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Mendelian randomization analysis of atopic dermatitis and esophageal cancer in East Asian and European populations

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ABSTRACT

Background: Emerging observational studies showed an association between atopic dermatitis (AD) and gastrointestinal cancers. However, it remains unclear whether this association is causal, particularly in the case of cancers like esophageal cancer, which exhibit ancestral genetic traits.

Methods: To assess the potential causal relationship between AD and esophageal cancer across diverse ancestral backgrounds, we conducted a 2-sample Mendelian randomization study. Independent genetic instruments for AD from the FinnGen consortium (N case = 7024 and N control = 198 740), BioBank Japan (N case = 2385 and N control = 209 651) and Early Genetics and Lifecourse Epidemiology (EAGLE) eczema consortium (N case = 18 900 and N control = 84 166, without the 23andMe study) were used to investigate the association with esophageal cancer in the UK Biobank study (N case = 740 and N control = 372 016) and BioBank Japan esophageal cancer sample (N case = 1300 and N control = 197 045).

Results: When esophageal cancer extracted from East Asian ancestry was used as a outcome factor, AD data extracted from BioBank Japan (OR = 0.90, 95% CI: 0.83-0.98), FinnGen consortium (OR = 0.86, 95% CI: 0.77-0.96), and EAGLE consortium (OR = 0.92, 95% CI: 0.81-1.06) were negatively associated with esophageal cancer susceptibility. However, AD as a whole did not show an association with esophageal cancer from European ancestry.

Conclusion: This study provides support for a causal relationship between AD and esophageal cancer in East Asian populations but not between AD and esophageal cancer from European ancestry. The specific associations between esophageal cancer and AD appear to exhibit significant disparities between the East Asian and European regions.

Keywords: Esophageal cancer, Atopic dermatitis, Mendelian randomization, European ancestry, East Asian ancestry

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INTRODUCTION

Esophageal cancer is one of the most aggressive malignant tumors, characterized by a notably low five-year overall survival rate.[1] Traditional and molecular epidemiology have demonstrated that esophageal cancer has distinct characteristics in East Asian and Western populations.[2-4] The majority of esophageal cancer cases are concentrated in East Asia, with approximately 90% of them being attributed to esophageal squamous cell carcinoma (ESCC).[5] While esophageal adenocarcinoma (EAC) is the major histology type in North American and European populations.[6,7] Despite advances in the treatment of esophageal cancer, the five-year survival rate for esophageal cancer patients remains relatively low.[8,9] Hence, the etiology of esophageal cancer and its protective factors continue to require investigation.

The hyperimmune response in allergic individuals has recently been recognized to enhance immune surveillance, thereby reducing the risk of cancer.[10,11] Correspondingly, allergic disease may serve as a protective mechanism against cancer by clearing potential carcinogens.[12] Atopic dermatitis (AD) is a long-lasting pruritic disease that causes inflammation, redness, and irritation of the skin.[13] An observational study has identified that individuals with a history of AD appear to exhibit a reduced risk of cancer.[14] Nonetheless, it remains uncertain whether a causal connection exists between AD and esophageal cancer. In a recent Mendelian randomization (MR) study, Shuai et al[15] suggested a protective effect of allergic disease against gastrointestinal tract cancers. However, this significance is only evident in East Asian esophageal cancer originating from BioBank Japan (BBJ). Moreover, Shuai et al[15] used a merged dataset encompassing various allergic diseases and did not conduct a stratified analysis.

The MR approach investigates causal relationships between exposure and outcome variables and is not susceptible to reverse causation or confounding factors.[16] Given the significant genetic discrepancies between East Asian and Western esophageal cancer, we performed a two-sample MR analysis, by using recently published large-scale Genome-wide association study (GWAS) summary statistics data and a two-sample MR approach, to explore the causal relationship between atopic dermatitis and esophageal cancer based on East Asian and Western populations.

