.11-1.38)	<0.001*
Control	1.00		1.00	
Drinking alcohol ≥ 1 time a week (n = 38,974)				
Asthma	1.21 (0.97-1.52)	0.099	1.19 (0.95-1.49)	0.140
Control	1.00		1.00	
Under weight (BMI < 18.5, n = 4,939)				
Asthma	0.60 (0.29-1.25)	0.176	0.59 (0.28-1.23)	0.157
Control	1.00		1.00	
Normal weight (BMI ≥ 18.5 to < 23, n = 63,586)				
Asthma	1.25 (1.05-1.48)	0.012*	1.24 (1.05-1.48)	0.013*
Control	1.00		1.00	
Overweight (BMI ≥ 23 to < 25, n = 48,238)				
Asthma	1.20 (1.00-1.45)	0.053	1.20 (0.99-1.44)	0.063

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Control	1.00		1.00	
Obese I (BMI ≥ 25 to < 30, n = 58,393)				
Asthma	1.37 (1.15-1.62)	<0.001*	1.35 (1.13-1.60)	0.001*
Control	1.00		1.00	
Obese II (BMI ≥ 30, n = 5,972)				
Asthma	0.73 (0.39-1.36)	0.321	0.73 (0.39-1.36)	0.325
Control	1.00		1.00	

* Non stratified Cox-proportional hazard regression model, Significance at P < 0.05

† Adjusted model for age, sex, income, region of residence, Charlson Comorbidity Index, obesity (BMI), smoking, alcohol intake, atopic dermatitis histories.

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Figure Legends

Figure 1 Schematic illustration of the participant selection process used in the present study. Of a total of 514,866 participants, 90,564 asthma patients were matched with 90,564 control participants for age, sex, income, and region of residence.

Figure 2 Kaplan-Meier survival curve of asthma for sudden sensorineural hearing loss (a 1 – survival function curve).

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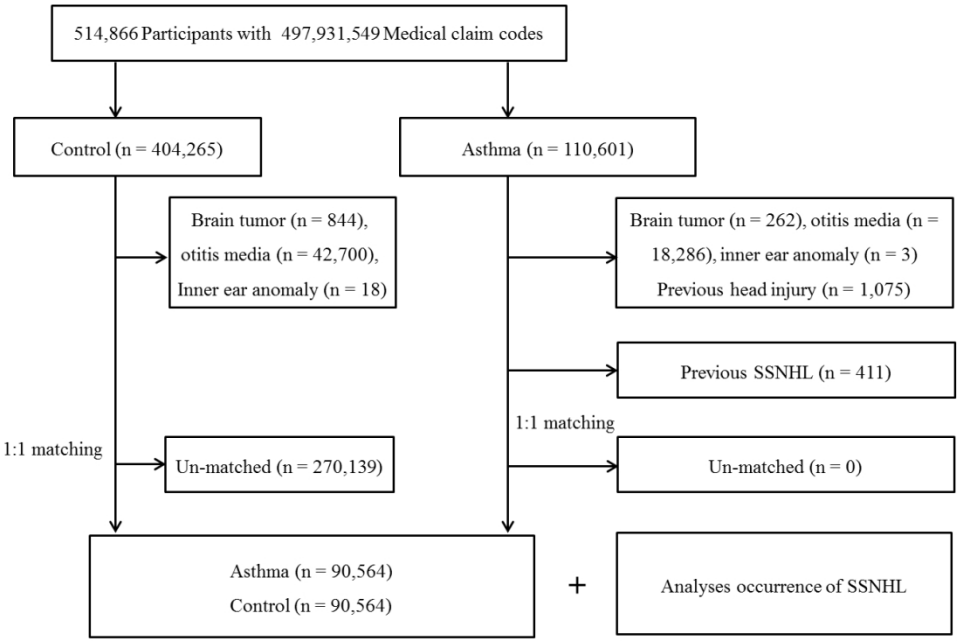
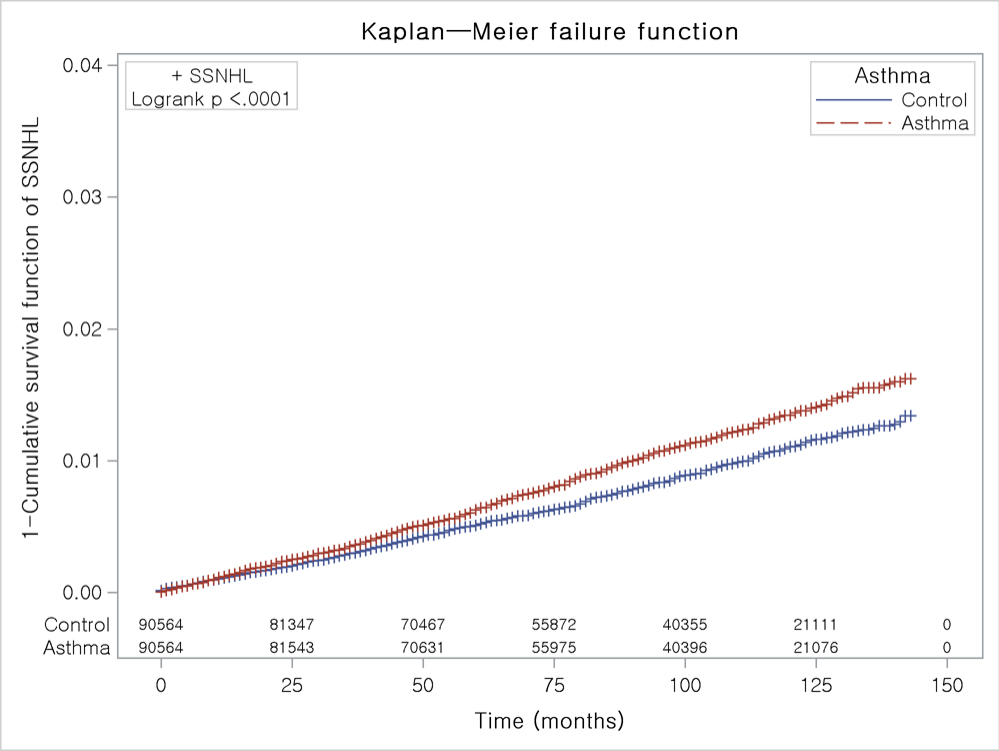

514,866 Participants with 497,931,549 Medical claim codes
Control (n = 404,265)
Asthma (n = 110,601)
Brain tumor (n = 844), otitis media (n = 42,700), Inner ear anomaly (n = 18)
Brain tumor (n = 262), otitis media (n = 18,286), inner ear anomaly (n = 3) Previous head injury (n = 1,075)
Previous SSNHL (n = 411)
1:1 matching
Un-matched (n = 270,139)
1:1 matching
Un-matched (n = 0)
Asthma (n = 90,564)
Control (n = 90,564)
+
Analyses occurrence of SSNHL



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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1-2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6-7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7-8
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	7-8
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	7-8
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8
Bias	9	Describe any efforts to address potential sources of bias	8-9
Study size	10	Explain how the study size was arrived at	7-8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8-9
		(*b*) Describe any methods used to examine subgroups and interactions	8-9
		(*c*) Explain how missing data were addressed	7-8
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	7-8
		(*e*) Describe any sensitivity analyses	N/A

Continued on next page

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Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7-8
		(b) Give reasons for non-participation at each stage	7-8
		(c) Consider use of a flow diagram	7-8
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10
		(b) Indicate number of participants with missing data for each variable of interest	10
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	7-8
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	10
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10
		(*b*) Report category boundaries when continuous variables were categorized	10
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12-13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-12
Generalisability	21	Discuss the generalisability (external validity) of the study results	11-12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	4

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Increased risk of sudden sensorineural hearing loss in asthma: A longitudinal follow-up study using a national sample cohort

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Increased risk of sudden sensorineural hearing loss in asthma: A longitudinal follow-up study using a national sample cohort

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Running head: Asthma and otitis media

Key words: asthma; otitis media; cohort studies; epidemiology

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Abstract

Objective: To investigate the risk of sudden sensorineural hearing loss (SSNHL) in asthma patients.

Design: A longitudinal follow-up study using a retrospective cohort

Setting: The 2002 – 2013 Korean National Health Insurance Service-Health Screening Cohort

Participants and Interventions: The ≥ 40 years old Korean population were enrolled. The asthma patients were 1:1 matched with the control group for age, sex, income, and region of residence.

Main outcome measure: The occurrence of SSNHL was followed in both asthma and control groups. The stratified Cox proportional hazard model was used. Age, sex, income, and region of residence were stratified, and Charlson comorbidity index scores, obesity, smoking, alcohol consumption, and atopic dermatitis histories were adjusted. Subgroup analysis was performed according to age, sex, obesity, smoking, and alcohol consumption.

Results: The results showed that 1.0% (877/ 90,564) of the asthma group and 0.8% (706/90,564) of the control group exhibited SSNHL ($P < 0.001$). The asthma group demonstrated a higher hazard ratio (HR) for SSNHL than the control group (adjusted HR = 1.23, 95% CI = 1.11 – 1.36, $P < 0.001$). According to age and sex, the female subgroup showed elevated HRs for SSNHL in asthma patients. Both the nonsmoker and current smoker groups demonstrated higher HRs for SSNHL in asthma patients than in controls. According to alcohol consumption or obesity, the < 1 time a week alcohol consumption group and normal weight and severe obesity groups showed higher HRs for SSNHL in asthma patients than in the controls.

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Conclusions: Adult asthma patients had a higher risk of SSNHL than the control participants matched for demographic and socioeconomic factors.

Key words: Hearing loss; Asthma; Risk factors; Cohort studies; Epidemiologies

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Background

Asthma is one of the most common airway disorders, and it is characterized by airway hyperresponsiveness and relapsing airway symptoms of wheezing and sputum [1]. The prevalence of asthma was estimated to be approximately 4.2% (95% confidence intervals [CI] = 3.1 – 5.6) in the ≥ 20-year-old population in East Asia [2]. Asthma has several endotypes encompassing heterogeneous phenotypes with different etiologies [3 4]. Genetic susceptibility, host factors, and environmental factors were suggested to cause asthma [5]. For host factors, in addition to allergic sensitization, obesity was reported to increase the risk of asthma [6]. For environmental factors, pollen, other aeroallergens, and smoking could elevate the risk of asthma [7]. These contributing factors result in airway inflammation and alter airway tone and reactivity, which evoke asthmatic symptoms [3]. A growing number of researchers, not only those investigating airway pathophysiology, have proposed systemic or extrapulmonary manifestations of inflammation in asthma patients [8]. For instance, asthma was suggested to be associated with cardiovascular and cerebrovascular disorders [9 10].

Similarly, the pathophysiology of asthma, such as systemic inflammation and persistent hypoxia, could also implicate sensorineural hearing loss. The cochlea is an organ that is vulnerable to inflammation or ischemic insertion, which could result in hearing loss [11]. Owing to the blood supply requirements for the extensive collateral microvasculature [12], chronic hypoxia conditions can deteriorate cochlear function [11]. In addition, inner ear inflammation and immune dysfunction can impact sensorineural hearing loss in patients with allergy [13]. Among these sensorineural hearing loss cases, the sudden onset of sensorineural hearing loss across 3 continuous frequencies within 3 days for 30 dB HL is defined as sudden sensorineural hearing loss (SSNHL) [14]. The incidence of SSNHL was estimated to be approximately 5 – 20 per 100,000 persons/year worldwide [15]. The pathophysiology of

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SSNHL is largely unknown and multifactorial. Approximately 71.0 – 87.4% of SSNHL occurred without any organic causes [16 17]. Less than 10% of SSNHL patients had brain tumors invading the internal auditory canal and causing inner ear anomaly [16]. Inner ear pathophysiology related to inflammation, immune system dysfunction, and vascular causes were suggested as contributing factors for SSNHL[17 18]. Based on a shared pathophysiologic mechanism with cardiovascular and cerebrovascular disorders, a number of previous studies reported an increased risk of these diseases in SSNHL patients [19]. Asthma also shares common pathophysiologies with SSNHL, namely, inflammation and immune system dysfunction. Therefore, there may be a relationship between asthma and SSNHL.

This study aimed to evaluate the risk of SSNHL in asthmatic adults. To the best of our knowledge, no prior study has investigated the association between SSNHL and asthma. When PubMed and EMBASE databases were searched for the keywords "asthma" AND "sudden hearing loss", no articles were retrieved until July 1, 2019. To minimize possible confounding effects, comorbidities and lifestyle factors associated with asthma were adjusted in this study. Moreover, SSNHL was confined to idiopathic cases by excluding cases of brain tumor, inner ear anomaly, and head injury.

Methods

Patient and Public Involvement statement

The Ethics Committee of Hallym University (2017-I102) approved the use of these data. Written informed consent was waived by the institutional review board.

