Causal Relationships of 38 Risk Factors with Chronic Rhinosinusitis: A Mendelian Randomization Study

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Research Article

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Abstract

Background

At present, the identification of risk factors associated with chronic rhinosinusitis (CRS) remains elusive. Our goal was to systematically investigate modifiable risk factors linked to CRS.

Methods

We conducted univariable Mendelian randomization (MR) based on genome-wide association studies (GWAS) to assess the causal relationships between 38 risk factors and CRS. The primary statistical analysis employed the inverse variance weighted (IVW) method, complemented by MR Egger and weighted median methods, in addition to multiple sensitivity analyses. Following this, we performed multivariable MR to consider the potential confounding effects of gastroesophageal reflux disease (GERD) and evaluate direct causal relationships between risk factors and CRS.

Results

Univariable MR results indicated that cigarettes per day, short sleep duration, overall health rating (OHR), hypertension, allergic rhinitis (AR), GERD, bronchial asthma (asthma), atopic dermatitis (AD), and rheumatoid arthritis (RA) were linked to an increased risk of CRS. Conversely, coffee intake, years of schooling, and apolipoprotein A-I were associated with a reduced risk of CRS. No other risk factors showed an association with CRS. When we adjusted for GERD using multivariable MR, the associations of OHR, RA, asthma, AD, and RA with CRS remained statistically significant. However, the previously observed effects of cigarettes per day, coffee intake, short sleep duration, years of schooling, apolipoprotein A-I, and hypertension were no longer apparent.

Conclusions

Our study suggests direct causal relationships between genetically predicted OHR, RA, asthma, AD, and increased risk of CRS. These findings will significantly contribute to advancing the exploration of CRS etiology.

1. Introduction

Chronic rhinosinusitis (CRS) is a prevalent inflammatory disorder affecting the upper respiratory tract, characterized by persistent inflammation of the sinus mucosa lasting for more than 12 weeks[1]. In Europe, the prevalence of CRS is approximately 10%, while in the United States, it ranges from 12–14%[2,3]. CRS is associated with allergic rhinitis (AR), chronic obstructive pulmonary disease (COPD), and asthma[4]. It also

serves as a significant risk factor for frequent acute exacerbations of COPD and suboptimal control of asthma[5,6]. Additionally, CRS is linked to an increased risk of chronic headaches, myocardial infarction, stroke, and depression[7]. This condition significantly impacts patients' quality of life and imposes a substantial economic burden[8]. Despite extensive research, the precise pathogenesis of CRS remains incompletely elucidated, and the therapeutic efficacy of glucocorticoids or surgery is unsatisfactory. Even after receiving adequate treatment, a substantial proportion of patients still experience suboptimal disease control[3]. Therefore, it is imperative to investigate the risk factors associated with CRS, as this will facilitate etiology-based behavioral interventions for this condition.

A substantial body of evidence from observational studies and meta-analyses consistently indicates an association between CRS and lifestyle factors, including smoking, alcohol consumption, and physical activity[9−11]. Moreover, numerous studies have identified a correlation between metabolic factors such as hypertension, diabetes, hyperlipidemia, and obesity and an increased risk of developing CRS[12]. However, it is crucial to recognize that the existing evidence primarily derives from observational studies. The utilization of observational epidemiological research methods to identify risk factors directly associated with CRS poses significant challenges due to the effect of potential confounding factors and reverse causality. Therefore, there is a need to explore more robust approaches for conducting relevant research.

Mendelian randomization (MR) is a research methodology that utilizes genetic variations as instrumental variables (IVs) to infer causal associations. These genetic variations adhere to the principles of Mendelian random distribution during conception and remain unaffected by confounding factors. This process is also irreversible[13]. Consequently, MR studies can effectively mitigate the influence of confounding factors and avoid reverse causality[14]. However, to date, only a limited number of MR studies have examined the associations between a small set of risk factors and CRS[15]. In response to this gap, our study aims to comprehensively investigate the causal relationship between 38 genetically predicted risk factors and CRS using a two-sample MR approach. Furthermore, to account for the potential effects of gastroesophageal reflux disease (GERD) on these risk factors, we conducted multivariable MR analyses.

