Wang et al. World Allergy Organization Journal (2022) 15:100630
http://doi.org/10.1016/j.waojou.2022.100630

WORLD ALLERGY ORGANIZATION JOURNAL

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Smoking behavior might affect allergic rhinitis and vasomotor rhinitis differently: A mendelian randomization appraisal

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ABSTRACT

Background: Allergic rhinitis and vasomotor rhinitis are harassing numerous patients and their risk factors have not been well investigated. Here, we try to identify their risk factors and distinguish these 2 diseases.

Methods: A two-sample Mendelian randomization (MR) study was implemented to discover the risk factors of allergic and vasomotor rhinitis. Based on previous studies, we selected 15 potential risk factors and the genome-wide summary statistics were extracted from the non-FinnGen consortium. The genome-wide summary statistics of rhinitis were obtained from the FinnGen consortium. Both univariable MR and multivariable MR analyses were performed to identify the causal risk factors. The Cochrane's Q value was calculated to appraise the heterogeneity. MR-Egger intercept and MR-RPESSO were utilized to appraise the pleiotropy.

Results: In the univariable model, the number of cigarettes per day can decrease the risk of allergic rhinitis (IVW OR = 0.29[0.18, 0.47], p-value = 2.70×10^{-7}) while increasing the risk of vasomotor rhinitis (IVW OR = 1.30[1.04, 1.62], p-value = 0.022). Besides, no other risk factors could affect the risk of either allergic or vasomotor rhinitis. After adjusting for age of smoking initiation and alcohol intake, the cigarettes per day could still decrease the risk of allergic rhinitis (IVW OR = 4.66×10^{-3} [1.99×10^{-4}, 0.11], p-value = 0.003) while not affecting the risk of vasomotor rhinitis (IVW OR = 0.92[0.44, 1.96], p-value = 0.834).

Conclusion: Smoking can affect the risk of allergic and vasomotor rhinitis differently where it decreases the risk of allergic rhinitis and increases the risk of vasomotor rhinitis.

Keywords: Allergic rhinitis, Vasomotor rhinitis, Mendelian randomization, Risk factors

INTRODUCTION

The incidence of rhinitis has been reported to harass 14% of adults and 13% of children in the United States.[1] Furthermore, rhinitis can coexist with asthma and usually is a strong risk factor for new-onset asthma, exerting a heavy burden on society.[2] Thus, it is necessary to identify the risk factors for rhinitis and control them. It has been

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http://doi.org/10.1016/j.waojou.2022.100630

Received 7 September 2021; Received in revised from 10 January 2022; Accepted 18 January 2022
Online publication date xxx

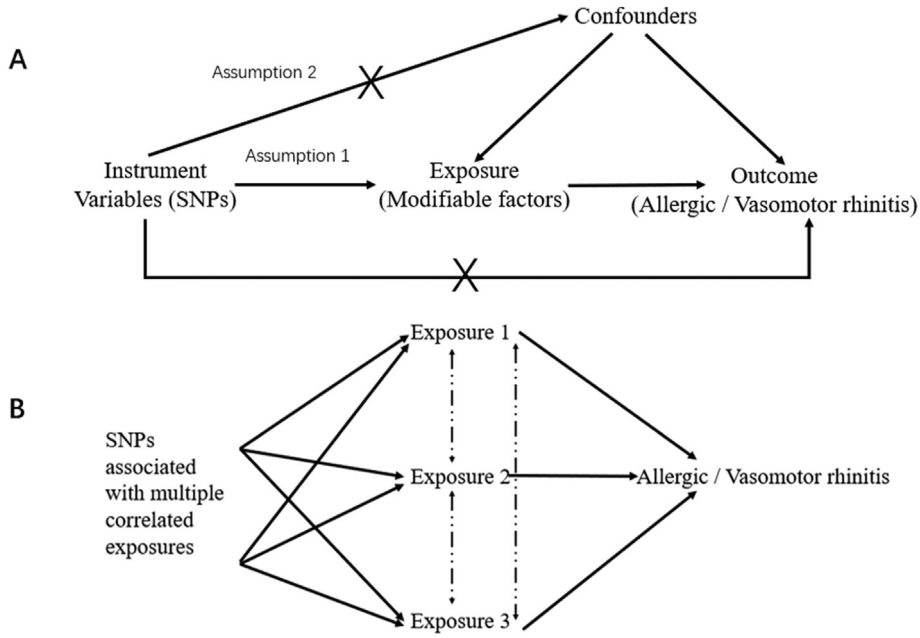

Fig. 1 The basic principles of two-sample Mendelian randomization and multivariable Mendelian randomization

