J Korean Med Sci. 2024 Oct 7;39(38):e273
https://doi.org/10.3346/jkms.2024.39.e273
eISSN 1598-6357·pISSN 1011-8934

JKMS

Original Article
Medicine General & Health Policy

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Sex Differences in Chronic Cough Epidemiology: The Korean Cough Study Group

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Received: Mar 25, 2024
Accepted: Jul 21, 2024
Published online: Aug 26, 2024

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ABSTRACT

Background: Chronic cough is a common symptom encountered by healthcare practitioners. The global prevalence of chronic cough is 9.6%, with a female predominance. The aim of our study is to reveal the sex differences in prevalence and severity of chronic cough in South Korea, stratified by age and etiology.
Methods: This study included adult patients with chronic cough who were recruited from 19 respiratory centers in South Korea. Patients completed the cough numeric rating scale (NRS) and COugh Assessment Test (COAT) questionnaire to assess the severity and

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Funding

This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korean government (MSIT: grant No. 2021R1G1A1095110 and RS-2024-00359875). The funding bodies played no role in the study design, data collection, analysis, interpretation, and writing of the manuscript.

Disclosure

The authors have no potential conflicts of interest to disclose.

Data Sharing Statement

The dataset generated during this study is available from the corresponding author upon reasonable request.

multidimensional impact of cough.

Results: Among the 625 patients, 419 (67.0%) were females, with a male-to-female ratio of 1:2.03. The mean age was 49.4 years, and the median duration of cough was 12 weeks. The mean NRS and COAT scores were 5.5 ± 1.8 and 9.5 ± 3.6, respectively. Female patients were older (45.3 ± 15.4 vs. 51.6 ± 15.2, $P < 0.001$) and more likely to have asthma/cough variant asthma (CVA) (26.7% vs. 40.8%, $P = 0.001$) than male patients. There was no difference in the duration or severity of cough between sexes, regardless of the cause. The male-to-female ratio was lower for upper airway cough syndrome (UACS), asthma/CVA, and gastro-esophageal reflux disease (GERD), but not for eosinophilic bronchitis (EB) or unexplained cough. The mean age of female patients was higher in UACS and asthma/CVA, but not in EB, GERD, or unexplained cough. The majority (24.2%) fell within the age category of 50s. The proportion of females with cough increased with age, with a significant rise in the 50s, 60s, and 70–89 age groups. The severity of cough decreased in the 50s, 60s, and 70–89 age groups, with no significant sex differences within the same age group.

Conclusion: The sex disparities in prevalence and severity of cough varied significantly depending on the age category and etiology. Understanding the specific sex-based difference could enhance comprehension of cough-related pathophysiology and treatment strategies.

Keywords: Chronic Cough; Female; Prevalence; Severity; Etiology; South Korea

INTRODUCTION

Cough is a common symptom that physicians in various healthcare settings, ranging from clinics to tertiary hospitals, can easily encounter. Cough is classified based on its duration as acute, subacute, or chronic. Chronic cough is defined as a cough lasting more than 8 weeks.[1,2] Common causes of chronic cough include cough-variant asthma (CVA), upper airway cough syndrome (UACS), eosinophilic bronchitis (EB), and cough-related gastro-esophageal reflux disease (GERD).[3,4] Chronic cough is associated with significant physical, psychological, and social morbidities, as well as a reduced quality of life.[5,6] Global surveys indicate that the overall prevalence of chronic cough is 9.6%, suggesting that a considerable number of people suffer from this condition.[7] Prior global epidemiologic studies consistently documented a female predominance of approximately two-thirds in the male-to-female ratio. This trend is particularly evident in the European population and indicates higher cough sensitivity in females.[8] However, a recent study from China revealed no discernible disparities between males and females, with a male-to-female sex ratio of approximately 1:1.[9] The aim of this study is to evaluate the sex difference pattern in South Korea, stratified by age and etiology. Gaining insight into the actual status of sex-related disparities in chronic cough further enhances our understanding of the underlying mechanism behind its development, which can benefit treatment strategies.