2. Methods

2.1 Study design

Single nucleotide polymorphisms (SNPs) were employed as IVs for risk factors. The selected SNPs needed to satisfy the three fundamental assumptions of MR (Fig. 1): (i) robust correlation between SNPs and risk factors, (ii) no association between SNPs and confounding factors affecting the exposure-outcome relationship, and (iii) SNPs solely influencing outcomes through the mediation of risk factors rather than other mechanisms[13]. The study encompassed a total of 38 modifiable risk factors, categorized into four groups: lifestyle, metabolic comorbidities, ambient air pollution, and other risk factors. Data used in this research are publicly available and have received ethical approval in the

primary literature, eliminating the need for additional ethical endorsement. This study was conducted following the Strengthening the Reporting of Observational Studies in Epidemiology Using Mendelian Randomization guidelines[16].

2.2 Data sources

The 38 risk factors included in this study can be categorized into four domains: lifestyle factors encompassing diet, physical activity, sleep traits, overall health rating, and education; metabolic complications involving serum lipids, serum glucose level, serum uric acid level, hypertension, and obesity traits; ambient air pollution, including pm2.5, pm10, pm2.5-10, nitrogen dioxide air pollution, and nitrogen oxides air pollution; as well as other potentially relevant risk factors such as allergic rhinitis (AR), GERD, bronchial asthma (asthma), atopic dermatitis (AD), and rheumatoid arthritis (RA). The IVs for modifiable risk factors were obtained from the largest genome-wide association studies (GWAS) of individuals of European ancestry, including the UK Biobank, the GWAS & Sequencing Consortium of Alcohol and Nicotine use (GSCAN), the Social Science Genetic Association Consortium (SSGAC), and the Genetic Investigation of Anthropometric Traits (GIANT) consortium. To minimize the potential for sample overlap with exposure GWASs, we extracted genetic variables for CRS from the recently released FinnGen R10 dataset. The data sources for exposures and outcomes are summarized in Table 1.

Table 1
An overview of the data sources.

Phenotype	Population	Sample Size	Number of SNPs	Consortium	PMID
Exposure (risk factors)					
Diet					
Alcoholic drinks per week	European	335,394	11,887,865	GSCAN	30643251
Smoking initiation	European	607,291	11,802,365	GSCAN	30643251
Cigarettes per Day	European	337,334	11,913,712	GSCAN	30643251
Coffee intake	European	428,860	9,851,867	UK Biobank	NA
Tea intake	European	447,485	9,851,867	UK Biobank	NA
Relative carbohydrate intake	European	268,922	11,417,549	NA	32393786
Relative fat intake	European	268,922	11,417,549	NA	32393786
Relative protein intake	European	268,922	11,417,549	NA	32393786
Relative sugar intake	European	235,391	11,417,549	NA	32393786
Physical activity					
Moderate physical activity	European	440,266	9,851,867	UK Biobank	NA
Vigorous physical activity	European	440,512	9,851,867	UK Biobank	NA
Sleep traits					
Insomnia	European	336,965	10,894,596	UK Biobank	NA
Daytime napping	European	452,633	13,304,133	UK Biobank	33568662
Morningness	European	449,734	11,977,112	UK Biobank	30696823
Long sleep duration	European	446,118	14,661,602	UK Biobank	30846698
Short sleep duration	European	446,118	14,661,602	UK Biobank	30846698
Education					
Years of schooling	European	766,345	10,101,242	SSGAC	30038396
Physical condition					
Overall health rating	European	460,844	9,851,867	UK Biobank	NA

Abbreviations: GSCAN, GWAS & Sequencing Consortium of Alcohol and Nicotine use; SSGAC, Social Science Genetic Association Consortium; GUGC, Global Urate Genetics Consortium; GIANT, Genetic Investigation of Anthropometric Traits.

Phenotype	Population	Sample Size	Number of SNPs	Consortium	PMID
Exposure (risk factors)					
Diet					
Serum lipids					
HDL cholesterol	European	403,943	12,321,875	UK Biobank	32203549
LDL cholesterol	European	440,546	12,321,875	UK Biobank	32203549
Triglycerides	European	441,016	12,321,875	UK Biobank	32203549
Apolipoprotein B	European	439,214	12,321,875	UK Biobank	32203549
Apolipoprotein A-I	European	393,193	12,321,875	UK Biobank	32203549
Glucose					
Type 2 diabetes	European	655,666	5,030,727	NA	30054458
Blood pressure					
Hypertension	European	461,880	9,851,867	UK Biobank	NA
Uric acid					
Serum uric acid	European	110,347	2,450,548	GUGC	23263486
Obesity traits					
Body mass index	European	681,275	2,336,260	GIANT	30124842
Waist-hip ratio	European	224,459	2,562,516	GIANT	25673412
Ambient air pollution					
Particulate matter air pollution (pm2.5)	European	423,796	9,851,867	MRC-IEU	NA
Particulate matter air pollution (pm10)	European	423,796	9,851,867	MRC-IEU	NA
Particulate matter air pollution 2.5-10um	European	423,796	9,851,867	MRC-IEU	NA
Nitrogen dioxide air pollution	European	456,380	9,851,867	MRC-IEU	NA
Nitrogen oxides air pollution	European	456,380	9,851,867	MRC-IEU	NA

