Community Dental Health (2024) **41,** 145–151
Received 8 December 2023; Accepted 12 April 2024; Online 1 May 2024

doi:10.1922/CDH_00274Hua07

Is there a causal relationship between autoimmune diseases and oropharyngeal cancer?

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Background: Autoimmune diseases (AIDs) are linked to oropharyngeal cancer (OPC), but the exact nature of this association remains unclear. This study aims to examine the potential causal effect of AIDs on the risk of developing OPC. ***Method***: Information regarding AIDs was collected from the UK Biobank dataset and the Finn Gen study. OPC data were sourced from the IEU Open GWAS project. All data were derived from European populations. Inverse variance weighted (IVW) to two-sample Mendelian randomization (MR) was complemented by weighted median and MR Egger validation analyses. ***Result***: The development of asthma (AS), multiple sclerosis (MS), and rheumatoid arthritis (RA) influenced the risk of developing OPC. However, the reverse MR analysis did not provide evidence for the impact of OPC on AIDs. Sensitivity analysis using MR corroborated the IVW results. The IVW results indicate OR values of 1.004 for AS, 0.936 for MS, and 1.0002 for RA. ***Conclusion***: This MR study supports a causal relationship between asthma and rheumatoid arthritis for OPC in a European population. Multiple sclerosis was protective against OPC.

Keywords*: Causality, Mendelian randomization, Oropharyngeal cancer, Autoimmune diseases*

Introduction

Oropharyngeal cancer (OPC) includes malignancies of the tonsils, base of the tongue, soft palate, and uvula. The prognosis for OPC is relatively poor. The five-year survival rate for OPC cases during the period of 2009-2013 was approximately 55% to 60% (Langdon *et al*., 2020; Lechner *et al*., 2022). It is crucial to comprehend the reasons for OPC as a result. Genetics, environment, immunological dysregulation, and inflammatory responses are common pathophysiologies of autoimmune diseases; further research is necessary to fully understand the specific mechanisms underlying each type of autoimmune disease, as they differ from one another (Qi *et al*., 2023).

Autoimmune diseases (AIDs) comprise conditions such as asthma (AS), multiple sclerosis (MS), rheumatoid arthritis (RA), psoriasis (Pso), hypothyroidism (HT), ulcerative colitis (UC), osteoarthritis (OA), and others in which the immune system unintentionally targets and destroys healthy tissues in the body and organs (Zhou *et al*., 2022). Genetics, the environment, immunological dysregulation and inflammatory responses are common pathophysiologies of AIDs. Further research is necessary to fully understand the specific causal mechanisms underlying each type of AID, as they differ from one to the next (Stojanovich and Marisavljevich, 2008). A systematic review and meta-analysis suggested that patients with autoimmune diseases have a higher risk of developing head and neck cancer than the general population (Batista *et al*., 2023). Some research links AIDs to OPC, indicating that people with AIDs may be more susceptible to HPV infection (Burd and Dean, 2016). While epidemiologic research indicates a possible link between OPC and AIDs, it is unclear if there is a direct causal relationship between the two because these results are sometimes confounded by other factors. Therefore, it is crucial to investigate the causal link between OPC and AIDs and rule out confounding.

Mendelian randomization (MR) is a statistical model that uses genetic variation as an instrumental variable and has been widely used in causality analysis studies in recent years with the boom in genome-wide association analysis data. The basic principle of MR analysis is to use the relationship between genes and phenotypes thereby determining whether there is a causal relationship between a gene and a trait. This approach is based on the second law of Mendelian genetics viz. Genetic variation is randomly distributed between individuals and populations to produce an experimental process similar to a randomized controlled trial. Compared with traditional epidemiology, MR has the following advantages: First, it avoids the interference of confounding factors, because the genetic variants that carry the determining phenotypes are randomly distributed in the population, so it can exclude the interference of confounding factors in the observational study, and thus infer causality more accurately. Second, it improves the credibility of causal inference: MR is free of selection error and information error. Third, MR can be used to validate the results of observational studies, and fourth, it has a wider range than trials and is more time and labor efficient than traditional observational studies. The data used in this study were derived from publicly available genome-wide association analysis summary data (GWAS-Summary data), a type of genetic data widely used in genetic research. GWAS are large-scale studies that examine genetic variation across

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many individuals to identify genetic variants associated with specific traits or diseases. This data usually contain a list of genetic variants, known as single nucleotide polymorphisms (SNPs), and their corresponding p-values, which reflect the strength of association between each variant in a case sample and the trait or disease being studied. (MR) studies use instrumental variables (IVs) methods to control for confounding factors, assess the influence of exposure on outcome, and explore the connections between genes and phenotypes to ascertain if the observed association between exposure and outcome is likely to be causal (Ference, 2022; Sekula *et al*, 2016). This study aimed to determine if there was a cause-and-effect link between AIDs (AS, MS, RA, Pso, HT, UC, OA) and OPC using a bidirectional two-sample MR.