METHODS

Study design and population

The detailed study design has been described previously.[10] Briefly, adult patients (> 18 years of age) with chronic cough lasting more than 8 weeks were recruited from 19 respiratory centers in South Korea from March 1, 2016 to February 28, 2018. Participants who were currently smoking and those who lost follow-up for the evaluation of treatment responsiveness were

Author Contributions

Conceptualization: Kang J,[1] Seo WJ, Koo HK. Data curation: Tai Joon An. Formal analysis: Kang J,[1] Seo WJ, Koo HK. Investigation: An TJ, Joo H, Lee H, Kim Y, Jeong I, Park J, Kim SK, Shin JW, Rhee CK, Kim YH, Min KH, Moon JY, Kim DK, Jang SH, Yoo KH, Kim JW, Yoon HK, Koo HK. Methodology: Kang J,[1] Kim JG, Chung SJ, Kang HK, Lee SS. Writing - original draft: Kang J,[1] Seo WJ, Koo HK. Writing - review & editing: Kang J,[2] Kim JG, Chung SJ, Kang HK, Lee SS, An TJ, Joo H, Lee H, Kim Y, Jeong I, Park J, Kim SK, Shin JW, Rhee CK, Kim YH, Min KH, Moon JY, Kim DK, Jang SH, Yoo KH, Kim JW, Yoon HK.

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also included in the present study. Only chronic cough patients who sought medical attention for the first time were included, while those who were already receiving regular follow-up were excluded. Pulmonary specialists in each hospital evaluated the cause of chronic cough according to the Korean cough guideline.[2] Following a comprehensive history taking that included patients' medical information, such as smoking habits, accompanying symptoms, and medication usage, all patients underwent chest radiography as the initial diagnostic test. Subsequently, additional diagnostic tests for common causes were performed in a step-wise manner, based on symptoms suggesting potential etiologies. Patients with suspected abnormalities on plain chest radiography or with chronic respiratory disease, such as overt asthma, chronic obstructive pulmonary disease, bronchiectasis, tuberculosis-destroyed lungs, or lung cancer, were excluded. Additionally, pregnant women and patients taking cough-inducing medications were excluded. Age ranges were categorized into six groups by 10-year increments (≤ 29, 30–39, 40–49, 50–59, 60–69, and ≥ 70 years). Participants completed the cough numeric rating scale (NRS) and COugh Assessment Test (COAT) questionnaire during their first visit. The cough NRS ranges from 0 (no cough at all) to 10 (maximal cough). The COAT is a simplified version of the Leicester Cough Questionnaire developed to evaluate the severity and multidimensional impact of cough.[11] The COAT consists of five components: cough frequency, limitation of daily activities, sleep disturbance, fatigue, and hypersensitivity to irritants. All factors are scored on a unified scale ranging from 0 to 4, resulting in total scores ranging from 0 to 20. A higher score indicates a more severe cough.

Statistical analysis

Patient characteristics are presented as means and standard deviations, or medians with 1st and 3rd interquartile ranges (IQRs) for continuous variables, and as relative frequencies for categorical variables. The student's *t*-test was used to compare the continuous response variables, such as age and the COAT scores. The χ^2 test was used to compare the categorical variables, such as sex and comorbidities. In order to account for the differences in age and smoking status among each etiology and sex, age and smoking status were incorporated into logistic regression models for sex in multivariable analyses. All statistical analyses were performed using the R Project software (version 4.3.1, https://www.r-project.org/).

Ethics statement

This study was conducted in accordance with the Declaration of Helsinki, and the Institutional Review Board (IRB) of Inje University Ilsan Paik Hospital approved the study protocol (IRB No. ISPAIK 2017-12-025) and waived the need for informed consent as none of the patients were at risk.

RESULTS

Baseline characteristics

This study included 625 patients with chronic cough who completed both questionnaires and the necessary diagnostic work-up (**Table 1**). The mean age was 49.5 years, and the median duration of cough was 12 weeks (IQR, 8–28). A total of 206 (33.0%) males and 419 (67.0%) females were enrolled, resulting in male-to-female ratio of 1:2.03. The mean COAT score was 9.5 ± 3.6, and the mean NRS score was 5.5 ± 1.8. Considering the causes of chronic cough, 287 patients (45.9%) were diagnosed with UACS, 226 (36.2%) with asthma/CVA, 45 (7.2%) with EB, and 84 (13.4%) with GERD (**Fig. 1**). Twenty patients (3.2%) were unable