Abbreviations: GSCAN, GWAS & Sequencing Consortium of Alcohol and Nicotine use; SSGAC, Social Science Genetic Association Consortium; GUGC, Global Urate Genetics Consortium; GIANT, Genetic Investigation of Anthropometric Traits.

Phenotype	Population	Sample Size	Number of SNPs	Consortium	PMID
Exposure (risk factors)					
Diet					
Other risk factors					
Allergic rhinitis	European	112,583	9,851,867	MRC-IEU	NA
Gastroesophageal reflux	European	602,604	2,320,781	NA	34187846
Bronchial asthma	European	449,500	24,162,338	UK Biobank	34594039
Atopic dermatitis	European	796,661	16,121,213	NA	34454985
Rheumatoid arthritis	European	58,284	13,108,512	NA	33310728
Outcome					
Chronic rhinosinusitis	European	326,444	21,304,282	FinnGen	NA

Abbreviations: GSCAN, GWAS & Sequencing Consortium of Alcohol and Nicotine use; SSGAC, Social Science Genetic Association Consortium; GUGC, Global Urate Genetics Consortium; GIANT, Genetic Investigation of Anthropometric Traits.

2.3 Instrumental variables selection

According to the fundamental principles of MR, IVs are selected in three steps based on their strong correlation with exposures while being independent of outcomes and confounding factors. (i) We selected SNPs significantly associated with exposures based on a genome-wide significance threshold of 5×10^{-8}. To ensure the robustness of our findings, we adjusted the threshold to 5×10^{-6} for relative dietary intake, pm2.5, pm10, and pm2.5-10, as fewer SNPs were included under the initial 5×10^{-8} threshold. (ii) The included SNPs exhibit minimal likelihood of linkage disequilibrium ($r^2 < 0.001$, window size = 10,000 kb). (iii) We refrained from including SNPs exhibiting palindromic structures and weak IVs. We employed the F-statistic to evaluate the presence of weak instrumental bias in the selected SNPs, with an F-value exceeding 10 indicating a robust instrumental variable that is minimally affected by weak variable bias[17]. The formula for computing the F-statistic is expressed as follows: $F= \frac{R^2}{1-R^2} \times \frac{N-K-1}{K}$, where $R^2 = \frac{2\times\beta^2\times EAF\times 1-EAF)}{2\times\beta^2\times EAF\times 1-EAF +2\times SE^2\times N\times EAF\times 1-EAF}$. N represents the number of participants in exposure GWAS studies, K represents the count of SNPs in IVs, and R^2 signifies the proportion of variance in exposure explained by IVs[18].

2.4 Statistical analysis and data visualization

We employed the inverse variance weighted (IVW) method of random effects as the primary statistical analysis approach in this study, complemented by the weighted median and MR Egger methods[19-21].

The use of the random effects IVW method effectively mitigates the impact of heterogeneity on causality[19]. To ensure the robustness of our results, we conducted a comprehensive set of sensitivity analyses, which included Cochran's Q test, MR Egger intercept test, Mendelian Randomization Pleiotropy RESidual Sum and Outlier (MR-PRESSO) global test, as well as leave-one-out analysis. We employed Cochran's Q test to assess heterogeneity among SNPs. When the random effects IVW method was applied, the causal relationship remained unaffected by heterogeneity ($p < 0.05$). The MR Egger intercept is employed to ascertain the presence of horizontal pleiotropy. If a statistically significant detection of horizontal pleiotropy ($p < 0.05$) occurred, it suggested that the causal relationship might be influenced by potential confounding factors[22]. The MR-PRESSO method was subsequently used to detect and evaluate potential outliers with pleiotropy and to assess whether the causal estimate significantly changed upon their exclusion[23]. Leave-one-out analysis was employed to determine if the causal effects were primarily driven by a single SNP. We visualized the results using scatter plots. All statistical analyses and data visualization were conducted using R Programming Software (version 4.3.1). The "TwoSampleMR" package was employed for univariable MR analyses, while the "MendelianRandomization" package was used for multivariable MR analyses. To address the issue of multiple testing bias, we applied the Bonferroni correction[24]. A significance level of $p < 0.001$ (0.05/38) was considered indicative of a statistically significant association, while a p-value ranging from 0.05 to 0.001 was suggestive of an association. Causal association results were expressed as odds ratios (OR) and 95% confidence intervals (95%CI).

