

Investigating epidemiological relevance of secretory otitis media and neighboring organ diseases through an Internet search

Cheng Guo^{Equal first author, 1}, Linlin Pan^{Equal first author, 1}, Ling Chen¹, Jinghua Xie¹, Zhuozheng Liang², Yongjin Huang¹, Long He^{Corresp. 1}

¹ Department of otorhinolaryngology head and neck surgery, Guangzhou First People's Hospital, the Second Affiliated Hospital of South China University of Technology, Guangzhou, Guangdong Province, China

² Intensive Care Unit, of The First People's Hospital of Foshan, Foshan, Guangdong Province, China

Corresponding Author: Long He
Email address: eyhelong@scut.edu.cn

Background. This study aimed to investigate the epidemiological relationship between secretory otitis media (SOM) and its neighboring organ diseases, as well as the changes of their incidence during the COVID-19 epidemic in 2020 based on the Internet big data.

Methods. We used the Baidu Index Platform to obtain the search volume for the terms “secretory otitis media (SOM)”, “tonsillitis”, “pharyngolaryngitis”, “adenoid hypertrophy (AH)”, “nasopharyngeal carcinoma (NPC)”, “nasal septum deviation (NSD)”, “rhinosinusitis”, “allergic rhinitis (AR)” and “gastroesophageal reflux disease (GERD)” in Mandarin from January 2011 to December 2021. We analyzed the correlations between them by Spearman’s correlation coefficients and compared the search data in 2019 and 2021 to assess the effects of isolation on SOM of 2020.

Results. Except for AR, the seasonal variations of the trendlines of SOM and other diseases coincided well ($P < 0.05$). During the 11-year timeframe, the monthly searches for rhinosinusitis, NSD, tonsillitis, pharyngolaryngitis, and NPC were statistically correlated with SOM ($R = 0.825, 0.594, 0.650, 0.636, 0.664$, respectively, $P < 0.05$). No correlation was found between SOM and AR, SOM and AH, or SOM and GERD ($R = -0.028; R = 0.259, R = 0.014$, respectively, $P > 0.05$). The total search volumes for SOM, rhinosinusitis, NPC, and AH decreased in 2020 compared to 2019.

Discussion. SOM was found to have an epidemiological relationship with rhinosinusitis, NSD, tonsillitis, pharyngolaryngitis, and NPC. Reduction in public gatherings effectively reduced the morbidities of SOM.

Investigating epidemiological relevance of secretory otitis media and neighboring organ diseases through an Internet search

Cheng Guo^{1†}, Linlin Pan^{1†}, Ling Chen^{1†}, Jinghua Xie¹, Zhuozheng Liang², Yongjin Huang¹, Long He¹

¹ Department of Otolaryngology, Head and Neck Surgery, Guangzhou First People's Hospital, the Second Affiliated Hospital of South China University of Technology, Guangdong Province, China

² Intensive Care Unit of The First People's Hospital of Foshan, Guangdong Province, China

† These authors contributed equally to this work

Corresponding Author:

Long He¹

1 Panfu Road, Yuexiu District, Guangzhou 510180, China

Email address: eyhelong@scut.edu.cn

Abstract

Background. This study aimed to investigate the epidemiological relationship between secretory otitis media (SOM) and its neighboring organ diseases, as well as the changes of their incidence during the COVID-19 epidemic in 2020 based on the Internet big data.

Methods. We used the Baidu Index Platform to obtain the search volume for the terms “secretory otitis media (SOM)”, “tonsillitis”, “pharyngolaryngitis”, “adenoid hypertrophy (AH)”, “nasopharyngeal carcinoma (NPC)”, “nasal septum deviation (NSD)”, “rhinosinusitis”, “allergic rhinitis (AR)” and “gastroesophageal reflux disease (GERD)” in Mandarin from January 2011 to December 2021. We analyzed the correlations between them by Spearman’s correlation coefficients and compared the search data in 2019 and 2021 to assess the effects of isolation on SOM of 2020.

Results. Except for AR, the seasonal variations of the trendlines of SOM and other diseases coincided well ($P < 0.05$). During the 11-year timeframe, the monthly searches for rhinosinusitis, NSD, tonsillitis, pharyngolaryngitis, and NPC were statistically correlated with SOM ($R = 0.825, 0.594, 0.650, 0.636, 0.664$, respectively, $P < 0.05$). No correlation was found between SOM and AR, SOM and AH, or SOM and GERD ($R = -0.028; R = 0.259, R = 0.014$, respectively, $P > 0.05$). The total search volumes for SOM, rhinosinusitis, NPC, and AH decreased in 2020 compared to 2019.

Discussion. SOM was found to have an epidemiological relationship with rhinosinusitis, NSD, tonsillitis, pharyngolaryngitis, and NPC. Reduction in public gatherings effectively reduced the morbidities of SOM.

Introduction

Secretory otitis media (SOM) is a frequently diagnosed disease characterized by middle-ear effusions (MEEs), which reduce tympanic membrane mobility, hearing loss, and ear swelling¹. Compared with adults, children have a high incidence, with about 90% of preschoolers experiencing at least one episode of SOM. Most children with SOM will self-heal. However, Chronic SOM may lead to speech retardation, academic performance decline, and other problems. The pathogenesis of SOM is related to adenoid hypertrophy(AH), nasopharyngeal carcinoma(NPC), rhinosinusitis, allergic rhinitis(AR)², nasal septum deviation (NSD), gastroesophageal reflux disease(GERD) and so on³.

Traditionally, epidemiologic data were provided by clinicians and preventive health professionals, and then collected and disclosed by health authorities. It consumes more time and resources, leading to delayed surveillance of emerging infectious diseases. With the widespread of the Internet, people access to health information easier and faster, and these changes have provided new sights to detect and monitor disease outbreaks. Internet search data can provide real-time information and have good consistency with traditional healthcare surveillance systems. In recent years, internet search data were used for investigate the epidemic characteristics of diseases in recent years⁴. For example, through the analysis of Internet search data, scholars found that influenza, depression, sleep-disordered breathing, and other diseases have seasonal onset⁵, and AH and rhinosinusitis are correlated⁶. Moreover, Internet search data can also be applied to predict the incidence of HIV and syphilis⁷.

