Exploratory Research and Hypothesis in Medicine **2022** vol. 000(000) | 000–000 Epub
DOI: 10.14218/ERHM.2022.00104

Review Article

Prevalence, Economic Burden, and Neurophenotype of Asthma

Cai Chen[1*], Guoqing Zhao[1,2], Danyang Lv[1], Jianpeng An[3], Chongxuan Tian[2], Yuhang Zhao[2], Ningling Zhang[1], Xingwei Wang[1], Xikun Zhang[1] and Fulai Peng[1*]

[1]*Shandong Institute of Advanced Technology, Chinese Academy of Sciences, Jinan, China;* [2]*Biomedical Engineering Institute, School of Control Science and Engineering, Shandong University, Jinan, China;* [3]*Orthopedics Department of Integrated Traditional Chinese and Western Medicine, Air Force Medical Center, PLA, Beijing, China*

Received: September 20, 2022 | **Revised:** October 06, 2022 | **Accepted:** November 07, 2022 | **Published:** December 13, 2022

Abstract

Asthma has become a serious global public health issue affecting approximately 14% of children worldwide. Asthma patients often accompany various mental disorders, such as depression, anxiety, and panic attacks, which could aggravate asthma symptoms. It can be summarized that in addition to pathological cellular and molecular immune processes, asthma also has a neural phenotype. The first part of this review summarizes the prevalence and economic burden of asthma in recent years. Then, the neurophenotype of asthma is described in terms of brain structural changes, molecular expression, and prevalence. Our literature search shows that the frontal lobe plays an essential role in asthma-related neurophenotypes. Finally, we assume that an electroencephalogram signal could be one of the directions of asthma neurophenotype diagnosis.

Introduction

Asthma is a heterogeneous disease characterized by chronic airway inflammation and influenced by environmental, neurological, and psychological factors. Chronic inflammation is associated with airway hyperresponsiveness often with widespread and variable reversible expiratory airflow limitation, thus resulting in recurrent wheezing, shortness of breath, chest tightness, and coughing.[1] Cyclic asthma symptoms often lead to insomnia, daytime fatigue, reduced activity, and disruption to school and work.[2] We summarized the prevalence, economic burden, neurophenotype, and future direction of asthma to emphasize its importance in the population. Relevant studies and publications were identified using the search terms asthma, prevalence, economic burden, and brain in the literature databases of MEDLINE, Web of Science, PubMed, and Google Scholar.

Keywords: Asthma; Neurophenotype; Electroencephalogram signal; Economic burden; Brain structure.

Abbreviations: EEG, electroencephalogram; fMRI, functional magnetic resonance imaging; HPAA, hypothalamic-pituitary-adrenal axis; OR, odd ratio; OSA, obstructive pulmonary disease; REP, respiratory associated evoked potentials; Th2, type 2 helper T cells.

[*]**Correspondence to**: Cai Chen, Shandong Institute of Advanced Technology, Chinese Academy of Sciences, Jinan, 250000, China. ORCID: https://orcid.org/0000-0001-5381-2457. Tel: +86-15905415351, Fax: 053180986098. E-mail: 1649011989@qq.com; Fulai Peng, Shandong Institute of Advanced Technology, Chinese Academy of Sciences, Jinan, 250000, China. Tel: +86-13355317860, Fax: 053180986098, ORCID: https://orcid.org/0000-0001-7591-4331. E-mail: fl.peng@sdiat.ac.cn

How to cite this article: Chen C, Zhao G, Lv D, An J, Tian C, Zhao Y, *et al*. Prevalence, Economic Burden, and Neurophenotype of Asthma. *Explor Res Hypothesis Med* 2022;000(000):000–000. doi: 10.14218/ERHM.2022.00104.

Prevalence of asthma

Asthma is one of the world's fastest-growing diseases affecting roughly one-third of the global population. It is estimated that more than 339 million people worldwide suffered from asthma in 2016,[3] of which mainland China accounted for 10%.[4,5] Asthma affects approximately 14% of children worldwide, and approximately 2.5 million patients die each year from severe exacerbations.[6]

Table 1 summarizes the prevalence of asthma in various countries and regions. The prevalence of asthma in the United States increased by 15.1% in 2010, with children aged 0–17 years accounting for 27.2%.[7] Bloom CI *et al* conducted a population-based cohort 2006–2016 based on United Kingdom electronic healthcare records and found overall asthma prevalence was 6.5% in 2016 (7.2% in 2006).[8] According to the 2001–2016 National Health and Nutrition Examination Survey, 9.9% of women aged 18–44 years and 10.9% of pregnant women suffered from asthma with the highest prevalence in 2015–2016 (12.0%) and the lowest in 2003–2004 (8.6%).[9] According to the Singapore National Health Survey, 10.5% of adults aged 18–69 years have asthma at some point in their lives.[10] According to the 2012 Canadian Aboriginal Survey, the overall prevalence of lifetime asthma diagnosis was 16.0%.[11] A study of 50,991 people in China found that the overall prevalence of asthma was 4.2%, only 28.8% of asthma patients had been diagnosed, and 15.5% of asthma patients had visited the emergency room at least once.[12] Likewise, according to the results of three large-scale asthma surveys in China, the prevalence of asthma in