This national cohort study relied on data from the Korean National Health Insurance Service-Health Screening Cohort (NHIS-HEALS). A detailed description of these data was provided in our previously published study [20]. This cohort based on the health claim code

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data and health screening database. This is a retrospective cohort study and participants did not intend to be collected or examined for study purpose.

Participant Selection

Of the 514,866 cases with 497,931,549 medical claim codes, we included participants who were diagnosed with asthma (ICD-10: J45) or status asthmaticus (J46) from 2002 through 2013 (n = 110,601) as reported in previous studies [21 22]. We excluded participants in both asthma and control groups who had a history of brain tumor (C70-C72), otitis media, or previous history of a head injury. Among them, we excluded participants who had a previous history of SSNHL. The numbers of excluded participants among asthma patients were 262 for the history of brain tumor, 18,286 for the history of otitis media, 1,075 for the previous history of a head injury, and 411 for previous history of SSNHL. The participants were followed through December 31, 2013. SSNHL was diagnosed according to ICD-10 codes (H912), the audiometry exam (claim codes: E6931-E6937, F6341-F6348) and steroid treatment [23].

The asthma group was matched 1:1 with participants (control group) who were not diagnosed with asthma from 2002 through 2013. From the total population (n = 404,265), the control group was selected. Among them, we excluded participants who had a history of brain tumor (n = 844), otitis media (n = 42,700), or inner ear anomaly (n = 18). Matching was performed for age, sex, income, and region of residence.

To prevent selection bias when enrolling the matched participants, the control participants were sorted using a random number order and then selected from top to bottom. We set the index date as the date of the diagnosis of asthma. It was assumed that the matched control participants were involved at the same time as the asthma participants (index date).

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Therefore, the control patients who died before the index date or who had a history of SSNHL before the index date were replaced. Participants with a history of SSNHL before the index date were excluded from the asthma group (n = 411). All asthma patients were matched with a control participant. The mean follow-up time from the index date to the last follow-up date (December 31, 2013) or the date of death was similar in both the asthma group (87.28 months, standard deviation [SD] =40.56) and control group (87.02 months, SD =40.78). Finally, 1:1 matching resulted in the inclusion of 90,564 asthma patients and 90,564 control participants (Figure 1).

Variables

Age, sex, income, and region of residence were defined as reported previous studies [22 24]. Brain tumor histories were included according to ICD-10 codes (C70-C72). Inner ear anomaly histories were included according to ICD-10 codes of Q16. Head injury histories were included according to ICD-10 codes of S00-S09 with claim codes of brain CT (HA 401-HA 472).

For tobacco smoking, patients were categorized according to their current smoking status (nonsmoker and former/current smoker)[25]. For alcohol consumption, patients were categorized according to frequency (< 1 time a week and ≥ 1 time a week)[25]. For obesity, patients were categorized as having a BMI (body mass index, kg/m^2) of < 18.5 (underweight), ≥ 18.5 to < 23 (normal), ≥ 23 to < 25 (overweight), ≥ 25 to < 30 (obese I), and ≥ 30 (obese II) following WPRO 2000 [26]. The Charlson comorbidity index (CCI) was used for 16 comorbidities, excluding pulmonary disease as a continuous variable (0 [no comorbidity] through 28 [multiple comorbidities]) [27]. Atopic dermatitis was defined according to the ICD-10 code of L20.

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Statistical Analyses

Chi-square tests were used to compare the general characteristics between the asthma and control groups.

Stratified Cox proportional hazard models were used to assess hazard ratios (HRs) for SSNHL with respect to asthma. In this analysis, crude (simple) and adjusted models (for CCI score, obesity, smoking, alcohol consumption, and atopic dermatitis histories) were used, and 95% CIs were calculated. In these analyses, age, sex, income, and region of residence were stratified. Kaplan-Meier analysis and the Log rank test were used. The proportional hazard assumption was tested using log minus log plot (Figure 2).

For subgroup analyses, we divided the participants by age and sex (<60 years old and ≥60 years old; male and female) to confirm that these relations were reliable according to age and sex. In another subgroup analysis, we analyzed HRs according to smoking status, alcohol consumption status, and obesity because we believe that these lifestyle factors could influence the occurrence of SSNHL.

Two-tailed analyses were conducted, and P values less than 0.05 were considered to indicate significance. The results were statistically analyzed using SPSS version 22.0 (IBM, Armonk, NY, USA) and SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

The duration from the index date to SSNHL (≥ 1 time) was 86.66 months (SD = 40.88) in the asthma group and 86.82 months (SD = 40.67) in the control group. The rates of SSNHL were higher in the asthma group (1.0% [877/90,564]) than in the control group (0.8% [706/90,564], P < 0.001, Table 1). No differences in the general characteristics of the

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participants (age, sex, income, and region of residence) were found due to the matching procedure (P = 1.000). However, the CCI score was different between the asthma and control groups (P < 0.001), the rate of atopic dermatitis was higher in the asthma group than in the control group (P < 0.001), and the distributions of obesity and alcohol consumption were different between the asthma and control groups (P < 0.001).

The adjusted HR of SSNHL was 1.23 (95% CI = 1.11-1.36) in the asthma group (P < 0.001, Table 2). Kaplan-Meier analysis showed consistent results (Figure 3). In subgroup analyses according to age and sex, the adjusted HRs were 1.29 (95% CI = 1.08-1.54) in < 60-year-old women and 1.24 (95% CI = 1.01-1.52) in ≥60-year-old women.

According to smoking status, both the nonsmoker and former/current smoker subgroups showed elevated HRs for SSNHL in the asthma group compared to the control group (Table 3). The adjusted HRs were 1.20 (95% CI = 1.08-1.33) in nonsmokers and former smokers and 1.45 (95% CI = 1.09-1.93) in current smokers. According to alcohol consumption, the alcohol consumption subgroup demonstrated increased HR for SSNHL in the asthma group (adjusted HR = 1.24, 95% CI = 1.11 – 1.38). For obesity, the normal weight group and obese I group demonstrated increased HR for SSNHL in the asthma group (adjusted HR = 1.24, 95% CI = 1.05 – 1.48 of normal weight and adjusted HR = 1.35, 95% CI =1.13 – 1.60 for obese I).

Discussion

The risk of developing SSNHL was 1.23 times higher in adult asthma patients than in the control group matched for demographic and socioeconomic factors. This association was independent of comorbidities such as allergies and lifestyle factors of obesity, alcohol consumption, and smoking. The metabolic syndrome components, including obesity and past

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medical histories using CCI scores were adjusted because these factors have been suggested as predictors of SSNHL and asthma[28 29]. According to sex, the female subgroup demonstrated a higher risk of SSNHL in the asthma patients than in the matched controls. The novelty of this study is that it delineates the risk of SSNHL in asthma patients. Clinicians need to be aware of the potential risk of SSNHL when managing asthmatic patients. A few plausible mechanisms could mediate this risk.

The allergic response in asthma patients could impact the elevated risk of SSNHL. Previous studies have demonstrated the etiologic role of allergy for SSNHL [13 30 31]. A few case reports have described SSNHL following IgE-mediated inflammatory responses [30 31]. In a cross-sectional study, patients in the adult asthma group showed higher serum IgE levels than the age-matched control group ($P < 0.001$) [13]. An allergy history was reported in 61.9% of asthma patients, which was higher than that reported in the control group (21.8%) [13]. The histamine and the degranulated mediators of mast cells could induce the vasodilation of inner ear vessels, impeding lymphatic circulation in the inner ear [32]. Circulating immune complexes could also occlude the strial capillaries and induce cochlear ischemia [33]. In addition, an allergic response could evoke inflammatory cascades via lymphocytes and macrophages of the inner ear, leading to inflammation and dysfunction of the inner ear [34].

In addition to an allergic response, other inflammatory mechanisms in asthma patients could induce inner ear inflammation and result in SSNHL. Only approximately 50% of asthma patients had Th2-high responses, while others had Th2-low cytokine profiles with neutrophilia and systemic inflammation [35]. This systemic inflammation might be linked to extrapulmonary disorders, including cardiovascular and metabolic diseases [6 10]. For instance, asthma patients with obesity demonstrated high levels of serum C-reactive protein,

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representing a systemic inflammatory response [36]. Similarly, these inflammatory conditions could influence inner ear inflammation and SSNHL.

The recurrent hypoxic conditions in asthma patients could act as an insult to the cochlear blood supply and cause SSNHL. Several previous studies have reported auditory dysfunction in patients with chronic lung disease [37-39]. The transient evoked otoacoustic emission (TEOAE), which primarily originates from outer hair cells, was found to be decreased in children with chronic lung disease compared to age- and sex-matched controls [37]. These results implied that outer hair cell functions were impaired following chronic exposure to hypoxia. Another case-control study demonstrated elevated hearing thresholds in pure tone audiometry and delayed interpeak latencies in the auditory brainstem response (ABR) in chronic obstructive lung disease patients [38]. Because the ABR records the evoked auditory response from multiple auditory brainstem nuclei, the abnormality in ABR implied the involvement of retrocochlear dysfunction as well as cochlear OHC dysfunction following hypoxic conditions. Because asthma is a pulmonary disorder with reversible airway obstruction, the impact of hypoxia might be less than that of other chronic lung diseases. However, the accumulated effects of recurrent hypoxic attack could result in cochlear dysfunction. Indeed, a previous study reported elevated hearing thresholds at high frequencies (10 – 20 kHz) in asthma patients [39]. The high frequencies are tonotopically allocated to the basal turn of the cochlea, which is susceptible to hypoxic injuries [40].

According to lifestyle factors, the participants without lifestyle risk factors, less alcohol consumption and normal BMI showed consistent results for the relationship between asthma and SSNHL in the present study. The non-significant association of asthma with SSNHL in participants with life style risk factors can be explained by the comorbid conditions susceptible to both asthma and SSNHL. Because smoking and alcohol consumption were

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supposed to increase the risk of SSNHL, the contribution of asthma on the development of SSNHL could not be as high as to reach the statistical significance[41-43]. The participants in Obese I (BMI ≥ 25 to < 30) also showed positive association of asthma with SSNHL in this study. In addition, the HR of obese I participants was higher than that of normal weight participants. The distinctive features of obese asthma could induce the elevated risk of SSNHL in this population[44]. The obese asthmatic patients were reported to suffer more symptoms, frequent and severe exacerbations, and refractory to some asthma medications[44].

Limitations

This study used a large, representative population cohort, which provided adequate statistical power. The large number of participants in the cohorts permitted the unbiased selection of control groups matched for both demographic and socioeconomic factors. In addition, comorbid conditions were adjusted using CCI. Lifestyle factors such as obesity, alcohol consumption, and smoking were also adjusted and analyzed using subgroups. The diagnoses of asthma and SSNHL were based on objective criteria according to ICD-10 codes and medication histories. However, this study had a few limitations, which should be noted. Because the study population of the present study was Korean, the ethnic or regional differences could be limit the generalizability of the present association between asthma and SSNHL. In addition, the duration and severity of asthma were heterogeneous, and pulmonary function test results were absent. Similarly, the degree and prognosis of hearing loss in SSNHL were not considered. Further studies are warrant to clarify the specific types of asthma which pose higher risk of SSNHL and the characteristics and prognosis of SSNHL in asthmatic patients.

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Conclusions

Asthma was associated with an increased risk of SSNHL in the adult asthma population compared to controls matched for demographic and socioeconomic factors. The potential contribution of asthma on the development of SSNHL will need to be considered when treating both asthma and SSNHL patients.

Competing interests

The authors declare they have no competing interests.

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Contributors

H.G.C. designed the study; C.M., and C.H.L. analyzed the data; S.Y.K. and H.G.C. drafted and revised the paper; and H.G.C. drew the figures. All authors have read and agreed to the published version of the manuscript.

Conflict of Interest

The authors report no potential conflicts of interest to disclose.

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Data Sharing

Release of the data by the researcher is not allowed legally. All data are available from the database of Korea Centers for Disease Control and Prevention (kdca.go.kr). The Korea Centers for Disease Control and Prevention provides all of these data for any researcher who promises to follow the research ethics guidelines, with some cost. If you want to access the data of this article, you could download it from the website after promising to follow the research ethics guidelines.

Ethical Approval

The Ethics Committee of Hallym University (2017-I102) approved the use of these data. Written informed consent was waived by the institutional review board.

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Figure Legends

Fig. 1. Schematic illustration of the participant selection process used in the present study. Of a total of 514,866 participants, 90,564 asthma patients were matched with 90,564 control participants for age, sex, income, and region of residence.

Fig. 2. The log minus log plot for a proportional hazard assumption for sudden sensorineural hearing loss of asthma and control groups.

Fig. 3. Kaplan-Meier survival curve of asthma for sudden sensorineural hearing loss (a 1 – survival function curve).