Method

The instrumental variables (IVs) used in this study were chosen based on three primary hypotheses: 1. The independence assumption: IVs were not related to any confounding factors. 2. The correlation assumption: IVs were correlated with the exposure. 3. The exclusion restriction assumption: IVs could only affect the result through exposure factors. In MR research, IV is an instrumental variable used to infer the effect of exposure factors on outcomes. This variable must be associated with the exposure factor while not directly affecting the outcome, only through its effect on the exposure factor and thus the outcome. Thus, the IV can simulate the effect of randomized treatments and help exclude confounding and reverse causation. Genotypes are often used as IVs because they are determined at the time of fertilization and are usually not affected by the environment. This allows genotypes to be used as natural IVs to simulate randomized treatments in order to infer the causal effects of exposure factors on outcomes. Single Nucleotide Polymorphisms (SNPs) are common genetic variants that represent two different bases at a single location in the genome. In MR studies, researchers may select SNPs associated with exposure factors as IVs to explore the effect of that genotype on an outcome. By identifying SNPs associated with exposure factors and utilizing these SNPs as IVs, the researcher can use the random distribution of genotypes to infer the causal effect of the exposure factor on an outcome for MR analysis. Taken together, concepts such as IV and SNP have been used in MR studies to establish a framework for causal inference to better understand the relationship between complex diseases and health outcomes by utilizing the random distribution of genotypes and the relationship between genes and diseases to infer the impact of exposure factors on outcomes.

Our analysis was conducted using the Two Sample MR R package (version 0.5.7) within the R statistical software (version 4.3.1). Initially, the SNPs associated with the exposure factors were screened using a significance threshold of $P<5*10^{-6}$ to minimize the influence of confounding factors. SNPs were then filtered out using the PLINK clumping algorithm, which included a chain imbalance parameter of $r^2 < 0.001$ and a clumping distance cutoff of 10,000 kb. Additionally, the validity of instrumental variables (IVs) was assessed by calculating the R^2 and F-statistic using specific formulas to ensure that the correlation assumptions of the IVs were satisfied: $F=R^2(N-2)/(1-R^2)$;
$R^2=(2\times EAF\times(1-EAF)\times beta2)/(2\times EAF\times(1-EAF)\times beta2)+(2\times EAF\times(1-EAF)\times N\times SE(beta)2)$, $R^2=2\times EAF\times(1-EAF)\times beta2$(SNPs<10), where $F < 10$ was considered to have a weak IV bias (Papadimitriou *et al*., 2020). Matching was subsequently conducted in the final dataset to eliminate SNPs with a palindromic structure. The primary research method employed was Inverse Variance Weighted (IVW), complemented by Weighted Median and MR Egger to validate the analysis. The Wald value was computed for each SNP, and the meta beta value was determined using IVW for each SNP, which was then converted to an odds ratio (OR). Cochran's Q test and MR Egger regression were utilized to validate diversity and multiplicity. The MR-PRESSO test was employed to identify abnormal SNPs, and a leave-one-out test was conducted to evaluate the impact of each SNP on the outcomes for sensitivity analysis. A statistical significance level of $P < 0.05$ was considered significant. Various visual representations, including scatterplots, leave-one-out plots, funnel plots, and forest plots, were generated using the Two Sample MR package.

Summary statistics for the seven autoimmune and inflammatory diseases and oral potentially malignant disorders included in the investigation were obtained from the GWAS Catalog (https://www.ebi.ac.uk/gwas/downloads/summary-statistics), IEU Open GWAS project, UK Biobank dataset (http://www.ukbiobank.ac.uk/), and FinnGen dataset (https://www.FinnGen.fi/en) (Kurki *et al.*, 2023). The research used openly available, publicly aggregated data that did not require ethical approval. The original publication provides detailed information on the diagnostic criteria and procedures used for population recruitment. Furthermore, minimal overlap was observed among the populations in the GWAS data. Phenoscanner (http://www.phenoscanner.medschl.cam.ac.uk/) was used to identify SNPs for pleiotropy; pleiotropic SNPs were included in the analysis and later removed if sensitivity analyses revealed horizontal pleiotropy.