METHODS

Study design and datasets

The single-nucleotide polymorphisms (SNPs) utilized in MR analyses to establish a causal effect must satisfy 3 fundamental assumptions: (1) the genetic instruments should exhibit a strong association with the exposure; (2) the SNPs should not be linked to any confounding factor influencing the risk factor-outcome relationship; (3) the SNPs should not influence the outcome via any pathway other than the target exposure. Determining causality becomes challenging in the absence of fulfilling any of the assumptions mentioned above.[17] The detailed study design of our analysis is outlined in Fig. 1. The current investigation provided relevant primary data source in Table 1. We have retrieved the GWAS summary statistics for AD from the FinnGen consortium (N case = 7024 and N control = 198 740), BBJ (N case = 2385 and N control = 209 651) and Early Genetics and Lifecourse Epidemiology (EAGLE) eczema consortium (N case = 10 788 and N control = 30 047, without the 23andMe study).[18] In order to explore the causal relationship between esophageal cancer and AD among individuals of European and East Asian ancestry, we extracted data from the UK Biobank (UKB) (N case = 740 and N control = 372 016) and BBJ (N case = 1300 and N control = 197 045) to represent the esophageal cancer GWAS datasets for these 2 distinct ancestries. Ethical approval was waived because the original GWAS study previously obtained ethical clearance from the relevant ethics committees and institutional review boards.

Selection of instrumental variables

The selection of optimal instrumental variables in this study adhered to high-quality criteria to uphold the study's integrity and precision. Initially, we identified SNP associated with AD at a genome-wide significance level ($P < 1 \times 10^{-5}$) and regarded them as instrumental variables.
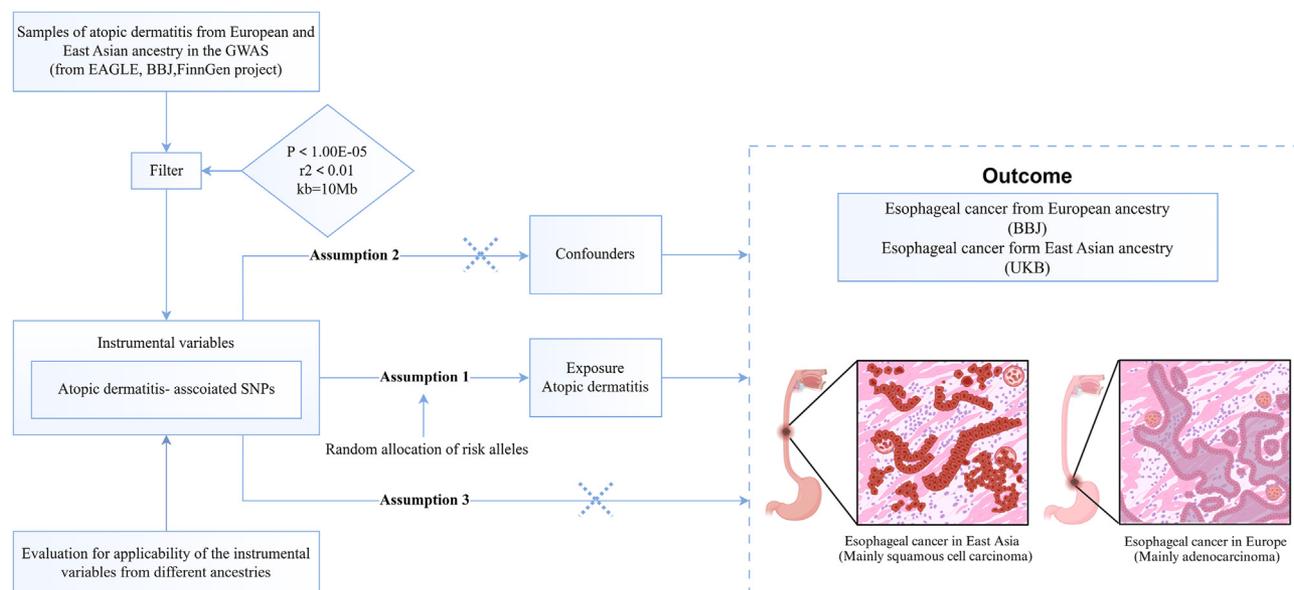
Fig. 1 The overview of study design and assumptions of the Mendelian randomization (MR) design. Assumption 1: Instrumental variables are strongly associated with atopic dermatitis. Assumption 2: Instrumental variables are independent of any confounders. Assumption 3: Instrumental variables affect esophageal cancer susceptibility varying from different ancestry. SNPs, single-nucleotide polymorphisms; EAGLE, Early Genetics and Lifecourse Epidemiology; GWAS, Genome-wide association study; UKB, UK Biobank; BBJ, BioBank Japan