https://doi.org/10.3346/jkms.2024.39.e273

Table 1. Baseline characteristics of study population stratified by sex

Characteristics	Total (N = 625)	Male (n = 206)	Female (n = 419)	*P* value
Demographics				
Age	49.5 ± 15.5	44.0 ± 14.7	52.3 ± 14.8	< 0.001
Smoking status				< 0.001
Never smoker	373 (59.7)	102 (49.5)	271 (64.7)	
Ex-smoker	68 (10.9)	63 (30.6)	5 (1.2)	
Current smoker	20 (3.2)	15 (7.3)	5 (1.2)	
Duration of cough	12 (8, 28)	12 (8, 24.25)	12 (8, 28)	0.570
Cough severity				
NRS	5.5 ± 1.8	5.4 ± 1.9	5.5 ± 1.7	0.775
COAT	9.5 ± 3.6	9.5 ± 3.5	9.4 ± 3.6	0.885
Etiology				
UACS	287 (45.9)	95 (46.1)	192 (45.8)	> 0.999
Asthma/CVA	226 (36.2)	55 (26.7)	171 (40.8)	0.001
EB	45 (7.2)	20 (9.7)	25 (6.0)	0.124
GERD	84 (13.4)	28 (13.6)	56 (13.4)	> 0.999
Unexplained cough	20 (3.2)	8 (3.9)	12 (2.9)	0.661
Multiple cause	134 (21.4)	36 (17.5)	98 (23.4)	0.112

Values are presented as mean ± standard deviation or number (%).
NRS = numeric rating scale, COAT = COugh Assessment Test, UACS = upper airway cough syndrome, CVA = cough variant asthma, EB = eosinophilic bronchitis, GERD = gastro-esophageal reflux disease.

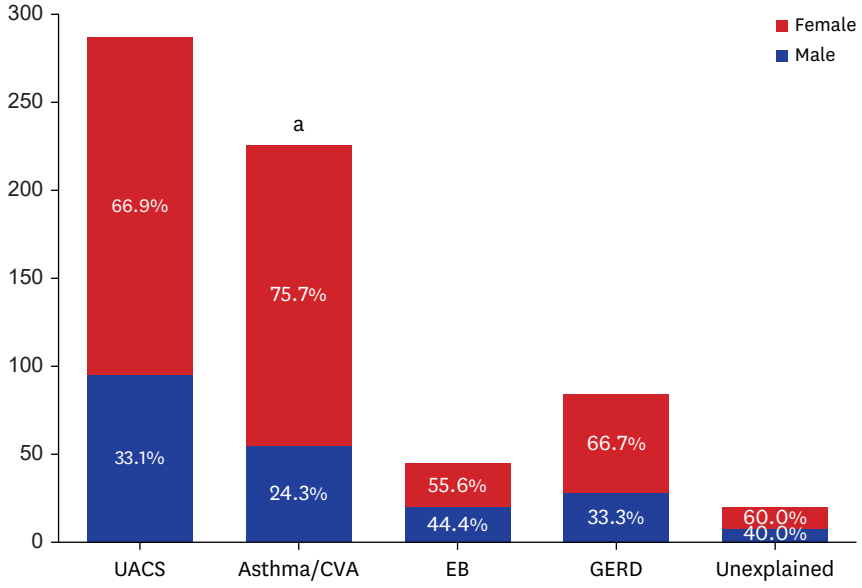

Fig. 1. Prevalence of each etiology of chronic cough stratified by sex. The 287 patients (45.9%) were diagnosed with UACS, 226 (36.2%) with asthma/CVA, 45 (7.2%) with EB, and 84 (13.4%) with GERD. The proportion of females is significantly higher in the asthma/CVA population.
UACS = upper airway cough syndrome, CVA = cough variant asthma, EB = eosinophilic bronchitis, GERD = gastro-esophageal reflux disease.
[a]Indicates statistically significant differences in the female proportion.

