Spontaneous pneumothorax risk factor mapping: a Mendelian randomization study

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Abstract. Objective: To investigate the causal relationship between risk factors and spontaneous pneumothorax using Mendelian randomization. Methods: Risk factors for spontaneous pneumothorax were identified through searches of English and Chinese databases. Single nucleotide polymorphism information was extracted from the GWAS database, with risk factor as exposure and spontaneous pneumothorax as outcome, and five methods, namely, inverse variance weighting, MR-Egger, weighted median, simple model and weighted model, were used to evaluate the causality between risk factors and spontaneous pneumothorax. Heterogeneity and leave-one-out tests were used for sensitivity analysis to evaluate the robustness of the causal relationship. Results: The search yielded 117 risk factors, and 50 risk factors for which genetic data were available were included. Height, COVID, lymphocytes, standing tall, snoring, exertion lung volume, squamous lung cancer, first second expiratory volume with exertion, and asthma were positively associated with SP, and hip circumference and exertion lung volume were negatively associated with SP. Chronic obstructive pulmonary disease and diaphragmatic hernia may be associated with SP. Conclusion: This study identified significant causal relationship between lymphocyte count, standing tall, asthma and spontaneous pneumothorax from genetic point of view, and provided basis for its prevention and treatment.

1. Introduction

Spontaneous Pneumothorax (SP) is a lung disease in which a rupture of lung tissue and pleura allows air to enter the pleural cavity without an obvious external cause[1]. It is categorized into Primary Spontaneous Pneumothorax (PSP) and Secondary Spontaneous Pneumothorax (SSP), and the cause of Primary Spontaneous Pneumothorax is still unknown[2]. Some studies have shown that cigarette smoking, marijuana use[3, 4], changes in atmospheric pressure, air pollution[5, 6], high lean body mass, low body mass index (BMI), are closely associated with SP[7]. Secondary spontaneous pneumothorax is often associated with underlying lung diseases, commonly chronic obstructive pulmonary disease (COPD)[8], cystic pulmonary fibrosis (CPF)[9], lung tumors, and lung infections[10]. SP recurs in 17%-54% of patients within 1 year of successful conservative treatment[11, 12]. Therefore, identifying patients with SP who have an occult underlying disease and definitively treating the disease, such as with surgery, is the key to improving the success rate of treatment. Traditional observational studies have not been able to determine whether the association between SP and certain risk factors and comorbidities is causal due to susceptibility to confounding. Mendelian randomization (MR) is a research method for making reliable causal inferences by using genetic variation as a tool for exposure[13]. Because genetic variants are randomly combined at the time of conception, they are independent of environmental factors and are not affected by the onset and progression of disease. The two-sample MR approach utilizes different combined genetic sources of exposure and outcome to infer exposure-outcome causality with better statistical power and less confounding bias[14]. There are no MR studies of SP. In this study, we assessed the causal associations between retrieved risk factors and SP using MR using Genome-Wide Association Study Aggregate (GWAS) data.

2. Methods

2.1. Literature search

We searched PubMed, CNKI, Wanfang, and CQVIP databases built to October 2023 for a total of 2644 research papers on risk factors for spontaneous pneumothorax. The Chinese search terms were (subject: spontaneous pneumothorax (fuzzy)) AND (subject: risk factors (fuzzy)). The English search terms are ((((((((((Pneumothorax) OR (Spontaneous Pneumothorax)) OR (Pneumothorax, Spontaneous)) OR (Tension Pneumothorax)) OR (Pneumothorax, Tension)) OR