Secondly, we applied the "clump" method to select independent SNPs, defined as those with a linkage disequilibrium (LD) r2 < 0.001 and the distance >10,000 kb. Thirdly, it was crucial to ensure that the effect of each SNP on the exposure aligned with its effect on the outcome.[19] Using the PhenoScanner database, no pleiotropic SNPs were found in our study. The selected instrumental SNPs were expected to exhibit a strong and specific association with the exposure of interest. In accordance with prior research, instrumental variables and the exposure were deemed to have a weak correlation if the F-statistic exceeded 10, indicating robust instrument validity.[20]

Applicability of the instrumental variables from different ancestral population

To assess the applicability of the instrumental variables for AD identified in individuals of European ancestry to the East Asian population, and vice versa, we examined the impact of genetic instruments for AD from the Biobank Japan, as well as data from European sources, including FinnGen and the EAGLE consortium, on AD in different ancestry groups. The selection criteria for instrumental variables at this part included SNPs associated with AD at a genome-wide significance level

$(P < 5 \times 10^{-8})$, with the other conditions remaining the same as previously mentioned.

Mendelian randomization analysis

Firstly, we harmonized the effect of SNP associated with AD and esophageal cancer across different ancestral populations. Second, we evaluated a causal relationship between AD and esophageal cancer for different ancestry. To satisfy the foundational MR assumptions and provide a comprehensive assessment of the causal effect between exposures and outcomes, we employed 4 distinct MR approaches: inverse variance-weighted (IVW) method, MR-Egger regression method, a weighted median method, and weighted mode method.[21-24]

Sensitivity analyses

To evaluate the robustness of our Mendelian randomization results, sensitivity analyses, including heterogeneity tests, pleiotropy tests, and leave-one-out analyses, were conducted and visualized. The heterogeneity of the selected SNPs was assessed using the Cochran Q test.[25] If p-values exceeded 0.05 and there was no indication of heterogeneity, the primary method used in this study was the fixed-effects IVW approach. The

Trait	Database	Year	Consortium	Population	SNP	Sample size
Exposure						
Atopic dermatitis	finn-b-L12_ATOPIC	2021	FinnGen Biobank	European	16 380 443	205 764
Atopic dermatitis	Sakaue S; Nat Genet[26]	2021	NA	East Asian	12 456 275	168 103
Atopic dermatitis	EAGLE eczema consortium	2016	EAGLE consortium	European	11 059 641	40 835
Outcome						
Esophageal cancer	ieu-b-4960	2021	UKB	European	8 970 465	372 756
Esophageal cancer	bbj-a-117	2019	BBJ	East Asian	8 885 106	197 045

Table 1. Details of studies included in the Mendelian randomization analyses for the association between AD and esophageal cancer. SNPs, single-nucleotide polymorphisms; EAGLE, Early Genetics and Lifecourse Epidemiology; BBJ, BioBank Japan; UKB, UK Biobank

MR estimates might be overestimated due to an overall imbalance in horizontal pleiotropy. Thus, we performed a pleiotropy test to confirm the absence of horizontal pleiotropy in our results. The impact of pleiotropic SNPs on the MR analyses was assessed through examination of the MR-Egger intercept.[23] R software (version 4.3.1, MR package) was employed to perform all statistical analyses.

RESULTS

Evaluation for applicability of the instrumental variables

Since our two-sample MR analysis may involve exposure and outcome data from different ancestries, we evaluated the suitability of instrumental variables for AD from the relevant ancestral populations (Supplementary Table 1). A significant elevated risk of AD among Japanese individuals with risk alleles of AD indicated the validity of the genetic instrument from FinnGen and the EAGLE consortium (OR = 2.27, 95% CI: 1.69-3.04, p = 4.0×10^{-8} and OR = 2.53, 95% CI: 1.72-3.71, p = 1.8×10^{-6} respectively). Moreover, the genetic instrument from the BioBank Japan also demonstrated its validity in the population with AD from FinnGen and the EAGLE consortium (OR = 1.29, 95% CI: 1.08-1.53, p = 4.0×10^{-3} and OR = 1.46, 95% CI: 1.19-1.79, p = 2.3×10^{-4} respectively).