to determine their cause of cough, while 134 participants (21.4%) had multiple causes. **Supplementary Table 1** provides a summary of the baseline characteristics of enrolled patients according to each etiology. The mean age of UACS patients was 49.6 ± 15.2 years, and 66.9% of them were female. In UACS patients, asthma/CVA, EB, and GERD were present in 30.3%, 4.2%, and 9.8% of cases, respectively, and 40.8% had multiple causes. In asthma/CVA, the mean age (52.0 ± 14.8 years) and proportion of females (75.7%) were both higher compared to the overall population. A total of 38.5% and 9.7% of asthma/CVA patients had UACS and GERD, respectively, and 42.9% had multiple causes. The mean age

https://doi.org/10.3346/jkms.2024.39.e273

for patients with EB was 47.5 ± 15.4 years, and 55.6% of them were female. UACS and GERD were present in 26.7% and 8.9% of EB patients, respectively, and 42.2% had multiple causes. The mean age of patients with GERD was 49.9 ± 14.8 years, and 66.7% of patients were female. UACS, asthma/CVA, and EB were identified in 33.3%, 26.2%, and 4.8% of GERD patients, respectively, and 50.0% had multiple causes. In patients without a definite cause of cough, the mean age (48.4 ± 15.3 years) and the proportion of females (60.0%) did not differ significantly; however, the COAT score was lower (7.2 ± 3.1). The proportion of sexes (73.1%) in patients with multiple causes was not different, but the mean age (52.5 ± 14.3) and the COAT scores (9.0 ± 2.9) were higher compared to the overall population. The proportions of patients with multiple causes were 87.3%, 72.4%, 14.2%, and 31.3% in UACS, asthma/CVA, EB, and GERD, respectively. A Venn diagram for the causes of cough is presented in **Supplementary Fig. 1**.

Sex differences in etiology

Female patients were significantly older than male patients (52.3 ± 14.8 vs. 44.0 ± 14.7, $P < 0.001$), and more likely to have asthma/CVA (40.8% vs. 26.7%, $P = 0.001$; **Table 1**). The duration of cough was not different between male and female patients (12 [8, 24.25] vs. 12 [8, 28] weeks, $P = 0.570$). The severity of cough, as measured by the NRS (5.4 ± 1.9 vs. 5.5 ± 1.7, $P = 0.775$) or COAT (9.5 ± 3.5 vs. 9.4 ± 3.6, $P = 0.885$), did not differ statistically between the sexes. **Table 2** provides a summary of the baseline characteristics of enrolled patients according to each etiology stratified by sex. Except for asthma/CVA (26.7% vs. 40.8%; $P = 0.001$), the proportions of UACS (46.1% vs. 45.8%; $P > 0.999$), EB (9.7% vs. 6.0%; $P = 0.124$), GERD (13.6% vs. 13.4%; $P > 0.999$), unexplained cough (3.9% vs. 2.9%; $P = 0.661$), and multiple causes (17.5% vs. 23.4%; $P = 0.112$) were not different between sexes. Multivariable analyses were performed adjusted for age and smoking status due to the demographic differences between the sexes. Female sex was only significantly associated with asthma/CVA in univariable and multivariable analyses (**Supplementary Table 2**). The male-to-female ratio was statistically lower for UACS (1:2.02, $P < 0.001$), asthma/CVA (1:3.11, $P < 0.001$), and GERD (1:2.00, $P = 0.002$) but not for EB (1:1.25, $P = 0.456$) or unexplained cough (1:1.50, $P = 0.564$) (**Fig. 1**). The Venn diagrams comparing the etiology of cough in males and females are presented in **Fig. 2**. The sex differences for each cause of cough are summarized in **Table 2**. The mean age of female patients was significantly higher than that of males in UACS (52.3 ± 14.8 vs. 44.0 ± 14.7, $P < 0.001$) and asthma/CVA (53.3 ± 14.2 vs. 47.8 ± 16.0, $P = 0.016$), but not in EB (48.6 ± 16.5 vs. 46.2 ± 14.3, $P = 0.623$), GERD (50.1 ± 15.5 vs. 49.5 ± 13.5, $P = 0.856$), unexplained cough (51.8 ± 13.0 vs. 43.1 ± 17.8, $P = 0.221$), and multiple causes (53.5 ± 14.6 vs. 50.0 ± 13.3, $P = 0.213$). Regardless of the cause, the mean duration of cough was not significantly different between the sexes. The mean COAT scores of female patients were significantly higher than those of males in EB (10.3 ± 3.7 vs. 8.4 ± 2.3, $P = 0.045$). However, the mean COAT scores were lower in unexplained cough (5.6 ± 1.2 vs. 9.6 ± 3.7, $P = 0.032$). The density plots for age and COAT distribution are depicted in **Supplementary Figs. 2** and **3**, respectively.