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Table 1 General Characteristics of Participants

Characteristics	Total participants		
	Asthma (n, %)	Control group (n, %)	P-value
Age (years old)			1.000
40-44	5,316 (5.9)	5,316 (5.9)	
45-49	11,747 (13.0)	11,747 (13.0)	
50-54	14,272 (15.8)	14,272 (15.8)	
55-59	14,013 (15.5)	14,013 (15.5)	
60-64	14,084 (15.6)	14,084 (15.6)	
65-69	13,553 (15.0)	13,553 (15.0)	
70-74	9,982 (11.)	9,982 (11.)	
75-79	5,552 (6.1)	5,552 (6.1)	
80+	2,045 (2.3)	2,045 (2.3)	
Sex			1.000
Male	40,842 (45.1)	40,842 (45.1)	
Female	49,722 (54.9)	49,722 (54.9)	
Income			1.000
1 (lowest)	15,966 (17.6)	15,966 (17.6)	
2	13,041 (14.4)	13,041 (14.4)	
3	14,266 (15.8)	14,266 (15.8)	
4	18,676 (20.6)	18,676 (20.6)	
5 (highest)	28,615 (31.6)	28,615 (31.6)	
Region of residence			1.000
Urban	38,170 (42.1)	38,170 (42.1)	
Rural	52,394 (57.9)	52,394 (57.9)	
CCI score			<0.001*

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0	89,184 (98.5)	87,800 (96.9)	
1	122 (0.1)	538 (0.6)	
2	180 (0.2)	474 (0.5)	
≥ 3	1,078 (1.2)	1,752 (1.9)	
Atopic dermatitis	10,622 (11.7)	7,324 (8.1)	<0.001*
BMI			<0.001*
< 18.5 (underweight)	2,483 (2.7)	2,456 (2.7)	
≥ 18.5 to < 23 (normal)	30,140 (33.3)	33,446 (36.9)	
≥ 23 to < 25 (overweight)	23,826 (26.3)	24,412 (27.0)	
≥ 25 to < 30 (obese I)	30,706 (33.9)	27,687 (30.6)	
≥ 30 (obese II)	3,409 (3.8)	2,563 (2.8)	
Smoking			0.551
Nonsmoker or past smoker	75,610 (83.5)	75,704 (83.6)	
Current smoker	14,954 (16.5)	14,860 (16.4)	
Drinking alcohol			<0.001*
< 1 time a week	71,773 (79.3)	70,381 (77.7)	
≥ 1 time a week	18,791 (20.7)	20,183 (22.3)	
SSNHL	877 (1.0)	706 (0.8)	<0.001*

SSNHL: sudden sensory neural hearing loss

*Chi-square test. Significance at $P < 0.05$

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Table 2 Crude and adjusted hazard ratios (95% confidence interval) of asthma for SSNHL according to age and sex

Characteristics	Hazard ratios for SSNHL			
	Crude†	P-value	Adjusted†‡	P-value
Total participants (n = 181,128)				
Asthma	1.24 (1.12-1.37)	<0.001*	1.23 (1.11-1.36)	<0.001*
Control	1.00		1.00	
Age < 60 years old, men (n = 40,166)				
Asthma	1.27 (1.03-1.56)	0.024*	1.22 (0.99-1.51)	0.058
Control	1.00		1.00	
Age < 60 years old, women (n = 50,530)				
Asthma	1.28 (1.08-1.53)	0.006*	1.29 (1.08-1.54)	0.005*
Control	1.00		1.00	
Age ≥ 60 years old, men (n = 41,518)				
Asthma	1.15 (0.93-1.43)	0.187	1.15 (0.93-1.43)	0.195
Control	1.00		1.00	
Age ≥ 60 years old, women (n = 48,914)				
Asthma	1.24 (1.01-1.52)	0.039*	1.24 (1.01-1.52)	0.038*
Control	1.00		1.00	

* Cox-proportional hazard regression model, Significance at P < 0.05

† Stratified model for age, sex, income, and region of residence.

‡ Adjusted model for Charlson Comorbidity Index, obesity (BMI), smoking, alcohol intake, atopic dermatitis histories.

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Table 3 Crude and adjusted hazard ratios (95% confidence interval) of asthma for SSNHL according to smoking, drinking alcohol, and obesity

Characteristics	Hazard ratios for SSNHL			
	Crude	P-value	Adjusted†	P-value
Non or past smoker (n = 151,314)				
Asthma	1.21 (1.09-1.35)	<0.001*	1.20 (1.08-1.33)	0.001*
Control	1.00		1.00	
Current smoker (n = 29,814)				
Asthma	1.47 (1.11-1.95)	0.007*	1.45 (1.09-1.93)	0.010*
Control	1.00		1.00	
Drinking alcohol < 1 time a week (n = 142,154)				
Asthma	1.24 (1.11-1.39)	<0.001*	1.24 (1.11-1.38)	<0.001*
Control	1.00		1.00	
Drinking alcohol ≥ 1 time a week (n = 38,974)				
Asthma	1.21 (0.97-1.52)	0.099	1.19 (0.95-1.49)	0.140
Control	1.00		1.00	
Under weight (BMI < 18.5, n = 4,939)				
Asthma	0.60 (0.29-1.25)	0.176	0.59 (0.28-1.23)	0.157
Control	1.00		1.00	
Normal weight (BMI ≥ 18.5 to < 23, n = 63,586)				
Asthma	1.25 (1.05-1.48)	0.012*	1.24 (1.05-1.48)	0.013*
Control	1.00		1.00	
Overweight (BMI ≥ 23 to < 25, n = 48,238)				
Asthma	1.20 (1.00-1.45)	0.053	1.20 (0.99-1.44)	0.063

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Control	1.00		1.00	
Obese I (BMI ≥ 25 to < 30, n = 58,393)				
Asthma	1.37 (1.15-1.62)	<0.001*	1.35 (1.13-1.60)	0.001*
Control	1.00		1.00	
Obese II (BMI ≥ 30, n = 5,972)				
Asthma	0.73 (0.39-1.36)	0.321	0.73 (0.39-1.36)	0.325
Control	1.00		1.00	

* Non stratified Cox-proportional hazard regression model, Significance at P < 0.05

† Adjusted model for age, sex, income, region of residence, Charlson Comorbidity Index, obesity (BMI), smoking, alcohol intake, atopic dermatitis histories.

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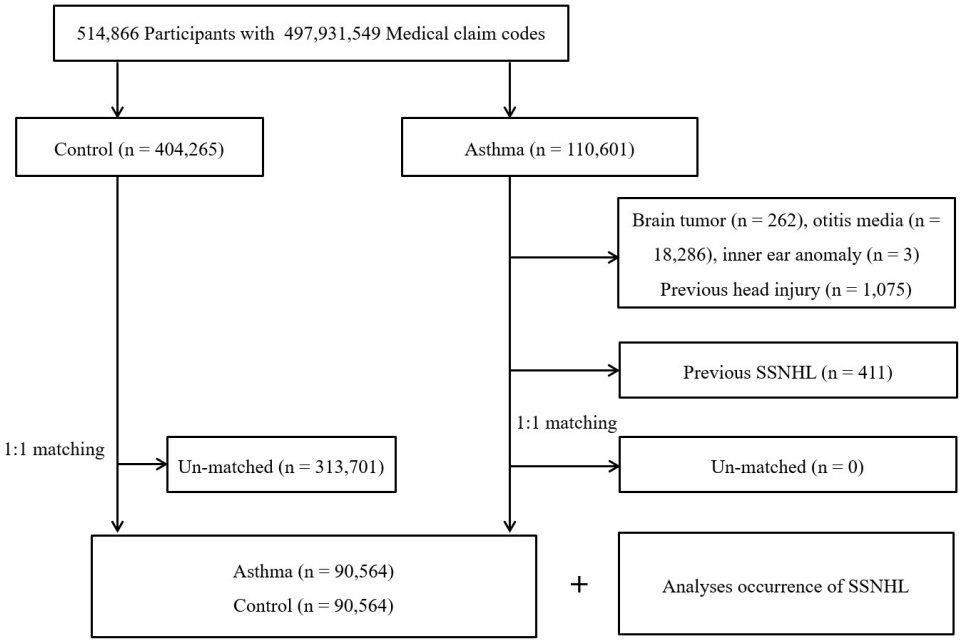

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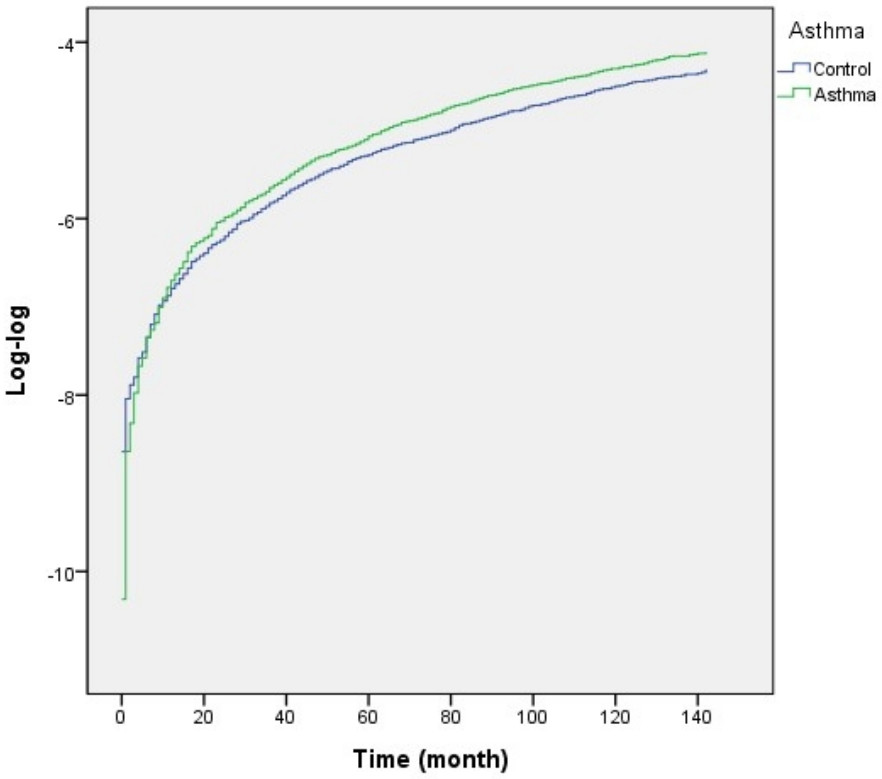

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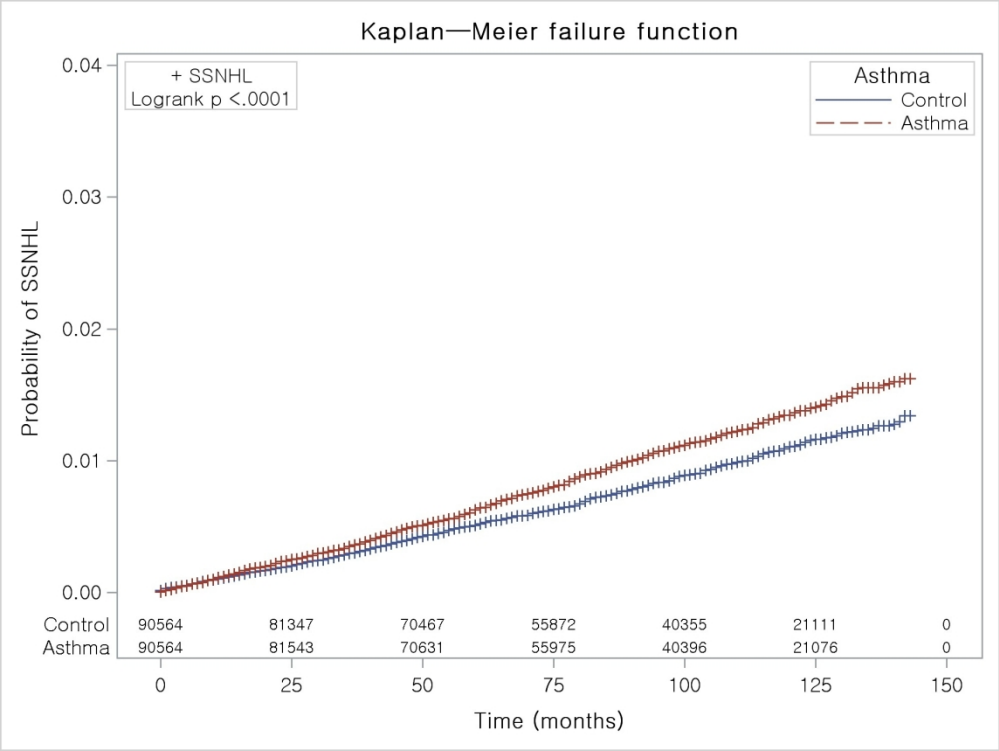

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1-2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6-7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7-8
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	7-8
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	7-8
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8
Bias	9	Describe any efforts to address potential sources of bias	8-9
Study size	10	Explain how the study size was arrived at	7-8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8-9
		(*b*) Describe any methods used to examine subgroups and interactions	8-9
		(*c*) Explain how missing data were addressed	7-8
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	7-8
		(*e*) Describe any sensitivity analyses	N/A

Continued on next page

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Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8-9
		(b) Give reasons for non-participation at each stage	8-9
		(c) Consider use of a flow diagram	8-9
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9
		(b) Indicate number of participants with missing data for each variable of interest	9
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	7-8
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	9
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9
		(*b*) Report category boundaries when continuous variables were categorized	9
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9
Discussion			
Key results	18	Summarise key results with reference to study objectives	10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12
Generalisability	21	Discuss the generalisability (external validity) of the study results	12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Increased risk of sudden sensorineural hearing loss in asthma: A longitudinal follow-up study using a national sample cohort

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Increased risk of sudden sensorineural hearing loss in asthma: A longitudinal follow-up study using a national sample cohort

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Running head: Asthma and otitis media

Key words: asthma; otitis media; cohort studies; epidemiology

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Abstract

Objective: To investigate the risk of sudden sensorineural hearing loss (SSNHL) in asthma patients.