Table 1. Asthma prevalence rate in different countries

	Author	Country	Time horizon	Population	Rate (%)
1	Akinbami *et al*[7]	United States	2001–2010	25.7 million	12
2	Bloom *et al*[8]	United Kingdom	2006–2016	–	6.5
3	Chuchalin *et al*[9]	Russia	2010–2011	7,164	25.7
4	Karunanayake *et al*[10]	Canada	2012	24,803	16
5	Marques *et al*[11]	Brazil	2012–2015	109,104	16
6	Huang *et al*[12]	China	2012–2015	57 ,779	4.2
7	Veettil *et al*[15]	Qatar	2016–2017	54,704	6.1
8	Sisay *et al*[16]	Ethiopia	2018	257	29.6
9	Raherison-Semjen *et al*[17]	France	2018	19,676	12.8
10	Molnár *et al*[18]	Hungary	2018–2019	3,836	12.6

childhood in China increased by nearly 50% every decade.[13] Currently, there is a gap between the level of asthma treatment in China and the level of treatment recommended by the Global Asthma Prevention Initiative. In Beijing, China, only 34.9% of asthma patients were under control.[14] In 2016–2017, a cross-sectional study in Qatar involving 54,704 children aged 5–12 years revealed a 6.1% prevalence of asthma.[15] Sisay *et al* found prevalence of bronchial asthma among adult patients was 29.6% based on hospital based cross-sectional study invloved in 257 participants.[16] Raherison-Semjen pointed that the prevalence of asthma in France has remained stable since 2006, and prevalence of lifetime asthma was 12.8% in 2018.[17] According to a questionnaire-based study conducted in Hungary, the current prevalence of wheezing and physician-diagnosed asthma are 9.5% and 6.3%, respectively.[18]

Economic burden of asthma

Asthma imposes a heavy financial burden on society and the healthcare system (Table 2).[19–24] In the United States, the total cost of asthma treatment was US $81.9 billion in 2013, and the annual cost of asthma per person was US $3,266.[19] According to a Japanese study, the cost of treating severe asthma is approximately double that of mild/moderate asthma with the average cost of hospitalized asthma patients reaching US $4,073.[20]

In addition, Lee *et al* estimated the prevalence of asthma in South Korea at 3.7% using a national asthma sample analysis in 2014, and the total cost of asthma was US $645.9 million with direct and indirect costs of US $553.9 million and US $92 million, respectively.[25] Finkelstein *et al* also found the annual economic burden of asthma in Singapore to be US $1.5 billion, 79 % of which was due to lost productivity, and the total annual cost of asthma in adults was estimated at US $1.25 billion.[26] In 2015, the per capita direct medical expenses of children with asthma in China were approximately US $75, accounting for 1.06% of China's per capita gross domestic product, or US $7,020.[21] According to a report published in Lung India, the annual cost of treatment per asthma patient was US $240 resulting in a high cost of US $556 billion based on a conservative estimate of a 2% prevalence in India.[22] Bavbek *et al* discovered that total direct medical costs per patient in Turkey were US $4,369.76 per year with medication/equipment (52.4%) being the main cost driver for severe asthma management, followed by hospitalization/intervention (26.4%), and comorbidities (15.2%).[23] Moreover, the total annual cost of pediatric asthma in Iran was US $367 with medication being the most expensive (69%).[24] A study of 20 institutions in Spain by Moreno *et al* found that the average direct cost, the cost per exacerbation, and average total annual cost was US $7,472, US $1,410, and US $8,554, respectively.[27]

Over the last few decades, the prevalence, morbidity, and mortality rates of childhood asthma have increased significantly worldwide. Although asthma is the most common chronic disease in children, underdiagnosis and undertreatment persist. Asthma prevalence varies widely around the world (Tables 1 and 2). Additionally, it varies by several orders of magnitude between countries. Asthma hospitalizations could increase due to increased asthma severity, poor disease management, and poverty. The economic burden of asthma is also high in developed countries, which consumes 1–2% of the healthcare budgets for asthma.

The brain is sensitive to hypoxia, and the lack of hypoxia caused by repeated asthma attacks could impair brain function, consequently leading to brain damage. Asthma patients have often been accompanied by various mental disorders, such as depres-

Table 2. Average annual cost of asthma

	Author	Country	Year	Cost (USD)
1	Nurmagambetov *et al*[19]	United States	2013	3,266
2	To *et al*[20]	Japan	2014–2018	4,073
3	Wu *et al*[21]	China	2015	75
4	Koul *et al*[22]	India	2018	556
5	Bavbek *et al*[23]	Turkey	2016	4,369
6	Sharifi *et al*[24]	Iran	2010–2012	367

Table 3. Abnormal areas for asthma

Authors	Tools	Abnormal areas for asthma
Huang *et al*[32]	MRI	Cerebellum, frontal lobe, temporal lobe, and occipital lobe.
Gao *et al*[33]	DIT	Bilateral frontal gyrus, right temporal and parietal cortices, and limbic regions.
Ritz *et al*[34]	fMRI	Dorsal anterior cingulate cortex and frontal lobe.
Li *et al*[35]	fMRI	Superior frontal gyrus, occipital lobes, and inferior temporal gyrus.
Carlson *et al*[36]	MRI	Hippocampal volume.

