Nutrición Hospitalaria

Correlación entre el riesgo de cáncer de esófago y la situación socioeconómica y nueve factores que pueden cambiar el estilo de vida en poblaciones europeas y de Asia oriental: evidencia de un estudio exhaustivo de aleatoriedad de Mendel

Association of socioeconomic status and nine modifiable lifestyle factors on esophageal cancer risk in European and East Asian populations — Evidence from a comprehensive Mendelian randomization study

10.20960/nh.05819

06/06/2025

OR 5819

Association of socioeconomic status and nine modifiable lifestyle factors on esophageal cancer risk in European and East Asian populations — Evidence from a comprehensive Mendelian randomization study

Correlación entre el riesgo de cáncer de esófago y la situación socioeconómica y nueve factores que pueden cambiar el estilo de vida en poblaciones europeas y de Asia oriental: evidencia de un estudio exhaustivo de aleatoriedad de Mendel

Ruizhi Ye[1,2], Fengming Zhang[1], Guangxian You[1]

[1]Radiotherapy Department. Taizhou Cancer Hospital, and [2]Taizhou Key Laboratory of Minimally Invasive Interventional Therapy & Artificial Intelligence. Taizhou, Zhejiang. People's Republic of China

Received: 06/03/2025
Accepted: 06/04/2025
Correspondence: Guangxian You, M.D. Radiotherapy Department. Taizhou Cancer Hospital. No. 50 Zhenxin Road, Xinhe Town, Wenling. Taizhou 317502, Zhenjiang Province. People's Republic of China
e-mail: 13676668511@163.com

Authors´ contribution: Ruizhi Ye and Guangxian You conceptualized and designed the study. Fengming Zhang was responsible for data collection. Ruizhi Ye conducted the analysis, while all authors contributed to the interpretation of the results. Guangxian You provided expert guidance and made critical revisions to the manuscript. Ruizhi Ye and Guangxian You drafted the initial manuscript. All authors critically reviewed multiple drafts and

contributed significant intellectual input. Ruizhi Ye and Guangxian You had full access to all the study data and were accountable for the data integrity, the accuracy of the analyses, and the final decision to submit the manuscript for publication.

Acknowledgements: The authors extend their gratitude to the organizations that provided the GWAS data.

Ethics approval and consent to participate: Formal ethical approval was not required, as the data utilized were anonymized and obtained from publicly accessible sources.

Availability of data and materials: All GWAS summary statistics utilized in this study are publicly accessible and available for download by qualified researchers.

Conflict of interest: The authors declare no conflict of interest.

Artificial intelligence: The authors declare not to have used artificial intelligence (AI) or any AI-assisted technologies in the elaboration of the article.

ABSTRACT

Background and aims: the intricate relationships between socioeconomic factors, modifiable lifestyle choices, and esophageal cancer risk remain uncertain. We aim to investigate the associations of socioeconomic status, modifiable lifestyle factors, and esophageal cancer risk.

Methods: we employed multiple Mendelian randomization (MR) analyses, including three different MR approaches. GWAS databases from European and East Asian populations, encompassing variables such as household income, educational attainment, and the Townsend deprivation index (TDI), were analyzed. The risk of esophageal cancer was assessed using data from three distinct cohorts of European and East Asian descent (Database 1: n = 476,306; Database 2: n = 372,756; Database 3: n = 160,589). Nine modifiable lifestyle factors were incorporated in the multivariable and mediation MR analyses. Meta-analysis was employed to synthesize results across the three datasets.

Results: higher household income was connected with a reduced esophageal cancer risk (odds ratio (OR) = 0.698, 95 % confidence interval (95 % CI): 0.556-0.876, p = 0.002). Body mass index (BMI) partially mediated the relationship between household income and the risk of esophageal cancer (OR = 0.914, 95 % CI: 0.841-0.992, p = 0.031, mediation ratio: 27.23 %). However, no significant evidence was found to support a direct association between educational attainment, TDI, and esophageal cancer risk.

Conclusions: these findings suggest that higher household income is inversely associated with esophageal cancer risk, with BMI acting as a partial mediator of this relationship. Accordingly, targeted early screening and preventive measures for esophageal cancer should be prioritized among low-income populations, particularly those with obesity.