MR analysis

The MR analysis was conducted with AD from European and East Asian ancestry as exposure and esophageal cancer also from the 2 ancestries as outcomes (Fig. 2). Details of instrumental variables finally used in this study were shown in Supplementary Table 2, and the F statistics for each exposure were greater than 10. When esophageal cancer extracted from East Asian ancestry (BBJ) was used as a outcome factor, 32 valid SNPs (OR$_{IVW}$ = 0.89, 95% CI: 0.81-0.98, p = 0.027) were extracted with AD from the work of Sakaue et al[26] being the exposure, 39 valid SNPs (OR$_{IVW}$ = 0.92, 95% CI: 0.81-1.06, p = 0.284) were extracted with AD from EAGLE consortium being the exposure, and 49 valid SNPs (OR$_{IVW}$ = 0.86, 95% CI: 0.77-0.96,
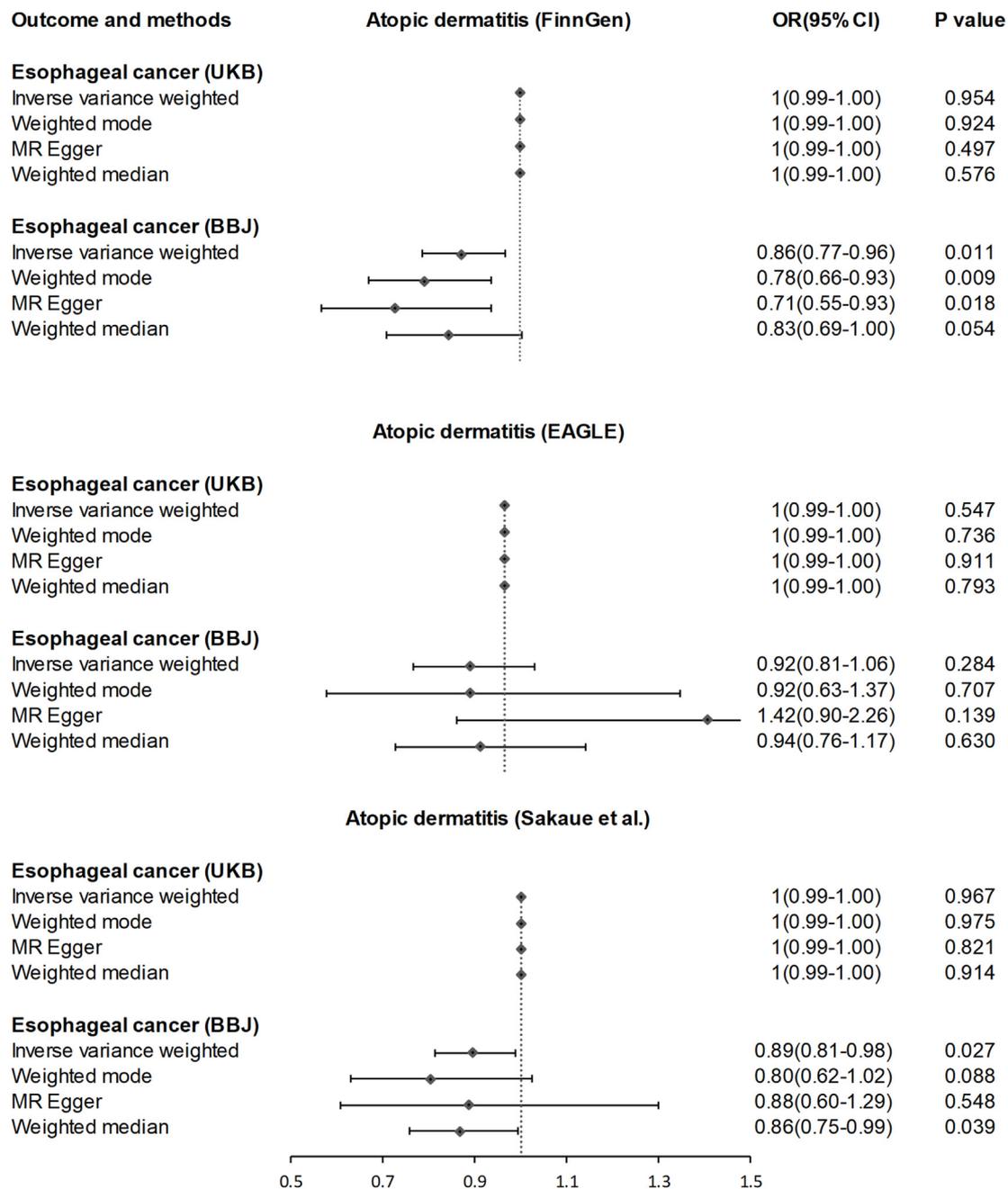
Fig. 2 Association of genetic susceptibility to atopic dermatitis with Mendelian randomizations of esophageal cancer from various ancestries. CI, confidence interval; OR, odds ratio; BBJ, BioBank Japan; UKB, UK Biobank; Statistical significance: p < 0.05

p = 0.011) were extracted with AD from FinnGen consortium being the exposure.