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(Pneumothorax, Tension)) OR (Pneumothorax, Tension)). Tension)) OR (Pressure Pneumothorax)) OR (Pneumothorax, Pressure)) OR (Pneumothorax, Primary Spontaneous)) OR (Primary Spontaneous Pneumothorax)) OR (Spontaneous Pneumothorax, Primary)) AND ((((((((((((((((((Risk Factors) OR (Factor, Risk)) OR (Risk Factor)) OR (Social Risk Factors)) OR (Factor, Social Risk)) OR (Factors, Social Risk)) OR (Risk Factor, Social)) OR (Risk Factors, Social)) OR (Social Risk Factor)) OR (Social Risk Factor)) OR (Health Correlates)) OR (Correlates, Health)) OR (Population at Risk)) OR (Populations at Risk)) OR (Risk Scores)) OR (Risk Score)) OR (Score, Risk)) OR (Risk Factor Scores)) OR (Risk Factor Score)) OR (Score, Risk Factor)). A combination of subject and free word searches were used to read, sort, and remove duplicates from all literature. Referring to the 2010 British Thoracic Society guidelines for spontaneous pneumothorax[15], the diagnostic criteria for spontaneous pneumothorax were sudden onset of chest pain on one side of the patient followed by chest tightness, dyspnea, cyanosis, and inability to lie flat.X-ray chest radiographs showed a line of pneumothorax, and CT scans showed pneumoperitoneum in the chest cavity with aspiration of gas by thoracentesis. Research literature that met the diagnostic criteria for spontaneous pneumothorax were included. Literature on traumatic pneumothorax and animal studies were excluded. Three persons completed the literature screening and a third person judged in case of disagreement.

2.2. Exposure, endings, instrumental variable screening

The databases used in this study were GWASCatalog (https://www.ebi.ac.uk/gwas/)[16] and IEUOpenGWAS (https://gwas.mrcieu.ac.uk/) [17]. The literature search yielded 116 risk factors. After excluding 66 risk factors with no or limited (nSNP≥3) genetic tools, 50 risk factors were finally obtained as exposures for inclusion in the MR analysis. The GWAS ID for the ending spontaneous pneumothorax was ukb-b-3693 from the European Population Study 2018, containing cases 1097 cases, controls 461,836, and SNPs of 9,851,867.

2.3. MR analysis

A two-sample Mendelian randomization method was used for the study. Risk factors were extracted as exposures with published information, number of included studies, sample size and risk estimates. Genome-wide significant SNPs were screened as candidate instrumental variables (Pvalue < 5e-08) from their GWAS pooled data. To ensure that the selected instrumental variables were independent of each other, the candidate instrumental variables were clustered together by chained disequilibrium (kb=5000, r2=0.01), and the SNP loci were screened to be independent of each other.MR analyses were performed using five methods, namely, IVW, MR-Egger, Weighted median, Simple mode, and Weighted mode. IVW and MR-Egger were the main analyses, and the remaining methods validated the causal effect results of the first two. Sensitivity analysis was performed using heterogeneity test and leave-one-out sensitivity test. Multiplicity test used MR-PRESSO method to detect and remove outliers. Heterogeneity of the snp used for a trait was measured with Cochranes' Q statistic, and possible pleiotropy was tested using the MR-Egger regression model with an intercept of $p < 0.05$. The results were expressed as risk ratios (ORs) and 95% confidence intervals (95% CIs). Weassessed the direction of the credibility of the findings based on the strength of association, the fit of the MR hypothesis, and the consistency of the effect. To assess the strength of instrumental variables, f-statistics were estimated based on sample size, number of snp used, and variance explained by the included snp. The reporting and analysis process followed the Interpretation of Reporting Specifications for Mendelian Randomization Studies [18].

2.4. Statistics

Statistical analyses for this study were performed using the TwoSampleMR, MVMR, MRPRESSO, VROOM, TIDYR, and READR packages in R version 4.2.0 software (R Foundation for statistical Computing). The statistical power of the MR analysis was estimated using the mRnd webtool. Associations with p-values < 0.05 in the ivw random effects and MR-PRESSO models were considered robust associations, and associations with p-values < 0.05 in the ivw random effects or MR-PRESS O models and in the same direction in all analyses were considered suggestive associations. For preliminary analyses, we calculated Wald ratios for each test SNP and combined them using inverse variance weighting (IVW) methods to obtain overall estimates. The IVW method provided the most accurate and robust estimates when the three key assumptions about the instrumental variables were met. To address the problem of multiple testing, the p-value threshold using a conservative bonferron correction was set at 0.0033. At this threshold, results with $p < 0.0033$ were considered statistically significant and strong evidence of causality.

3. RESULTS

The flow of the study is shown in Figure 1.