3. Results

We conducted a comprehensive MR analysis of 38 potential risk factors associated with CRS. All IVs utilized in the analysis exhibited F-statistics exceeding 10, and no weak IVs were identified (Supplementary Table 1). Additionally, apart from tea intake, there was no evidence of horizontal pleiotropy detected using the MR Egger intercept test. Despite the detection of partial heterogeneity through Cochran's Q test, it had no impact on the random-effects IVW method employed in this study (Supplementary Table 2).

3.1 Causal effects of lifestyle factors on CRS

The results obtained through the IVW approach demonstrated a significant association between genetically predicted years of schooling and an increased risk of CRS. Additionally, a significant inverse relationship was observed between OHR and the risk of CRS. Genetically predicted cigarettes per day and short sleep duration were suggestively associated with an increased risk of CRS, whereas coffee intake was suggestively associated with a decreased risk of CRS (Fig. 2). Leave-one-out analysis did not find causation driven by a single SNP (Supplementary Fig. 1). Furthermore, no causal relationship was found between genetically predicted alcoholic drinks per week, smoking initiation, tea intake, relative carbohydrate intake, relative sugar intake, physical activity, insomnia, daytime napping, morningness, long sleep duration, and CRS. These causal relationships persisted even after the removal of outliers

identified by MR PRESSO. There was a suggestive association between relative fat and protein intake and a reduced risk of CRS; however, this association became non-significant after excluding an outlier identified by MR PRESSO (Supplementary Table 1).

3.2 Causal effects of metabolic comorbidities on CRS

The results of the IVW method showed that apolipoprotein A-I was suggestively associated with a reduced risk of CRS, while hypertension was suggestively associated with an increased risk of CRS (Fig. 2). These causal relationships remained significant even after the removal of outliers. Leave-one-out analysis did not reveal any single SNP driving causation (Supplementary Fig. 2). Additionally, no causal relationship was found between genetically predicted high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), triglycerides, apolipoprotein B, type 2 diabetes, serum uric acid, body mass index (BMI), waist-hip ratio, and CRS (Supplementary Table 1).

3.3 Causal effects of ambient air pollution and other risk factors on CRS

The IVW method revealed a significant association between genetic prediction of AR, GERD, asthma, and RA with an increased risk of CRS (Fig. 2). Moreover, the results obtained from the MR Egger and weighted median methods were consistent with those from IVW. These causal relationships persisted even after removing the outliers identified by MR PRESSO. While the association between RA and CRS reduced from significance to suggestiveness, it remained consistent in direction. The IVW method showed a suggestive association between AD and CRS, which increased to significance after removing the outliers identified by MR PRESSO (Supplementary Table 1). Leave-one-out analysis did not provide any evidence of causation attributed to a single SNP (Supplementary Fig. 3). No association was found between the five risk factors representing ambient air pollution and CRS (Supplementary Table 1).

3.4 Multivariable MR analysis

Given the established association between GERD and CRS, we employed multivariable MR adjustment to account for potential pleiotropy related to GERD. This allowed us to evaluate the direct causal impact of various risk factors (including cigarettes per day, coffee intake, short sleep duration, years of schooling, OHR, apolipoprotein A-I, hypertension, AR, GERD, asthma, AD, and RA) on CRS. The results obtained from the IVW method demonstrated that the significant associations between OHR, AR, asthma, AD, RA, and an increased risk of CRS remained robust even after adjusting for the impact of GERD. Furthermore, these associations were not substantially altered in terms of effect sizes (Fig. 3). The findings from MR Egger and weighted median analyses were generally consistent with those obtained through IVW, thereby providing additional validation for the robustness of our results (Supplementary Table 3). However, upon adjusting for potential pleiotropic effects of GERD, the associations between cigarettes per day, coffee intake, short sleep duration, years of schooling, apolipoprotein A-I, hypertension, and the risk of CRS were no longer statistically significant (Fig. 3). This suggests that the causal associations between these risk factors and CRS identified by univariable MR are entirely mediated by GERD.