When esophageal cancer extracted from European ancestry (UKB) was used as a outcome factor, 31 valid SNPs (ORIVW = 1.00, 95% CI: 0.99–1.00, p = 0.249) were extracted with AD from the work of Sakaue et al being the exposure, 46 valid SNPs (ORIVW = 1.00, 95% CI: 0.99–1.00, p = 0.547) were extracted with AD from EAGLE consortium

being the exposure, and 62 valid SNPs (ORIVW = 1.00, 95% CI: 0.99–1.00, p = 0.954) were extracted with AD from FinnGen consortium being the exposure.

Sensitivity and pleiotropy analysis

The MR sensitivity analysis and heterogeneity test showed with AD as exposure factor, the Cochran's Q statistic and MR Egger regression

Exposure	Outcome	Heterogeneity test			Horizontal pleiotropy test		
		Method	Cochran's Q	Q_ pval	Egger_intercept	Se	pval
Atopic dermatitis	Esophageal cancer	MR Egger	31.479	0.725			
(EAGLE)	(UKB)	IVW	35.165	0.601	−0.052	0.027	0.063
	Esophageal cancer	MR Egger	35.375	0.819			
	(BBJ)	IVW	35.518	0.843	−0.001	0.001	0.707
Atopic dermatitis	Esophageal cancer	MR Egger	59.631	0.38			
(FinnGen)	(UKB)	IVW	60.286	0.393	0.001	0.001	0.432
	Esophageal cancer	MR Egger	44.783	0.102			
	(BBJ)	IVW	45.151	0.117	0.018	0.035	0.601
Atopic dermatitis	Esophageal cancer	MR Egger	31.574	0.248			
(Sakaue et al.)	(UKB)	IVW	31.634	0.289	0.001	0.031	0.964
	Esophageal cancer	MR Egger	18.532	0.932			
	(BBJ)	IVW	18.534	0.949	< 0.001	< 0.001	0.823

Table 2. Heterogeneity test and horizontal pleiotropy test. *IVW, inverse-variance weighted; MR, Mendelian randomization; BBJ, BioBank Japan; UKB, UK Biobank; Statistical significance: p < 0.05*

intercept were not significant (p > 0.05), indicating no heterogeneity or horizontal pleiotropy (Table 2). The visualization analysis showed that the association between AD from European and East Asian ancestry and esophageal cancer from these 2 ancestries were not driven by a single SNP, but by all functional SNPs together. Funnel plot, leave-one-out analysis, scatter plot, and forest plot of MR are presented in Supplementary Figs. 1–6.

DISCUSSION

Currently, there are few studies exploring the potential causal relationship and pathogenic association involving esophageal cancer from different ancestry. Due to the substantial genetic variability observed in esophageal cancer across different geographic regions, the potential causal relationship and pathogenic association involving esophageal cancer may differ for different ancestry.[2,27] Currently, our MR analysis aims to investigate the causal connection between AD and esophageal cancer within diverse ancestral populations. Our investigation has revealed a noteworthy observation within the East Asian population. Specifically, individuals with a genetic predisposition to AD demonstrated a significantly reduced risk of developing esophageal cancer. However, this association was not evident within the European ancestry and there was no potential causal relationship.

Allergic diseases often coexist due to shared genetic risk variants that disrupt the regulation of immune-related gene expression.[28] Moreover, individuals with hyperimmune response resulting from allergic conditions may experience enhanced immune surveillance, consequently reducing their risk of developing cancer.[11] Existing research had provided limited insights into the relationship between AD and non-allergic comorbidities. Understanding these non-allergic comorbidities has the potential to improve treatment outcomes.[29] While current data from observational studies were largely inconsistent for specific cancers, AD appears to have an overall preventive effect on gastrointestinal cancers.[30,31] The disparities in findings could be attributed to external confounding factors, including variations in ancestry.