Patterns of cough according to age category and sex

According to age category, patients were divided into six groups, with the majority (24.2%) being in the 50–59 year age group (**Table 3**). The proportion of female sex increased with age category and was significantly higher in the age groups of 50–59 years (odds ratio [OR], 1.90; 95% confidence interval [CI], 1.06–3.41), 60–69 years (OR, 2.68; 95% CI, 1.40–5.13), and 70–89 years (OR, 2.36; 95% CI, 1.14–4.91) (**Supplementary Fig. 4**). Except for a higher prevalence of asthma/CVA in the 40–89 years age group and multiple causes in the 60–89 years age group, the prevalence of each cause was similar across all age groups (**Supplementary Table 3**). The

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Table 2. Baseline characteristics according to etiology stratified by sex

Characteristics	Male (n = 206)	Female (n = 419)	*P* value
Upper airway cough syndrome			
Number	95 (46.1)	192 (45.8)	> 0.999
Age	44.0 ± 14.7	52.3 ± 14.8	< 0.001
Never smoker	57 (60.0)	144 (75.0)	0.013
Duration	12 (8, 24)	12 (8, 38)	0.318
Severity: COAT	9.7 ± 3.3	9.5 ± 3.4	0.624
Asthma/cough variant asthma			
Number	55 (26.7)	171 (40.8)	0.001
Age	47.8 ± 16.0	53.3 ± 14.2	0.016
Never smoker	41 (74.5)	149 (87.1)	0.045
Duration	16 (9, 38)	16 (8, 52)	0.52
Severity: COAT	8.9 ± 3.6	9.4 ± 3.2	0.404
Eosinophilic bronchitis			
Number	20 (9.7)	25 (6.0)	0.124
Age	46.2 ± 14.3	48.6 ± 16.5	0.623
Never smoker	9 (45.0)	15 (60.0)	0.483
Duration	14 (9.75, 24)	20 (11.25, 24)	0.476
Severity: COAT	8.4 ± 2.3	10.3 ± 3.7	0.045
Gastro-esophageal reflux disease			
Number	28 (13.6)	56 (13.4)	> 0.999
Age	49.5 ± 13.5	50.1 ± 15.5	0.856
Never smoker	18 (64.3)	37 (66.1)	> 0.999
Duration	12 (12, 36)	20 (12, 40)	0.324
Severity: COAT	9.6 ± 3.7	8.7 ± 3.6	0.358
Unexplained cough			
Number	8 (3.9)	12 (2.9)	0.661
Age	43.1 ± 17.8	51.8 ± 13.0	0.221
Never smoker	10 (83.3)	12 (80.0)	> 0.999
Duration	12 (11, 50)	12 (11.25, 60)	0.286
Severity: COAT	9.6 ± 3.7	5.6 ± 1.2	0.032
Multiple cause			
Number	36 (17.5)	98 (23.4)	0.112
Age	50.0 ± 13.3	53.5 ± 14.6	0.213
Never smoker	34 (94.4)	85 (86.7)	0.344
Duration	17 (10, 52)	16 (8, 52)	0.515
Severity: COAT	8.7 ± 3.0	9.1 ± 2.9	0.569

Values are presented as mean ± standard deviation or number (%).
COAT = COugh Assessment Test.