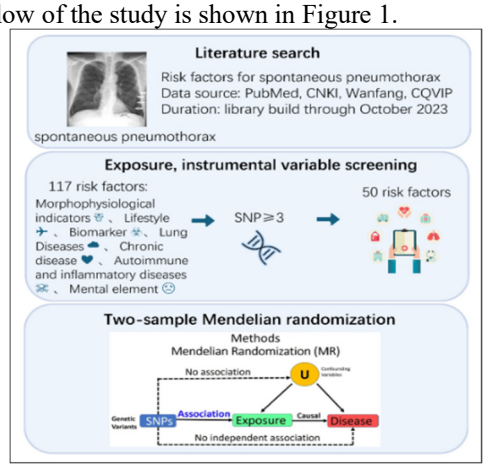

Fig. 1 Research Flow Chart

3.1. Exposure Tool Variable Screening

Fifty risk factors (nSNP≥3) were finally obtained as exposures for inclusion in the MR analysis, and their IEUIDs, sample sizes, populations, SNPs, nSNPs, and F-statistics are detailed in Table 1.

Table 1. Risk factor exposure instrument variables

Expose	IEUID	Sample size	Crowds	SNPs	nSNP	F-statistics
bald head	ukb-a-303	154988	European	124	124	97
body fat percentage	ukb-a-264	331117	European	122	84	54
height	ieu-a-96	60586	European	379	15	197
weight	ukb-b-11842	461632	European	1034	225	76
BMI	ieu-a-2	339224	European	42	41	66
hip measurement	ieu-a-59	93963	European	15	15	50
exertion spirometry	ukb-a-336	307638	European	90	90	58
First Second Expiratory Volume	ukb-b-8428	148653	European	43	43	58
spirometry	ebi-a-gcst007429	321047	European	124	124	56
Number of cigarettes smoked per day	ieu-b-142	249,752	European	62	11	101
caffeine	ukb-b-5237	428860	European	1277	16	73
snore	ebi-a-gcst009761	407066	European	13	13	40
stand on high	ukb-a-389	336474	European	226	226	137
lactate dehydrogenase	bbj-a-30	126319	European	78	3	64
urea	ebi-a-gcst90018948	344052	European	69	69	95
lymphocyte	ebi-a-gcst90002316	524923	European	177	177	129
hemoglobin	ebi-a-gcst90002310	563946	European	179	179	118
C-reactive protein	ebi-a-gcst90014002	389,057	European	99	99	257
suffer from insomnia	ukb-b-3957	462341	European	169	19	45
irritability	ukb-a-47	90282	European	15	11	37
apprehensive	ebi-a-gcst90041879	444404	European	23	20	42
lung cancer	ebi-a-gcst004748	29266	European	8	7	83
squamous lung cancer	ieu-a-989	62467	European	4	4	65
COVID	ebi-a-gcst90013414	10,056	European	3	3	88
bronchitis	ukb-b-3467	462933	European	425	372	30
pulmonary emphysema	ukb-b-7280	462933	European	348	297	38
pleurisy	ukb-b-16652	462933	European	595	516	30
TB	ukb-b-15622	462933	European	493	428	69
pleural effusion	ukb-b-9925	463010	European	467	401	30
bronchitis	ebi-a-gcst90014325	408422	European	491	423	69
bronchiectasis	ukb-b-18163	462933	European	798	668	49
chronic obstructive pulmonary disease	ukb-b-13447	462,933	European	565	480	31
coronary heart disease	ieu-a-7	456348	European	1131	10	61
heart attack	ebi-a-gcst90018877	456348	European	4	20	64
Type 1 diabetes	ebi-a-gcst90014023	520580	European	30	30	275
Type 2 diabetes	ukb-e-250_AFR	6636	European	50	39	31
high blood pressure	finn-b-I9_HYPTENSESS	870217	Mixed	73	10	65
inflammatory bowel disease	ieu-a-294	65642	European	65	63	110
rheumatoid arthritis	finn-b-RHEUMA_SEROPOS_OTH	4539	European	4	4	192
systemic lupus erythematosus	ebi-a-gcst90011866	12,653	European	15	9	46
celiac disease	ieu-a-276	15,283	European	6	4	334
non-toxic multinodular goiter	finn-b-E4_GOITREMULTINOD	3432	European	15	8	59
palmar fasciitis fibromatosis	finn-b-M13_DUPUTRYEN	2588	European	3	3	136
multiple sclerosis	ebi-a-gcst003566	15283	European	17	8	112
Crohn's disease	ieu-a-30	20,883	European	74	23	71
myasthenia gravis	ebi-a-gcst90093061	38,243	European	32	4	43
esophagitis	ukb-b-19354	463010	European	369	312	31
general anesthetic	ukb-b-10263	463,010	European	359	309	33
ectopic pregnancy	ukb-b-12801	462933	European	477	401	35
diaphragmatic hernia	ukb-e-K44_AFR	6636	European	64	55	36