Nowadays, the biggest search engines in the world are Baidu and Google. Baidu is by far the dominant search engine since Google pulled out of China in 2010. Some researchers who conducted studied using internet data have verified that the Baidu index (BI) is reliable as the incidence index of diseases⁶.

The novel coronavirus disease 2019 (COVID-19), a highly contagious respiratory disease, emerged in Wuhan, Hubei Province, China in December 2019. Chinese government locked down Wuhan from January to April 2020 to prevent COVID-19 and urged people to stay at home. This provides an opportunity to investigate the effect of isolation on the incidence of diseases such as SOM, rhinosinusitis, NSD, AR, AH, NPC, tonsillitis, pharyngolaryngitis, and GERD.

This study aims to use BI to analyze the correlation between SOM and neighboring organ diseases and to analyze the impact of isolation on the incidence of SOM and neighboring organ diseases during the COVID-19 epidemic in 2020.

Materials & Methods

2.1 Data from the Baidu index

Most of the Chinese search engine users are inclined to use Baidu to retrieve numerous search terms. The weighted sum of the BI can reflect the characteristics of people's behaviors. The search data for the terms "secretory otitis media", "tonsillitis", "pharyngolaryngitis", "adenoid hypertrophy", "nasopharyngeal carcinoma", "nasal septum deviation," "rhinosinusitis", "allergic

rhinitis” and “gastroesophageal reflux disease” in Chinese from January 2011 to December 2021 were retrieved from the BI. To observe the influence of COVID-19 isolation, the first 5 months of the above data in 2019, 2020, and 2021 were included in our study’s timeframe to compare search volumes from the same period among these years. We calculated the monthly search volume by multiplying the number of days in the month by the average daily search volume, and then adding it to the annual search volume. Following data normalization against the total search volume, results are presented as percentages ranging from 0 to 100%.

2.2 Data analysis

The main variables were the percentages of monthly search volume and the average monthly search for “tonsillitis”, “pharyngolaryngitis”, “AH”, “NPC”, “NSD”, “rhinosinusitis”, “AR” and “GERD”. Statistical analyses were performed using SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA). The continuous variables in this research were not normally distributed based on the results of Shapiro-Wilk test for normality. Thus, we used Spearman’s correlation coefficients to analyze the correlation between variables. Paired comparisons among the first 5 months of the data in 2019, 2020, and 2021 were performed with nonparametric Friedman test. $P < 0.05$ was considered significant. Microsoft Excel Software and RStudio 2022 were used to draw line graphs and heatmaps.

Results

A total of 132 monthly search volume values were obtained. In our study, tonsillitis, acute tonsillitis, and chronic tonsillitis were merged into “tonsillitis”; likewise, “acute pharyngitis”, “chronic pharyngitis”, “pharyngitis”, “laryngitis”, “chronic pharyngolaryngitis”, and “pharyngolaryngitis” were included in “pharyngolaryngitis”. In order to find out the relationship between SOM and nasal disease, laryngeal disease, oropharyngeal diseases, and GERD, SOM was compared with the other eight search terms. The tendency charts of the nine search terms from 2011 to 2021 are presented in Figure 1. Except for AR, the trendlines of SOM and the other seven diseases coincided well. As shown in Figure 1, the seasonal variations of the trendlines between SOM and NSD, tonsillitis, and pharyngolaryngitis were strongly correlated ($R = 0.584, 0.588, 0.502$, respectively, all $P < 0.05$), while the relationship between SOM and rhinosinusitis, NPC, AH, GERD was weak ($R = 0.475, 0.358, 0.351, 0.339$, respectively, all $P < 0.05$).

The average monthly search volumes for the nine keywords during the 11-year timeframe are shown in Figure 2. The monthly searches for rhinosinusitis, NSD, tonsillitis, pharyngolaryngitis, and NPC showed a similar trend, which correlated significantly with SOM ($R = 0.825, 0.594, 0.650, 0.636, 0.664$, respectively, all $P < 0.05$). As shown in Figure 2, the highest and lowest average monthly search volumes for SOM, rhinosinusitis, NSD, tonsillitis, and pharyngolaryngitis were in February and March. Furthermore, the curve was more gradual from April to December. However, no correlation was detected between SOM and AR, SOM and AH, or SOM and GERD ($R = -0.028, 0.259, 0.014$, respectively, all $P > 0.05$).

As shown in Figure 3, the search volumes for SOM, rhinosinusitis, NPC, and AH decreased during the first 5 months of 2020 compared with the same period in 2019 ($P < 0.05$). In addition,

the total search volumes for NSD and pharyngolaryngitis were found to decrease during the first 5 months of 2021 compared with 2019 ($P < 0.05$). For AR, tonsillitis, and GERD, no statistical correlation was found between SOM and any one of them ($P > 0.05$). The correlation between SOM and other search volumes can be observed intuitively in the heatmaps in Figure 4 and Figure 5.

Discussion

In this study, we explored the correlation and seasonal prevalence of SOM with rhinosinusitis, AH, NPC, AR, NSD, pharyngolaryngitis, and GERD by using the BI. The correlation was further verified by the feature that isolation during the COVID-19 epidemic reduced the incidence of rhinosinusitis and AH. Our results indicated that the monthly search volume of SOM was statistically consistent with the monthly search volume of rhinosinusitis, AH, NPC, NSD, pharyngolaryngitis, tonsillitis, and GERD. During COVID-19 isolation from January to May 2020, monthly searches for SOM decreased in parallel with that for rhinosinusitis, AH, and NPC. However, there was no correlation between SOM and GERD, AR, NSD, pharyngolaryngitis and tonsillitis.

With the popularization of the Internet, an increasing number of people can access medical and health knowledge through an Internet search. Therefore, data from Online surveillance tools began to be used to predict disease prevalence and analyze epidemic characteristics. Compared to traditional healthcare surveillance systems, surveillance systems based on Internet search data are more convenient, economical, and fast. Mounting evidence has shown that Internet search data can be used to monitor and predict influenza, AIDS, gonorrhea, syphilis, and other infectious diseases⁷. In addition, the sensitivity and specificity of monitoring or forecasting results based on Internet search data are comparable to those of traditional surveillance systems.