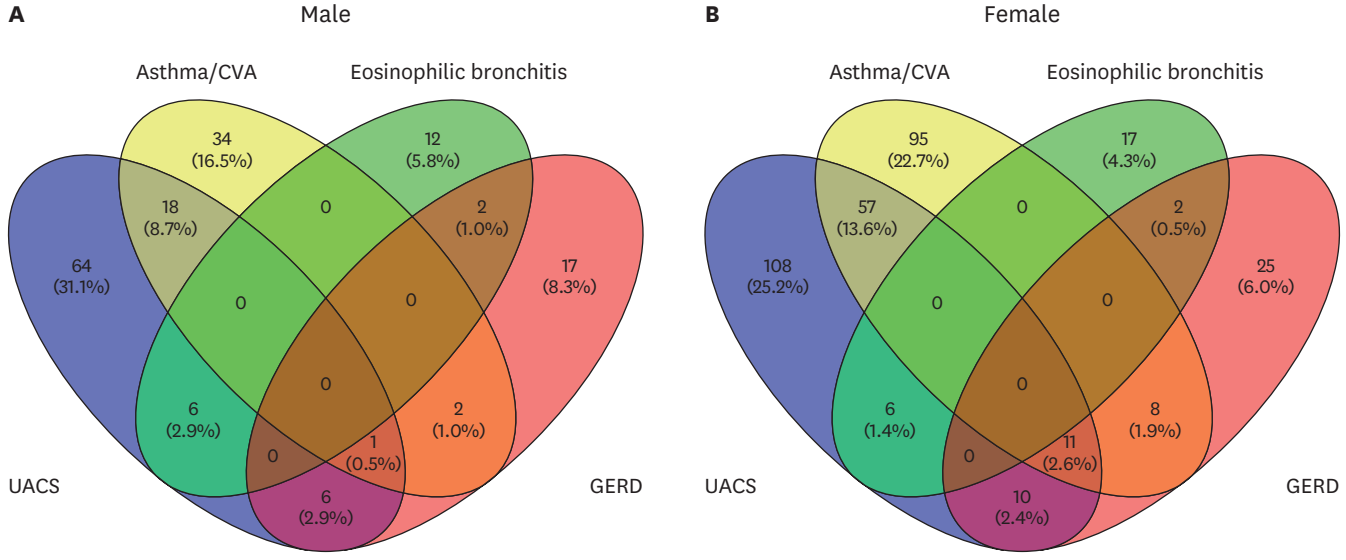

Fig. 2. Venn diagram of etiologies stratified by sex.
UACS = upper airway cough syndrome, CVA = cough variant asthma, GERD = gastro-esophageal reflux disease.

https://doi.org/10.3346/jkms.2024.39.e273

Table 3. Male and female proportions of study participants according to age category

Age, yr	Total	Sex difference		
		Male	Female	*P* value
10–29	72 (11.5)	31 (43.1)	41 (56.9)	Ref
30–39	116 (18.6)	50 (43.1)	66 (56.9)	0.995
40–49	111 (17.8)	42 (37.8)	69 (62.2)	0.482
50–59	151 (24.2)	43 (28.5)	108 (71.5)	0.032
60–69	109 (17.4)	24 (22.0)	85 (78.0)	0.003
70–89	66 (10.6)	16 (24.2)	50 (75.8)	0.021

Values are presented as number (%).
Reference group: 10–29 years.
Female proportion was significantly higher than that in males in the 50–59, 60–69, and 70–89 years.