4. Discussion

In this study, we leveraged publicly available GWAS data to conduct a comprehensive investigation into the correlation between 38 modifiable risk factors and CRS. Our study unveiled significant associations between genetically predicted OHR, GERD, AR, asthma, AD, RA, and an increased risk of CRS. However, we did not observe any significant causal relationship between other modifiable risk factors and CRS. These findings significantly enhance our understanding of the etiology of CRS.

Our univariable MR analysis revealed significant associations between cigarettes per day, coffee intake, short sleep duration, years of schooling, apolipoprotein A-I, hypertension, and CRS. However, these associations vanished when employing multivariable MR to account for potential confounding effects arising from GERD. These findings suggest that the observed associations between these risk factors and CRS do not imply direct causal relationships. Numerous observational studies have consistently demonstrated a robust correlation between tobacco exposure and the onset of CRS[2,25]. Although some researchers have suggested smoking as a potential risk factor for CRS, this hypothesis remains controversial and lacks widespread acceptance[7]. Our study also demonstrated a consistent association between smoking and an elevated risk of CRS, in line with previous observational studies. However, our findings further revealed that this relationship was fully mediated by GERD rather than being a direct causal association. Therefore, our study suggests that smoking does not appear to be a significant risk factor for CRS. Similarly, the results of multivariable MR also revealed that the associations between coffee intake, short sleep duration, years of schooling, apolipoprotein A-I, hypertension, and CRS were fully mediated by GERD, rather than indicating direct causal relationships.

The association between GERD and CRS has been substantiated by several recent observational studies, meta-analyses, and MR studies[26–28]. Furthermore, two recent MR studies have demonstrated a significant association between GERD and an increased risk of CRS, even after controlling for various potential confounding factors[29,30]. Remarkably, one of these MR studies also observed that antireflux treatment with omeprazole reduced the risk of CRS, which further supports the conclusions drawn from our research[29]. While the precise mechanism remains elusive, it is postulated that gastric content reflux, nerve conduction disorders, and Helicobacter pylori infection may potentially contribute to this phenomenon[31–33].

Our study unveiled a noteworthy correlation among OHR, AR, asthma, AD, and RA, indicating an increased risk of CRS. Notably, this correlation remained strong even after accounting for the potential confounding impact of GERD. This implies that these factors independently function as mediators in the development of CRS, establishing them as individual risk factors for CRS. Several observational studies have consistently highlighted connections between AR, asthma, and CRS[7,34]. Moreover, a prior MR study has firmly established a causal link among these conditions[15]. Our findings align with this conclusion, as we have replicated it using the latest CRS data from FinnGen R10. This not only reinforces the reliability of our results but also enhances the overall robustness and reproducibility of this identified relationship. AR, asthma, and CRS are respiratory conditions marked by dysregulated immune responses. While AR and

CRS are identified as upper airway disorders, asthma is categorized as a lower airway disease. This classification implies a potential connection involving immune dysregulation in both the upper and lower respiratory tracts. This phenomenon could be attributed to the spread of inflammation in both the upper and lower airways. A more plausible explanation is that they share a common pathophysiology[35]. Moreover, our study revealed a noteworthy correlation among AD, a skin immune disorder-related condition, RA, a systemic immune disorder, and an elevated risk of CRS. This suggests a connection not only between the immunity of the upper and lower airways but also between the airways and the skin, and even systemic immunity. While the mechanism remains unclear, our study offers compelling genetic evidence supporting a causal relationship.

Interestingly, in contrast to numerous observational studies and a prior MR inquiry[15,36,37], our research discovered no evidence supporting an association between BMI and CRS. Observational studies often grapple with confounding factors and may encounter issues of reverse causality. The previous MR study merely hinted at an association between BMI and CRS. Diverging from the earlier MR study, our investigation leans on the latest and comprehensive GWAS data, bolstering the reliability of our findings. Given the exploratory nature of our study, caution is imperative when excluding potential CRS-related risk factors. To validate our conclusion in the future, a larger sample size and a more stringent experimental design will be indispensable.

Our study possesses several notable strengths. Firstly, we utilized the MR research methodology to comprehensively investigate the causal effects of 38 risk factors on CRS from a genetic perspective, thus avoiding the influence of confounding factors and the issue of reverse causality. Secondly, we conducted multiple sensitivity analyses to ensure the robustness of our findings. Additionally, we employed multivariable MR to account for potential confounding by GERD, which further increased our confidence in the validity of our conclusions.