The correlation between SOM and rhinosinusitis is well-established². Finkelstein et al. showed that 66% of adults with SOM had rhinosinusitis, especially ethmoid sinus lesions⁸. Previous studies reported that 23% of patients with chronic rhinosinusitis suffered from SOM⁹. Some research exploring the correlation between SOM and nasal polyps indicated that the incidence of SOM was high in severe nasal polyps, such as patients with asthma and aspirin intolerance¹⁰. However, the specific pathogenesis is still unclear. The scholar analyzed two possibilities: mechanical blockage of the eustachian tube and simultaneous inflammation of the mucous membrane of the middle ear and nasal¹¹. Surprisingly, our study also discovered that the incidence of rhinosinusitis is coincide with SOM. A multicenter prospective study confirmed that patients with sinusitis with eustachian tube dysfunction (ETD) typically experience improved eustachian tube function after surgery¹². However, Daval Mary et al. suggested no significant correlation between the incidence of SOM and the severity of nasal polyps and nasal blockage. SOM may develop or persist even after nasal congestion improves with surgical or conservative medical treatment¹³. Therefore, it was speculated that the correlation between sinusitis and SOM was mainly due to hypersecretion of the nasal mucosa and middle ear mucosa stimulated by inflammation.

Adenoids are immune organs in childhood that gradually increase until 7-10 years old, but then begin to shrink with age. However, repeated inflammatory stimulation can lead to AH. The correlation between the incidence of SOM and AH has been verified ¹⁴. Our study discovered that the occurrence of SOM and AH were consistent, and the difference was statistically significant. Many studies have shown that the nasopharyngeal bacteria of patients with SOM have homology with the middle ear effusion bacteria. Obstruction of the eustachian tube (ET) caused by adenoid enlargement led to the accumulation of nasopharyngeal secretions and microorganisms. Retrograde microbial infection is the main cause of SOM caused by AH ^{15,16}. Pharyngolaryngitis and tonsillitis are often accompanied by bacterial infection in the pharynx. Our study showed that SOM is associated with pharyngolaryngitis, and we speculate that it is not only related to retrogressive infection of pharyngeal bacteria along ET, but also related to mucosal swelling around ET and ETD caused by repeated inflammatory stimulation. However, the correlation between adenoid enlargement and mechanical obstruction of ET and SOM remains ambiguous. Relevant studies have demonstrated that the mucous membrane of the middle ear has the same secretory function as the nasopharynx ¹⁷. When inflammation stimulates adenoid enlargement, it may also induce hypersecretion of middle ear mucosa, subsequently leading to SOM ^{18,19}.

NPC is a common malignant tumor occurring in the nasopharynx, usually in the pharyngeal recess ²⁰. Due to tumor compression and invasion, the function of ET is affected, and patients with NPC are prone to have SOM. However, studies have shown that for many newly diagnosed NPC, the etiology of ETD is still unknown ²¹. Yunxian Mo et al. evaluated the ET function of NPC patients by Valsalva maneuver combined with MRI and found that ETD was significantly more common when tumors involved structures near the ET, especially the tensor veli palatine muscle ²². It has also been suggested that SOM was caused by nerve injury that innervates the tensor veli palatine muscle. The primary treatment for NPC is radiotherapy ²³. Radiotherapy can cause many local complications, such as otitis media, sensorineural hearing loss, and rhinosinusitis. Although modern intensity-modulated radiotherapy (IMRT) can reduce the incidence of these complications, researchers have shown that SOM is still a common late toxicity of the middle ear after radiotherapy ¹⁸. Among the susceptibility factors to post-irradiation SOM, rhinosinusitis and ETD have been fully confirmed. The nasopharyngeal and middle ear bacteriology of patients with post-irradiation sinusitis and SOM have homology, and SOM is alleviated by nasal irrigation. This indicates that there may be a correlation between SOM and bacterial infection from the paranasal sinuses after irradiation ²⁴. Rinsing the nasal cavity with normal saline can relieve the symptoms of rhinosinusitis and SOM ²⁵. However, Chung-Han Hsin et al. found that post-irradiation SOM is not related to rhinosinusitis. They also believed that nasal irrigation had no effect on alleviating SOM symptoms, and incorrect nasal irrigation will cause retrograde movement of nasal microorganisms to the middle ear and aggravated SOM ²⁶.

The NSD may be associated with middle ear diseases. Ural et al. found that 89.4% of patients with NSD had middle ear disease, and 50.4% of them had otitis media on the same side as the nasal congestion ²⁷. Our study found a correlation between the incidence of NSD and SOM. Submucous resection (SMR) of the nasal septum can improve the negative pressure regulation of the

middle ear in patients with septal deviation and ETD²⁸. The relationship between septal deviation and SOM is considered to be ET. However, it is not clear how septal deviation affects the function of ET. Most studies suggest that NSD affects the function of ET by affecting the airflow in the nasopharynx²⁹. When the gas flows through the narrow space, the velocity becomes faster and the laminar flow becomes turbulent, resulting in high local negative pressure and impaired ET function. Another opinion is that patients with nasal congestion develop greater negative pressure during strenuous breathing. McNicoll & Scanlad examined nasal airflow by xenon 133 scintigraphy and found that patients with NSD and ETD had disordered nasal airflow before SMR, and the middle ear cavity could not be inflated. After SMR, the nasopharyngeal airflow disorder disappeared, and the middle ear cavity could be well inflated²⁸. W.K.LOW et al. found that the difference in bilateral nasal patency caused by NSD was negatively correlated with the negative pressure in the middle ear on the side of the blocked nasal passage. Correcting this asymmetric nasal patency through SMR could improve the corresponding negative pressure in the middle ear³⁰. Therefore, they hypothesized that the asymmetry of bilateral nasal airflow caused by the NSD leads to turbulence in the nasopharynx, making it easier for microorganisms to deposit in the nasopharynx and around the pharyngeal orifice of ET, resulting in inflammation and mechanical obstruction around the ET. In addition, turbulence dries the air and affects the function of the mucous layer in the nasopharynx and ET. However, other studies have shown that NSD has little impact on the function of ET, and only severe deviation can affect the middle ear function.