DIT, diffusion tensor imaging; fMRI, functional magnetic resonance imaging; MRI, magnetic resonance imaging.

sion, anxiety, and panic attacks, which could aggravate asthma symptoms. Airway inflammation in asthma patients could be transmitted to the central nervous system resulting in the secretion of mediators in the airway nerves, which could play critical roles in neuroimmune interactions and worsen airway inflammation.[28] Furthermore, psychological disorders, such as depression and anxiety, could exacerbate asthmatic bronchoconstriction by altering the function of the brain's regions involved in respiratory control.[29] These observations thus suggest that nerves could be involved in the modulation of asthmatic airway events, as the brain must transmit stress- and mood-related stimuli from the environment, hence signaling inflammatory mechanisms in the lungs and exacerbating the underlying disease.

Asthma neurophenotype

Therefore, it could be concluded that the neuron phenotype of asthma involves structural and functional changes in the brain's regions, pathological cellular, and molecular immune processes, as well as also has external manifestations of psychological or neurological disease.[30] Neurophenotype refers to the pattern of symptom expression caused by the interaction between the immune response that regulates inflammation and the neural process. It should be pointed out that the neurophenotype of asthma refers to neural processes, especially those related to mood, that regulate airway inflammation and clinical expression of the severity of asthma.[31] Although relevant scholars have recognized the neurophenotype of asthma, current research on the pathophysiology of asthma and the manifestation of asthma symptoms has almost exclusively focused on the lung. This paper would describe the neural phenotype of asthma in terms of brain structural changes, molecular expression, and epidemiology.

Brain structural changes

Neuroimaging and clinical studies have revealed that the neurophenotypes of asthma patients include structural and functional changes (Table 3). According to Rosenkranz *et al*, the neurophenotype of asthma could be identified by the neural responses of the brain's circuits known to be involved in emotional information processing.[32] People with higher anterior insula activation had higher lung inflammatory signals in response to asthma-related psychological stimuli. Huang *et al* also conducted research based on functional magnetic resonance imaging (fMRI) and found the regional homogeneity values of the left posterior cerebellar lobe and left upper frontal gyrus among healthy people were significantly higher in asthmatic patients.[32] In contrast, the values of the right middle temporal gyrus and right inferior temporal gyrus were lower. Likewise, Gao *et al* discovered that asthma patients had abnormal structural connectivity in the bilateral frontal gyrus, right temporal, parietal cortices, and limbic regions, which hinted those changes in the function of the emotion-related brain regions in asthma patients.[33] Ritz *et al* found that asthma patients with high airway inflammation had reduced activation in many cortical and subcortical regions associated with emotional processing and respiratory control.[34] Li *et al* discovered regional abnormalities in the left angular gyrus, right anterior cuneus, and inferior temporal gyrus within the default mode network based on a low-frequency fluctuation amplitude, degree centrality, and functional connectivity.[35] A study involving 1,287 adults found that people with asthma had a significantly smaller hippocampal volume than people without the condition.[36]

Table 3 summarizes the abnormal areas for asthmatic patients. We could find that the frontal lobe played a vital role in asthma-related neurophenotypes. Frontal lobe development is essential for acquiring, executing, and controlling a wide range of functions from basic motor response to complex decision-making. Disruptions in the fronto-subcortical circuitry that governs motivated behavior appear to contribute to a variety of developmental disorders, including attention-deficit/hyperactivity disorder and anxiety, as well as vulnerability to psychopathology.

Molecular expression

Rosenkranz *et al* found that emotional responses were associated with significant changes in the fMRI signals in the anterior cingulate cortex and insula, and emotional responses were negatively correlated with lung function in asthma patients.[37] Furthermore, the induction of asthma-related psychological stimuli in the anterior insula increased the response to the inflammatory signals in the lungs, which correlated with disease severity. In chronic stress asthma patients, acute psychological stress exacerbated airway inflammation, which was associated with signal crossing interactions between the anterior cingulate cortex and the insula in response to psychological stress. During psychosocial stress induction, activation of the medial and anterior cingulate cortex was associated with increased expression of interleukin 23 subunit alpha and interleukin-1 receptor type 1 mRNA in the sputum cells of asthmatics after stress.[38] Moreover, Caulfield *et al* found that brain stem serotonin transporter mRNA expression decreased by approximately 30% in adult mice that experienced an asthma attack during adolescence, while the hippocampal serotonin receptor 1A and corticotropin-releasing hormone receptor 1 expressions increased by approximately 50%.[39]