Inconsistent findings have been documented in studies of the incidence of esophageal cancer and allergic disease, while in East Asian populations, atopy has often been reported as a protective factor against esophageal cancer. In a large cohort study from Korea including data extracted from 9 892 633 Korean adults who underwent a medical check-up, the adjusted incidence rate ratio of esophageal cancer in patients with AD was 0.91 (95% CI, 0.69–1.19).[31] A Shang Hai-population study that included 163 incident cases of esophageal cancer and 275 controls found that a history of allergy was associated with a reduced risk (adjusted OR = 0.6, 95% CI = 0.4–0.9).[32] However, a large Sweden population-based study included 42 663 men and 50 323 women patients hospitalized for asthma and found that patients with asthma had an increased risk of incident esophageal adenocarcinoma (adjusted OR = 1.5, 95% CI = 0.9–2.5).[33]

From a genetic perspective, our findings substantiate the protective role of AD against esophageal cancer within the Asian genetic lineage, indicating a favorable effect of AD in preventing esophageal cancer in Asian populations. While the mechanisms through AD or other allergic diseases exert this effect remain unclear. At present, several potential mechanisms have been proposed. The first mechanism is the chronic inflammation hypothesis, where the inflammation associated with allergic diseases may promote cancer progression by inducing oxidative damage, leading to mutations in tumor suppressor genes or post-translational modifications of proteins involved in DNA repair or cell apoptosis control.[11,34] This chronic inflammation hypothesis predicts an increased risk of cancer associated with allergic inflammation. However, the immune surveillance hypothesis suggests that allergies result from a general enhancement of the immune response, which has a tendency to detect and eliminate dysfunctional cells.[35] Additionally, the physical effects of allergic reactions in specific tissues and the Th2 skewing hypothesis propose that the allergic state may enable the body to clear mutagenic triggers before malignant transformation occurs.[36,37]

Furthermore, the vast majority of participants in current GWAS studies have European ancestry. Conducting GWAS in non-European

populations is essential for elucidating the disease biology in East Asian populations.[38] Esophageal cancer, as a regionally heterogeneous cancer, has demonstrated genetic background differences between the various races through GWAS studies.[27,39] Observational studies have demonstrated that risk factors for esophageal cancer may vary among different ancestries (eg, the impact of tobacco on esophageal squamous cell carcinoma appears to be weaker in Asians compared to Europeans).[38] Therefore, it is necessary to conduct further investigations into the risk or protective factors for esophageal cancer among different races. In this study, we conducted a Mendelian randomization investigation of the associations between AD and esophageal cancer in European and East Asian populations. Our findings indicate that in the European population, there is virtually no causal relationship between genetic susceptibility to AD and esophageal cancer. However, in the East Asian population, suggestive associations between AD and esophageal cancer were observed, regardless of the AD genetic liability in either European or East Asian populations. This, to some extent, suggests that different immune states may have varying effects on genetically heterogeneous tumors from different ancestries.

The major strength of this study is that, for the first time, as far as our knowledge extends, we have utilized MR approach to assess the causal relationship of AD on esophageal cancer development across different ancestry backgrounds, which could provide insights for future research on esophageal cancer originating from different ancestries. The advantages of this approach include its resistance to confounding, reverse causality, and non-differential measurement error, as opposed to observational studies.[40] Additionally, we conducted multiple sensitivity analyses to ensure the consistency of causal estimates and confirm the robustness of the current study's findings. We acknowledge the limitations of our study. Firstly, the sample sizes for esophageal cancer GWAS data are limited for both ancestral backgrounds. Second, there is a lack of esophageal cancer subtypes available for MR assessment, as esophageal squamous cell carcinoma and adenocarcinoma constitute the majority of the European and East Asian

esophageal cancer GWAS samples we extracted, potentially leading to a loss of statistical power when analyzed separately. Third, the present study employed binary variables as the exposure for Mendelian randomization, which may have inherent limitations.[41] Lastly, this study is limited to assessing the causal relationship between AD and esophageal cancer based on genetic factors across different ancestries, and future research should consider evaluating the influence of different racial environments (such as diet and lifestyle) on AD and esophageal cancer.

CONCLUSION

This study provides support for a causal relationship between AD and esophageal cancer in East Asian populations but not between AD and esophageal cancer from European ancestry. The specific associations between esophageal cancer and AD appear to exhibit significant disparities between the East Asian and European regions. This finding holds crucial significance in discovering the connections between tumor heterogeneity across different ancestries and immune states. Further research is warranted to investigate the underlying pathological and physiological mechanisms of this relationship.