reported that genetic factors might play an important role in the pathogenesis of rhinitis, together with those environmental factors.[3] For example, single nucleotide polymorphism (SNP) located in the interleukin, chemokine, and receptor coding genes might affect the pathogenesis of rhinitis and so do the epigenetic factors.[3] A recent cohort study, consisting of 11 506 adults in Northern Europe, found that smoking and living in new buildings could increase the risk of rhinitis.[4] However, Skaaby et al reported that smoking might lower the risk of hay fever and allergic sensitization.[5] Besides, obesity was reported to be associated with allergic rhinitis where the impact of obesity on allergic rhinitis is not clear.[6] Considering the association between environmental risk factors and rhinitis tends to be biased by the unknown confounders such as socioeconomic status, it is necessary to overcome the unknown confounders and reverse causation when attempting to identify causal risk factors for rhinitis.

Mendelian randomization (MR) is a method for causal inference using genetic variants as the instrumental variables and has achieved great success in many fields.[7] Since the gametes are randomly allocated at conception, the SNP's different effect on the exposure can simulate the different levels of the exposure and they can divide the population into different groups the same as the randomized controlled trial (RCT).[8] Nowadays, MR studies based on the two-sample setting are developing rapidly thanks to the accumulation of summary statistics derived from publicly available genome-wide association studies (GWAS). Meanwhile, a few MR studies focused on allergic rhinitis and hay fever have been reported and they added evidence to observational studies. Feng et al supported that serum 25-hydroxyvitamin D could not affect the risk of allergic rhinitis, allergic sensitization, and non-allergic rhinitis, and Skaaby et al also found the null association between vitamin B12 and allergic rhinitis, together with folate concentrations.[9,10] Meanwhile, Tea et al and Frederikke et al ruled out the causal relationship between alcohol intake and allergic rhinitis.[11]

However, recent MR studies are only focused on a small number of risk factors and the main outcome is allergic rhinitis and no study has treated vasomotor rhinitis as the outcome yet. It is known that vasomotor rhinitis is a kind of rhinitis with high heterogeneity and many aspects of it are still under investigation.[12] Thus, we hope to perform a comprehensive MR study to identify

modifiable risk factors for rhinitis, including both allergic rhinitis and vasomotor rhinitis.

METHODS

Mendelian randomization design

This study consisted of 2 parts including univariable and multivariable MR analyses. Initially, the potential causal risk factors of rhinitis were identified and we further judged whether these factors independently affected the risk of rhinitis. This study is reported mainly based on "STrengthening the Reporting of OBservational studies in Epidemiology" (STROBE).[13]

Univariable MR analysis

The Mendelian randomization analysis is performed based on the following 3 principles:[1] The genetic variant is closely associated with the exposure;[2] The genetic variant is not associated with potential confounders;[3] The genetic variant is not associated with the outcome except via the way of the exposure[7] (Fig. 1A). Usually, the first assumption can be well satisfied using the GWAS summary statistics and the last 2 assumptions sometimes cannot be well tested. As the genetic variants (SNP) are closely associated with the exposure, they would affect the exposure firstly. Also, the only pathway is "genetic variants → exposure → outcome" if we observed the significant results since the genetic variants are not directly associated with potential confounders and outcomes. Thus, the observed associations from MR should be causal.

Initially, we extracted SNPs associated with the exposure from the GWAS summary statistics if reaching the genome-wide significance (p-value $< 5 \times 10^{-8}$). Then, we removed the SNP with its minor allele frequency less than 0.01. The SNPs in close linkage disequilibrium (LD) with the most significant one in the given region would be removed as well. The palindromic SNPs (A/T or C/G) were also excluded. Before MR analysis, we also appraise the weak instrument bias using the F statistics ($F = beta^2/se^2$) for each SNP and calculate a general F statistic for all SNPs.[14] The SNP with less statistical power would be excluded. To avoid the bias caused by the violation of assumption 2, we conducted a phenome-wide association study to find the SNPs associated with potential confounders and removed these SNPs.[15] A Bonferroni correction p-value was adopted to define SNP not associated with the outcome (outcome p-value $>$ 0.05/number of SNPs).

Multivariable Mandelian randomization analysis

The multivariable MR (MVMR) analysis would be performed only if the exposure-outcome association is significant in the univariable MR analysis (Fig. 1B). We will include other exposures closely associated with the significant one in the multivariable regression model. Before MVMR analysis, we would also calculate the MVMR F statistics for each exposure, and the exposure would be removed if its F statistic is less than 10.