Design: A longitudinal follow-up study using a retrospective cohort

Setting: The 2002 – 2013 Korean National Health Insurance Service-Health Screening Cohort

Participants and Interventions: The ≥ 40 years old Korean population were enrolled. The asthma patients were 1:1 matched with the control group for age, sex, income, and region of residence.

Main outcome measure: The occurrence of SSNHL was followed in both asthma and control groups. The stratified Cox proportional hazard model was used. Age, sex, income, and region of residence were stratified, and Charlson comorbidity index scores, obesity, smoking, alcohol consumption, and atopic dermatitis histories were adjusted. Subgroup analysis was performed according to age, sex, obesity, smoking, and alcohol consumption.

Results: The results showed that 1.0% (877/ 90,564) of the asthma group and 0.8% (706/90,564) of the control group exhibited SSNHL ($P < 0.001$). The asthma group demonstrated a higher hazard ratio (HR) for SSNHL than the control group (adjusted HR = 1.23, 95% CI = 1.11 – 1.36, $P < 0.001$). According to age and sex, the female subgroup showed elevated HRs for SSNHL in asthma patients. Both the nonsmoker and current smoker groups demonstrated higher HRs for SSNHL in asthma patients than in controls. According to alcohol consumption or obesity, the < 1 time a week alcohol consumption group and normal weight and severe obesity groups showed higher HRs for SSNHL in asthma patients than in the controls.

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Conclusions: Adult asthma patients had a higher risk of SSNHL than the control participants matched for demographic and socioeconomic factors.

Key words: Hearing loss; Asthma; Risk factors; Cohort studies; Epidemiologies

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Background

Asthma is one of the most common airway disorders, and it is characterized by airway hyperresponsiveness and relapsing airway symptoms of wheezing and sputum [1]. The prevalence of asthma was estimated to be approximately 4.2% (95% confidence intervals [CI] = 3.1 – 5.6) in the ≥ 20-year-old population in East Asia [2]. Asthma has several endotypes encompassing heterogeneous phenotypes with different etiologies [3 4]. Genetic susceptibility, host factors, and environmental factors were suggested to cause asthma [5]. For host factors, in addition to allergic sensitization, obesity was reported to increase the risk of asthma [6]. For environmental factors, pollen, other aeroallergens, and smoking could elevate the risk of asthma [7]. These contributing factors result in airway inflammation and alter airway tone and reactivity, which evoke asthmatic symptoms [3]. A growing number of researchers, not only those investigating airway pathophysiology, have proposed systemic or extrapulmonary manifestations of inflammation in asthma patients [8]. For instance, asthma was suggested to be associated with cardiovascular and cerebrovascular disorders [9 10].

Similarly, the pathophysiology of asthma, such as systemic inflammation and persistent hypoxia, could also implicate sensorineural hearing loss. The cochlea is an organ that is vulnerable to inflammation or ischemic insertion, which could result in hearing loss [11]. Owing to the blood supply requirements for the extensive collateral microvasculature [12], chronic hypoxia conditions can deteriorate cochlear function [11]. In addition, inner ear inflammation and immune dysfunction can impact sensorineural hearing loss in patients with allergy [13]. Among these sensorineural hearing loss cases, the sudden onset of sensorineural hearing loss across 3 continuous frequencies within 3 days for 30 dB HL is defined as sudden sensorineural hearing loss (SSNHL) [14]. The incidence of SSNHL was estimated to be approximately 5 – 20 per 100,000 persons/year worldwide [15]. The pathophysiology of

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SSNHL is largely unknown and multifactorial. Approximately 71.0 – 87.4% of SSNHL occurred without any organic causes [16-18]. Less than 10% of SSNHL patients had brain tumors invading the internal auditory canal and causing inner ear anomaly [16]. Inner ear pathophysiology related to inflammation, immune system dysfunction, and vascular causes were suggested as contributing factors for SSNHL[17 19]. Based on a shared pathophysiologic mechanism with cardiovascular and cerebrovascular disorders, a number of previous studies reported an increased risk of these diseases in SSNHL patients [20]. Asthma also shares common pathophysiologies with SSNHL, namely, inflammation and immune system dysfunction. Therefore, there may be a relationship between asthma and SSNHL.

This study aimed to evaluate the risk of SSNHL in asthmatic adults. To the best of our knowledge, no prior study has investigated the association between SSNHL and asthma. When PubMed and EMBASE databases were searched for the keywords "asthma" AND "sudden hearing loss", no articles were retrieved until July 1, 2019. To minimize possible confounding effects, comorbidities and lifestyle factors associated with asthma were adjusted in this study. Moreover, SSNHL was confined to idiopathic cases by excluding cases of brain tumor, inner ear anomaly, and head injury.

Methods

Patient and Public Involvement statement

The Ethics Committee of Hallym University (2017-I102) approved the use of these data. Written informed consent was waived by the institutional review board.

This national cohort study relied on data from the Korean National Health Insurance Service-Health Screening Cohort (NHIS-HEALS). A detailed description of these data was provided in our previously published study [21]. This cohort based on the health claim code

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data and health screening database. This is a retrospective cohort study and participants did not intend to be collected or examined for study purpose.

Participant Selection

Of the 514,866 cases with 497,931,549 medical claim codes, we included participants who were diagnosed with asthma (ICD-10: J45) or status asthmaticus (J46) from 2002 through 2013 (n = 110,601) as reported in previous studies [22 23]. We excluded participants in both asthma and control groups who had a history of brain tumor (C70-C72), otitis media, or previous history of a head injury. Among them, we excluded participants who had a previous history of SSNHL. The numbers of excluded participants among asthma patients were 262 for the history of brain tumor, 18,286 for the history of otitis media, 1,075 for the previous history of a head injury, and 411 for previous history of SSNHL. The participants were followed through December 31, 2013. SSNHL was diagnosed according to ICD-10 codes (H912), the audiometry exam (claim codes: E6931-E6937, F6341-F6348) and steroid treatment [24].

The asthma group was matched 1:1 with participants (control group) who were not diagnosed with asthma from 2002 through 2013. From the total population (n = 404,265), the control group was selected. Among them, we excluded participants who had a history of brain tumor (n = 844), otitis media (n = 42,700), or inner ear anomaly (n = 18). Matching was performed for age, sex, income, and region of residence.

To prevent selection bias when enrolling the matched participants, the control participants were sorted using a random number order and then selected from top to bottom. We set the index date as the date of the diagnosis of asthma. It was assumed that the matched control participants were involved at the same time as the asthma participants (index date).

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Therefore, the control patients who died before the index date or who had a history of SSNHL before the index date were replaced. Participants with a history of SSNHL before the index date were excluded from the asthma group (n = 411). All asthma patients were matched with a control participant. The mean follow-up time from the index date to the last follow-up date (December 31, 2013) or the date of death was similar in both the asthma group (87.28 months, standard deviation [SD] =40.56) and control group (87.02 months, SD =40.78). Finally, 1:1 matching resulted in the inclusion of 90,564 asthma patients and 90,564 control participants (Figure 1).

Variables

Age, sex, income, and region of residence were defined as reported previous studies [23 25]. Brain tumor histories were included according to ICD-10 codes (C70-C72). Inner ear anomaly histories were included according to ICD-10 codes of Q16. Head injury histories were included according to ICD-10 codes of S00-S09 with claim codes of brain CT (HA 401-HA 472).

For tobacco smoking, patients were categorized according to their current smoking status (nonsmoker and former/current smoker)[26]. For alcohol consumption, patients were categorized according to frequency (< 1 time a week and ≥ 1 time a week)[26]. For obesity, patients were categorized as having a BMI (body mass index, kg/m^2) of < 18.5 (underweight), ≥ 18.5 to < 23 (normal), ≥ 23 to < 25 (overweight), ≥ 25 to < 30 (obese I), and ≥ 30 (obese II) following WPRO 2000 [27]. The Charlson comorbidity index (CCI) was used for 16 comorbidities, excluding pulmonary disease as a continuous variable (0 [no comorbidity] through 28 [multiple comorbidities]) [28]. Atopic dermatitis was defined according to the ICD-10 code of L20.

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Statistical Analyses

Chi-square tests were used to compare the general characteristics between the asthma and control groups.

Stratified Cox proportional hazard models were used to assess hazard ratios (HRs) for SSNHL with respect to asthma. In this analysis, crude (simple) and adjusted models (for CCI score, obesity, smoking, alcohol consumption, and atopic dermatitis histories) were used, and 95% CIs were calculated. In these analyses, age, sex, income, and region of residence were stratified. Kaplan-Meier analysis and the Log rank test were used. The proportional hazard assumption was tested using log minus log plot (Figure 2).

For subgroup analyses, we divided the participants by age and sex (<60 years old and ≥60 years old; male and female) to confirm that these relations were reliable according to age and sex. In another subgroup analysis, we analyzed HRs according to smoking status, alcohol consumption status, and obesity because we believe that these lifestyle factors could influence the occurrence of SSNHL.

Two-tailed analyses were conducted, and P values less than 0.05 were considered to indicate significance. The results were statistically analyzed using SPSS version 22.0 (IBM, Armonk, NY, USA) and SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

The duration from the index date to SSNHL (≥ 1 time) was 86.66 months (SD = 40.88) in the asthma group and 86.82 months (SD = 40.67) in the control group. The rates of SSNHL were higher in the asthma group (1.0% [877/90,564]) than in the control group (0.8% [706/90,564], P < 0.001, Table 1). No differences in the general characteristics of the

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participants (age, sex, income, and region of residence) were found due to the matching procedure (P = 1.000). However, the CCI score was different between the asthma and control groups (P < 0.001), the rate of atopic dermatitis was higher in the asthma group than in the control group (P < 0.001), and the distributions of obesity and alcohol consumption were different between the asthma and control groups (P < 0.001).

The adjusted HR of SSNHL was 1.23 (95% CI = 1.11-1.36) in the asthma group (P < 0.001, Table 2). Kaplan-Meier analysis showed consistent results (Figure 3). In subgroup analyses according to age and sex, the adjusted HRs were 1.29 (95% CI = 1.08-1.54) in < 60-year-old women and 1.24 (95% CI = 1.01-1.52) in ≥60-year-old women.

According to smoking status, both the nonsmoker and former/current smoker subgroups showed elevated HRs for SSNHL in the asthma group compared to the control group (Table 3). The adjusted HRs were 1.20 (95% CI = 1.08-1.33) in nonsmokers and former smokers and 1.45 (95% CI = 1.09-1.93) in current smokers. According to alcohol consumption, the alcohol consumption subgroup demonstrated increased HR for SSNHL in the asthma group (adjusted HR = 1.24, 95% CI = 1.11 – 1.38). For obesity, the normal weight group and obese I group demonstrated increased HR for SSNHL in the asthma group (adjusted HR = 1.24, 95% CI = 1.05 – 1.48 of normal weight and adjusted HR = 1.35, 95% CI =1.13 – 1.60 for obese I).

Discussion

The risk of developing SSNHL was 1.23 times higher in adult asthma patients than in the control group matched for demographic and socioeconomic factors. This association was independent of comorbidities such as allergies and lifestyle factors of obesity, alcohol consumption, and smoking. The metabolic syndrome components, including obesity and past

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medical histories using CCI scores (diabetes) were adjusted because these factors have been suggested as predictors of SSNHL and asthma[29 30]. According to sex, the female subgroup demonstrated a higher risk of SSNHL in the asthma patients than in the matched controls. The novelty of this study is that it delineates the risk of SSNHL in asthma patients. Clinicians need to be aware of the potential risk of SSNHL when managing asthmatic patients. A few plausible mechanisms could mediate this risk.