It is known that the occurrence of asthma is closely related to the peripheral immune and inflammatory pathway. Airway inflammation is one of the important clinical features for asthma. Under the interaction of autoimmunity and adaptive immunity, external antigen stimulation causes eosinophilia, type 2 helper T cells (Th2) to migrate to the airway epithelium and subcutaneous mucosa, and

release interleukin (leukin), which leads to subepithelial fibrosis, bronchial remodeling, and airway hyperresponsiveness. In addition, some studies have confirmed that depression is an inflammatory disease.[40] The level of peripheral immune inflammation in depressed patients is significantly higher than that in healthy people,[40] including the increased expression of proinflammatory cytokines and their receptors.[41] Such a disturbed level of peripheral immune inflammation could directly affect the structure and function of the brain. Notably, stress is a common risk factor for asthma and depression. For asthma, stress does not simply suppress the immune system of asthmatic patients, but breaks the balance of the Th1/Th2 cytokines, thus making them shift to the Th2 type.[42] For depression, stress (especially early life events and lack of interpersonal interaction) could enhance the inflammatory response. The high comorbidity rate of asthma and depression highly would suggest that there could be some common pathogenesis between them. The relationship between asthma and its neurophenotype might be explained by the hypothalamic-pituitary-adrenal axis (HPAA). For example, some researchers found that mothers who experienced perinatal stress had a significantly increased risk of asthma in their offspring.[43] Hence, the HPAA would be an important component of the stress system, and the release of proinflammatory cytokines during asthma inflammation could cause the activation of the stress system. In addition, stress and negative emotions increase inflammatory mediators. Depression related studies also suggested that depression was associated with the HPAA dysfunction, and the levels of stress hormones, such as cortisol, were significantly increased in patients with depression. These findings together suggested that inflammatory cytokines and HPAA activity were promising biomarkers for asthma with depression.

Epidemiology

A recent meta-analysis showed that anxiety disorders were prevalent in nearly 23% of asthmatic adolescents compared with a prevalence of 7–8% in the general youth population.[44] Adolescents with asthma also had higher morbidity rates and were more likely to suffer from a major depressive disorder than the control. Additionally, Scott *et al* found that age- and sex-adjusted pooled estimates of the prevalence of mental disorders were 1.6 for asthma, 1.5 for anxiety disorders, and 1.7 for alcohol use disorders compared with patients without asthma.[45] A study evaluating the relationship between asthma and anxiety in Japanese elementary school students showed that the multifactor PR for anxiety in asthmatic boys was 1.56 compared to non-asthmatic boys.[46] This association was more pronounced in older boys, where PR was 1.32 for younger boys, and 1.87 for older boys. A multi-ethnic adult survey also showed an association between asthma and mental disorders, particularly anxiety disorders (odd ratio (OR) = 2.7), depression (OR = 1.6), and bipolar disorder (OR = 2.1).[47] Likewise, a study involving 1,358 adults with asthma and non-asthmatic cross-sectional studies showed that severe asthma increased the odds of depression by 53%. In contrast, mild to moderate asthma was associated with an 11-fold increased likelihood of suicidal ideation.[48] Adolescents with asthma had a 22.7% prevalence of anxiety disorders and higher levels of anxiety symptoms than adolescents without asthma.[49]

Future direction

In summary, the incidence of asthma is becoming more and more serious, and the population base of asthma patients is large and growing rapidly. Consequently, the severe situation of the heavy economic burden and low degree of disease control would affect the living standards and mental health of the patients. Asthma hypoxia might also cause brain damage, initiate mental disorders, and induce abnormal brain electrical activity. Electroencephalogram (EEG) signals could capture the abnormal areas of the brain and quantify the changes from the perspective of bioelectrical signals.

An EEG is an essential bioelectrical signal of the human body, which contains a large amount of physiological information about the body. It can be obtained by collecting and recording potential changes in the superficial skin of the head (Fig. 1). Brain signals change with the cognitive processes of the brain, which could respond quickly to external stimuli and provide accurate human data. Furthermore, EEG signals contain a large amount of physiological information and disease information, which could provide a basis for the diagnosis or effective treatment for certain brain diseases.[50]

However, to date, only a few studies on EEG signals related to asthma have been reported. The respiratory associated evoked potentials (REP) study showed that six out of 11 patients with severe asthma were missing P1 in early REP.[51] Nicot *et al* found less REP component in children with asthma than in healthy subjects.[52] Asthma patients exhibited significant enhancement of power and functional connectivity in both the default mode network and the resting salient state network. Several studies have also shown that EEG signals could help to analyze other respiratory-related diseases.[53] EEG signals have been used for sleep monitoring, especially for lung diseases, such as chronic obstructive pulmonary disease (OSA). Moreover, one study has shown that OSA patients with hypoventilation had changes in awake EEG with increased EEG power, increased microstates C, and decreased microstates D.[54] A systematic study of spindle oscillations in patients with sleep disorders showed lower spindle wave density/spindle frequency activity and slower mean spindle frequency than controls. Compared with other brain examinations, EEG signals are cheaper, easier to operate than magnetic resonance imaging and positron radiography, and non-invasive real-time access to EEG signals. The authors think that EEG signals could be used to study the neurophenotype of asthmatic patients with better performance.

Conclusions

Asthma is one of the world's fastest-growing diseases affecting roughly one-third of the global population. This paper reviewed the prevalence, economic burden, and neurophenotype of asthma. We found the frontal lobe plays an essential role in asthma-related neurophenotypes. Additionally, an EEG could be used as one of the tools to analyze the neurophenotype of asthma.

Acknowledgments

The authors would like to thank all the reviewers who participated in the review.