Results

We examined the causal association between AIDs and OPC by analyzing seven distinct exposure factors (Table 1). All 14 instrumental variable analyses demonstrated F-statistics exceeding 10. In general, an F-statistic of more than 10 is considered to be stronger evidence that the effect of IV on the association between exposure and outcome is significant, which strengthens the inference of causality, and there was no evidence of weak instrumental variable bias.

The MR analysis identified a direct cause-and-effect connection between AS, MS, RA, and OPC with MS being protective against OPC. The IVW results demonstrated a significant correlation between AS and OPC (IVW: OR=1.004, 95%CI: 1.0009-1.0068), MS and OPC (IVW: OR=0.936, 95%CI: 0.892-0.982), and RA and OPC (IVW: OR=1.0002, 95%CI: 1.00002-1.00033), consistent with the findings of the Weighted Median and MR Egger's analyses. The IVW findings for the remaining four AIDs did not demonstrate any impact on

the likelihood of developing OPC. This was consistent with the Weighted Median and MR Egger methods, both of which showed no evidence of heterogeneity or pleiotropy and demonstrated statistical robustness. Our MR analysis of the causal relationship between the seven AIDs and OPC is displayed in Table 2. Scatter plots and LOO tests showed that the results were stable (Figure 1, Figure 2). All statistical results were reliable (Figure 3). The Supplementary Information contains comprehensive study data. All SNPs derived from the seven MR analyses focusing on AIDs-OPC, exhibited F-statistics greater than 10 and showed no evidence of weak instrumental variable bias. Our original data has been uploaded to Figshare (DOI:10.6084/m9.figshare.25611201), an open-access data storage and sharing platform designed to make it easy for researchers to store, manage, and share their research data, code, and other academic achievements.

Our retrospective MR analysis, with OPC as the exposure variable and AIDs as the outcomes, and using the IVW, Weighted Median, and MR Egger methods all consistently suggested that OPC did not increase the risk of developing AIDs. Comprehensive results are provided in the supplementary table on Figshare. In the seven MR analyses (OPC-AIDs) the F-statistics for all SNPs exceeded 10, suggesting the absence of weak instrumental variable bias.

Discussion

Mendelian randomisation uses genetic variation associated with modifiable risk factors to explore their potential causal relationship with a specific outcome. Unlike conventional observational studies, MR minimizes the influence of confounding factors such as lifestyle and socioeconomic variables. MR utilizes SNPs that are typically strongly associated with the exposure being investigated and are not prone to confounding or reverse causation (Lawlor *et al.*, 2008; Sekula *et al*., 2016). In this study, we observed indications of a causal association between two autoimmune diseases (asthma and rheumatoid arthritis) and OPC in a two-sample MR analysis. Multiple sclerosis was protective against OPC. Four other AIDs (Psoriasis, hypothyroidism, ulcerative colitis and osteoarthritis) did not demonstrate a causal relationship with OPC. Furthermore, reverse MR analyses did not reveal a causal link between OPC and AIDs (Davies *et al.*, 2018; Skrivankova *et al*., 2021).