We acknowledge several limitations of our study. Firstly, it's important to note that our study was conducted exclusively on a European population, limiting the generalizability of our findings to this specific demographic. Future investigations are needed to determine whether these conclusions can be extrapolated to other populations. Furthermore, our study focused on examining the association between risk factors and overall CRS, without conducting subgroup analyses due to data constraints, both with and without nasal polyps. Lastly, while our study established direct causal associations between several risk factors and CRS from a genetic perspective, it did not elucidate the specific underlying mechanisms, which will require further investigation in future studies.

5. Conclusion

This study identified OHR, GERD, AR, asthma, AD, and RA as significant risk factors for CRS. No other modifiable risk factors affecting CRS were observed. These findings enhance our understanding of the connections between these diseases and CRS, providing valuable insights into clarifying the etiology of CRS.

Declarations

Ethical approval

The data utilized in this study were sourced from publicly available GWAS statistics. Ethical approval and informed consent from participants had already been secured for all original studies. Consequently, no additional ethical approval or informed consent was necessary for this study.

Data availability

The GWAS summary statistics utilized in this MR study were sourced from publicly available GWAS databases, and their specific sources have been indicated in the article.

Author contributions

Guobing Jia designed the research and wrote the manuscript; Guo Tao assisted in collecting data; Lei Liu assisted in analyzing data; Chengshi He assisted in designing the study and proofreading the manuscript. All authors read and approved the submitted version.

Conflict of interests

The authors claim that no interests were involved in this study.

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Figures
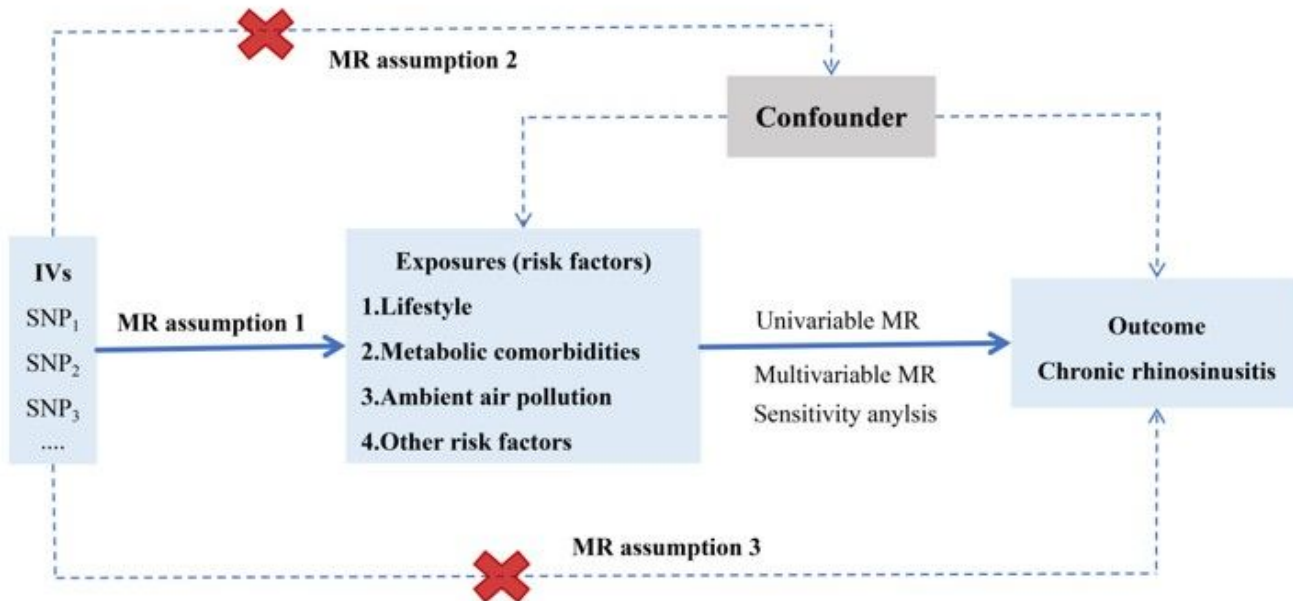
Figure 1

An overview of the MR study design: MR assumption 1, MR assumption 2, and MR assumption 3 represent the three basic assumptions of MR. MR assumption 1 states that the selected SNPs exhibit a robust correlation with risk factors. MR assumption 2 asserts that the selected SNPs show no association with confounding factors that could affect the relationship between exposure and outcome. MR assumption 3 emphasizes that the selected SNPs can solely influence outcomes through the mediation of risk factors rather than any other mechanisms.