Gastroesophageal reflux (GER) is the reflux of stomach contents into the esophagus. GERD is characterized by the abnormal reflux of stomach contents into the esophagus causing symptoms such as heartburn or complications such as esophageal injury³¹. GERD not only causes esophageal lesions, but is also associated with many diseases of the ear, nose, and throat^{32,33}. Although GERD has been listed as one of the pathogenesis factors of SOM, the pathophysiological mechanism remains unclear. A Korean study showed that adults with GERD had a 1.84 times higher prevalence of chronic SOM than those without GERD³⁴. Our study found that the incidence of SOM and GERD had the same trend. Previous studies found that many middle ear effusions of SOM existed with pepsin/pepsinogen and hydrochloric acid (HCl), with gastric juice as the main component of the effusions. It was speculated that the inflammatory stimulation of pepsin/pepsinogen and HCl on the middle ear mucosa led to mucosal edema and hypersecretion. The damage to the ET was the key factor for SOM. It has been verified in rat experiments that pepsin and HCl can affect the function of ET and mucociliary clearance³⁵. Pepsinogen can only be activated into bioactive pepsin under an acidic environment, but the pH of the middle ear effusion is alkaline, and the pepsinogen in the middle ear effusion cannot be activated. However, no relevant study has confirmed the causal relationship between pepsin/pepsinogen in middle ear effusion and SOM.

AR refers to symptoms such as nasal congestion, itching, sneezing, and runny nose caused by allergies to certain substances. The association between AR and SOM is controversial. It has been established that AR is a risk factor for the pathogenesis of SOM. Some researchers have found that allergen exposure can induce ET obstruction and SOM symptoms in AR patients³⁶. In

addition, the finding of effector T helper 2 (Th2) cells, a cell whose expression is significantly higher in allergic patients, in the middle ear effusion of SOM patients indicates that allergic inflammation may be also present in the middle ear of SOM³⁷. In response to these findings, some studies treated patients with AR and SOM with nasal steroid sprays and azelastine hydrochloride and found it could relieve patients' SOM symptoms³⁸. The mucosa of the nasal cavity and the middle ear are contiguous and both can produce an allergic inflammatory response. However, in the study of nasal polyps and SOM, some researchers found that the risk of SOM in patients with specific nasal polyps was not different from that in patients with non-specific nasal polyps, denying the role of allergic reactions in SOM¹¹. In our study, the incidence trend of SOM was not consistent with that of AR. Overall, the correlation between allergic diseases and SOM needs to be further studied.

In 2019, there was an outbreak of COVID-19 in China. In order to prevent the spread, the Chinese government imposed lockdown measures from January to May 2020, which advocated wearing masks and home isolation. The incidence of NPC, AH, and rhinosinusitis all coincided with a decline in the incidence of SOM during this period. The reduction of crowd gatherings and the wearing of masks have greatly reduced the spread of microorganisms during COVID-19. However, considering the repeated local epidemics of COVID-19 in China, this may result in the weak evidence base of the impact of COVID-19 isolation on SOM and neighboring organ diseases in the first five months of 2021. SOM and lesions of surrounding structures also decreased. It is known that microorganisms may play a crucial role in the pathogenesis of secretory otitis media and peripheral organ lesions.

Notwithstanding, our current study has certain limitations. Firstly, since rhinosinusitis and pharyngolaryngitis include acute, chronic, and other types, it would have been optimum to proceed the accounting for these diverse subtypes. However, considering that people may not be able to distinguish among subtypes when searching, we combined the keywords "tonsillitis", "acute tonsillitis" and "chronic tonsillitis" into "tonsillitis", and "acute pharyngitis", "chronic pharyngitis", "pharyngitis", "chronic pharyngolaryngitis", and "pharyngolaryngitis" into "pharyngolaryngitis", making the study of subtypes complicated. Secondly, on account of the Internet search engines users are basically young people. Whereas, children, the elderly, and those in underdeveloped areas who rarely use search engines, may lead to age bias. Thirdly, the fluctuations in BI search behaviors may be influenced by media reports and social propaganda, events. Finally, in view of the symptoms of these diseases have some overlaps, which led to the precise motivations behind these search behaviors being unable to be determined. Further big data analysis or accurate data to improve the reliability of utilizing the search query data as the monitoring method is in urgent. With the further popularization of the Internet and the spread of medical science, insufficient clinical data could be effectively compensated by Internet-based surveillance systems, thus providing a novel field for monitoring disease morbidity and exploring the relationships among diseases.

Conclusions

In summary, in seasonal variation, SOM was strongly correlated with NSD, tonsillitis and pharyngolaryngitis, and weakly correlated with rhinosinusitis, AH, NPC and GERD, but not significantly correlated with AR. The decrease in public gatherings significantly reduced the morbidities of SOM, rhinosinusitis, NPC, and AH, but not those of GERD, AR, NSD, pharyngolaryngitis and tonsillitis.

Acknowledgements

Ethics approval: Ethics committee approval was not required for this study because it was based on Internet search data.

Consent to participate: The study was based on Internet search data, and no personal information was revealed, thereby maintaining confidentiality.

Funding: No funding was received for conducting this study.

Competing interests: The authors have no relevant financial or non-financial interests to disclose.

Data, materials and/or code availability: The data sets used and/or analyzed in the present study are available from the author on reasonable request.

References

1. Chen T, Li G, Liu W, Fan Z, Li L. Surfactant Protein A Can Affect Macrophage Phagocytosis: An Important Pathogenic Mechanism of Otitis Media with Effusion. *J Assoc Res Otolaryngol*. 2023;
2. Rosenfeld RM, Shin JJ, Schwartz SR et al. Clinical Practice Guideline: Otitis Media with Effusion (Update). *Otolaryngol Head Neck Surg*. 2016;154(1 Suppl):S1-S41
3. Sone M, Kato T, Arao H et al. Exploratory findings of audiometry in adult patients with otitis media with high pepsinogen concentrations: a preliminary study. *Acta Otolaryngol*. 2013;133(1):35-41
4. Milinovich GJ, Williams GM, Clements AC, Hu W. Internet-based surveillance systems for monitoring emerging infectious diseases. *Lancet Infect Dis*. 2014;14(2):160-8
5. Ingram DG, Matthews CK, Plante DT. Seasonal trends in sleep-disordered breathing: evidence from Internet search engine query data. *Sleep Breath*. 2015;19(1):79-84
6. Yang Y, Li X, Ma Q, Fu Z, Su K. Detecting epidemiological relevance of adenoid hypertrophy, rhinosinusitis, and allergic rhinitis through an Internet search. *Eur Arch Otorhinolaryngol*. 2022;279(3):1349-1355
7. Huang R, Luo G, Duan Q et al. Using Baidu search index to monitor and predict newly diagnosed cases of HIV/AIDS, syphilis and gonorrhea in China: estimates from a vector autoregressive (VAR) model. *BMJ Open*. 2020;10(3):e036098
8. Finkelstein Y, Ophir D, Talmi YP et al. Adult-onset otitis media with effusion. *Arch Otolaryngol Head Neck Surg*. 1994;120(5):517-27
9. Dang PT, Gubbels SP. Is nasopharyngoscopy necessary in adult-onset otitis media with effusion? *Laryngoscope*. 2013;123(9):2081-2