DATA SOURCE DESCRIPTION

Genetic instrumental variables for modifiable risk factors

We extracted the instrumental variables from GWAS results and removed SNPs in high linkage disequilibrium ($r^2 < 0.01$) to get independent instrumental variables using 1000 genome Phase 3 European samples as the reference panel (https://www.internationalgenome.org/). All instrumental variables reached the genome-wide significance (GWAS p-value $< 5 \times 10^{-8}$) and each minor allele frequency was more than 0.01. Genetic variants associated with the number of cigarettes smoked per day (CPD, a continuous variable) were all obtained from the recent GWAS result derived from GWAS & Sequencing Consortium of Alcohol and Nicotine use (GSCAN).[16] Meanwhile, the IVs for the age of smoking initiation and alcoholic drinks per week were also obtained from the GSCAN. We obtained genetic variants associated with BMI, waist circumference, hip circumference, and waist-to-hip ratio (WHR) from the Genetic Investigation of ANthropometric Traits (GIANT) consortium.[17,18] The instrumental variables for lipidemic traits, including HDL, LDL, total cholesterol, and triglycerides, were extracted from the Global Lipids Genetics Consortium (GLGC).[19] We obtained instrumental variables for HbA1c[20] and fasting glucose[21] from the Meta-Analyses of Glucose and Insulin-related traits Consortium (MAGIC). The genetic variants associated with systolic blood pressure (SBP) and

diastolic blood pressure (DBP) were extracted from a GWAS meta-analysis in over 1 million individuals from UK Biobank (UKB) and International Consortium for Blood Pressure (ICBP).[22]

Genetic instrumental variables for allergic and vasomotor rhinitis

The GWAS results of allergic and vasomotor rhinitis were obtained from the FinnGen Consortium (https://r4.finngen.fi/). The definitions of these 2 diseases are based on the international code of diseases (ICD) where allergic rhinitis included participants diagnosed by ICD-10 J301, J302, J303, J304 in ICD-10 and 477 in ICD-9. As for vasomotor rhinitis, it includes participants diagnosed by J300 in ICD-10. The samples were genotyped with Illumina (Illumina Inc., San Diego, CA, USA) and Affymetrix arrays (Thermo Fisher Scientific, Santa Clara, CA, USA). The individuals with ambiguous gender, high genotype missingness (>5%), excess heterozygosity (±4SD), and non-Finnish ancestry were excluded. Meanwhile, variants with high missingness (>2%), low HWE *P*-value (<1e-6), and low minor allele count (<3) were excluded. The Sequencing Initiative Suomi (SISu) was used as the reference panel for genotype imputation (http://sisuproject.fi/). The genotype imputation was conducted using the software Beagle 4.1.[23] The GWAS was performed under the mixed model logistic regression provided by the SAIGE software, adjusting for sex, age, 10 PCs, genotyping batch, and genetic relatedness. The allergic rhinitis samples consisted of 4300 cases and 171,926 controls and there were 744 cases and 174,935 controls in the samples of vasomotor rhinitis.

Each GWAS study was performed under the license of its corresponding Independent Ethics Committee and related information can be founded in the original GWAS publications. All GWAS

Exposure	Consortium	NSNP	Sample size	R2(%)	F
Cigarettes per day	GSCAN	25	842,717	4.32	1521.92
Age of smoking initiation	GSCAN	2	842,717	0.01	42.14
Alcoholic drinks per day	GSCAN	13	842,717	0.03	19.45
BMI	GIANT	42	344,369	2.65	223.17
Waist circumference	GIANT	23	344,369	1.78	271.32
Hip circumference	GIANT	26	344,369	1.75	235.90
WHR	GIANT	9	344,369	1.64	637.96
HDL	GLGC	57	188,578	7.54	269.71
LDL	GLGC	39	188,578	5.31	271.10
TC	GLGC	42	188,578	9.60	476.70
TG	GLGC	31	188,578	6.21	402.71
HbA1c	MAGIC	20	159,940	1.23	99.57
Fasting glucose	MAGIC	25	151,188	1.34	82.12
SBP	UKB + ICBP	313	757,601	4.64	117.72
DBP	UKB + ICBP	349	757,601	4.73	107.73

Table 1. A summary of GWAS summary statistics for different risk factors. *Notes: (1) Exposure: the risk factors; BMI = body mass index; WHR = waist-to-hip ratio; HDL = high-density lipoprotein; LDL = low-density lipoprotein; TC = total cholesterol; TG = triglycerides; HbA1c = glycated hemoglobin; SBP = systolic blood pressure; DBP = diastolic blood pressure. (2) Consortium: The name of GWAS consortium. (3) NSNP: the number of SNPs in the MR analysis. (4) Sample size: the sample size of each GWAS. (5) R2(%): the genetic explanation of each risk factor. (5) F: the general F statistic for each risk factor*

summary statistics are freely downloadable and can be used without restriction.