The allergic response in asthma patients could impact the elevated risk of SSNHL. Previous studies have demonstrated the etiologic role of allergy for SSNHL [13 31 32]. A few case reports have described SSNHL following IgE-mediated inflammatory responses [31 32]. In a cross-sectional study, patients in the adult asthma group showed higher serum IgE levels than the age-matched control group ($P < 0.001$) [13]. An allergy history was reported in 61.9% of asthma patients, which was higher than that reported in the control group (21.8%) [13]. The histamine and the degranulated mediators of mast cells could induce the vasodilation of inner ear vessels, impeding lymphatic circulation in the inner ear [33]. Circulating immune complexes could also occlude the strial capillaries and induce cochlear ischemia [34]. In addition, an allergic response could evoke inflammatory cascades via lymphocytes and macrophages of the inner ear, leading to inflammation and dysfunction of the inner ear [35].

In addition to an allergic response, other inflammatory mechanisms in asthma patients could induce inner ear inflammation and result in SSNHL. Only approximately 50% of asthma patients had Th2-high responses, while others had Th2-low cytokine profiles with neutrophilia and systemic inflammation [36]. This systemic inflammation might be linked to extrapulmonary disorders, including cardiovascular and metabolic diseases [6 10]. For instance, asthma patients with obesity demonstrated high levels of serum C-reactive protein,

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representing a systemic inflammatory response [37]. Similarly, these inflammatory conditions could influence inner ear inflammation and SSNHL.

The recurrent hypoxic conditions in asthma patients could act as an insult to the cochlear blood supply and cause SSNHL. Several previous studies have reported auditory dysfunction in patients with chronic lung disease [38-40]. The transient evoked otoacoustic emission (TEOAE), which primarily originates from outer hair cells, was found to be decreased in children with chronic lung disease compared to age- and sex-matched controls [38]. These results implied that outer hair cell functions were impaired following chronic exposure to hypoxia. Another case-control study demonstrated elevated hearing thresholds in pure tone audiometry and delayed interpeak latencies in the auditory brainstem response (ABR) in chronic obstructive lung disease patients [39]. Because the ABR records the evoked auditory response from multiple auditory brainstem nuclei, the abnormality in ABR implied the involvement of retrocochlear dysfunction as well as cochlear OHC dysfunction following hypoxic conditions. Because asthma is a pulmonary disorder with reversible airway obstruction, the impact of hypoxia might be less than that of other chronic lung diseases. However, the accumulated effects of recurrent hypoxic attack could result in cochlear dysfunction. Indeed, a previous study reported elevated hearing thresholds at high frequencies (10 – 20 kHz) in asthma patients [40]. The high frequencies are tonotopically allocated to the basal turn of the cochlea, which is susceptible to hypoxic injuries [41].

According to lifestyle factors, the participants without lifestyle risk factors, less alcohol consumption and normal BMI showed consistent results for the relationship between asthma and SSNHL in the present study. The non-significant association of asthma with SSNHL in participants with life style risk factors can be explained by the comorbid conditions susceptible to both asthma and SSNHL. Because smoking and alcohol consumption were

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supposed to increase the risk of SSNHL, the contribution of asthma on the development of SSNHL could not be as high as to reach the statistical significance[42-44]. The participants in Obese I (BMI ≥ 25 to < 30) also showed positive association of asthma with SSNHL in this study. In addition, the HR of obese I participants was higher than that of normal weight participants. The distinctive features of obese asthma could induce the elevated risk of SSNHL in this population[45]. The obese asthmatic patients were reported to suffer more symptoms, frequent and severe exacerbations, and refractory to some asthma medications[45].

Limitations

This study used a large, representative population cohort, which provided adequate statistical power. The large number of participants in the cohorts permitted the unbiased selection of control groups matched for both demographic and socioeconomic factors. In addition, comorbid conditions were adjusted using CCI. Lifestyle factors such as obesity, alcohol consumption, and smoking were also adjusted and analyzed using subgroups. The diagnoses of asthma and SSNHL were based on objective criteria according to ICD-10 codes and medication histories. However, this study had a few limitations, which should be noted. Although many comorbid conditions were considered, the metabolic syndrome components could not be fully evaluated in the current study. Because the study population of the present study was Korean, the ethnic or regional differences could be limit the generalizability of the present association between asthma and SSNHL. In addition, the duration and severity of asthma were heterogeneous, and pulmonary function test results were absent. Similarly, the degree and prognosis of hearing loss in SSNHL were not considered. Further studies are warrant to clarify the specific types of asthma which pose higher risk of SSNHL and the characteristics and prognosis of SSNHL in asthmatic patients.

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Conclusions

Asthma was associated with an increased risk of SSNHL in the adult asthma population compared to controls matched for demographic and socioeconomic factors. The potential contribution of asthma on the development of SSNHL will need to be considered when treating both asthma and SSNHL patients.

Competing interests

The authors declare they have no competing interests.

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Contributors

H.G.C. designed the study; C.M., and C.H.L. analyzed the data; S.Y.K. and H.G.C. drafted and revised the paper; and H.G.C. drew the figures. All authors have read and agreed to the published version of the manuscript.

Conflict of Interest

The authors report no potential conflicts of interest to disclose.

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Role of the Funder: The funders had no role in the design of the study and collection, analysis, and interpretation of data and in writing the manuscript.

Data Sharing

Release of the data by the researcher is not allowed legally. All data are available from the database of Korea Centers for Disease Control and Prevention (kdca.go.kr). The Korea Centers for Disease Control and Prevention provides all of these data for any researcher who promises to follow the research ethics guidelines, with some cost. If you want to access the data of this article, you could download it from the website after promising to follow the research ethics guidelines.

Ethical Approval

The Ethics Committee of Hallym University (2017-I102) approved the use of these data. Written informed consent was waived by the institutional review board.

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Figure Legends

Fig. 1. Schematic illustration of the participant selection process used in the present study. Of a total of 514,866 participants, 90,564 asthma patients were matched with 90,564 control participants for age, sex, income, and region of residence.

Fig. 2. The log minus log plot for a proportional hazard assumption for sudden sensorineural hearing loss of asthma and control groups.

Fig. 3. Kaplan-Meier survival curve of asthma for sudden sensorineural hearing loss (a 1 – survival function curve).

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Table 1 General Characteristics of Participants

Characteristics	Total participants		
	Asthma (n, %)	Control group (n, %)	P-value
Age (years old)			1.000
40-44	5,316 (5.9)	5,316 (5.9)	
45-49	11,747 (13.0)	11,747 (13.0)	
50-54	14,272 (15.8)	14,272 (15.8)	
55-59	14,013 (15.5)	14,013 (15.5)	
60-64	14,084 (15.6)	14,084 (15.6)	
65-69	13,553 (15.0)	13,553 (15.0)	
70-74	9,982 (11.)	9,982 (11.)	
75-79	5,552 (6.1)	5,552 (6.1)	
80+	2,045 (2.3)	2,045 (2.3)	
Sex			1.000
Male	40,842 (45.1)	40,842 (45.1)	
Female	49,722 (54.9)	49,722 (54.9)	
Income			1.000
1 (lowest)	15,966 (17.6)	15,966 (17.6)	
2	13,041 (14.4)	13,041 (14.4)	
3	14,266 (15.8)	14,266 (15.8)	
4	18,676 (20.6)	18,676 (20.6)	
5 (highest)	28,615 (31.6)	28,615 (31.6)	
Region of residence			1.000
Urban	38,170 (42.1)	38,170 (42.1)	
Rural	52,394 (57.9)	52,394 (57.9)	
CCI score			<0.001*

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0	89,184 (98.5)	87,800 (96.9)	
1	122 (0.1)	538 (0.6)	
2	180 (0.2)	474 (0.5)	
≥ 3	1,078 (1.2)	1,752 (1.9)	
Atopic dermatitis	10,622 (11.7)	7,324 (8.1)	<0.001*
BMI			<0.001*
< 18.5 (underweight)	2,483 (2.7)	2,456 (2.7)	
≥ 18.5 to < 23 (normal)	30,140 (33.3)	33,446 (36.9)	
≥ 23 to < 25 (overweight)	23,826 (26.3)	24,412 (27.0)	
≥ 25 to < 30 (obese I)	30,706 (33.9)	27,687 (30.6)	
≥ 30 (obese II)	3,409 (3.8)	2,563 (2.8)	
Smoking			0.551
Nonsmoker or past smoker	75,610 (83.5)	75,704 (83.6)	
Current smoker	14,954 (16.5)	14,860 (16.4)	
Drinking alcohol			<0.001*
< 1 time a week	71,773 (79.3)	70,381 (77.7)	
≥ 1 time a week	18,791 (20.7)	20,183 (22.3)	
SSNHL	877 (1.0)	706 (0.8)	<0.001*

SSNHL: sudden sensory neural hearing loss

*Chi-square test. Significance at P < 0.05

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Table 2 Crude and adjusted hazard ratios (95% confidence interval) of asthma for SSNHL according to age and sex

Characteristics	Hazard ratios for SSNHL			
	Crude†	P-value	Adjusted†‡	P-value
Total participants (n = 181,128)				
Asthma	1.24 (1.12-1.37)	<0.001*	1.23 (1.11-1.36)	<0.001*
Control	1.00		1.00	
Age < 60 years old, men (n = 40,166)				
Asthma	1.27 (1.03-1.56)	0.024*	1.22 (0.99-1.51)	0.058
Control	1.00		1.00	
Age < 60 years old, women (n = 50,530)				
Asthma	1.28 (1.08-1.53)	0.006*	1.29 (1.08-1.54)	0.005*
Control	1.00		1.00	
Age ≥ 60 years old, men (n = 41,518)				
Asthma	1.15 (0.93-1.43)	0.187	1.15 (0.93-1.43)	0.195
Control	1.00		1.00	
Age ≥ 60 years old, women (n = 48,914)				
Asthma	1.24 (1.01-1.52)	0.039*	1.24 (1.01-1.52)	0.038*
Control	1.00		1.00	

* Cox-proportional hazard regression model, Significance at P < 0.05

† Stratified model for age, sex, income, and region of residence.

‡ Adjusted model for Charlson Comorbidity Index, obesity (BMI), smoking, alcohol intake, atopic dermatitis histories.

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Table 3 Crude and adjusted hazard ratios (95% confidence interval) of asthma for SSNHL according to smoking, drinking alcohol, and obesity

Characteristics	Hazard ratios for SSNHL			
	Crude	P-value	Adjusted†	P-value
Non or past smoker (n = 151,314)				
Asthma	1.21 (1.09-1.35)	<0.001*	1.20 (1.08-1.33)	0.001*
Control	1.00		1.00	
Current smoker (n = 29,814)				
Asthma	1.47 (1.11-1.95)	0.007*	1.45 (1.09-1.93)	0.010*
Control	1.00		1.00	
Drinking alcohol < 1 time a week (n = 142,154)				
Asthma	1.24 (1.11-1.39)	<0.001*	1.24 (1.11-1.38)	<0.001*
Control	1.00		1.00	
Drinking alcohol ≥ 1 time a week (n = 38,974)				
Asthma	1.21 (0.97-1.52)	0.099	1.19 (0.95-1.49)	0.140
Control	1.00		1.00	
Under weight (BMI < 18.5, n = 4,939)				
Asthma	0.60 (0.29-1.25)	0.176	0.59 (0.28-1.23)	0.157
Control	1.00		1.00	
Normal weight (BMI ≥ 18.5 to < 23, n = 63,586)				
Asthma	1.25 (1.05-1.48)	0.012*	1.24 (1.05-1.48)	0.013*
Control	1.00		1.00	
Overweight (BMI ≥ 23 to < 25, n = 48,238)				
Asthma	1.20 (1.00-1.45)	0.053	1.20 (0.99-1.44)	0.063

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Control	1.00		1.00	
Obese I (BMI ≥ 25 to < 30, n = 58,393)				
Asthma	1.37 (1.15-1.62)	<0.001*	1.35 (1.13-1.60)	0.001*
Control	1.00		1.00	
Obese II (BMI ≥ 30, n = 5,972)				
Asthma	0.73 (0.39-1.36)	0.321	0.73 (0.39-1.36)	0.325
Control	1.00		1.00	

* Non stratified Cox-proportional hazard regression model, Significance at P < 0.05

† Adjusted model for age, sex, income, region of residence, Charlson Comorbidity Index, obesity (BMI), smoking, alcohol intake, atopic dermatitis histories.