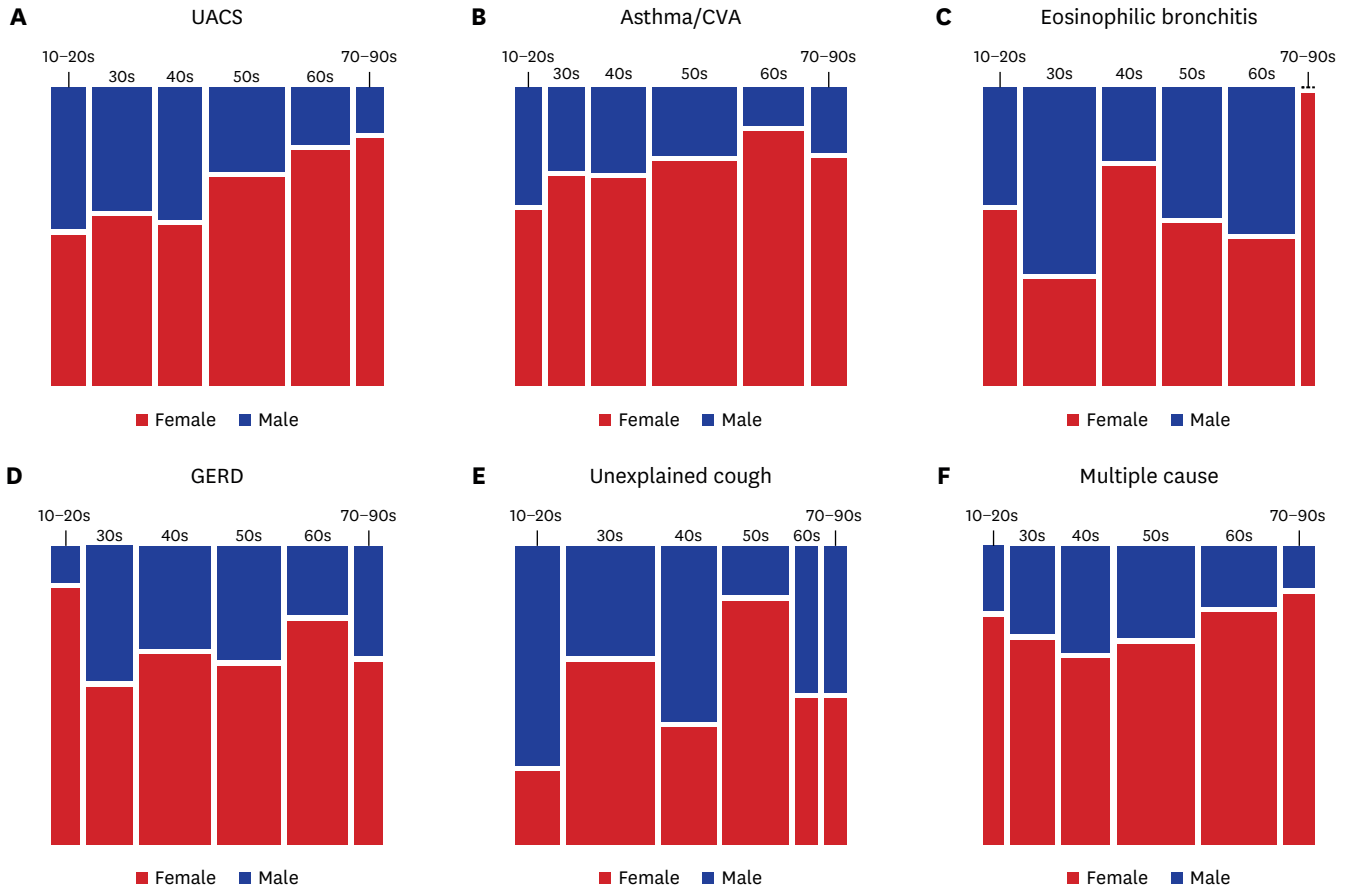

Fig. 3. Proportion of male-to-female sex by age category in each etiology. The proportion of females with (**A**) UACS serially has increased from the age group of 50–59 years. The proportion of females in (**B**) asthma/CVA increased similarly and was significantly higher in the 60–69 year age group. The proportion of females with (**C**) eosinophilic bronchitis, (**D**) GERD, and (**E**) unexplained cough showed no significant pattern. In patients with (**F**) multiple causes, the proportion of females decreased from the 30–39 year age group, reaching the lowest point in the 40–49 year age group, and subsequently began to increase in the 50-59 year age group, resembling a U-shaped pattern.
UACS = upper airway cough syndrome, CVA = cough variant asthma, GERD = gastro-esophageal reflux disease.

proportion of females with UACS serially increased starting from the age group of 50–59 years, which was statistically significant. The proportion of females with asthma/CVA increased in a similar manner, with a significantly higher rate in the 60–69 year age group. On the contrary, in patients with multiple causes, the proportion of females decreased starting from the 30–39 year age group, reaching the lowest proportion in the 40–49 year age group, and then began to increase in the 50–59 year age group, resembling a U-shaped pattern (**Fig. 3**). The ORs for females in each age category for each etiology are summarized in **Supplementary Table 4**.

https://doi.org/10.3346/jkms.2024.39.e273

DISCUSSION

The chronic cough population in Korea was predominantly female, with male-to-female ratio of 1:2.03. Female patients were older and had a higher prevalence of asthma/CVA than male patients. However, cough duration and severity were not different between the sexes. Patients with UACS and asthma/CVA were also predominantly female, and female patients were older than male patients with similar cough severity. The male-to-female ratio was comparable for EB, and there was no significant difference in age between the sexes; however, female patients had more severe cough compared to that in males. In GERD, females were more prevalent than males, and neither the mean age nor the COAT score differed between males and females. The male-to-female ratio was also comparable for unexplained cough, and the mean age did not differ between the sexes, however, females had a lower COAT score than males.