10. Taylor B, Evans JN, Hope GA. Upper respiratory tract in cystic fibrosis. Ear-nose-throat survey of 50 children. *Arch Dis Child*. 1974;49(2):133-6
11. Parietti-Winkler C, Baumann C, Gallet P, Gauchard G, Jankowski R. Otitis media with effusion as a marker of the inflammatory process associated to nasal polyposis. *Rhinology*. 2009;47(4):396-9
12. Chen X, Dang H, Chen Q et al. Endoscopic sinus surgery improves Eustachian tube function in patients with chronic rhinosinusitis: a multicenter prospective study. *Rhinology*. 2021;59(6):560-566
13. Daval M, Picard H, Bequignon E et al. Chronic otitis media with effusion in chronic sinusitis with polyps. *Ear Nose Throat J*. 2018;97(8):E13-E18
14. Low WK, Lim TA, Fan YF, Balakrishnan A. Pathogenesis of middle-ear effusion in nasopharyngeal carcinoma: a new perspective. *J Laryngol Otol*. 1997;111(5):431-4
15. Tawfik SA, Ibrahim AA, Talaat IM, El-Alkamy SS, Youssef A. Role of bacterial biofilm in development of middle ear effusion. *Eur Arch Otorhinolaryngol*. 2016;273(11):4003-4009
16. Pagella F, Colombo A, Gatti O, Giourgos G, Matti E. Rhinosinusitis and otitis media: the link with adenoids. *Int J Immunopathol Pharmacol*. 2010;23(1 Suppl):38-40
17. Marple BF. Allergic rhinitis and inflammatory airway disease: interactions within the unified airspace. *Am J Rhinol Allergy*. 2010;24(4):249-54
18. Hsin CH, Chen TH, Liang KL, Tseng HC, Liu WS. Postirradiation otitis media with effusion in nasopharyngeal carcinoma patients treated by intensity-modulated radiotherapy. *Laryngoscope*. 2013;123(9):2148-53
19. Young YH. Irradiated ears in nasopharyngeal carcinoma survivors: A review. *Laryngoscope*. 2019;129(3):637-642
20. Chen YP, Chan A, Le QT et al. Nasopharyngeal carcinoma. *Lancet*. 2019;394(10192):64-80
21. Su CY, Hsu SP, Chee CY. Electromyographic study of tensor and levator veli palatini muscles in patients with nasopharyngeal carcinoma. Implications for eustachian tube dysfunction. *Cancer*. 1993;71(4):1193-200
22. Mo Y, Zhuo S, Tian L et al. Functional MRI of the Eustachian Tubes in Patients With Nasopharyngeal Carcinoma: Correlation With Middle Ear Effusion and Tumor Invasion. *AJR Am J Roentgenol*. 2016;206(3):617-22
23. Wei WI, Sham JS. Nasopharyngeal carcinoma. *Lancet*. 2005;365(9476):2041-54
24. Hsin CH, Tseng HC, Lin HP, Chen TH. Sinus mucosa status in patients with nasopharyngeal carcinoma treated with intensity-modulated radiotherapy: A 5-year follow-up. *Head Neck*. 2016;38(1):29-35
25. Liang KL, Kao TC, Lin JC et al. Nasal irrigation reduces postirradiation rhinosinusitis in patients with nasopharyngeal carcinoma. *Am J Rhinol*. 2008;22(3):258-62
26. Hsin CH, Tseng HC, Lin HP, Chen TH. Post-irradiation otitis media, rhinosinusitis, and their interrelationship in nasopharyngeal carcinoma patients treated by IMRT. *Eur Arch Otorhinolaryngol*. 2016;273(2):471-7
27. Ural A, Minovi A, Çobanoğlu B. Upper airway obstructions and chronic otitis media: a clinical

- study. *Am J Otolaryngol*. 2014;35(3):329-31
28. Upadhy I, Datar J. Treatment options in otitis media with effusion. *Indian J Otolaryngol Head Neck Surg*. 2014;66(Suppl 1):191-7
29. Maier W, Krebs A. [Is surgery of the inner nose indicated before tympanoplasty? Effects of nasal obstruction and reconstruction on the eustachian tube]. *Laryngorhinootologie*. 1998;77(12):682-8
30. Low WK, Willatt DJ. The relationship between middle ear pressure and deviated nasal septum. *Clin Otolaryngol Allied Sci*. 1993;18(4):308-10
31. Dent J, Brun J, Fendrick A et al. An evidence-based appraisal of reflux disease management--the Genval Workshop Report. *Gut*. 1999;44 Suppl 2(Suppl 2):S1-16
32. Ozmen S, Yücel OT, Sinici I et al. Nasal pepsin assay and pH monitoring in chronic rhinosinusitis. *Laryngoscope*. 2008;118(5):890-4
33. Lechien JR, Akst LM, Saussez S et al. Involvement of Laryngopharyngeal Reflux in Select Nonfunctional Laryngeal Diseases: A Systematic Review. *Otolaryngol Head Neck Surg*. 2021;164(1):37-48
34. Yeo CD, Kim JS, Lee EJ. Association of gastroesophageal reflux disease with increased risk of chronic otitis media with effusion in adults: A nationwide population-based cohort study. *Medicine (Baltimore)*. 2021;100(33):e26940
35. White DR, Heavner SB, Hardy SM, Prazma J. Gastroesophageal reflux and eustachian tube dysfunction in an animal model. *Laryngoscope*. 2002;112(6):955-61
36. Skoner DP, Doyle WJ, Fireman P. Eustachian tube obstruction (ETO) after histamine nasal provocation--a double-blind dose-response study. *J Allergy Clin Immunol*. 1987;79(1):27-31
37. Nguyen LH, Manoukian JJ, Sobol SE et al. Similar allergic inflammation in the middle ear and the upper airway: evidence linking otitis media with effusion to the united airways concept. *J Allergy Clin Immunol*. 2004;114(5):1110-5
38. Bhargava R, Chakravarti A. A double-blind randomized placebo-controlled trial of topical intranasal mometasone furoate nasal spray in children of adenoidal hypertrophy with otitis media with effusion. *Am J Otolaryngol*. 2014;35(6):766-70

Figure 1

Monthly search volume (in percentage).