Statistical methods

The inverse-variance weighted (IVW) method was adopted to combine each IV's effect size, and MR-Egger and median-based methods were used as the complement to the IVW. We calculated Cochrane's Q value to assess the heterogeneity. As for horizontal pleiotropy, the MR-Egger intercept and MR-PRESSO methods were utilized.[24,25] If the outliers were detected, they would be removed and we would reassess the MR causal estimation. If heterogeneity still exists, the median-based estimation will be adopted as the main effect size. If there is horizontal pleiotropy, the MR-Egger estimation will be the main effect size.

In the univariable MR analysis, we tested the causal relationship between 15 exposures and 2 kinds of rhinitis (allergic rhinitis and vasomotor rhinitis). The exposure-outcome association is defined to be significant if its Bonferroni corrected p-value is less than 0.05. The Bonferroni corrected p-value is calculated using the following formula: corrected p-value = p * (1/n) where p is the original MR p-value and n is the number of statistical tests (n = 14). The univariable MR analysis was performed using the R packages "TwoSampleMR" and "MendelianRandomization". The MR-PRESSO was conducted using the R package "MRPRESSO".[25] The IVW model was the main method in MVMR analysis and the MR-Egger method was the complementary method. The MVMR was performed using the R packages "MendelianRandomization" and "MVMR".

The mRnd was used to calculate the statistical power for Mendelian randomization (https://

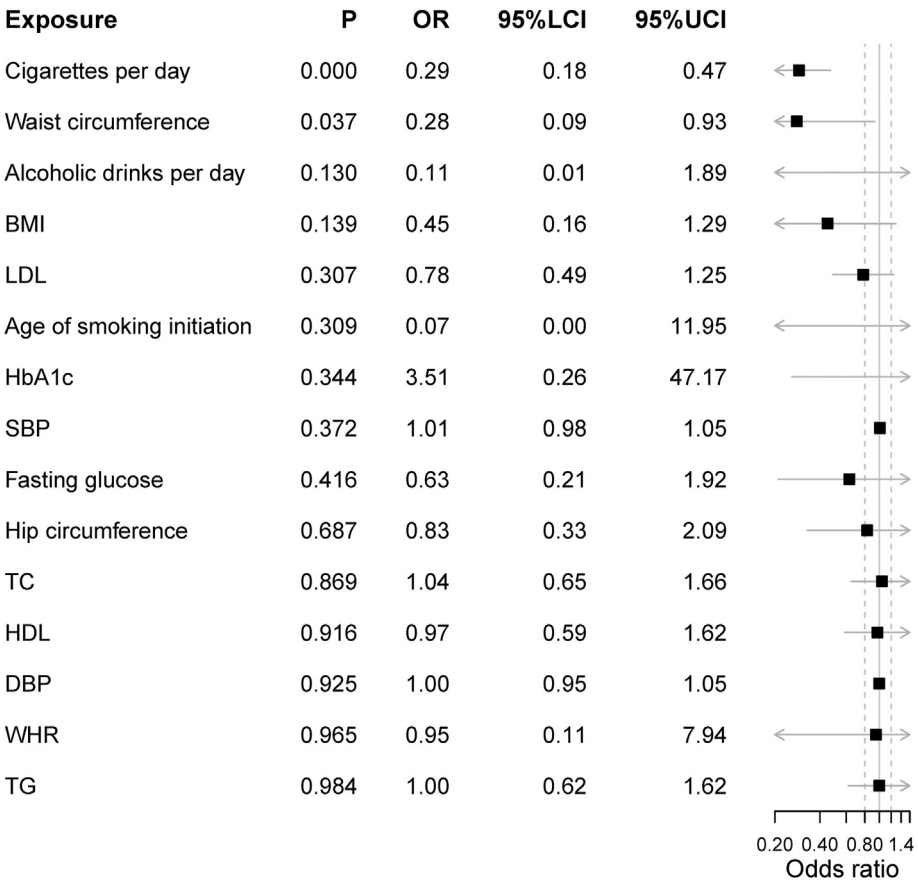

Fig. 2 The forest plot of different risk factors' effect on allergic rhinitis. Notes: (1) Exposure: the risk factors; BMI = body mass index; WHR = waist-to-hip ratio; HDL = high-density lipoprotein; LDL = low-density lipoprotein; TC = total cholesterol; TG = triglycerides; HbA1c = glycated hemoglobin; SBP = systolic blood pressure; DBP = diastolic blood pressure. (2) P: the p-value of each MR result. (3) OR: the odds ratio. (4) 95%LCI: the lower limit of 95% confidence interval. (5) 95%UCI: the upper limit of 95% confidence interval