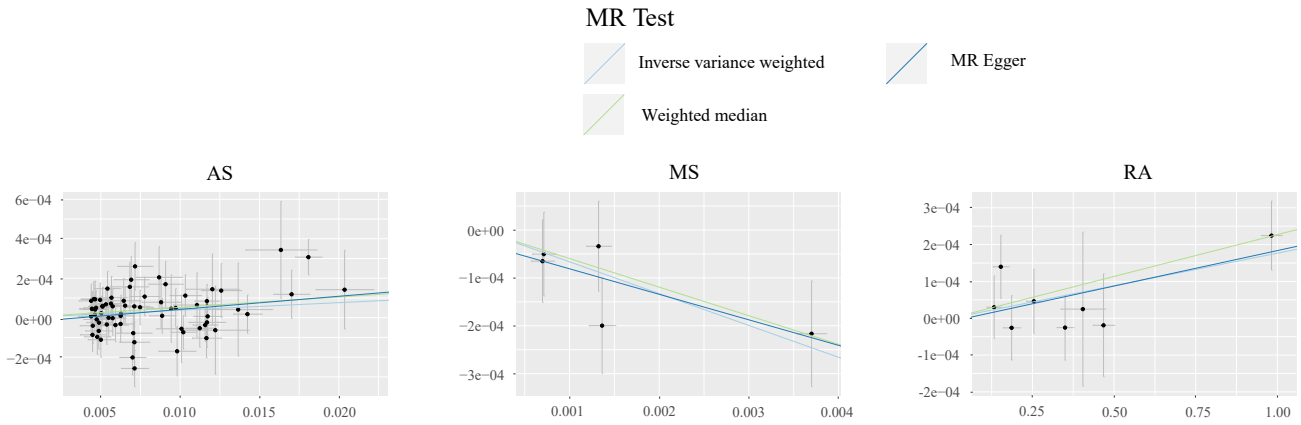
Numerous studies have demonstrated that the immune system is crucial to the pathophysiology of both cancer and AIDs, and that people with these conditions are more likely to develop cancer (Franks and Slansky, 2012). AS is a chronic inflammatory condition, and numerous research studies indicate that prolonged inflammation is associated with an increased vulnerability to cancer. Approximately 15-20% of solid tumors may be attributed to chronic inflammation (Coussens and Werb, 2002; Lin *et al*., 2015; Multhoff *et al.*, 2011; Woo *et al*., 2021). The immune regulators IL-1, TNF, and IL-6 play promote inflammation-induced tumor formation by stimulating transcription factors (NF-κB, STAT-3, and HIF-1) involved in tumor-associated inflammation at different stages of tumorigenesis (Karin, 2006; Multhoff *et al*., 2011; Woo *et al*., 2021). Guo et al. (2023) discovered that individuals with a history of AS had a 1.36-fold higher risk of developing cancer compared to those without. Our analysis supports a causal link between asthma and OPC.

Table 1. Characteristics of the autoimmune disease and oropharyngeal cancer GWAS cohorts.

Disease	*GWAS ID*	*No. Cases*	*No. Controls*	*No. SNPs*
Oropharyngeal cancer	ieu-b-4968	494	372016	8283869
Asthma	ukb-a-66	39049	298110	10894596
Multiple sclerosis	ukb-b-17670	1679	461254	9851867
Rheumatoid arthritis	finn-b-RHEUMA_SEROPOS_OTH	4539	214196	16380466
Psoriasis	ukb-b-10537	5314	457619	9851867
Hypothyroidism	ukb-b-4226	9674	453336	9851867
Ulcerative colitis	ukb-b-7584	2439	460494	9851867
Osteoarthritis	ukb-b-14486	38472	424461	9851867

Table 2. Mendelian randomization analysis of the causal relationship between seven autoimmune diseases and oropharyngeal cancer.

Exposure	*nsnps*	*Inverse Variance Weighted*		*Weighted median*		*MR Egger*	
		OR	*95%CI*	*OR*	*95%CI*	*OR*	*95%CI*
Asthma	70	1.004	1.0009-1.0068	1.01	1.00-1.01	1.01	1.00-1.01
Multiple sclerosis	5	0.936	0.892-0.982	0.94	0.89-0.99	0.95	0.87-1.03
Rheumatoid arthritis	8	1.0002	1.00002-1.00033	1.0002	1.00-1.00	1.0002	1.00-1.00
Psoriasis	21	1.01	0.999-1.020	1.01	1.00-1.02	1.01	1.00-1.02
Hypothyroidism	35	1.01	0.997-1.022	1.00	0.99-1.02	1.02	1.00-1.06
Ulcerative colitis	9	0.97	0.896-1.061	0.97	0.89-1.05	0.79	0.54-1.16
Osteoarthritis	6	0.99	0.959-1.015	0.98	0.96-1.00	0.95	0.89-1.00



x-axes represent the genetic association with the risk of the autoimmune disease
y-axes represent the genetic association with the risk of oropharyngeal disease

***Figure 1**. Mendelian randomisation effects of asthma, multiple sclerosis and rheumatoid arthritis on oropharyngeal cancer.*