Funding

The research was supported by the project of the Natural Science Foundation of Shandong Province (ZR2020QF024; ZR2021QH290), Jinan 20 Universities (2019GXRC040), Jinan 5150 Program for Talents Introduction, Major Basic Research Project of Shandong Natural Science Foundation (ZR2021ZD40), Key Research and Development Plan of Shandong Province (2021CXGC011304), and Shandong Institute of Advanced Technology, Chinese Academy of Sciences (YJZX003, YQCX20220106).

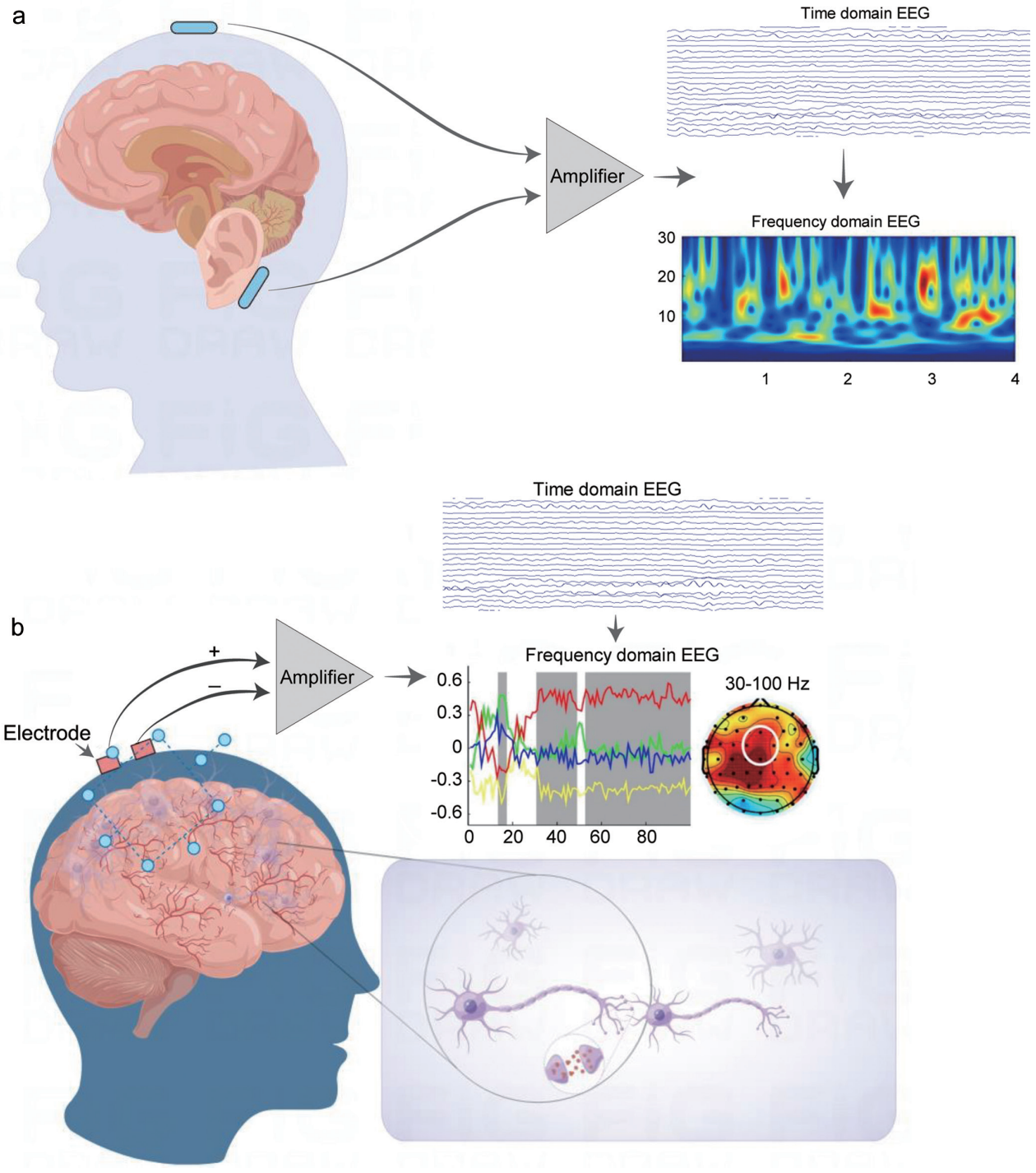

Fig. 1. Electroencephalogram signal acquisition. (a) unipolar lead; (b) bipolar lead.

Conflict of interest

The authors declare that they have no conflicts of interest.

Author contributions

Guarantor of the integrity of the entire study (CC); study concept and design, and manuscript editing (CC and FLP); literature research (GQZ, XWW, XKZ, and ZYW); data acquisition (YS, JPA, and CC); data analysis (CC, FLP, and DYL); manuscript preparation (CC, FLP, and ZLZ); manuscript revision/review (CC). All authors participated in this study and consented to publish this article in the Journal. The contribution list is shown in the following form.

Ethical Statement

This study was approved by the Ethics Committee of the Shandong Institute of Advanced Technology, Chinese Academy of Sciences. All procedures performed in the studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Consent to Publish

All authors consent to publish this article.