Authors' contributions
L-YX contributed to the study design, supervised the data analysis process, and mainly revised the manuscript. G-YM

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REFERENCES

1. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA A Cancer J Clin*. May 2021;71(3):209–249.

2. Zhang H-Z, Jin G-F, Shen H-B. Epidemiologic differences in esophageal cancer between Asian and Western populations. *Chin J Cancer*. Jun 2012;31(6):281–286.

3. Li M, Zhang Z, Wang Q, Yi Y, Li B. Integrated cohort of esophageal squamous cell cancer reveals genomic features underlying clinical characteristics. *Nat Commun*. Sep 7 2022;13(1):5268.

4. Dong J, Buas MF, Gharahkhani P, et al. Determining risk of barrett's esophagus and esophageal adenocarcinoma based on epidemiologic factors and genetic variants. *Gastroenterology*. Apr 2018;154(5):1273–1281.e1273.

5. Chen W, Zheng R, Baade PD, et al. Cancer statistics in China, 2015. *CA A Cancer J Clin*. Mar-Apr 2016;66(2):115–132.

6. Arnold M, Ferlay J, van Berge Henegouwen MI, Soerjomataram I. Global burden of oesophageal and gastric cancer by histology and subsite in 2018. *Gut*. Sep 2020;69(9): 1564–1571.

7. Bosetti C, Levi F, Ferlay J, et al. Trends in oesophageal cancer incidence and mortality in Europe. *Intern J Cancer*. Mar 1 2008;122(5):1118–1129.

8. Kelly RJ. Emerging multimodality approaches to treat localized esophageal cancer. *J Natl Compr Cancer Netw : JNCCN*. Aug 1 2019;17(8):1009–1014.

9. Li X, Chen L, Luan S, et al. The development and progress of nanomedicine for esophageal cancer diagnosis and treatment. *Semin Cancer Biol*. Nov 2022;86(Pt 2):873–885.

10. Rigoni A, Colombo MP, Pucillo C. Mast cells, basophils and eosinophils: from allergy to cancer. *Semin Immunol*. Feb 2018;35:29–34.

11. Sherman PW, Holland E, Sherman JS. Allergies: their role in cancer prevention. *QRB (Q Rev Biol)*. Dec 2008;83(4):339–362.

12. D'Arcy M, Rivera DR, Grothen A, Engels EA. Allergies and the subsequent risk of cancer among elderly adults in the United States. *Cancer Epidemiol Biomarkers Prev: Pub American Assoc Cancer Res, Cospons American Soci Prevent Oncol*. Apr 2019;28(4):741–750.

13. Ständer S. Atopic dermatitis. *N Engl J Med*. Mar 25 2021;384(12):1136–1143.

14. Wang H, Diepgen TL. Atopic dermatitis and cancer risk. *Br J Dermatol*. Feb 2006;154(2):205–210.

15. Yuan S, Vithayathil M, Kar S, et al. Assessing the protective role of allergic disease in gastrointestinal tract cancers using Mendelian randomization analysis. *Allergy*. May 2021;76(5): 1559–1562.

16. Davies NM, Holmes MV, Davey Smith G. Reading Mendelian randomisation studies: a guide, glossary, and checklist for clinicians. *Br Med J*. Jul 12 2018;362:k601.

17. Lawlor DA, Harbord RM, Sterne JA, Timpson N, Davey Smith G. Mendelian randomization: using genes as instruments for making causal inferences in epidemiology. *Stat Med*. Apr 15 2008;27(8):1133–1163.

18. Paternoster L, Standl M, Waage J, et al. Multi-ancestry genome-wide association study of 21,000 cases and 95,000 controls identifies new risk loci for atopic dermatitis. *Nat Genet*. Dec 2015;47(12):1449–1456.

19. Kamat MA, Blackshaw JA, Young R, et al. PhenoScanner V2: an expanded tool for searching human genotype-phenotype associations. *Bioinformatics*. Nov 1 2019;35(22):4851–4853.

20. Pierce BL, Ahsan H, Vanderweele TJ. Power and instrument strength requirements for Mendelian randomization studies using multiple genetic variants. *Intern J Epidemiol*. Jun 2011;40(3):740–752.

21. Hemani G, Zheng J, Elsworth B, et al. The MR-Base platform supports systematic causal inference across the human phenome. *Elife*. May 30 2018;7.