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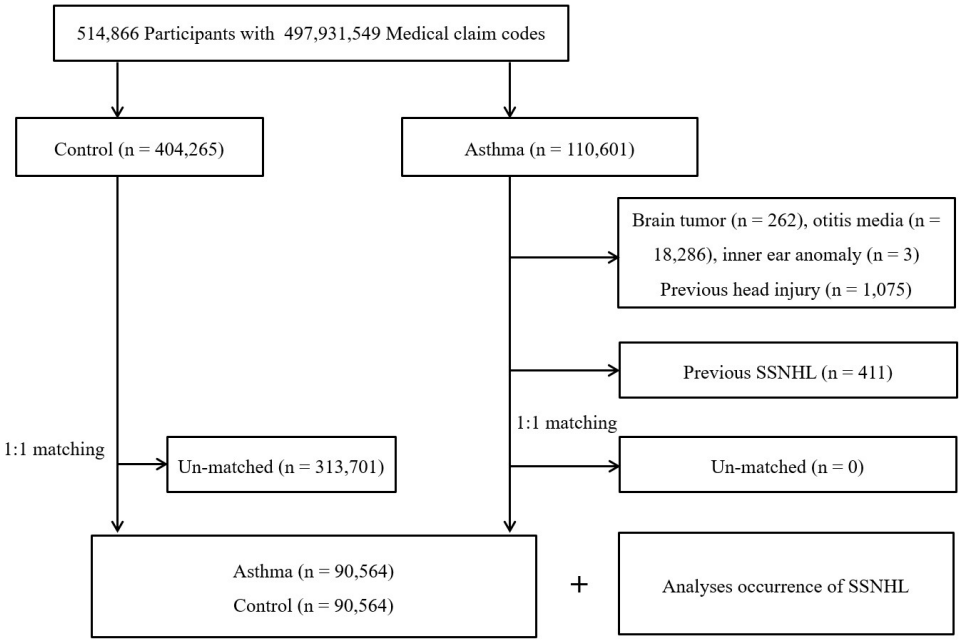

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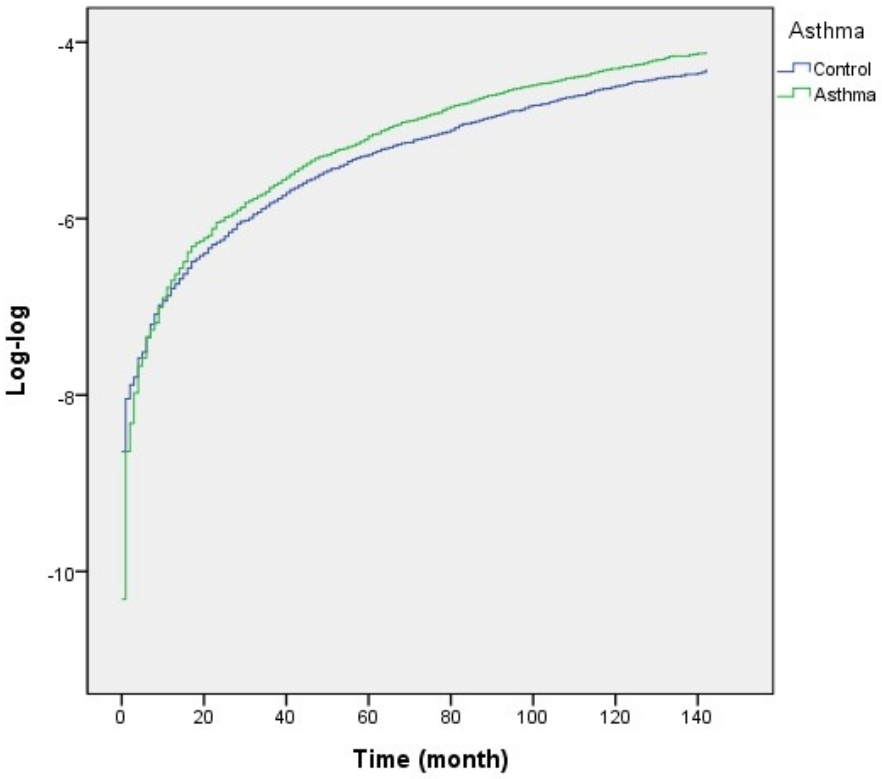

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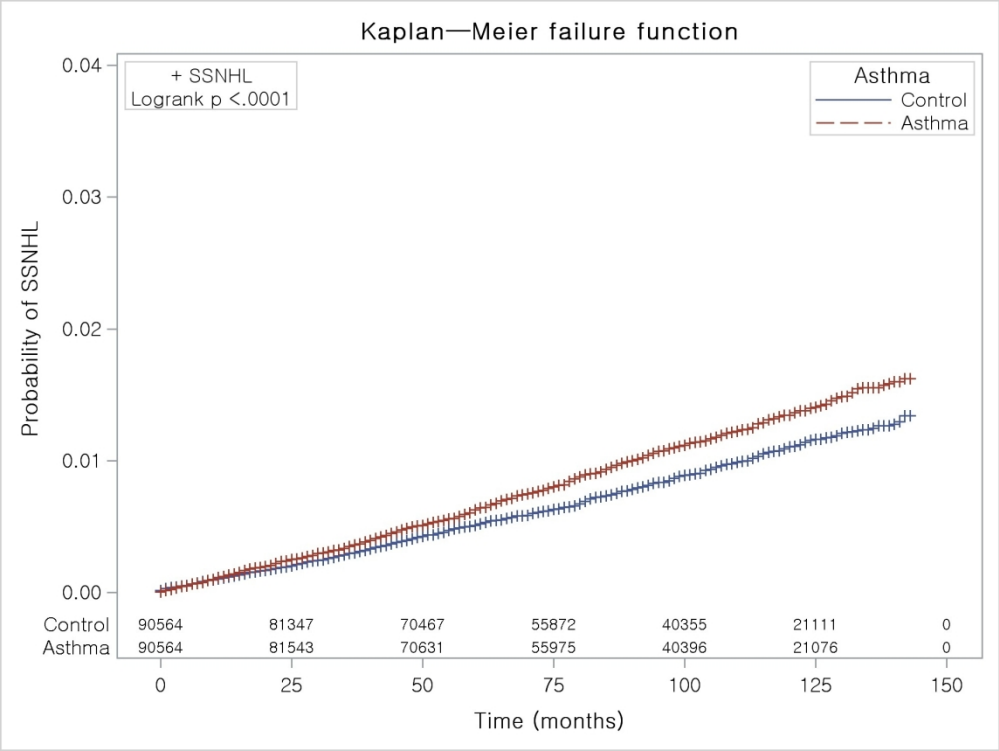

169x127mm (300 x 300 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1-2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6-7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7-8
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	7-8
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	7-8
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8
Bias	9	Describe any efforts to address potential sources of bias	8-9
Study size	10	Explain how the study size was arrived at	7-8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8-9
		(*b*) Describe any methods used to examine subgroups and interactions	8-9
		(*c*) Explain how missing data were addressed	7-8
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	7-8
		(*e*) Describe any sensitivity analyses	N/A

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Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8-9
		(b) Give reasons for non-participation at each stage	8-9
		(c) Consider use of a flow diagram	8-9
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9
		(b) Indicate number of participants with missing data for each variable of interest	9
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	7-8
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	9
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9
		(*b*) Report category boundaries when continuous variables were categorized	9
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9
Discussion			
Key results	18	Summarise key results with reference to study objectives	10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12
Generalisability	21	Discuss the generalisability (external validity) of the study results	12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Association of sudden sensorineural hearing loss with asthma: A longitudinal follow-up study using a national sample cohort

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Association of sudden sensorineural hearing loss with asthma: A longitudinal follow-up study using a national sample cohort

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Running head: Asthma and otitis media

Key words: asthma; otitis media; cohort studies; epidemiology

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Abstract

Objective: To investigate the risk of sudden sensorineural hearing loss (SSNHL) in asthma patients.

Design: A longitudinal follow-up study using a retrospective cohort

Setting: The 2002 – 2013 Korean National Health Insurance Service-Health Screening Cohort

Participants and Interventions: The ≥ 40 years old Korean population were enrolled. The asthma patients were 1:1 matched with the control group for age, sex, income, and region of residence.

Main outcome measure: The occurrence of SSNHL was followed in both asthma and control groups. The stratified Cox proportional hazard model was used. Age, sex, income, and region of residence were stratified, and Charlson comorbidity index scores, obesity, smoking, alcohol consumption, and atopic dermatitis histories were adjusted. Subgroup analysis was performed according to age, sex, obesity, smoking, and alcohol consumption.

Results: The results showed that 1.0% (877/ 90,564) of the asthma group and 0.8% (706/90,564) of the control group exhibited SSNHL ($P < 0.001$). The asthma group demonstrated a higher hazard ratio (HR) for SSNHL than the control group (adjusted HR = 1.23, 95% CI = 1.11 – 1.36, $P < 0.001$). According to age and sex, the female subgroup showed elevated HRs for SSNHL in asthma patients. Both the nonsmoker and current smoker groups demonstrated higher HRs for SSNHL in asthma patients than in controls. According to alcohol consumption or obesity, the < 1 time a week alcohol consumption group and normal weight and severe obesity groups showed higher HRs for SSNHL in asthma patients than in the controls.

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Conclusions: Adult asthma patients had a higher risk of SSNHL than the control participants matched for demographic and socioeconomic factors.

Key words: Hearing loss; Asthma; Risk factors; Cohort studies; Epidemiologies

Strengths and limitations of this study

- This study used a large, representative population cohort, which provided adequate statistical power.
- Comorbid conditions were adjusted for the analyses.
- However, because the study population of the present study was Korean, the ethnic or regional differences could limit the generalizability of the present association between asthma and SSNHL.
- The duration and severity of asthma were heterogeneous, and pulmonary function test results were absent.

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Background

Asthma is one of the most common airway disorders, and it is characterized by airway hyperresponsiveness and relapsing airway symptoms of wheezing and sputum [1]. The prevalence of asthma was estimated to be approximately 4.2% (95% confidence intervals [CI] = 3.1 – 5.6) in the ≥ 20-year-old population in East Asia [2]. Asthma has several endotypes encompassing heterogeneous phenotypes with different etiologies [3 4]. Genetic susceptibility, host factors, and environmental factors were suggested to cause asthma [5]. For host factors, in addition to allergic sensitization, obesity was reported to increase the risk of asthma [6]. For environmental factors, pollen, other aeroallergens, and smoking could elevate the risk of asthma [7]. These contributing factors result in airway inflammation and alter airway tone and reactivity, which evoke asthmatic symptoms [3]. A growing number of researchers, not only those investigating airway pathophysiology, have proposed systemic or extrapulmonary manifestations of inflammation in asthma patients [8]. For instance, asthma was suggested to be associated with cardiovascular and cerebrovascular disorders [9 10].

Similarly, the pathophysiology of asthma, such as systemic inflammation and persistent hypoxia, could also implicate sensorineural hearing loss. The cochlea is an organ that is vulnerable to inflammation or ischemic insertion, which could result in hearing loss [11]. Owing to the blood supply requirements for the extensive collateral microvasculature [12], chronic hypoxia conditions can deteriorate cochlear function [11]. In addition, inner ear inflammation and immune dysfunction can impact sensorineural hearing loss in patients with allergy [13]. Among these sensorineural hearing loss cases, the sudden onset of sensorineural hearing loss across 3 continuous frequencies within 3 days for 30 dB HL is defined as sudden sensorineural hearing loss (SSNHL) [14]. The incidence of SSNHL was estimated to be approximately 5 – 20 per 100,000 persons/year worldwide [15]. The pathophysiology of

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SSNHL is largely unknown and multifactorial. Approximately 71.0 – 87.4% of SSNHL occurred without any organic causes [16-18]. Less than 10% of SSNHL patients had brain tumors invading the internal auditory canal and causing inner ear anomaly [16]. Inner ear pathophysiology related to inflammation, immune system dysfunction, and vascular causes were suggested as contributing factors for SSNHL[17 19]. Based on a shared pathophysiologic mechanism with cardiovascular and cerebrovascular disorders, a number of previous studies reported an increased risk of these diseases in SSNHL patients [20]. Asthma also shares common pathophysiologies with SSNHL, namely, inflammation and immune system dysfunction. Therefore, there may be a relationship between asthma and SSNHL.

This study aimed to evaluate the risk of SSNHL in asthmatic adults. To the best of our knowledge, no prior study has investigated the association between SSNHL and asthma. When PubMed and EMBASE databases were searched for the keywords "asthma" AND "sudden hearing loss", no articles were retrieved until July 1, 2019. To minimize possible confounding effects, comorbidities and lifestyle factors associated with asthma were adjusted in this study. Moreover, SSNHL was confined to idiopathic cases by excluding cases of brain tumor, inner ear anomaly, and head injury.

Methods

Patient and Public Involvement statement

The Ethics Committee of Hallym University (2017-I102) approved the use of these data. Written informed consent was waived by the institutional review board.

This national cohort study relied on data from the Korean National Health Insurance Service-Health Screening Cohort (NHIS-HEALS). A detailed description of these data was provided in our previously published study [21]. This cohort based on the health claim code

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data and health screening database. This is a retrospective cohort study and participants did not intend to be collected or examined for study purpose.

Participant Selection

Of the 514,866 cases with 497,931,549 medical claim codes, we included participants who were diagnosed with asthma (ICD-10: J45) or status asthmaticus (J46) from 2002 through 2013 (n = 110,601) as reported in previous studies [22 23]. We excluded participants in both asthma and control groups who had a history of brain tumor (C70-C72), otitis media, or previous history of a head injury. Among them, we excluded participants who had a previous history of SSNHL. The numbers of excluded participants among asthma patients were 262 for the history of brain tumor, 18,286 for the history of otitis media, 1,075 for the previous history of a head injury, and 411 for previous history of SSNHL. The participants were followed through December 31, 2013. SSNHL was diagnosed according to ICD-10 codes (H912), the audiometry exam (claim codes: E6931-E6937, F6341-F6348) and steroid treatment [24].