Reference

[1] Wang R, Murray CS, Fowler SJ, Simpson A, Durrington HJ. Asthma diagnosis: into the fourth dimension. Thorax 2021;76(6):624–631. doi:10.1136/thoraxjnl-2020-216421, PMID:33504564.

[2] Al Kindi Z, McCabe C, Mc Cann M. School Nurses' Available Education to Manage Children with Asthma at Schools: A Scoping Review. J Pediatr Nurs 2021;60:46–57. doi:10.1016/j.pedn.2021.01.027, PMID:33610087.

[3] GBD 2016 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet 2017;390(10100):1211–1259. doi:10.1016/S0140-6736(17)32154-2, PMID:28919117.

[4] Chen ZH, Wang PL, Shen HH. Asthma research in China: a five-year review. Respirology 2013;18(Suppl 3):10–9. doi:10.1111/resp.12196, PMID:24188199.

[5] World Health Organization. WHO methods and data sources for country-level causes of death 2000-2016. Available from: https://terrance.who.int/mediacentre/data/ghe/GlobalCOD_method_2000_2016.pdf. Accessed November 29, 2022.

[6] Rehman A, Amin F, Sadeeqa S. Prevalence of asthma and its management: A review. J Pak Med Assoc 2018;68(12):1823–1827. PMID:30504949.

[7] Akinbami LJ, Moorman JE, Bailey C, Zahran HS, King M, Johnson CA, *et al*. Trends in asthma prevalence, health care use, and mortality in the United States, 2001-2010. NCHS Data Brief 2012;(94):1–8. PMID:22617340.

[8] Bloom CI, Saglani S, Feary J, Jarvis D, Quint JK. Changing prevalence of current asthma and inhaled corticosteroid treatment in the UK: population-based cohort 2006-2016. Eur Respir J 2019;53(4):1802130. doi:10.1183/13993003.02130-2018, PMID:30765507.

[9] Chuchalin AG, Khaltaev N, Antonov NS, Galkin DV, Manakov LG, Antonini P, *et al*. Chronic respiratory diseases and risk factors in 12 regions of the Russian Federation. Int J Chron Obstruct Pulmon Dis 2014;9:963–974. doi:10.2147/copd.s67283, PMID:25246783.

[10] Karunanayake CP, Amin K, Abonyi S, Dosman JA, Pahwa P. Prevalence and determinants of asthma among aboriginal adolescents in Canada. J Asthma 2020;57(1):40–46. doi:10.1080/02770903.2018.1541354, PMID:30628527.

[11] Marques GÁ, Wendt A, Wehrmeister FC. Temporal evolution of and factors associated with asthma and wheezing in schoolchildren in Brazil. J Bras Pneumol 2019;45(3):e20180138. doi:10.1590/1806-3713/e20180138, PMID:31271601.

[12] Huang K, Yang T, Xu J, Yang L, Zhao J, Zhang X, *et al*. Prevalence, risk factors, and management of asthma in China: a national cross-sectional study. Lancet 2019;394(10196):407–418. doi:10.1016/S0140-6736(19)31147-X, PMID:31230828.

[13] Li X, Song P, Zhu Y, Lei H, Chan KY, Campbell H, *et al*. The disease burden of childhood asthma in China: a systematic review and meta-analysis. J Glob Health 2020;10(1):010801. doi:10.7189/jogh.10.01081, PMID:32257166.

[14] Wang WY, Lin JT, Su N, Liu GL, Feng XK, He QY, *et al*. Survey on the prevalence rate of bronchial asthma in Beijing area among the residents aged over 14 years from 2010 to 2011. Zhonghua Yi Xue Za Zhi 2013;93(18):1383–1387. PMID:24025502.

[15] Veettil ST, Alnuaimi ASA. Epidemiology and utilization of primary health care services in Qatar by asthmatic children 5-12 years old: secondary data analysis 2016-2017. Asthma Res Pract 2019;5:3. doi:10.1186/s40733-019-0050-4, PMID:31452904.

[16] Shine S, Muhamud S, Demelash A. Prevalence and associated factors of bronchial asthma among adult patients in Debre Berhan Referral Hospital, Ethiopia 2018: a cross-sectional study. BMC Res Notes 2019;12(1):608. doi:10.1186/s13104-019-4670-9, PMID:31547859.

[17] Raherison-Semjen C, Izadifar A, Russier M, Rolland C, Aubert JP, Touboul C, *et al*. Self-reported asthma prevalence and management in adults in France in 2018: ASTHMAPOP survey. Respir Med Res 2021;80:100864. doi:10.1016/j.resmer.2021.100864, PMID:34773824.

[18] Molnár D, Gálffy G, Horváth A, Tomisa G, Katona G, Hirschberg A, *et al*. Prevalence of Asthma and Its Associating Environmental Factors among 6-12-Year-Old Schoolchildren in a Metropolitan Environment-A Cross-Sectional, Questionnaire-Based Study. Int J Environ Res Public Health 2021;18(24):13403. doi:10.3390/ijerph182413403, PMID:34949011.

[19] Nurmagambetov T, Kuwahara R, Garbe P. The Economic Burden of Asthma in the United States, 2008-2013. Ann Am Thorac Soc 2018;15(3):348–356. doi:10.1513/AnnalsATS.201703-259OC, PMID:29323930.