(A) SOM and nasal disease (AR, rhinosinusitis and NSD). (B) SOM and nasopharyngeal diseases (NPC and AH). (C) SOM and laryngeal diseases (tonsillitis and pharyngolaryngitis). (D) SOM and GERD during 2011–2021. Except for AR, the trendlines of SOM and the other seven diseases coincided well. AR allergic rhinitis, NSD nasal septum deviation, SOM secretory otitis media, NPC nasopharyngeal carcinoma, AH adenoid hypertrophy, GERD gastroesophageal reflux disease

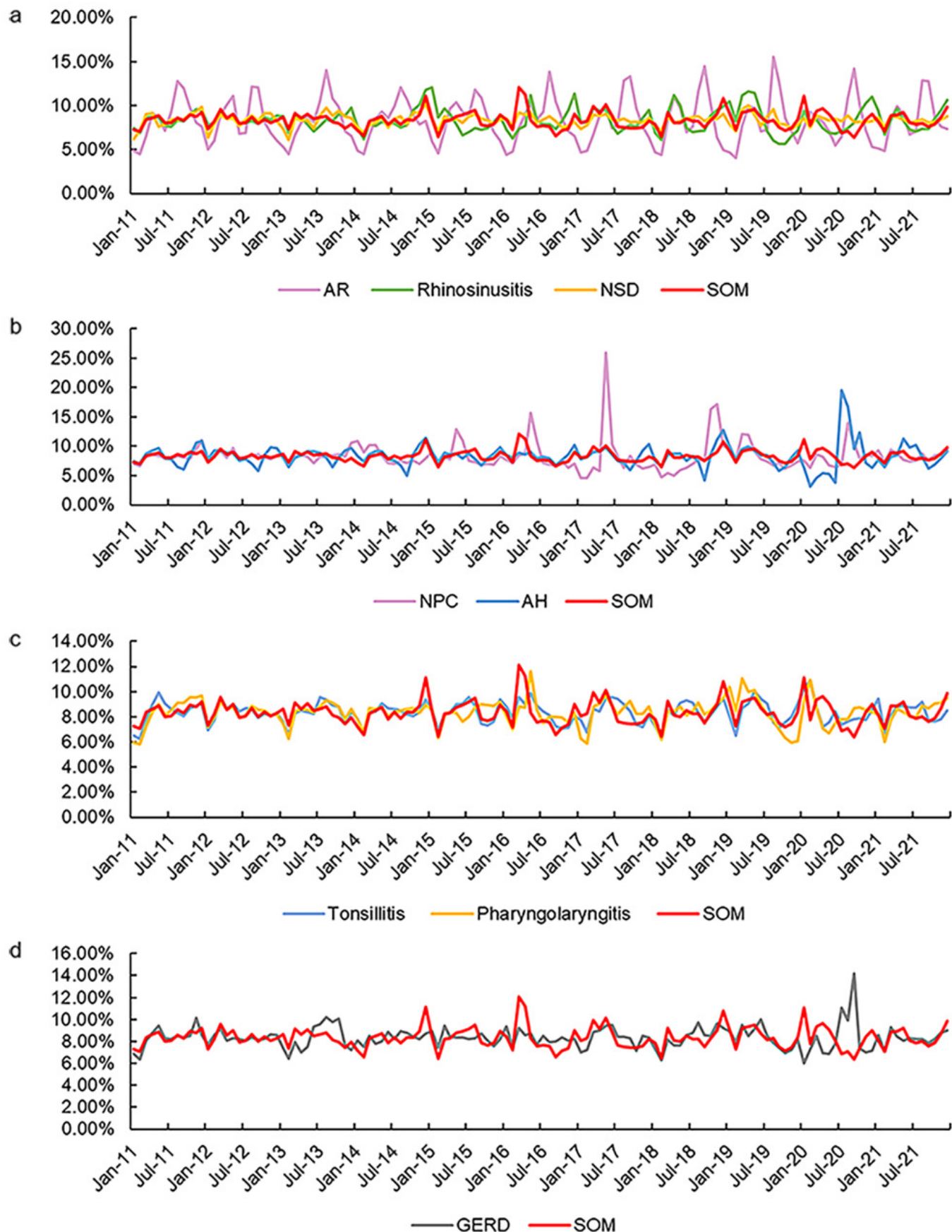


Figure 2

Average monthly search volume.

(A) SOM and nasal disease (AR, rhinosinusitis and NSD). (B) SOM and nasopharyngeal diseases (NPC and AH). (C) SOM and laryngeal diseases (tonsillitis and pharyngolaryngitis). (D) SOM and GERD during 2011–2021. SOM and rhinosinusitis, NSD, tonsillitis, pharyngolaryngitis, NPC all drastically decline from January to February and slowly decline from March to September and then increase from February to May and from November to December. *AR* allergic rhinitis, *NSD* nasal septum deviation, *SOM* secretory otitis media, *NPC* nasopharyngeal carcinoma, *AH* adenoid hypertrophy, *GERD* gastroesophageal reflux disease