3.2. Mendelian randomization

Among the 50 possible risk factors, four characteristics, lymphocytes, standing tall, hip circumference, and asthma, were significantly associated with the risk of SP, and five risk factors, height, COVID, snoring, forceful lung capacity (FVC), lung squamous carcinoma, and predicted first-second forceful expiratory volume of air (FEV1), had suggestive correlations (Table 2).

Table 2. Results of Mendelian Randomization for Two Samples of Risk Factors

Expose	IVW			MR Egger			WM			Cochran's Q	Q_pval	Pintercept
	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P			
bald head	1.002	1.000-1.002	0.193	1.003	1.000-1.003	0.133	1.001	0.999-1.007	0.162	102.135	0.137	0.208
body fat percentage	0.997	0.993-1.002	0.408	1.003	1.000-1.003	0.610	1.001	0.999-1.007	0.560	107.100	0.482	0.452
height	1.001	1.000-1.003	0.025	1.006	1.000-1.004	0.060	2	1.000-1.012	0.017	16.460	0.286	0.135
weight	1.000	0.999-1.001	0.629	1.002	0.998-1.002	0.135	1.000	0.999-1.005	0.953	881.726	0.286	0.667
BMI	1.000	0.999-1.001	0.846	1.001	0.998-1.002	0.484	1.000	0.998-1.004	0.961	5.874	0.998	0.154
hip measurement	0.998	0.997-1.000	0.018	0.999	0.996-1.000	0.032	0.998	0.986-0.999	0.039	20.040	0.089	0.075
exertion spirometry	0.998	0.997-1.000	0.009	0.996	0.996-1.00	0.272	0.998	0.990-1.003	0.029	76.460	0.845	0.645
First Second Expiratory Volume	1.001	1.000-1.002	0.045	1.003	1.000-1.003	0.163	1.001	0.999-1.007	0.156	32.490	0.854	0.365
spirometry	1.001	1.000-1.002	0.088	1.003	1.000-1.003	0.590	1.001	0.999-1.007	0.087	128.000	0.360	0.723
Daily cigarettes	1.001	1.000-1.002	0.021	1.003	0.999-1.007	0.574	1.001	1.000-1.003	0.272	4.441	0.925	0.620
caffeine	1.001	1.000-1.002	0.053	1.003	0.625-1.561	0.583	1.001	0.089-6.448	0.632	9.171	0.868	0.647
snore	1.010	1.002-1.019	0.013	1.012	1.000-1.024	0.713	1.012	0.952-1.076	0.037	20.040	0.094	0.431
stand on high	1.001	1.000-1.002	0.002	1.003	1.000-1.003	0.019	1.001	1.000-1.004	0.029	210.100	0.754	0.077
lactate dehydrogenase	1.001	1.000-1.002	0.133	1.003	1.000-1.003	0.573	1.001	0.999-1.007	0.100	0.813	0.666	0.586
urea	1.000	0.999-1.001	0.469	1.002	0.998-1.002	0.637	1.000	0.996-1.002	0.713	5.120	0.400	0.491
lymphocyte	1.001	1.000-1.002	0.007	1.002	1.000-1.002	0.002	1.001	1.001-1.004	0.048	25.476	0.992	0.881
hemoglobin concentration	1.001	1.000-1.002	0.073	1.003	1.000-1.003	0.178	1.001	0.999-1.007	0.166	186.300	0.320	0.254
C-reactive protein	2.718	2.030-3.641	0.007	3.003	1.649-4.481	0.064	3.003	1.709-4.324	0.083	72.090	0.977	0.227
suffer from insomnia	1.001	1.000-1.002	0.071	1.003	0.999-1.007	0.056	1.001	1.000-1.003	0.071	22.530	0.209	0.651
irritability	1.001	1.000-1.002	0.010	1.003	1.000-1.003	0.063	1.001	0.999-1.007	0.030	16.960	0.075	0.644
apprehensive	1.000	0.998-1.002	0.836	1.003	0.998-1.003	0.466	1.000	0.917-1.038	0.881	31.471	0.957	0.446
lung cancer	1.000	1.000-1.001	0.071	1.001	1.000-1.001	0.036	1.000	0.999-1.002	0.349	5.141	0.526	0.824
squamous lung cancer	1.001	1.000-1.002	0.001	1.003	1.000-1.003	0.063	1.001	0.999-1.007	0.005	0.622	0.891	0.623
COVID	1.001	1.000-1.001	0.047	1.001	1.000-1.001	0.058	1.001	1.001-1.013	0.024	4.692	0.096	0.280
bronchitis	2.768	0.000-3.910	0.068	0.082	0.000-1.730	0.036	1.479	0.733-2.990	0.275	384.859	0.081	0.927
pulmonary emphysema	0.433	0.000-5.469	0.560	0.032	0.000-0.751	0.048	0.985	0.837-3.411	0.949	284.622	0.672	0.210
pleurisy	0.605	0.000-4.427	0.457	26.488	0.000-113.574	0.747	1.287	0.551-3.004	0.560	550.275	0.253	0.708
TB	1.109	0.000-4.617	0.881	0.502	0.000-1.066	0.036	1.037	0.002-2.551	0.915	378.155	0.782	0.927
pleural effusion	0.083	0.000-3.743	0.561	0.059	0.000-5.221	0.953	1.786	0.430-5.221	0.145	432.239	0.851	0.354
bronchitis	1.000	1.000-1.001	0.000	1.001	1.000-1.001	0.004	1.000	1.000-1.002	0.000	689.584	0.128	0.083
bronchiectasis	1.048	0.000-1.272	0.279	3.956	0.366-4.277	0.056	4.616	0.923-23.074	0.057	663.868	0.527	0.114
chronic obstructive pulmonary disease	0.000	0.000-5.602	0.354	0.000	0.000-5.191	0.777	4.250	1.473-12.261	0.011	503.018	0.216	0.632
coronary heart disease	1.001	1.000-1.002	0.033	1.003	0.999-1.007	0.021	1.001	1.000-1.003	0.019	16.530	0.057	0.484
heart attack	0.999	1.000-1.002	0.030	1.003	1.000-1.003	0.048	1.001	0.999-1.007	0.014	24.460	0.179	0.404
Type 1 diabetes	1.001	1.000-1.002	0.050	1.003	1.000-1.003	0.095	1.001	0.999-1.007	0.115	27.581	0.843	0.608
Type 2 diabetes	1.001	1.000-1.002	0.050	1.003	1.000-1.003	0.095	1.001	0.999-1.007	0.115	554.554	0.894	0.626