cnsgenomics.shinyapps.io/mRnd/). All statistical analyses and data visualization were performed in R software 3.4.0 (www.r-project.org).

RESULTS

Valid IVs

Generally, we included 15 risk factors as the exposures. The number of genetic variants varies between 2 and 349, explaining 0.01%–6.21% of the exposure (Table 1). The genetic variants for each exposure were valid IVs.

In the univariable MR analysis, the F statistics for each IV are much greater than the empirical threshold 10 and the general F statistics for each exposure were greater than 10 as well (Supplementary Table 1-15).

In the multivariable MR analysis, the F statistics of CPD is 50.52 and the p-value of Q is 0.815, suggesting sufficient statistical power and validity.

ALLERGIC RHINITIS

Smoking and drinking

Of these 15 risk factors, only CPD was causally associated with allergic rhinitis after Bonferroni correction and it might be a protective factor (IVW OR = 0.29[0.18, 0.47], p-value = 2.70×10^{-7}, Bonferroni p-value = 4.05×10^{-6}) (Fig. 2). Therein, the risk of allergic rhinitis would reduce 71% if increasing per SD of CPD. However, the alcohol-intake seemed not to affect the allergic rhinitis (IVW OR = 0.11[0.01, 1.89], p-value = 0.130). After adjusting for the age of smoking initiation and alcohol intake, the CPD could still decrease the risk of allergic rhinitis (IVW OR = 4.66×10^{-3} [1.99×10^{-4}, 0.11], p-value = 0.003). The p-value of Cochrane's Q and MR-Egger intercept is greater than 0.05, suggesting no significant heterogeneity or pleiotropy.

Anthropometric traits

Besides, a higher waist circumference could also lower the risk of allergic rhinitis suggestively (IVW OR = 0.28[0.09, 0.93], p-value = 0.037, Bonferroni p-value = 0.560). However, the waist-to-hip ratio (WHR) might not affect it (IVW OR = 0.95[0.11, 7.94], p-value = 0.965), and so did the hip circumference (IVW OR = 0.83[0.33, 2.09], p-value = 0.687). These results suggested that waist circumference and hip circumference were 2 different indicators for the risk of allergic risk. Meanwhile, the BMI was not associated with the risk of allergic rhinitis (IVW OR = 0.45[0.16, 1.29], p-value = 0.139).

Blood lipids

We failed to observe any causal association between blood lipids and allergic rhinitis. Three kinds of cholesterol could not affect the risk of allergic rhinitis, including HDL (IVW OR = 0.97 [0.59, 1.62], p-value = 0.916), LDL (IVW OR = 0.78 [0.49, 1.25], p-value = 0.307) and total cholesterol (IVW OR = 1.04[0.65, 1.66], p-value = 0.869). Meanwhile, the triglycerides cannot affect it as well (IVW OR = 1.00[0.62, 1.62], p-value = 0.984).

Glycemic traits

Here, we included 2 glycemic traits, including HbA1c and fasting glucose. The HbA1c level cannot affect the risk of allergic rhinitis (IVW OR = 3.51[0.26, 47.17], p-value = 0.344) and the fasting glucose cannot affect it either (IVW OR = 0.63[0.21, 1.92], p-value = 0.416).

Blood pressure

Both kinds of blood pressure were not associated with the risk of allergic rhinitis, including SBP (IVW OR = 1.01[0.98, 1.05], p-value = 0.372) and DBP (IVW OR = 1.00[0.95, 1.05], p-value = 0.924).