[20] To Y, Taguchi Y, Shimazaki T, Arima K, Yu E, Sven D, *et al*. Real-world treatment and health care resource use among severe asthma patients in Japan. Respir Investig 2021;59(4):464–477. doi:10.1016/j.resinv.2021.02.010, PMID:33789828.

[21] Wu P, Xu B, Shen A, He Z, Zhang CJP, Ming WK, *et al*. The economic burden of medical treatment of children with asthma in China. BMC Pediatr 2020;20(1):386. doi:10.1186/s12887-020-02268-6, PMID:32811470.

[22] Koul PA, Dhar R. Economic burden of asthma in India. Lung India 2018;35(4):281–283. doi:10.4103/lungindia.lungindia_220_18, PMID:29970764.

[23] Bavbek S, Malhan S, Mungan D, Misirligil Z, Erdinc M, Gemicioglu B, *et al*. Economic burden of severe asthma in Turkey: a cost of illness study from payer perspective. Eur Ann Allergy Clin Immunol 2021;53(3):128–137. doi:10.23822/EurAnnACI.1764-1489.149, PMID:32372589.

[24] Sharifi L, Dashti R, Pourpak Z, Fazlollahi MR, Movahedi M, Chavoshzadeh Z, *et al*. Economic Burden of Pediatric Asthma: Annual Cost of Disease in Iran. Iran J Public Health 2018;47(2):256–263. PMID:29445636.

[25] Lee EW, Kim HS, Kim W, Nam JY, Park JH. Socioeconomic Burden of Disease Due to Asthma in South Korea. Asia Pac J Public Health 2020;32(4):188–193. doi:10.1177/1010539520920524, PMID:32468824.

[26] Finkelstein EA, Lau E, Doble B, Ong B, Koh MS. Economic burden of asthma in Singapore. BMJ Open Respir Res 2021;8(1):e000654. doi:10.1136/bmjresp-2020-000654, PMID:33737309.

[27] Melero Moreno C, Quirce S, Huerta A, Uría E, Cuesta M. Economic impact of severe asthma in Spain: multicentre observational longitudinal study. J Asthma 2019;56(8):861–871. doi:10.1080/02770903.2018.1499035, PMID:30003827.

[28] Kaczyńska K, Zając D, Wojciechowski P, Jampolska M. Regulatory Peptides in Asthma. Int J Mol Sci 2021;22(24):13656. doi:10.3390/ijms222413656, PMID:34948451.

[29] Satia I, Nagashima A, Usmani OS. Exploring the role of nerves in asthma; insights from the study of cough. Biochem Pharmacol 2020;179:113901. doi:10.1016/j.bcp.2020.113901, PMID:32156662.

[30] Satia I, O'Byrne PM. Identifying a Neurophenotype in Severe Asthma. Am J Respir Crit Care Med 2020;201(9):1024–1025. doi:10.1164/rccm.202002-0228ED, PMID:32049547.

[31] Rosenkranz MA, Busse WW, Sheridan JF, Crisafi GM, Davidson RJ. Are there neurophenotypes for asthma? Functional brain imaging of the interaction between emotion and inflammation in asthma. PLoS One 2012;7(8):e40921. doi:10.1371/journal.pone.0040921, PMID:22870208.

[32] Huang H, Li SY, Shi L, Huang X, Wang J. Altered spontaneous brain activity in patients with asthma: a resting-state functional MRI study us-