high blood pressure	1.000	1.000-1.002	0.128	1.003	1.000-1.003	0.448	1.001	0.999-1.007	0.085	4.026	0.910	0.880
inflammatory bowel disease	1.001	1.000-1.002	0.900	1.003	1.000-1.003	0.550	1.001	0.999-1.007	0.910	22.530	0.175	0.555
rheumatoid arthritis	1.000	1.000-1.001	0.212	1.001	1.000-1.001	0.359	1.000	0.999-1.003	0.152	6.213	0.102	0.503
systemic lupus erythematosus	1.001	1.000-1.002	0.731	1.003	1.000-1.003	0.495	1.001	1.000-1.007	0.907	4.277	0.831	0.531
celiac disease	1.001	1.000-1.002	0.367	1.003	1.000-1.003	0.140	1.001	0.999-1.007	0.330	5.874	0.118	0.154
non-toxic multinodular goiter	1.000	0.999-1.000	0.423	0.999	0.997-1.002	0.767	0.999	0.999-1.001	0.574	16.562	0.247	0.896
palmar fasciitis fibromatosis	1.000	0.999-1.000	0.058	1.001	0.999-1.000	0.625	1.000	0.999-1.002	0.174	11.766	0.294	0.979
multiple sclerosis	1.000	0.999-1.000	0.184	0.999	0.999-1.000	0.767	1.000	0.995-1.004	0.279	7.901	0.341	0.870
Crohn's disease	1.001	1.000-1.002	0.124	1.003	1.000-1.003	0.290	1.001	0.999-1.007	0.437	20.410	0.558	0.158
myasthenia gravis	1.001	1.000-1.002	0.523	1.003	1.000-1.003	0.539	1.001	0.999-1.007	0.171	3.488	0.322	0.585
esophagitis	0.003	0.000-5.139	0.298	0.054	0.000-1.061	0.251	0.652	0.380-3.329	0.081	307.864	0.349	0.825
general anesthetic	1.630	0.003-7.964	0.877	0.003	0.578-1.377	0.341	0.385	0.170-0.869	0.603	317.937	0.336	0.084
ectopic pregnancy	0.000	0.000-6.568	0.660	0.016	0.326-1.377	0.833	15.559	8.355-28.976	0.276	418.968	0.790	0.556
diaphragmatic hernia	0.004	0.000-16.161	0.191	0.005	0.000-1.061	0.540	0.580	0.559-0.600	0.000	61.081	0.864	0.970