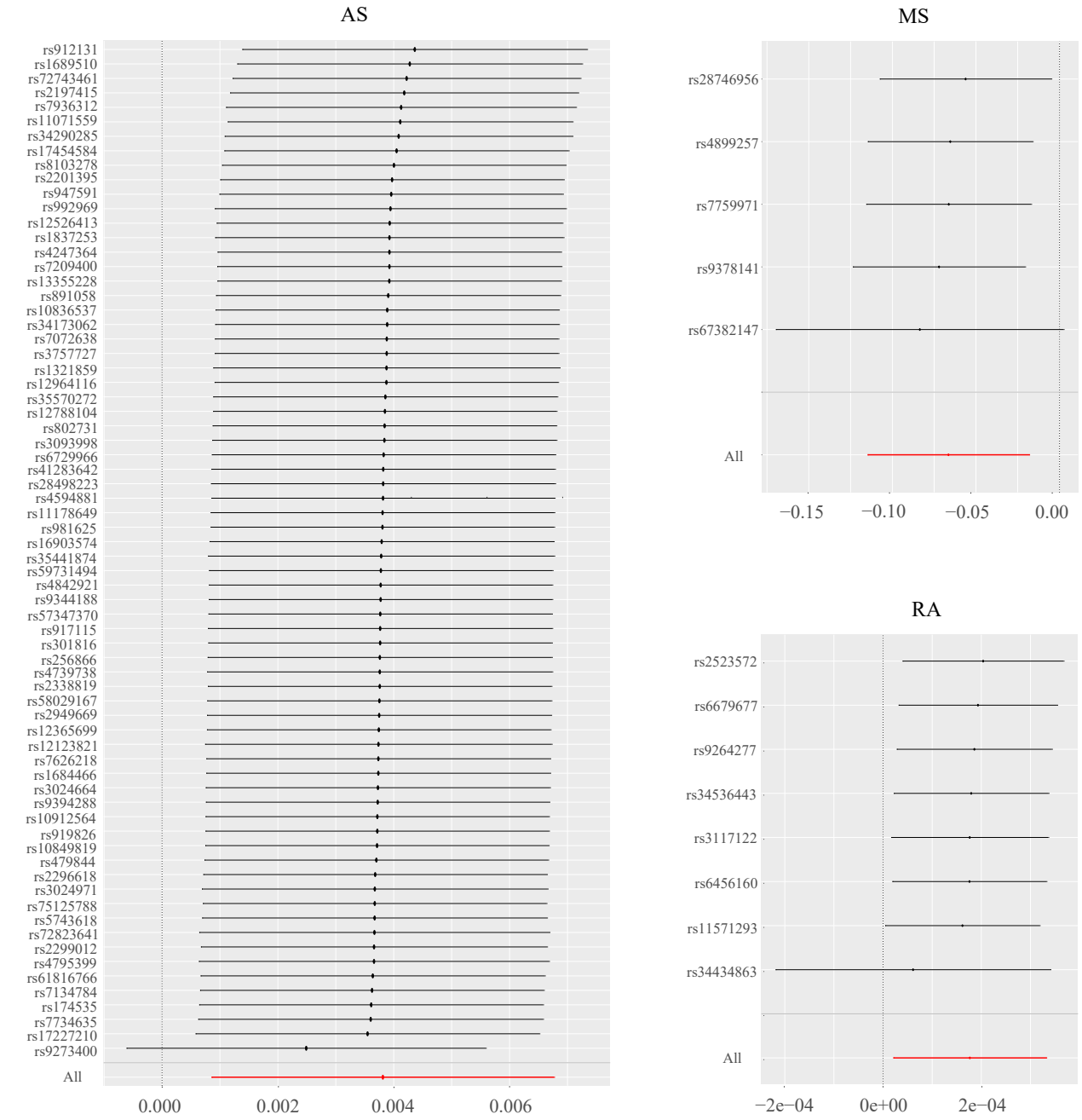


***Figure 2**. Leave one out analysis MR analysis for causal link between asthma, multiple sclerosis and rheumatoid arthritis on oropharyngeal cancer.*