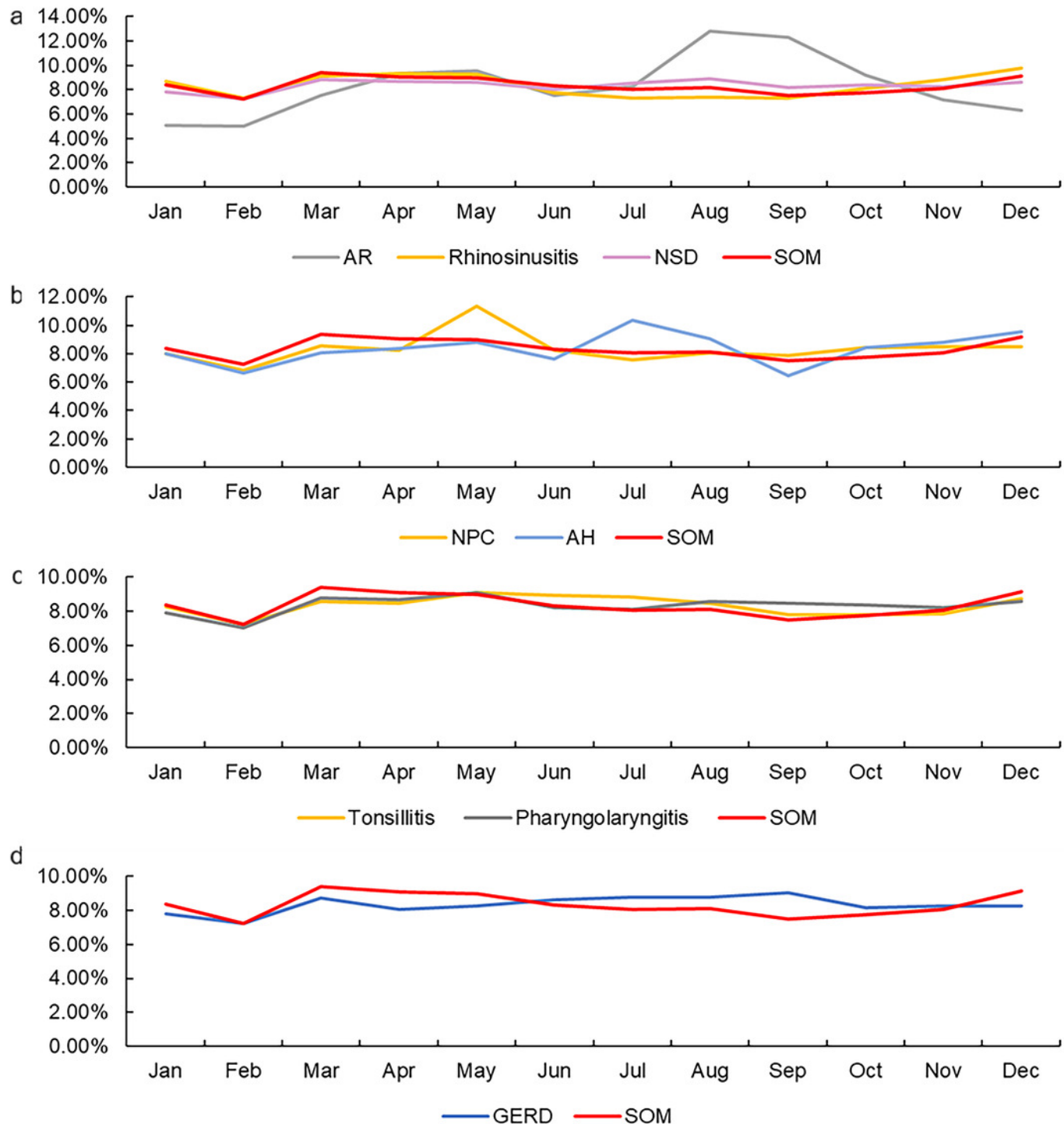


Figure 3

Comparison of the search volume during the first 5 months of 2019, 2020 and 2021.

(A) SOM. (B) AR. (C) rhinosinusitis. (D) NSD. (E) NPC. (F) AH. (G) tonsillitis. (H) pharyngolaryngitis. (I) GERD. The total search volumes for SOM, rhinosinusitis, NPC, AH, pharyngolaryngitis decreased during the first 5 months of 2020 compared with those months in 2019 ($P > 0.05$). However, no statistical relationship was found for these search volumes in 2021 compared with 2019. *AR* allergic rhinitis, *NSD* nasal septum deviation, *SOM* secretory otitis media, *NPC* nasopharyngeal carcinoma, *AH* adenoid hypertrophy, *GERD* gastroesophageal reflux disease