VASOMOTOR RHINITIS

Smoking and drinking

No risk factor was associated with vasomotor rhinitis after Bonferroni correction. However, it was suggestive that CPD could increase the risk of vasomotor rhinitis (IVW OR = 1.30[1.04, 1.62], p-value = 0.022, Bonferroni p-value = 0.325) (Fig. 3). After adjusting for the age of smoking initiation and alcohol intake, the CPD cannot affect the risk of vasomotor rhinitis (IVW OR = 2.40[0.45, 12.76], p-value = 0.316). In this study, the alcoholic drinks per day cannot affect the risk of

Exposure	P	OR	95%LCI	95%UCI
Cigarettes per day	0.022	1.30	1.04	1.62
Fasting glucose	0.058	1.57	0.99	2.49
WHR	0.158	1.88	0.78	4.54
TC	0.161	0.86	0.70	1.06
Age of smoking initiation	0.305	3.44	0.32	36.47
Alcoholic drinks per day	0.356	1.74	0.54	5.61
HbA1c	0.388	1.50	0.60	3.77
DBP	0.445	0.99	0.97	1.01
HDL	0.521	0.93	0.75	1.16
SBP	0.574	1.00	0.98	1.01
BMI	0.677	0.91	0.60	1.39
LDL	0.700	0.96	0.76	1.20
TG	0.737	0.96	0.73	1.25
Hip circumference	0.769	1.07	0.70	1.63
Waist circumference	0.834	0.92	0.44	1.96

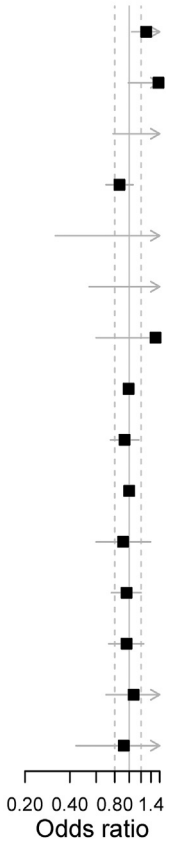

Fig. 3 The forest plot of different risk factors' effect on vasomotor rhinitis. Notes: (1) Exposure: the risk factors; BMI = body mass index; WHR = waist-to-hip ratio; HDL = high-density lipoprotein; LDL = low-density lipoprotein; TC = total cholesterol; TG = triglycerides; HbA1c = glycated hemoglobin; SBP = systolic blood pressure; DBP = diastolic blood pressure. (2) P: the p-value of each MR result. (3) OR: the odds ratio. (4) 95%LCI: the lower limit of 95% confidence interval. (5) 95%UCI: the upper limit of 95% confidence interval

vasomotor rhinitis (IVW OR = 1.74[0.54, 5.61], p-value = 0.356).

Anthropometric traits

Unlike allergic rhinitis, the vasomotor rhinitis cannot be affected by the waist circumference (IVW OR = 0.92[0.44, 1.96], p-value = 0.834). Besides, no other anthropometric traits are causally associated with vasomotor rhinitis, including BMI (IVW OR = 0.91[0.60, 1.39], p-value = 0.677), hip circumference (IVW OR = 1.07[0.70, 1.63], p-value = 0.769) and waist-to-hip ratio (IVW OR = 1.88[0.78, 4.54], p-value = 0.158).

Blood lipids

No causal association was observed between blood lipids and vasomotor rhinitis. Four blood lipids cannot influence the risk of vasomotor rhinitis, including HDL (IVW OR = 0.93[0.75, 1.16], p-value = 0.521), LDL (IVW OR = 0.96[0.76, 1.20], p-value = 0.700), total cholesterol (IVW OR = 0.86 [0.70, 1.06], p-value = 0.161), and triglycerides (IVW OR = 0.96[0.73, 1.25], p-value = 0.737).

Glycemic traits

Here, we included 2 glycemic traits but either can affect the risk of vasomotor rhinitis, including HbA1c (IVW OR = 1.50[0.60, 3.77], p-value = 0.388) and fasting glucose (IVW OR = 1.57[0.99, 2.49], p-value = 0.058).

Blood pressure

Two kinds of blood pressure were not associated with the risk of allergic rhinitis, including SBP (IVW OR = 0.996[0.98, 1.01], p-value = 0.574) and DBP (IVW OR = 0.99[0.97, 1.01], p-value = 0.445).

Sensitivity analysis and power calculation

A leave-one-out sensitivity analysis was performed for each exposure-outcome association. The outliers were removed in the further analysis and no IV could drive the results. The statistical power for CPD is 100%.

DISCUSSION

To summarize, we identified smoking might be the only common risk factor and it could affect the risk of allergic rhinitis and vasomotor rhinitis in the opposite direction. The CPD might decrease the risk of allergic rhinitis while increasing the risk of vasomotor rhinitis suggestively. Meanwhile, a higher waist circumference could marginally decrease the risk of allergic rhinitis. Besides, no other risk factors were causally associated with the risk of either allergic or vasomotor rhinitis. However, this study has its limitations[1]: The study population is limited to the Europeans and the conclusion cannot expand to other ethnicities easily;[2] Different risk factors might affect the risk of allergic and vasomotor rhinitis differently based on the age and sex, and immunity and clinical/functional outcomes are also important but we failed to consider them due to data limitations;[3] The statistical power for cigarettes per day is sufficient while relatively low for other traits and we cannot avoid the false negative results;[4] We failed to fully replicate our findings due to data limitations.