3.2.1 Morphophysiological indicators

Of the nine morphophysiologic index-related risk factors, including baldness, percent body fat, height, weight, BMI, hip circumference, exertional spirometry, first-second exertional expiratory volume, and lung function, four, height, hip circumference, exertional spirometry, and first-second exertional expiratory volume, were associated with SP. Specifically, height (IVWOR=1.001, P=0.025) and first-second expiratory volume with exertion (IVWOR=1.001, P=0.045) were positively associated with the risk of SP, whereas hip circumference (IVWOR=0.998, P=0.018) and expiratory lung capacity (IVWOR=0.998, P=0.009) were negatively associated with the risk. Although there was no heterogeneity in the above analyses, no signs of pleiotropy were found in the MR-Egger regression analyses (all $p > 0.05$). The other five factors showed limited evidence of association with SP risk.

3.2.2 Lifestyle

Among the lifestyle-related risk factors smoking and coffee have limited evidence of association with SP risk. Snoring (IVWOR=1.010, P=0.013), and standing on heights (IVWOR=1.001, P=0.002) were positively associated with SP risk.

3.2.3 Biomarkers

Lymphocyte count (IVWOR=1.001, P=0.007) was positively associated with SP risk. There was limited evidence of a causal relationship between other lactate dehydrogenase, urea, lymphocytes, hemoglobin concentration, and C-reactive protein and spontaneous pneumothorax.

3.2.4 Mental factors

Insomnia, irritability Limited evidence of a causal relationship between anxiety and spontaneous pneumothorax.

3.2.5 Lung diseases

COVID(IVWOR=1.001,P=0.047), squamous lung cancer (IVWOR=1.001,P=0.001), and asthma (IVWOR=1.000, P=0.000) were positively associated with SP risk. There was limited evidence of a causal relationship between lung cancer, bronchitis, emphysema, pleurisy, tuberculosis, pleural effusion, bronchiectasis, chronic obstructive pulmonary disease and spontaneous pneumothorax.

3.2.6 Chronic diseases

There is limited evidence of a causal relationship between coronary artery disease, type 1 diabetes, cardiac infarction, hypertension, diabetes, and spontaneous pneumothorax.

3.2.7 Autoimmune and inflammatory diseases

There is limited evidence for a causal relationship between inflammatory bowel disease, rheumatoid arthritis, systemic lupus erythematosus, celiac disease, nontoxic multinodular goiter, palmar fasciitis fibromatosis, multiple sclerosis, Crohn's disease, myasthenia gravis, baldness, esophagitis, and spontaneous pneumothorax.

3.2.8 Other factors

There is limited evidence of a causal relationship between general nesthesia, ectopic pregnancy, diaphragmatic hernia, and spontaneous pneumothorax.