Risk factors	nSNPs	OR(95%CI)	P-value		P(Egger intercept)
Lifestyle factors					
Cigarettes per day	22	1.12(1.00 to 1.25)	0.049		0.817
Coffee intake	38	0.64(0.47 to 0.88)	0.005		0.353
Short sleep duration	24	4.53(1.90 to 10.78)	0.001		0.833
Years of schooling	299	0.80(0.71 to 0.91)	4.14E-04		0.651
Overall health rating	102	2.51(1.73 to 3.63)	1.11E-06		0.717
Metabolic complications					
Apolipoprotein A−I	267	0.92(0.85 to 0.98)	0.016		0.738
Hypertension	217	1.43(1.08 to 1.88)	0.011		0.548
Other risk factors					
Allergic rhinitis	32	4.27(1.49 to 12.28)	0.007		0.853
Gastroesophageal reflux	75	1.25(1.11 to 1.41)	2.45E-04		0.404
Bronchial asthma	93	1.68(1.52 to 1.86)	3.27E-24		0.308
Atopic dermatitis	21	1.20(1.08 to 1.34)	0.001		0.146
Rheumatoid arthritis	85	1.10(1.07 to 1.13)	8.51E-10		0.270

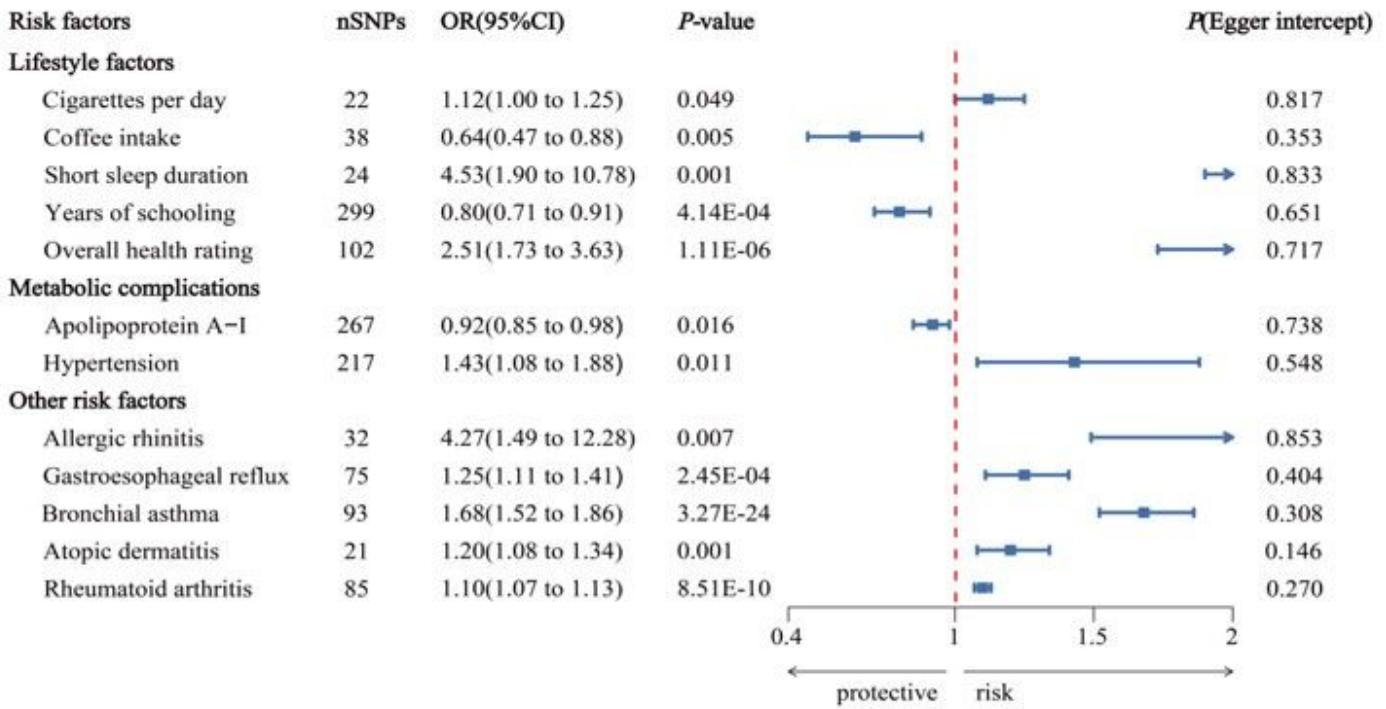0.4　　1　　1.5　　2

← protective　risk →

Figure 2

Associations of modifiable risk factors with CRS. Abbreviations: nSNPs, number of SNPs; OR (95%CI), odds ratios (95% confidence interval).