The recent consensus pertaining to the impact of smoking on allergic rhinitis is still controversial.[26] On one hand, smoking can increase the synthesis of immunoglobulin E and stimulate airway hyperresponsiveness and it can also hamper the immune functions, suggesting 2 opposite effects of smoking on the pathogenesis of allergic rhinitis. Our results lent strong support to it that smoking could lower the risk of allergic rhinitis.[5] Several reasons can account for it:[1] Patients with allergic rhinitis tend to quit smoking and thus it may introduce reversal causality;[5,2] Smoking might have a strong immunosuppressive effect smoking and thus decrease the risk of allergic rhinitis.[27] However, Holm et al reported that respiratory diseases, including asthma, wheeze, hay fever, and chronic bronchitis, could not significantly predict smoking cessation.[28] Our MR indicated smoking can decrease the risk of AR, suggesting its effect on suppressing immunity might be a major one. Thus, we deemed that the immunosuppressive effect of smoking might be the main mechanism that could explain the significant MR results.

Recently, Elisia et al reported that smoking can induce inflammation and compromise our innate immunity since higher CRP, fibrinogen, IL-6, IL-8, and leukocytes were observed in smokers.[29] Additionally, the smokers had lower NK cells and higher Tregs than non-smokers, indicating that smoking may disturb our immune function.[29] Groneberg et al reported that chronic exposure to smoking could elevate the levels of vasoactive intestinal peptide and neuropeptide tyrosine.[30] The vasoactive intestinal peptide is an inhibitory noncholinergic neurotransmitter that can cause bronchodilation and vasodilatation, and further lead to hypersecretion.[31] Thus, chronic exposure to smoking might cause vasodilation and further contribute to vasomotor rhinitis.

As per the abovementioned, we deemed that smoking could affect the risk of allergic rhinitis and vasomotor rhinitis via 2 different mechanisms where the former might be explained by the immunosuppressive effect of smoking and the latter by the vasodilation effect of smoking.

In our MR analysis, we did not find that alcohol intake could increase the risk of allergic/vasomotor rhinitis and this was in concordance with previous studies. For instance, A MR study did not observe the causal relationship between prenatal alcohol exposure and allergic rhinitis[32] and Skaaby et al further ruled out the causal relationship between alcohol intake and allergic sensitization.[11]

There is a lack of evidence on whether waist circumference could affect the risk of allergic rhinitis and Liu et al reported there was no difference in waist circumference between allergic rhinitis and controls.[33] However, Choi et al found that waist circumference and body mass index were greater among women without chronic rhinitis than among those with chronic rhinitis,[34] partly consistent with our findings. Here, that higher waist circumference could reduce the risk

of allergic rhinitis might be explained by the activated inflammation and compromised immunity caused by obesity since obesity could trigger the chronic mild systemic inflammation.[35] This was similar to the mechanism that smoking can suppress allergic rhinitis via its immunosuppressive effect. As for vasomotor rhinitis, no related studies have been reported. An up-to-date meta-analysis suggested that obesity/overweight might be associated with a higher risk of allergic rhinitis in children.[36] Obesity is measured by BMI and we hypothesized that different anthropometric traits might have different impacts on rhinitis. Also, we deemed that obesity's impact on rhinitis might be affected by age and it should be further investigated.

Our study did not suggest that blood lipids could serve as indicators for the risk of allergic/vasomotor rhinitis. However, Sheha et al found that TC (total cholesterol) was positively correlated with the severity of allergic rhinitis and dyslipidemia might play a potential role in the severity of allergic rhinitis symptoms and impairment of patients' quality of life via the interleukin-17A (IL-17A).[37] Meanwhile, Vinding et al discovered that high levels of HDL could lower the risk of allergic rhinitis while the triglycerides could elevate the risk of it.[38] These previous studies all indicated that blood lipids were associated with allergic rhinitis while failing to point out whether such association was causal. Although MR is an effective method for causal inference, it might suffer from some biases and the high false negative rate is one of them. Since the IV selection process was very strict and should meet the basic 3 principles, sometimes the statistical power could not be well satisfied. However, considering that the statistical power in our study was sufficient, we preferred to rule out the possibility that blood lipids could affect the risk of allergic/vasomotor rhinitis.