4. Discuss

This is the first study to comprehensively investigate potential risk factors for spontaneous pneumothorax using MR analysis. Using MR analysis, we found for the first time that 4 out of 50 risk factors were strongly associated with the risk of spontaneous pneumothorax, including lymphocyte count, standing on heights, hip circumference, and asthma. It was also observed that height, COVID , snoring, forceful lung volume, squamous lung cancer, and first second forceful expiratory volume were associated with the risk of spontaneous pneumothorax.

In previous studies, height[19] , weight[20] , and body mass index[21] have been identified as risk factors for spontaneous pneumothorax. In this study, a causal relationship between excessive height and increased risk of spontaneous pneumothorax was confirmed, and there was limited evidence of a causal relationship between body weight, body mass index and spontaneous pneumothorax. In addition the first finding confirms that standing in high places also increases the risk of developing spontaneous pneumothorax. This suggests that spontaneous pneumothorax may be related to the total height at the time of onset, and that spontaneous pneumothorax may occur even when standing in high places at lower heights. Previous case reports of sleep apnea syndrome combined with spontaneous pneumothorax[22] , this study found limited evidence of a causal relationship between sleep apnea syndrome and spontaneous pneumothorax, but snoring was causally associated with an increased risk of spontaneous pneumothorax. There are previous case reports of secondary school students who developed pneumothorax after blowing hard during a physical spirometry test[23] , and the present study also found that first second expiratory volume with exertion was positively associated with the risk of spontaneous pneumothorax, whereas expiratory spirometry was negatively associated with the risk. In normal subjects, first second expiratory force volume is equal to expiratory force volume, and in the presence of airway obstruction, first second expiratory force volume less than expiratory force volume[24], and in secondary pneumothorax with underlying disease expiratory force volume is associated with a downgraded risk of pneumothorax due to impaired ventilation. This study also found that hip circumference was negatively associated with the risk of spontaneous pneumothorax. Hip circumference is defined as the horizontal circumference of the most prominent part of the buttocks toward the back. The height-waist index and waist-hip ratio are greater in men than in women. These indices are calculated by dividing the waist-joint circumference by the height and hip circumference respectively, and multiplying the result by 100 for the height-waist index. Some studies have proved that the overall incidence of spontaneous pneumothorax is much higher in men than in women[25] . And pear-shaped and hourglass-shaped women with thin waist and wide hips and thick thighs live longer and healthier lives than rectangular-shaped, apple-shaped and inverted triangle-shaped women with thick waist and narrow hips and thin thighs[26] . The present study confirms that there is a positive causal relationship between lymphocyte count height and the occurrence of spontaneous pneumothorax, probably due to the fact that autoimmune and inflammatory diseases mainly invade human lymphocytes[27] , leading to the destruction of the human immune system, which results in the emergence of a variety of opportunistic lung infections and ultimately causes spontaneous pneumothorax. Bronchial asthma[28] is a common clinical condition, and its acute exacerbation is often combined with spontaneous pneumothorax, and the present study also confirms a causal relationship with the occurrence of spontaneous pneumothorax. A study at confirmed that mechanical ventilation in critically ill patients with novel coronavirus pneumonia (COVID-19) [29] had a 5.38% probability of being associated with pneumothorax, and we also confirmed that COVID was positively associated with the risk of spontaneous pneumothorax. Lung cancer[30] with spontaneous pneumothorax is rare, and only a few special reports have been published in China. In recent years, as the incidence of lung cancer increases, its incidence is bound to increase gradually, and we found that squamous lung cancer is one of the causes of spontaneous pneumothorax.

Limitations of this study remain. First, all GWAS data are mostly from European origin, and it remains to be determined whether the findings of this study are applicable to other populations, especially Asian populations. Therefore, future studies should consider including samples from different ethnic groups to increase the generalizability of the results. Second, because this study used pooled statistics rather than individual-level data, subgroup analyses were not possible, and large-scale clinical trials should be conducted to confirm the effects of these factors on spontaneous pneumothorax. In conclusion, this MR study provides evidence of a causal relationship between lymphocyte count, standing tall, hip circumference, asthma, height, COVID, snoring, forceful lung volume, squamous lung cancer, first-second forceful expiratory volume, and the risk of spontaneous pneumothorax, which could provide a basis for the development of public health policies.

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