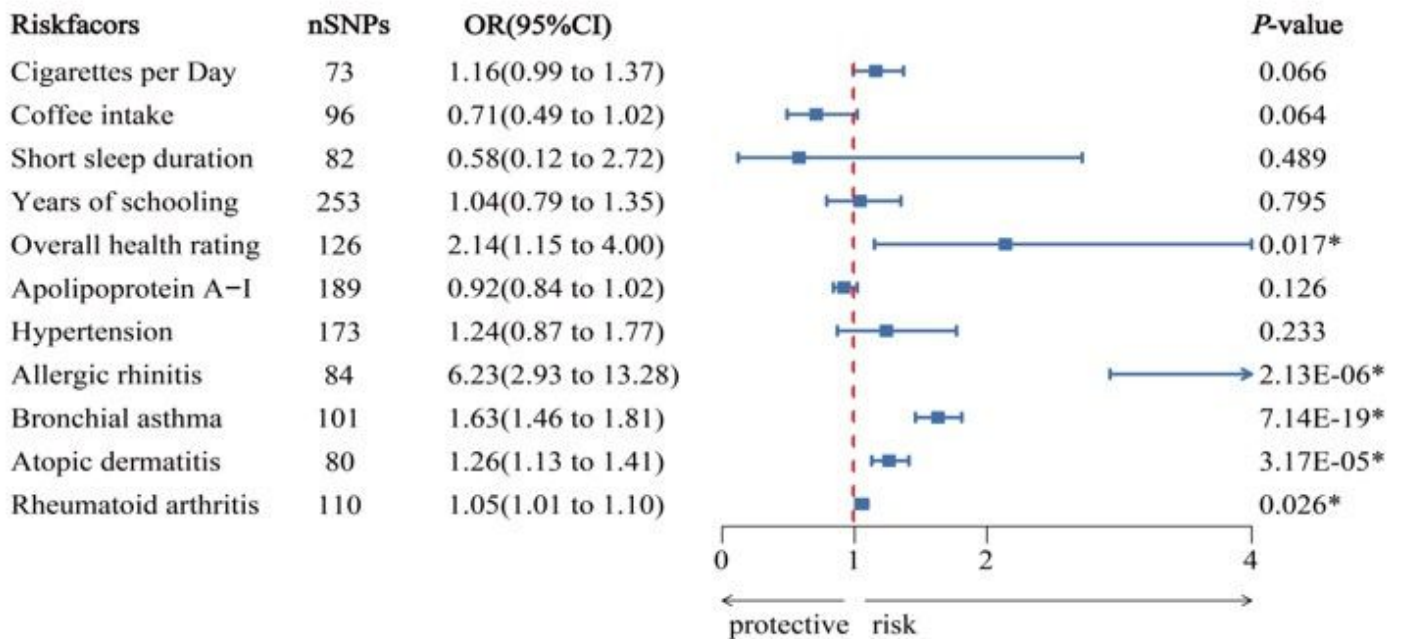| Riskfacors	nSNPs	OR(95%CI)		P-value
Cigarettes per Day	73	1.16(0.99 to 1.37)		0.066
Coffee intake	96	0.71(0.49 to 1.02)		0.064
Short sleep duration	82	0.58(0.12 to 2.72)		0.489
Years of schooling	253	1.04(0.79 to 1.35)		0.795
Overall health rating	126	2.14(1.15 to 4.00)		0.017*
Apolipoprotein A−I	189	0.92(0.84 to 1.02)		0.126
Hypertension	173	1.24(0.87 to 1.77)		0.233
Allergic rhinitis	84	6.23(2.93 to 13.28)		2.13E-06*
Bronchial asthma	101	1.63(1.46 to 1.81)		7.14E-19*
Atopic dermatitis	80	1.26(1.13 to 1.41)		3.17E-05*
Rheumatoid arthritis	110	1.05(1.01 to 1.10)		0.026*

0　　1　　2　　4

← protective　risk →

Figure 3

The associations between gastroesophageal reflux adjusted risk factors and CRS by multivariable MR.

Abbreviations: nSNPs, number of SNPs; OR (95%CI), odds ratios (95% confidence interval).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryFigures.docx
- SupplementaryTables.docx