The asthma group was matched 1:1 with participants (control group) who were not diagnosed with asthma from 2002 through 2013. From the total population (n = 404,265), the control group was selected. Among them, we excluded participants who had a history of brain tumor (n = 844), otitis media (n = 42,700), or inner ear anomaly (n = 18). Matching was performed for age, sex, income, and region of residence.

To prevent selection bias when enrolling the matched participants, the control participants were sorted using a random number order and then selected from top to bottom. We set the index date as the date of the diagnosis of asthma. It was assumed that the matched control participants were involved at the same time as the asthma participants (index date).

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Therefore, the control patients who died before the index date or who had a history of SSNHL before the index date were replaced. Participants with a history of SSNHL before the index date were excluded from the asthma group (n = 411). All asthma patients were matched with a control participant. The mean follow-up time from the index date to the last follow-up date (December 31, 2013) or the date of death was similar in both the asthma group (87.28 months, standard deviation [SD] =40.56) and control group (87.02 months, SD =40.78). Finally, 1:1 matching resulted in the inclusion of 90,564 asthma patients and 90,564 control participants (Figure 1).

Variables

Age, sex, income, and region of residence were defined as reported previous studies [23 25]. Brain tumor histories were included according to ICD-10 codes (C70-C72). Inner ear anomaly histories were included according to ICD-10 codes of Q16. Head injury histories were included according to ICD-10 codes of S00-S09 with claim codes of brain CT (HA 401-HA 472).

For tobacco smoking, patients were categorized according to their current smoking status (nonsmoker and former/current smoker)[26]. For alcohol consumption, patients were categorized according to frequency (< 1 time a week and ≥ 1 time a week)[26]. For obesity, patients were categorized as having a BMI (body mass index, kg/m^2) of < 18.5 (underweight), ≥ 18.5 to < 23 (normal), ≥ 23 to < 25 (overweight), ≥ 25 to < 30 (obese I), and ≥ 30 (obese II) following WPRO 2000 [27]. The Charlson comorbidity index (CCI) was used for 16 comorbidities, excluding pulmonary disease as a continuous variable (0 [no comorbidity] through 28 [multiple comorbidities]) [28]. Atopic dermatitis was defined according to the ICD-10 code of L20.

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Statistical Analyses

Chi-square tests were used to compare the general characteristics between the asthma and control groups.

Stratified Cox proportional hazard models were used to assess hazard ratios (HRs) for SSNHL with respect to asthma. In this analysis, crude (simple) and adjusted models (for CCI score, obesity, smoking, alcohol consumption, and atopic dermatitis histories) were used, and 95% CIs were calculated. In these analyses, age, sex, income, and region of residence were stratified. Kaplan-Meier analysis and the Log rank test were used. The proportional hazard assumption was tested using log minus log plot (Figure 2).

For subgroup analyses, we divided the participants by age and sex (<60 years old and ≥60 years old; male and female) to confirm that these relations were reliable according to age and sex. In another subgroup analysis, we analyzed HRs according to smoking status, alcohol consumption status, and obesity because we believe that these lifestyle factors could influence the occurrence of SSNHL.

Two-tailed analyses were conducted, and P values less than 0.05 were considered to indicate significance. The results were statistically analyzed using SPSS version 22.0 (IBM, Armonk, NY, USA) and SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

The duration from the index date to SSNHL (≥ 1 time) was 86.66 months (SD = 40.88) in the asthma group and 86.82 months (SD = 40.67) in the control group. The rates of SSNHL were higher in the asthma group (1.0% [877/90,564]) than in the control group (0.8% [706/90,564], P < 0.001, Table 1). No differences in the general characteristics of the

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participants (age, sex, income, and region of residence) were found due to the matching procedure (P = 1.000). However, the CCI score was different between the asthma and control groups (P < 0.001), the rate of atopic dermatitis was higher in the asthma group than in the control group (P < 0.001), and the distributions of obesity and alcohol consumption were different between the asthma and control groups (P < 0.001).

The adjusted HR of SSNHL was 1.23 (95% CI = 1.11-1.36) in the asthma group (P < 0.001, Table 2). Kaplan-Meier analysis showed consistent results (Figure 3). In subgroup analyses according to age and sex, the adjusted HRs were 1.29 (95% CI = 1.08-1.54) in < 60-year-old women and 1.24 (95% CI = 1.01-1.52) in ≥60-year-old women.

According to smoking status, both the nonsmoker and former/current smoker subgroups showed elevated HRs for SSNHL in the asthma group compared to the control group (Table 3). The adjusted HRs were 1.20 (95% CI = 1.08-1.33) in nonsmokers and former smokers and 1.45 (95% CI = 1.09-1.93) in current smokers. According to alcohol consumption, the alcohol consumption subgroup demonstrated increased HR for SSNHL in the asthma group (adjusted HR = 1.24, 95% CI = 1.11 – 1.38). For obesity, the normal weight group and obese I group demonstrated increased HR for SSNHL in the asthma group (adjusted HR = 1.24, 95% CI = 1.05 – 1.48 of normal weight and adjusted HR = 1.35, 95% CI =1.13 – 1.60 for obese I).

Discussion

The risk of developing SSNHL was 1.23 times higher in adult asthma patients than in the control group matched for demographic and socioeconomic factors. This association was independent of comorbidities such as allergies and lifestyle factors of obesity, alcohol consumption, and smoking. The metabolic syndrome components, including obesity and past

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medical histories using CCI scores (diabetes) were adjusted because these factors have been suggested as predictors of SSNHL and asthma[29 30]. According to sex, the female subgroup demonstrated a higher risk of SSNHL in the asthma patients than in the matched controls. The novelty of this study is that it delineates the risk of SSNHL in asthma patients. Clinicians need to be aware of the potential risk of SSNHL when managing asthmatic patients. A few plausible mechanisms could mediate this risk.

The allergic response in asthma patients could impact the elevated risk of SSNHL. Previous studies have demonstrated the etiologic role of allergy for SSNHL [13 31 32]. A few case reports have described SSNHL following IgE-mediated inflammatory responses [31 32]. In a cross-sectional study, patients in the adult asthma group showed higher serum IgE levels than the age-matched control group ($P < 0.001$) [13]. An allergy history was reported in 61.9% of asthma patients, which was higher than that reported in the control group (21.8%) [13]. The histamine and the degranulated mediators of mast cells could induce the vasodilation of inner ear vessels, impeding lymphatic circulation in the inner ear [33]. Circulating immune complexes could also occlude the strial capillaries and induce cochlear ischemia [34]. In addition, an allergic response could evoke inflammatory cascades via lymphocytes and macrophages of the inner ear, leading to inflammation and dysfunction of the inner ear [35].

In addition to an allergic response, other inflammatory mechanisms in asthma patients could induce inner ear inflammation and result in SSNHL. Only approximately 50% of asthma patients had Th2-high responses, while others had Th2-low cytokine profiles with neutrophilia and systemic inflammation [36]. This systemic inflammation might be linked to extrapulmonary disorders, including cardiovascular and metabolic diseases [6 10]. For instance, asthma patients with obesity demonstrated high levels of serum C-reactive protein,

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representing a systemic inflammatory response [37]. Similarly, these inflammatory conditions could influence inner ear inflammation and SSNHL.

The recurrent hypoxic conditions in asthma patients could act as an insult to the cochlear blood supply and cause SSNHL. Several previous studies have reported auditory dysfunction in patients with chronic lung disease [38-40]. The transient evoked otoacoustic emission (TEOAE), which primarily originates from outer hair cells, was found to be decreased in children with chronic lung disease compared to age- and sex-matched controls [38]. These results implied that outer hair cell functions were impaired following chronic exposure to hypoxia. Another case-control study demonstrated elevated hearing thresholds in pure tone audiometry and delayed interpeak latencies in the auditory brainstem response (ABR) in chronic obstructive lung disease patients [39]. Because the ABR records the evoked auditory response from multiple auditory brainstem nuclei, the abnormality in ABR implied the involvement of retrocochlear dysfunction as well as cochlear OHC dysfunction following hypoxic conditions. Because asthma is a pulmonary disorder with reversible airway obstruction, the impact of hypoxia might be less than that of other chronic lung diseases. However, the accumulated effects of recurrent hypoxic attack could result in cochlear dysfunction. Indeed, a previous study reported elevated hearing thresholds at high frequencies (10 – 20 kHz) in asthma patients [40]. The high frequencies are tonotopically allocated to the basal turn of the cochlea, which is susceptible to hypoxic injuries [41].

According to lifestyle factors, the participants without lifestyle risk factors, less alcohol consumption and normal BMI showed consistent results for the relationship between asthma and SSNHL in the present study. The non-significant association of asthma with SSNHL in participants with life style risk factors can be explained by the comorbid conditions susceptible to both asthma and SSNHL. Because smoking and alcohol consumption were

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supposed to increase the risk of SSNHL, the contribution of asthma on the development of SSNHL could not be as high as to reach the statistical significance[42-44]. The participants in Obese I (BMI ≥ 25 to < 30) also showed positive association of asthma with SSNHL in this study. In addition, the HR of obese I participants was higher than that of normal weight participants. The distinctive features of obese asthma could induce the elevated risk of SSNHL in this population[45]. The obese asthmatic patients were reported to suffer more symptoms, frequent and severe exacerbations, and refractory to some asthma medications[45].

Limitations

This study used a large, representative population cohort, which provided adequate statistical power. The large number of participants in the cohorts permitted the unbiased selection of control groups matched for both demographic and socioeconomic factors. In addition, comorbid conditions were adjusted using CCI. Lifestyle factors such as obesity, alcohol consumption, and smoking were also adjusted and analyzed using subgroups. The diagnoses of asthma and SSNHL were based on objective criteria according to ICD-10 codes and medication histories. However, this study had a few limitations, which should be noted. Although many comorbid conditions were considered, the metabolic syndrome components could not be fully evaluated in the current study. Because the study population of the present study was Korean, the ethnic or regional differences could be limit the generalizability of the present association between asthma and SSNHL. In addition, the duration and severity of asthma were heterogeneous, and pulmonary function test results were absent. Similarly, the degree and prognosis of hearing loss in SSNHL were not considered. Further studies are warrant to clarify the specific types of asthma which pose higher risk of SSNHL and the characteristics and prognosis of SSNHL in asthmatic patients.

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Conclusions

Asthma was associated with an increased risk of SSNHL in the adult asthma population compared to controls matched for demographic and socioeconomic factors. The potential contribution of asthma on the development of SSNHL will need to be considered when treating both asthma and SSNHL patients.

Competing interests

The authors declare they have no competing interests.

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Contributors

H.G.C. designed the study; C.M., and C.H.L. analyzed the data; S.Y.K. and H.G.C. drafted and revised the paper; and H.G.C. drew the figures. All authors have read and agreed to the published version of the manuscript.

Conflict of Interest

The authors report no potential conflicts of interest to disclose.

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Data Sharing

Release of the data by the researcher is not allowed legally. All data are available from the database of Korea Centers for Disease Control and Prevention (kdca.go.kr). The Korea Centers for Disease Control and Prevention provides all of these data for any researcher who promises to follow the research ethics guidelines, with some cost. If you want to access the data of this article, you could download it from the website after promising to follow the research ethics guidelines.

Ethical Approval

The Ethics Committee of Hallym University (2017-I102) approved the use of these data. Written informed consent was waived by the institutional review board.

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Figure Legends

Fig. 1. Schematic illustration of the participant selection process used in the present study. Of a total of 514,866 participants, 90,564 asthma patients were matched with 90,564 control participants for age, sex, income, and region of residence.

Fig. 2. The log minus log plot for a proportional hazard assumption for sudden sensorineural hearing loss of asthma and control groups.

Fig. 3. Kaplan-Meier survival curve of asthma for sudden sensorineural hearing loss (a 1 – survival function curve).