Exposure	Method	nsnp	OR(95%CI)	pval
Asthma	MR Egger	70	1.01(1.00 to 1.01)	0.077000000
Asthma	Weighted median	70	1.01(1.00 to 1.01)	0.020000000
Asthma	Inverse Variance Weighted	70	1.00(1.00 to 1.01)	0.011000000
Multiple sclerosis	MR Egger	5	0.95(0.87 to 1.03)	0.295146560
Multiple sclerosis	Weighted median	5	0.94(0.89 to 0.99)	0.031804904
Multiple sclerosis	Inverse Variance Weighted	5	0.94(0.89 to 0.98)	0.007041236
Rheumatoid arthritis	MR Egger	8	1.00(1.00 to 1.00)	0.179000000
Rheumatoid arthritis	Weighted median	8	1.00(1.00 to 1.00)	0.010000000
Rheumatoid arthritis	Inverse Variance Weighted	8	1.00(1.00 to 1.00)	0.026000000
Psoriasis	MR Egger	21	1.01(1.00 to 1.02)	0.148000000
Psoriasis	Weighted median	21	1.01(1.00 to 1.02)	0.134000000
Psoriasis	Inverse Variance Weighted	21	1.01(1.00 to 1.02)	0.080000000
Hypothyroidism	MR Egger	35	1.02(1.00 to 1.06)	0.191000000
Hypothyroidism	Weighted median	35	1.00(0.99 to 1.02)	0.846000000
Hypothyroidism	Inverse Variance Weighted	35	1.01(1.00 to 1.02)	0.127000000
ulcerative colitis	MR Egger	9	0.79(0.54 to 1.16)	0.271000000
ulcerative colitis	Weighted median	9	0.97(0.89 to 1.05)	0.410000000
ulcerative colitis	Inverse Variance Weighted	9	0.97(0.90 to 1.06)	0.556000000
Osteoarthritis	MR Egger	6	0.94(0.89 to 1.00)	0.140000000
Osteoarthritis	Weighted median	6	0.98(0.96 to 1.00)	0.118000000
Osteoarthritis	Inverse Variance Weighted	6	0.99(0.96 to 1.01)	0.350000000

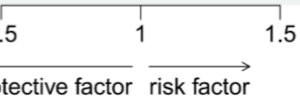


Figure 3. *Forest plots of causal relationship for the effect of autoimmune diseases on oropharyngeal cancer.*

Multiple sclerosis is a chronic autoimmune and inflammatory demyelinating disease of the central nervous system with Epstein-Barr virus (EBV) the primary infectious agent responsible (Bjornevik *et al*., 2022; Marcus, 2022; Soldan and Lieberman, 2023). Multiple reports correlate EBV with the onset of OPC, with EBV DNA identified in oropharyngeal malignancies. EBV is commonly found in the tonsils and the base of the tongue. It remains in the oral cavity, latent in the epithelial squamous cells. It then spreads through the oropharyngeal epithelium and undergoes a cycle of reactivation (Migliaro *et al*., 2022; Soldan and Lieberman, 2023; Turunen, Rautava, Grenman, Syrjanen, and Syrjanen, 2017). Certain oropharyngeal tumors exhibit elevated levels of EBV, while others lack detectable EBV. This may be due to a "hit-and-run" mechanism, in which EBV contributes to tumor formation and then evades detection (Guidry *et al*., 2018). Interestingly, our MR analysis suggests that MS is a protective factor for OPC. This may be because patients with MS are protected from cancer by increased immune surveillance, and the autoimmune changes that contribute to the pathogenesis of MS may be responsible for the reduced cancer risk (Bahar *et al*., 2023).

This research also supported a causal link between rheumatoid arthritis and OPC. RA is a systemic inflammatory auto immune disease of unknown cause, primarily affecting the joints with frequent extra-articular symptoms. RA is characterized by joint swelling and pain. Individuals with RA exhibit heightened levels of several cytokines, such as TGF-β, TNF-α, IL-6, and IL-1. In particular, TGF-β has both pro-inflammatory and systemic immunosuppressive properties, contributing to the development of fibrosis and cancer in RA (Massague and Sheppard, 2023; Patel *et al*., 2020). Guan and colleagues (2021) identify a correlation between TGF-β1 polymorphisms and HPV16 tumors and found that TGF-β shows an increased susceptibility to HPV infection (Guan *et al*., 2010; Mills and McGuirk, 2004). The incidence of OPC has increased, particularly caused by HPV16 infections, in some regions. This results in an increase in mortality among affected individuals (Chaturvedi *et al*., 2023). Additionally, a cohort study conducted by Cordtz et al. (2016) found that patients with RA undergoing treatment with biological DMARDs (bDMARDs) were more susceptible to OPC. These findings align with the results of our MR analysis, which suggests a causal relationship between RA and OPC. It is important for clinicians to be mindful of the potential increased risk of OPC in people with RA.