22. Lee CH, Cook S, Lee JS, Han B. Comparison of two meta-analysis methods: inverse-variance-weighted average and weighted sum of Z-scores. *Genomics informatics*. Dec 2016;14(4):173–180.

23. Bowden J, Davey Smith G, Burgess S. Mendelian randomization with invalid instruments: effect estimation and bias detection through Egger regression. *Intern J Epidemiol*. Apr 2015;44(2):512–525.

24. Bowden J, Davey Smith G, Haycock PC, Burgess S. Consistent estimation in mendelian randomization with some invalid instruments using a weighted median estimator. *Genetic Epidem*. May 2016;40(4):304–314.

25. Bowden J, Del Greco MF, Minelli C, Davey Smith G, Sheehan N, Thompson J. A framework for the investigation of pleiotropy in two-sample summary data Mendelian randomization. *Stat Med*. May 20 2017;36(11):1783–1802.

26. Sakaue S, Kanai M, Tanigawa Y, et al. A cross-population atlas of genetic associations for 220 human phenotypes. *Nat Genet*. Oct 2021;53(10):1415–1424.

27. Lindström S, Wang L, Feng H, et al. Genome-wide analyses characterize shared heritability among cancers and identify novel cancer susceptibility regions. *J Natl Cancer Inst*. Jun 8 2023;115(6):712–732.

28. Ferreira MA, Vonk JM, Baurecht H, et al. Shared genetic origin of asthma, hay fever and eczema elucidates allergic disease biology. *Nature Genetic*. Dec 2017;49(12):1752–1757.

29. Paller A, Jaworski JC, Simpson EL, et al. Major comorbidities of atopic dermatitis: beyond allergic disorders. *Am J Clin Dermatol*. Dec 2018;19(6):821–838.

30. Fereidouni M, Ferns GA, Bahrami A. Current status and perspectives regarding the association between allergic disorders and cancer. *IUBMB life*. Jul 2020;72(7):1322–1339.

31. Choi YJ, Han K, Jin EH, Lim JH, Shin CM, Lee DH. Allergic diseases and risk of malignancy of gastrointestinal cancers. *Cancers*. Jun 16 2023;15(12).

32. Dai Q, Zheng W, Ji BT, et al. Prior immunity-related medical conditions and oesophageal cancer risk: a population-based case-control study in Shanghai. *Eur J Cancer Prev: Off J European Cancer Prev Org*. Apr 1997;6(2):152–157.

33. Ye W, Chow WH, Lagergren J, et al. Risk of adenocarcinomas of the oesophagus and gastric cardia in patients hospitalized for asthma. *British J Cancer*. Nov 2 2001;85(9):1317–1321.

34. Siemes C, Visser LE, Coebergh JW, et al. C-reactive protein levels, variation in the C-reactive protein gene, and cancer risk: the Rotterdam Study. *J Clin Oncol: Off J American Soci Clinic Oncol*. Nov 20 2006;24(33):5216–5222.

35. Rittmeyer D, Lorentz A. Relationship between allergy and cancer: an overview. *Int Arch Allergy Immunol*. 2012;159(3):216–225.

36. Profet M. The function of allergy: immunological defense against toxins. *QRB (Q Rev Biol)*. Mar 1991;66(1):23–62.

37. Josephs DH, Spicer JF, Corrigan CJ, Gould HJ, Karagiannis SN. Epidemiological associations of allergy, IgE and cancer. *Clin Exp Allergy: J British Soci Allergy Clinic Immuno*. Oct 2013;43(10):1110–1123.

38. Ishigaki K, Akiyama M, Kanai M, et al. Large-scale genome-wide association study in a Japanese population identifies novel susceptibility loci across different diseases. *Nat Genet*. Jul 2020;52(7):669–679.

39. Sung H, Yang HH, Zhang H, et al. Common genetic variants in epigenetic machinery genes and risk of upper gastrointestinal cancers. *Int J Epidemiol*. Aug 2015;44(4):1341–1352.

40. Davey Smith G, Holmes MV, Davies NM, Ebrahim S. Mendel's laws, Mendelian randomization and causal inference in observational data: substantive and nomenclatural issues. *European J Epidemiol*. Feb 2020;35(2):99–111.

41. Burgess S, Labrecque JA. Mendelian randomization with a binary exposure variable: interpretation and presentation of causal estimates. *Eur J Epidemiol*. Oct 2018;33(10):947-952.