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Table 1 General Characteristics of Participants

Characteristics	Total participants		
	Asthma (n, %)	Control group (n, %)	P-value
Age (years old)			1.000
40-44	5,316 (5.9)	5,316 (5.9)	
45-49	11,747 (13.0)	11,747 (13.0)	
50-54	14,272 (15.8)	14,272 (15.8)	
55-59	14,013 (15.5)	14,013 (15.5)	
60-64	14,084 (15.6)	14,084 (15.6)	
65-69	13,553 (15.0)	13,553 (15.0)	
70-74	9,982 (11.)	9,982 (11.)	
75-79	5,552 (6.1)	5,552 (6.1)	
80+	2,045 (2.3)	2,045 (2.3)	
Sex			1.000
Male	40,842 (45.1)	40,842 (45.1)	
Female	49,722 (54.9)	49,722 (54.9)	
Income			1.000
1 (lowest)	15,966 (17.6)	15,966 (17.6)	
2	13,041 (14.4)	13,041 (14.4)	
3	14,266 (15.8)	14,266 (15.8)	
4	18,676 (20.6)	18,676 (20.6)	
5 (highest)	28,615 (31.6)	28,615 (31.6)	
Region of residence			1.000
Urban	38,170 (42.1)	38,170 (42.1)	
Rural	52,394 (57.9)	52,394 (57.9)	
CCI score			<0.001*

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0	89,184 (98.5)	87,800 (96.9)	
1	122 (0.1)	538 (0.6)	
2	180 (0.2)	474 (0.5)	
≥ 3	1,078 (1.2)	1,752 (1.9)	
Atopic dermatitis	10,622 (11.7)	7,324 (8.1)	<0.001*
BMI			<0.001*
< 18.5 (underweight)	2,483 (2.7)	2,456 (2.7)	
≥ 18.5 to < 23 (normal)	30,140 (33.3)	33,446 (36.9)	
≥ 23 to < 25 (overweight)	23,826 (26.3)	24,412 (27.0)	
≥ 25 to < 30 (obese I)	30,706 (33.9)	27,687 (30.6)	
≥ 30 (obese II)	3,409 (3.8)	2,563 (2.8)	
Smoking			0.551
Nonsmoker or past smoker	75,610 (83.5)	75,704 (83.6)	
Current smoker	14,954 (16.5)	14,860 (16.4)	
Drinking alcohol			<0.001*
< 1 time a week	71,773 (79.3)	70,381 (77.7)	
≥ 1 time a week	18,791 (20.7)	20,183 (22.3)	
SSNHL	877 (1.0)	706 (0.8)	<0.001*

SSNHL: sudden sensory neural hearing loss

*Chi-square test. Significance at P < 0.05

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Table 2 Crude and adjusted hazard ratios (95% confidence interval) of asthma for SSNHL according to age and sex

Characteristics	Hazard ratios for SSNHL			
	Crude†	P-value	Adjusted†‡	P-value
Total participants (n = 181,128)				
Asthma	1.24 (1.12-1.37)	<0.001*	1.23 (1.11-1.36)	<0.001*
Control	1.00		1.00	
Age < 60 years old, men (n = 40,166)				
Asthma	1.27 (1.03-1.56)	0.024*	1.22 (0.99-1.51)	0.058
Control	1.00		1.00	
Age < 60 years old, women (n = 50,530)				
Asthma	1.28 (1.08-1.53)	0.006*	1.29 (1.08-1.54)	0.005*
Control	1.00		1.00	
Age ≥ 60 years old, men (n = 41,518)				
Asthma	1.15 (0.93-1.43)	0.187	1.15 (0.93-1.43)	0.195
Control	1.00		1.00	
Age ≥ 60 years old, women (n = 48,914)				
Asthma	1.24 (1.01-1.52)	0.039*	1.24 (1.01-1.52)	0.038*
Control	1.00		1.00	

* Cox-proportional hazard regression model, Significance at P < 0.05

† Stratified model for age, sex, income, and region of residence.

‡ Adjusted model for Charlson Comorbidity Index, obesity (BMI), smoking, alcohol intake, atopic dermatitis histories.

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Table 3 Crude and adjusted hazard ratios (95% confidence interval) of asthma for SSNHL according to smoking, drinking alcohol, and obesity

Characteristics	Hazard ratios for SSNHL			
	Crude	P-value	Adjusted†	P-value
Non or past smoker (n = 151,314)				
Asthma	1.21 (1.09-1.35)	<0.001*	1.20 (1.08-1.33)	0.001*
Control	1.00		1.00	
Current smoker (n = 29,814)				
Asthma	1.47 (1.11-1.95)	0.007*	1.45 (1.09-1.93)	0.010*
Control	1.00		1.00	
Drinking alcohol < 1 time a week (n = 142,154)				
Asthma	1.24 (1.11-1.39)	<0.001*	1.24 (1.11-1.38)	<0.001*
Control	1.00		1.00	
Drinking alcohol ≥ 1 time a week (n = 38,974)				
Asthma	1.21 (0.97-1.52)	0.099	1.19 (0.95-1.49)	0.140
Control	1.00		1.00	
Under weight (BMI < 18.5, n = 4,939)				
Asthma	0.60 (0.29-1.25)	0.176	0.59 (0.28-1.23)	0.157
Control	1.00		1.00	
Normal weight (BMI ≥ 18.5 to < 23, n = 63,586)				
Asthma	1.25 (1.05-1.48)	0.012*	1.24 (1.05-1.48)	0.013*
Control	1.00		1.00	
Overweight (BMI ≥ 23 to < 25, n = 48,238)				
Asthma	1.20 (1.00-1.45)	0.053	1.20 (0.99-1.44)	0.063

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Control	1.00		1.00	
Obese I (BMI ≥ 25 to < 30, n = 58,393)				
Asthma	1.37 (1.15-1.62)	<0.001*	1.35 (1.13-1.60)	0.001*
Control	1.00		1.00	
Obese II (BMI ≥ 30, n = 5,972)				
Asthma	0.73 (0.39-1.36)	0.321	0.73 (0.39-1.36)	0.325
Control	1.00		1.00	

* Non stratified Cox-proportional hazard regression model, Significance at P < 0.05

† Adjusted model for age, sex, income, region of residence, Charlson Comorbidity Index, obesity (BMI), smoking, alcohol intake, atopic dermatitis histories.

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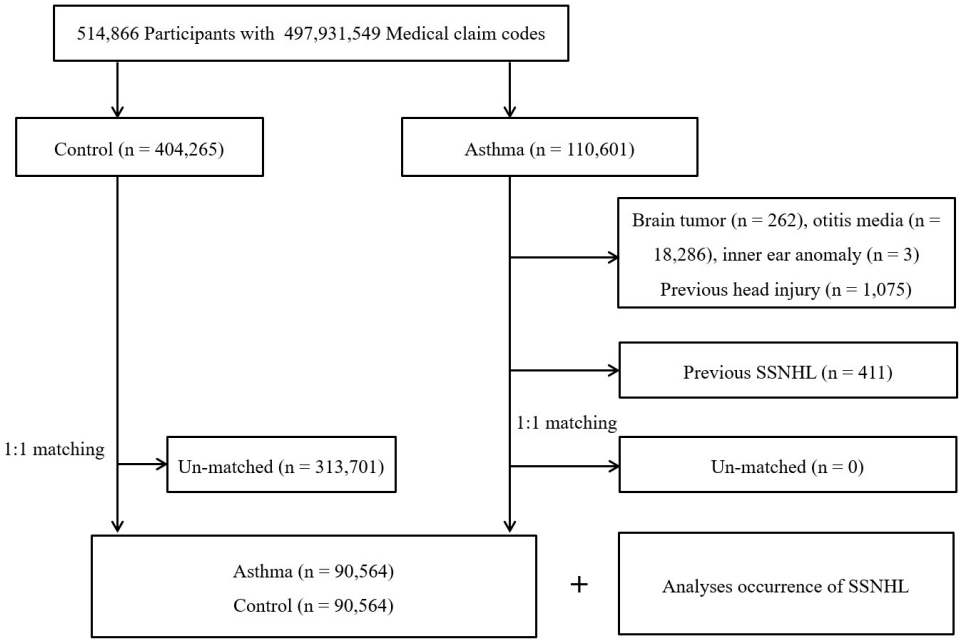

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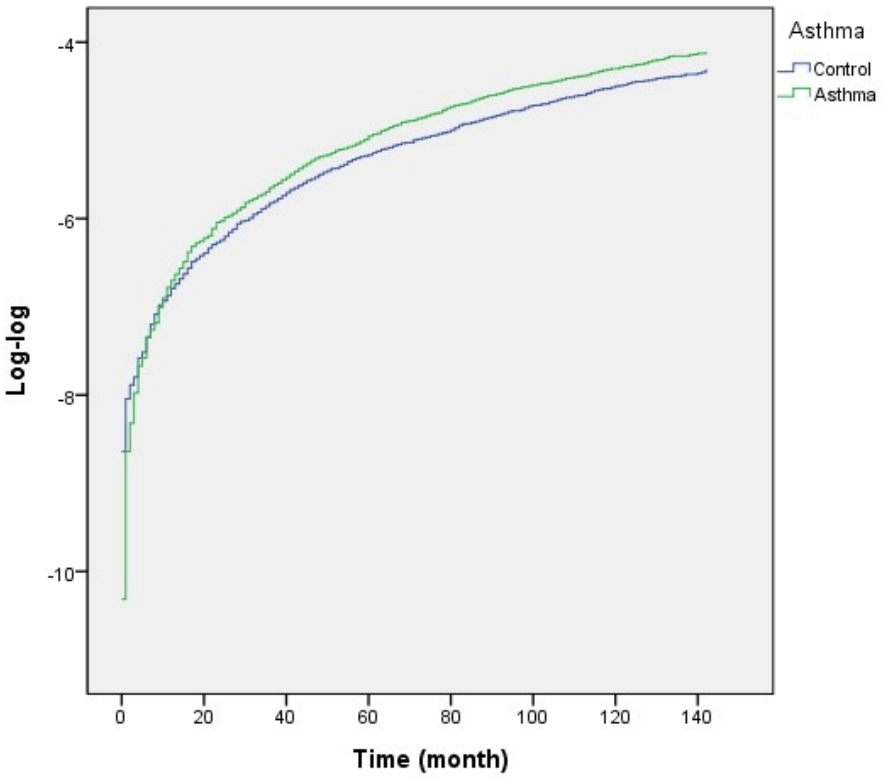

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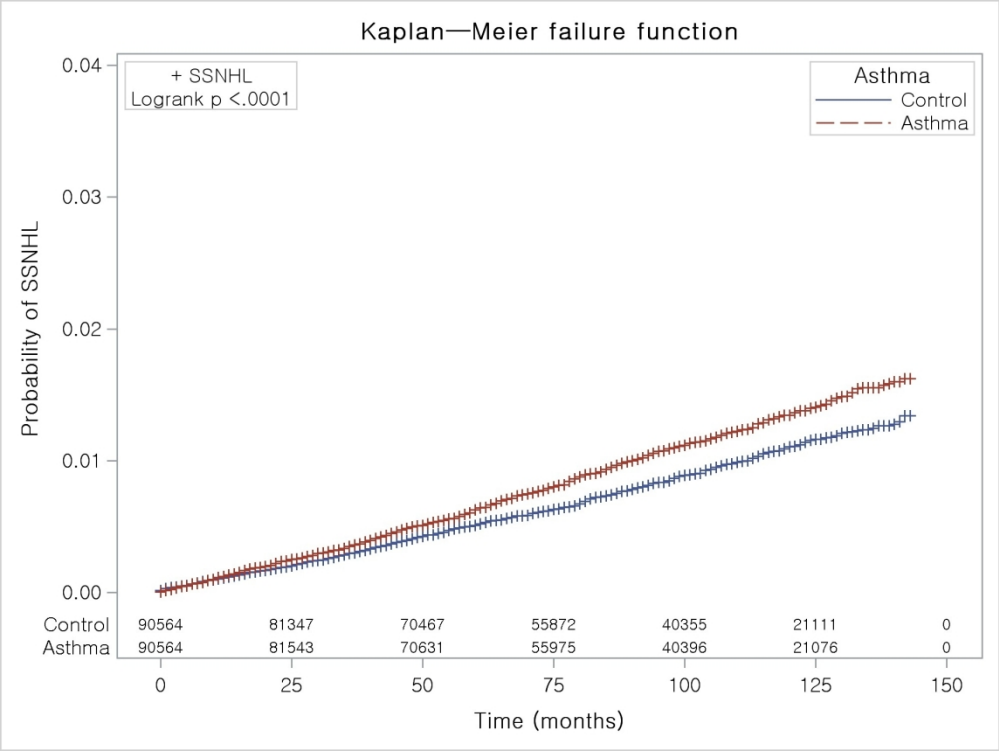

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1-2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6-7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7-8
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	7-8
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	7-8
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8
Bias	9	Describe any efforts to address potential sources of bias	8-9
Study size	10	Explain how the study size was arrived at	7-8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8-9
		(*b*) Describe any methods used to examine subgroups and interactions	8-9
		(*c*) Explain how missing data were addressed	7-8
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	7-8
		(*e*) Describe any sensitivity analyses	N/A

Continued on next page

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Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8-9
		(b) Give reasons for non-participation at each stage	8-9
		(c) Consider use of a flow diagram	8-9
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9
		(b) Indicate number of participants with missing data for each variable of interest	9
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	7-8
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	9
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9
		(*b*) Report category boundaries when continuous variables were categorized	9
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9
Discussion			
Key results	18	Summarise key results with reference to study objectives	10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12
Generalisability	21	Discuss the generalisability (external validity) of the study results	12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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