Psoriasis is a genetic disorder mediated by the immune system that can affect the skin and or joints (Boehncke and Schon, 2015). Our analysis revealed no association between OPC and Pso. Pso has been found to activate STAT3, and high nuclear STAT3 expression was associated with a favorable outcome in head and neck squamous cell carcinoma. Nevertheless, the effects of different stimulation modalities on STAT3 activation varied, meaning that inflammatory stimuli from cytokines (e.g., IL-17 and IL-22) may activate STAT3 without influencing the risk of OPC (Kishimoto *et al*., 2021).

Hypothyroidism occurs when the thyroid gland is unable to produce enough thyroid hormones, which lowers the body's metabolic rate and impairs a number of biological processes. HT was not linked to OPC in our analysis. Hellevik et al. (2009) discovered no connection between HT and overall cancer risk.

Ulcerative colitis is a chronic inflammatory disease of the colon, the etiology of which is unknown. Again, we found no causal link between UC and OPC. Whilst patients with inflammatory bowel disease have an increased risk of oral cancer the association with OPC is unknown (Adams and Bornemann, 2013; Katsanos *et al.*, 2016).

Osteoarthritis is a common joint disease, with both incidence and prevalence increasing with age (Mandl, 2019). No causal relationship was found between OA and OPC based on this MR analysis.

This two-sample two-way MR analysis found that AS and RA, predicted based on genetic levels, were causally associated with the development of OPC. The reverse analysis showed that OPC was not causally associated with these seven AIDs.

Multiple sensitivity analyses fulfilled the three major assumptions of MR to ensure the reliability of the results, this implies that the associations between Pso, HT, UC and OA and OPC suggested by previous epidemiologic results may be influenced by confounding factors. The advantages of our study are: First, we studied the causal relationship between diseases at the genetic level, which greatly eliminated the interference of confounding factors and the bias of reverse causality, and thus increased the validity of the results. Second, we used European populations for the exposure and outcome datasets and the datasets were independent of each other, which stratified the populations and reduced the duplication of populations, increasing the reliability of the results. Third, we excluded chain imbalance and abnormal SNPs and calculated F-statistics which were all greater than 10, demonstrating that there was no bias caused by weak instrumental variable IVs. After excluding heterogeneity and pleiotropy, we used IVW as the main research method, and two other MR analysis methods, Weighted Median and MR Egger, were also used to verify the results. However, we still need to recognize limitations of study in that only European populations were included in the analyses, and the results should be validated in other populations. Also, whilst our sensitivity analyses showed limited pleiotropic effects, we could not completely exclude horizontal pleiotropic effects that might have influenced our results.

In conclusion, this two-way two-sample MR examined the genetic correlation between seven AIDs and OPC. Two AIDs (asthma and rheumatoid arthritis) were causally linked to OPC, whereas multiple sclerosis was protective. Four AIDs (Psoriasis, ulcerative colitis, hypothyroidism and osteoarthritis) were not associated with OPC. Furthermore, the presence of OPC did not demonstrate any impact on the likelihood of developing AIDs. The application of MR analysis effectively mitigated the influence of potential confounding variables and reverse causality. Our findings provide new insights into the biological mechanisms of OPC, as well as advances in early detection, personalized treatment, and preventive measures. Due to the large number of causative factors for OPC and the fact that the mechanisms underlying the increased risk of OPC in patients with AIDs are not clear. We will continue to delve into the potential mechanism of action of this association in future studies.

Acknowledgments

We express our gratitude to The MRC Integrative Epidemiology Unit (IEU) at the University of Bristol for their valuable contribution to the IEU open GWAS project. We appreciate their efforts in extracting relevant GWAS summary-level data from the UK Biobank, FinnGen biobank, and published papers.

Disclosure statement

When this study was released, all of the data was sourced from original, published research that had undergone ethical review and approval by the relevant authorities.

Availability of data and materials

The authors will provide all raw data used in this work free of charge, and any other inquiries should be directed to the respective author.

Additional information

Funding

Natural Science Foundation of Gansu Province (21JR-7RA620).

Supplementary Information

Our original data has been uploaded to Figshare (www.figshare.com). (DOI:10.6084/m9.figshare.25611201)

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