ing regional homogeneity analysis. Neuroreport 2021;32(18):1403–1407. doi:10.1097/WNR.0000000000001736, PMID:34743166.
[33] Gao X, Xiao Y, Lv P, Zhang W, Gong Y, Wang T, *et al*. Altered brain network integrity in patients with asthma: A structural connectomic diffusion tensor imaging study. Respir Physiol Neurobiol 2019;266:89–94. doi:10.1016/j.resp.2019.05.004, PMID:31085322.
[34] Ritz T, Kroll JL, Patel SV, Chen JR, Yezhuvath US, Aslan S, *et al*. Central nervous system signatures of affect in asthma: associations with emotion-induced bronchoconstriction, airway inflammation, and asthma control. J Appl Physiol (1985) 2019;126(6):1725–1736. doi:10.1152/japplphysiol.01018.2018, PMID:30920889.
[35] Li S, Lv P, He M, Zhang W, Liu J, Gong Y, *et al*. Cerebral regional and network characteristics in asthma patients: a resting-state fMRI study. Front Med 2020;14(6):792–801. doi:10.1007/s11684-020-0745-1, PMID:32270434.
[36] Carlson SM, Kim J, Khan DA, King K, Lucarelli RT, McColl R, *et al*. Hippocampal volume in patients with asthma: Results from the Dallas Heart Study. J Asthma 2017;54(1):9–16. doi:10.1080/02770903.2016.1186174, PMID:27187077.
[37] Rosenkranz MA, Busse WW, Johnstone T, Swenson CA, Crisafi GM, Jackson MM, *et al*. Neural circuitry underlying the interaction between emotion and asthma symptom exacerbation. Proc Natl Acad Sci U S A 2005;102(37):13319–13324. doi:10.1073/pnas.0504365102, PMID:16141324.
[38] Rosenkranz MA, Esnault S, Christian BT, Crisafi G, Gresham LK, Higgins AT, *et al*. Mind-body interactions in the regulation of airway inflammation in asthma: A PET study of acute and chronic stress. Brain Behav Immun 2016;58:18–30. doi:10.1016/j.bbi.2016.03.024, PMID:27039241.
[39] Caulfield JI, Caruso MJ, Michael KC, Bourne RA, Chirichella NR, Klein LC, *et al*. Peri-adolescent asthma symptoms cause adult anxiety-related behavior and neurobiological processes in mice. Behav Brain Res 2017;326:244–255. doi:10.1016/j.bbr.2017.02.046, PMID:28284954.
[40] Köhler CA, Freitas TH, Maes M, de Andrade NQ, Liu CS, Fernandes BS, *et al*. Peripheral cytokine and chemokine alterations in depression: a meta-analysis of 82 studies. Acta Psychiatr Scand 2017;135(5):373–387. doi:10.1111/acps.12698, PMID:28122130.
[41] Miller AH, Raison CL. The role of inflammation in depression: from evolutionary imperative to modern treatment target. Nat Rev Immunol 2016;16(1):22–34. doi:10.1038/nri.2015.5, PMID:26711676.
[42] Marshall GD Jr, Agarwal SK. Stress, immune regulation, and immunity: applications for asthma. Allergy Asthma Proc 2000;21(4):241–246. doi:10.2500/108854100778248917, PMID:10951892.
[43] Leonard BE. Pain, Depression and Inflammation: Are Interconnected Causative Factors Involved? Mod Trends Pharmacopsychiatry 2015;30:22–35. doi:10.1159/000435930, PMID:26437055.
[44] Ghandour RM, Sherman LJ, Vladutiu CJ, Ali MM, Lynch SE, Bitsko RH, *et al*. Prevalence and Treatment of Depression, Anxiety, and Conduct Problems in US Children. J Pediatr 2019;206:256–267.e3. doi:10.1016/j.jpeds.2018.09.021, PMID:30322701.
[45] Scott KM, Von Korff M, Ormel J, Zhang MY, Bruffaerts R, Alonso J, *et al*. Mental disorders among adults with asthma: results from the World Mental Health Survey. Gen Hosp Psychiatry 2007;29(2):123–133. doi:10.1016/j.genhosppsych.2006.12.006, PMID:17336661.
[46] Kimura M, Ikeda A, Suzuki Y, Maruyama K, Wada H, Tanigawa T. The association between asthma and anxiety in elementary school students in Japan. Pediatr Pulmonol 2020;55(10):2603–2609. doi:10.1002/ppul.24986, PMID:32720730.
[47] Jeyagurunathan A, Abdin E, Shafie S, Sambasivam R, Yunjue Z, Chua BY, *et al*. Asthma Prevalence and its Risk Factors Among a Multi-Ethnic Adult Population. Yale J Biol Med 2021;94(3):417–427. PMID:34602881.
[48] Vázquez VS, de Lima VB, de Mello LM, Duarte DCB, Saback de Oliveira TD, Cruz ÁA. Depression, suicidal motivation and suicidal ideation among individuals with asthma: a cross-sectional study. J Thorac Dis 2021;13(10):6082–6094. doi:10.21037/jtd-20-3197, PMID:34795954.
[49] Dudeney J, Sharpe L, Jaffe A, Jones EB, Hunt C. Anxiety in youth with asthma: A meta-analysis. Pediatr Pulmonol 2017;52(9):1121–1129. doi:10.1002/ppul.23689, PMID:28749088.
[50] Han C, Peng F, Chen C, Li W, Zhang X, Wang X, *et al*. Research progress of epileptic seizure predictions based on electroencephalogram signals. Sheng Wu Yi Xue Gong Cheng Xue Za Zhi 2021;38(6):1193–1202. doi:10.7507/1001-5515.202105052, PMID:34970903.
[51] Davenport PW, Cruz M, Stecenko AA, Kifle Y. Respiratory-related evoked potentials in children with life-threatening asthma. Am J Respir Crit Care Med 2000;161(6):1830–1835. doi:10.1164/ajrccm.161.6.9903077, PMID:10852753.
[52] Nicot F, Renault F, Clément A, Fauroux B. Respiratory-related evoked potentials in children with asthma. Neurophysiol Clin 2007;37(1):29–33. doi:10.1016/j.neucli.2007.01.003, PMID:17418355.
[53] Gholami-Mahtaj L, Salimi M, Nazari M, Tabasi F, Bamdad S, Dehdar K, *et al*. Asthma induces psychiatric impairments in association with default mode and salience networks alteration: A resting-state EEG study. Respir Physiol Neurobiol 2022;300:103870. doi:10.1016/j.resp.2022.103870, PMID:35176500.
[54] Xiong X, Ren Y, Gao S, Luo J, Liao J, Wang C, *et al*. EEG microstate in obstructive sleep apnea patients. Sci Rep 2021;11(1):17178. doi:10.1038/s41598-021-95749-2, PMID:34433839.