Similar to blood lipids, we did not find that glycemic traits could affect the risk of allergic or vasomotor rhinitis. However, Hashimoto et al reported that the prevalence of allergic rhinitis is lower in subjects with higher levels of fasting plasma glucose,[39] and this conclusion was further confirmed by Hwang et al.[40] Considering the relatively low statistical power, we could not rule out the possibility that HbA1c and fasting glucose affect the risk of allergic or vasomotor rhinitis. The observational results might be biased by potential confounders or the reversal causation.

As for blood pressure, Sakallioglu et al demonstrated that blood pressure was not associated with rhinitis and should not be followed up[41] while Hwang et al found a lower prevalence of allergic rhinitis in the high blood pressure group.[40] Our MR results supported the former conclusion. Li et al did not observe the relationship between allergic rhinitis and blood pressure in adults but suggested an association in young women aged 20–39.[42] Thus, we hypothesized that the blood pressure's effect on rhinitis might be affected by ethnicity and age.

Overall, our MR analysis discovered that smoking can lower the risk of allergic rhinitis while increasing the risk of vasomotor rhinitis. Besides, a higher waist circumference could marginally lower the risk of allergic rhinitis. No other causal relationship was observed. Generally, we think our study has several strengths[1]: The sample size for each risk factor is large and guarantees the statistical power;[2] We strictly followed the basic principles of MR and the results can be convincing;[3] The outcomes include the allergic rhinitis and vasomotor rhinitis, and this is the first MR analysis to investigate the risk factors of vasomotor rhinitis;[4] Our results can be informative in distinguishing 2 rhinitis. However, the chances of both codes of AR and VMR coexistence are hard to give due to the unavailability of individual-level data. Intuitively, the coexistence chances should be low so that we obtained that the smoking should affect AR and VMR differently, even in the opposite direction. Besides, the generalizability of results should be interpreted with caution as we only tested them in European participants.

CONCLUSION

Smoking can lower the risk of allergic rhinitis while elevating the risk of vasomotor rhinitis. This result might help to distinguish 2 rhinitis in clinical practice.

Abbreviations
MR = Mendelian randomization; IVW = inverse-variance weighted; SNP = single nucleotide polymorphism; RCT = randomized controlled trials; GWAS = genome-wide association study; IV = instrumental variable; LD = linkage disequilibrium; MVMR = multivariable Mendelian randomization; OR = odds ratio; SD = standard deviation; BMI = body mass index; WHR = waist-to-hip ratio; HDL = high-density lipoprotein; LDL = low-density lipoprotein; TC = total cholesterol; TG = triglycerides; HbA1c = glycated hemoglobin; SBP = systolic blood pressure; DBP = diastolic blood pressure.

Funding
This work is supported by Science and Technology Plan Project of Liaoning Province [Grant number 20170058].

Authors' consent for publication
All authors have given consent for publication.

Author contributions
A.Y contributed to the study design, supervised the data analysis process, and mainly revised the manuscript. S.W and L.Q were responsible for data acquisition, statistical analysis, and data visualization; and S·W drafted the original manuscript. H.W and L.Q read and revised the original manuscript and gave substantial suggestions on statistics. All authors have approved the publication of this study. A.Y takes responsibility for the integrity of the data and the accuracy of the data analysis.

Ethics approval
All GWAS consortia have approved by corresponding ethical committees.

Availability of data and materials
GWAS summary statistics of smoking and drinking can be accessed via GSCAN (https://conservancy.umn.edu/handle/11299/201564).
GWAS summary statistics of smoking and drinking can be accessed via GIANT (http://portals.broadinstitute.org/collaboration/giant/index.php/GIANT_consortium_data_files).
GWAS summary statistics of blood lipids can be accessed via GLGC (http://lipidgenetics.org/#data-downloads-title).
GWAS summary statistics of glycemic traits can be accessed via MAGIC (https://magicinvestigators.org/downloads/).
GWAS summary statistics of glycemic traits can be accessed via the GWAS catalog (https://www.ebi.ac.uk/gwas/).
GWAS summary statistics of rhinitis can be accessed via FinnGen (https://r4.finngen.fi/).

Declaration of competing interest
No conflicts of interest to be disclosed.

Acknowledgments
We thank all GWAS consortia to make their GWAS summary statistics publicly available, including GSCAN, GIANT, GLGC, MAGIC, and FinnGen.

Appendix A. Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.waojou.2022.100630.

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