Global epidemiologic studies have repeatedly demonstrated sex-related differences in chronic cough.[12] In order to ascertain the pattern in one of the East Asian countries, we examined the sex-related differences in chronic cough in South Korea and analyzed the effect of age and etiology on this pattern. The male-to-female ratio in South Korea was 1:2.03, which is consistent with the ratios reported in previous global reports. To explain the cause of these sex-related disparities, several theories have been suggested. Fujimura et al.[13] performed a capsaicin cough challenge test on healthy nonsmokers and discovered that female participants displayed a reduced threshold, regardless of their age. Kelsall et al.[14] assessed cough frequency and cough reflex sensitivity in chronic cough patients, and discovered increased night-time cough frequency and cough reflex. Our study revealed that these sex-related disparities were attributable to asthma/CVA but not UACS, EB, or unexplained cough. Women have a higher likelihood of developing asthma, which is approximately 10.5% higher than that of men. Nevertheless, asthma is more prevalent and more severe in males under the age of 18 years.[15,16] The prevalence of asthma in women begins to rise after puberty and becomes more prevalent by the age of 20.[17] The difference continues to widen in adults over the age of 35 years and appears to narrow after menopause, although it does not entirely disappear.[18,19] Considering the consistent pattern change of the male-to-female ratio in asthma and chronic cough, a higher prevalence of asthma in female patients could be suggested as one of the causes of female predominance in chronic cough patients. Female hypersensitivity is commonly believed to influence cough duration and severity; however, no discernible distinction was found between males and females irrespective of the etiology, with the exception of asthma/CVA. Higher prevalence of asthma in female patients could be suggested as one of the causes of female predominance in chronic cough.

Our study found that the age group of 50–59 years had the highest prevalence of chronic cough, consistent with results in previous research.[12,20] This finding could be attributed to UACS. The proportion of females with chronic cough increased with age, although the severity of cough decreased with age. In addition, there was no sex difference within the same age group. There had been a limited study that specifically examined the disparities in quality of life between males and females due to chronic cough.

Sex-related differences in the prevalence of chronic cough may be due to genetic, hormonal, and socioeconomic factors.[21,22] Our study found that the percentage of females with chronic cough increased with age in all categories below 70–89 years. Given the consistent increasing trend, except in cases of multiple causes, linking these sex differences to hormonal or socioeconomic effects is challenging.

https://doi.org/10.3346/jkms.2024.39.e273

Several limitations should be acknowledged in this study. First, we could not evaluate the longitudinal change or treatment outcome of sex-related disparities due to the cross-sectional nature of this study design. Further follow-up data is required to ascertain this outcome. Second, because we used predefined data, we were unable to collect additional clinical information, including detailed medication histories and laboratory results. Third, in addition to age groups, various socioeconomic health determinants can have diverse impacts on disease; however, we were unable to evaluate this effect due to the lack of data. Lastly, we cannot be certain whether all of the comorbidities are responsible for the cough. Further study is needed to determine the generalizability of our results to other populations.

In conclusion, this study demonstrated that sex disparities in cough prevalence, demographic characteristics, and severity varied significantly according to age category and etiology. Our study findings could enhance the comprehension of cough-related pathophysiology, particularly with regard to age, sex, and etiology. Understanding and addressing the structure of sex-based differences could improve targeted screening and diagnostic strategies for chronic cough. Through this analysis, sex- and age-specific etiologic approach for chronic cough can be developed, which consequently can lead to more effective and personalized approaches for diagnosis, treatment, and management, ultimately leading to better patients' outcomes.

SUPPLEMENTARY MATERIALS

Supplementary Table 1
Baseline characteristics according to etiology

Supplementary Table 2
Univariable and multivariable analysis for sex

Supplementary Table 3
Prevalence of each etiology according to age category stratified by sex

Supplementary Table 4
Odds of each etiology for female relative to male in 10-year age increments

Supplementary Fig. 1
Venn diagram for causes of chronic cough.

Supplementary Fig. 2
The age distribution according to etiology stratified by sex.

Supplementary Fig. 3
The cough severity distribution by COAT score according to age stratified by sex.

Supplementary Fig. 4
Proportion of male-to-female sex by age category.

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