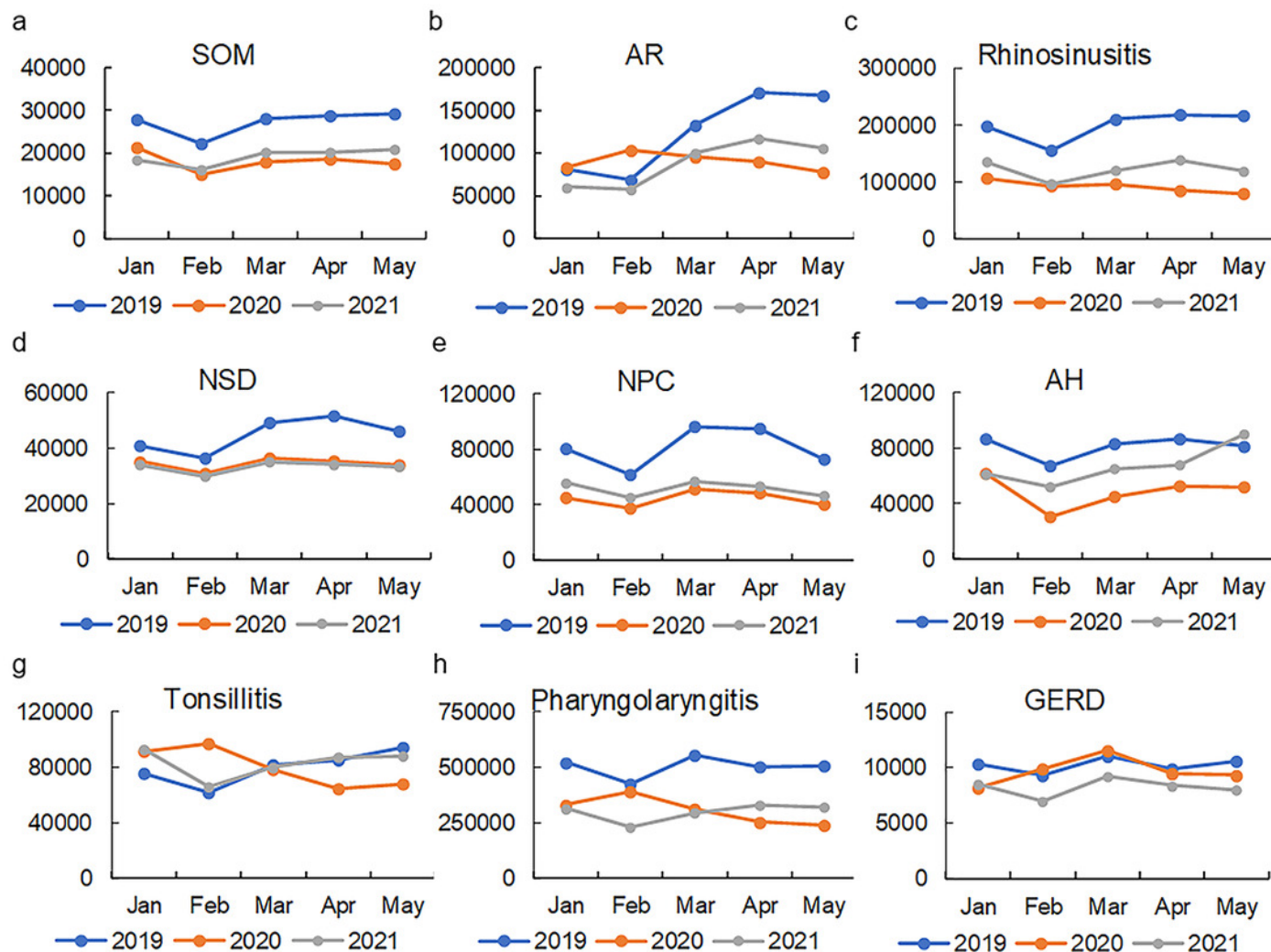


Figure 4

The heatmap shows the relationship between SOM and other eight diseases in monthly volume.

As we can show, the search variations for SOM and rhinosinusitis, NSD, AH, NPC, tonsillitis, pharyngolaryngitis, GERD are significantly relevant ($R = 0.475, 0.584, 0.351, 0.358, 0.358, 0.588, 0.502, 0.339$, respectively, all $P < 0.05$). The search variations for SOM and AR are not related ($R = 0.082, P > 0.05$). AR allergic rhinitis, NSD nasal septum deviation, SOM secretory otitis media, NPC nasopharyngeal carcinoma, AH adenoid hypertrophy, GERD gastroesophageal reflux disease.

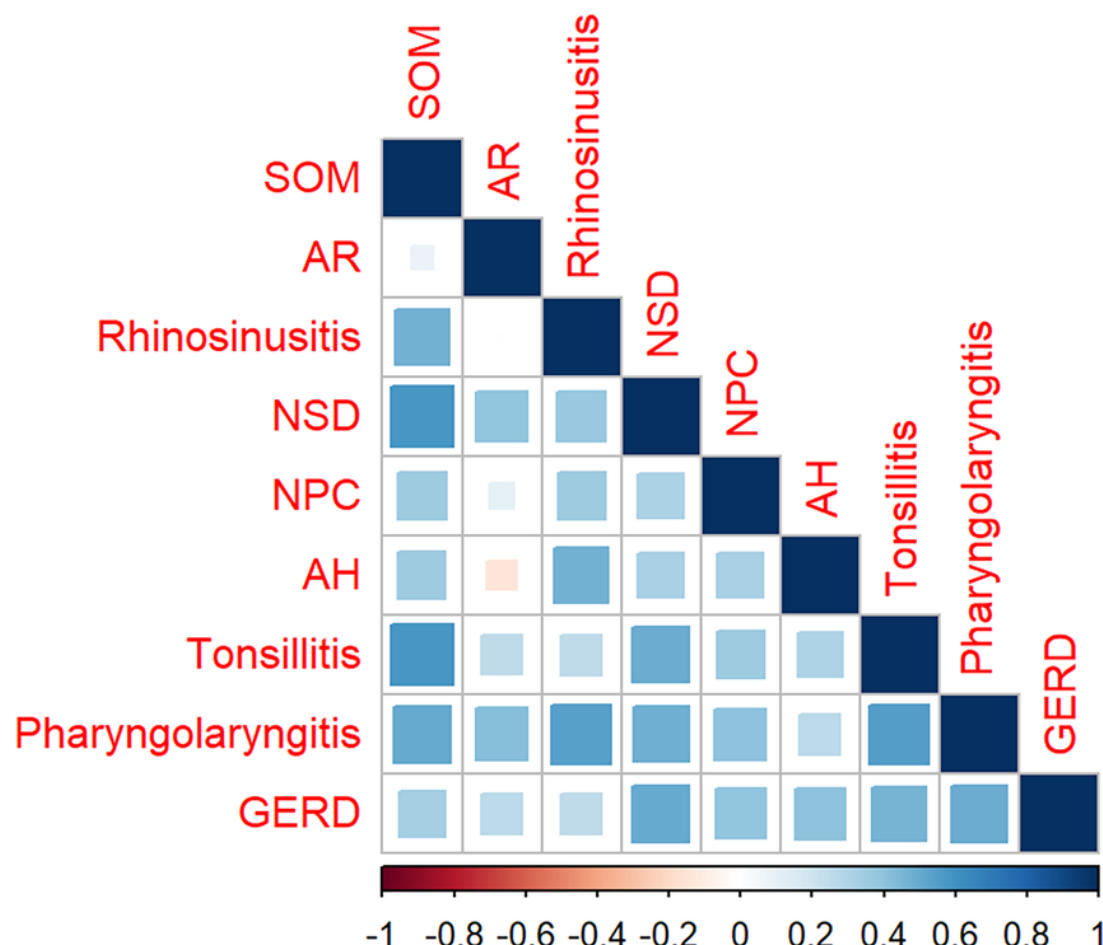


Figure 5

The heatmap shows the relationship between SOM and other eight diseases in average month volume.

The search variations for SOM and rhinosinusitis, NSD, tonsillitis, pharyngolaryngitis, NPC are strongly relevant ($R=0.584, 0.588, 0.502, P<0.01$, respectively). No statistical relationship was found between SOM and AR, AH or GERD ($R = -0.028, 0.259, 0.014$, respectively, all $P > 0.05$). *AR* allergic rhinitis, *NSD* nasal septum deviation, *SOM* secretory otitis media, *NPC* nasopharyngeal carcinoma, *AH* adenoid hypertrophy, *GERD* gastroesophageal reflux disease.