Keywords: Socioeconomic status. Modifiable lifestyle factors. Esophageal cancer. Mendelian randomization. Mediation effect.

RESUMEN

Introducción y objetivo: la compleja relación entre los factores socioeconómicos, las opciones de estilo de vida modificables y el riesgo de cáncer de esófago sigue siendo incierta. Nuestro objetivo es investigar la relación entre el estatus socioeconómico, los factores cambiables del estilo de vida y el riesgo de cáncer de esófago.

Método: utilizamos múltiples análisis aleatorios de Mendel (MR), incluidos tres métodos de MR diferentes. Se analizó la base de datos gwas de la población de Europa y Asia oriental, incluyendo variables como el ingreso familiar, el nivel de educación y el índice de pobreza de Thomson (TDI). Evaluar el riesgo de cáncer de esófago utilizando datos de tres cohortes diferentes de ascendencia europea y oriental (base de datos 1: n = 476.306; base de datos 2: n = 372.756; base de datos 3: n = 160.589). En el análisis de MR multivariable e intermediario se incluyeron nueve factores de estilo de vida modificables. Se utilizó un metaanálisis para sintetizar los resultados de los tres conjuntos de datos.

Resultados: mayor ingreso familiar asociado a una reducción del riesgo de cáncer esofágico (cociente de posibilidades (OR) = 0,698, intervalo de confianza del 95 % (IC del 95 %): 0,556-0,876, p = 0,002). El índice de masa corporal (IMC) mediaba parcialmente la relación entre los ingresos familiares y el riesgo de cáncer de esófago (OR = 0,914, IC del 95 %: 0,841-0,992, p = 0031, tasa de mediación: 27,23 %). Sin embargo, no se han encontrado evidencias significativas que respalden la asociación directa entre el nivel de educación, el TDI y el riesgo de cáncer de esófago.

Conclusiones: estos hallazgos sugieren que los ingresos familiares más altos están negativamente relacionados con el riesgo de cáncer de esófago, y el IMC es un mediador parcial de esta relación. Por lo tanto, las personas de bajos ingresos, especialmente las personas obesas, deben dar prioridad a la detección temprana y las medidas preventivas específicas contra el cáncer.

Palabras clave: Estatus socioeconómico. Factores de estilo de vida cambiables. Cáncer de esófago. Aleatorización mendeliana. Efecto de mediación.

INTRODUCTION

Esophageal cancer is a prevalent malignancy worldwide, ranking seventh in incidence and sixth in mortality among all cancers, with around 572,000 new cases and 508,000 deaths reported annually (1). The burden of esophageal cancer in China is particularly significant, accounting for over half of the global new cases and deaths (2). Within the country, esophageal cancer ranks sixth in incidence and fourth in mortality among all tumors (3). The disease exhibits pronounced gender disparities, with approximately 70 % of patients being male, and its incidence and mortality rates increase with age (4). SCC constitutes roughly 90 % of cases in China (5). Notably, recent years have witnessed a declining trend in the incidence and mortality of esophageal cancer, particularly among females (6). There are many risk factors of esophageal cancer such as alcohol consumption, tobacco use, gastroesophageal reflux disease, obesity, advanced age, male sex, Barrett's esophagus, and genetic predispositions (7). Additional contributing factors encompass achalasia, human papillomavirus (HPV) infection, ingestion of corrosive substances, sclerotherapy, and Plummer-Vinson syndrome (8). Despite the observed decline in incidence, esophageal cancer remains a significant public health challenge due to its poor prognosis and low survival rates (9). This highlights the urgent need for continued research and targeted interventions to mitigate its impact.

Socioeconomic status (SES) is intricately linked to the health of human being, including the risk of esophageal cancer (10). Research has consistently demonstrated that lower SES is connected with a heightened incidence and mortality of esophageal cancer, alongside various other adverse health outcomes (11). Individuals with lower SES often encounter compounded health risks, including poor dietary habits, limited health literacy, restricted access to medical resources, and elevated psychological stress, all of which collectively contribute to an increased vulnerability to malignancies such as esophageal cancer (12). Economic constraints play a critical role in shaping these risks. Financial limitations may compel individuals from low-SES backgrounds to adopt diets high in calories, salt, and fat but low in fiber—dietary patterns closely connected with the esophageal cancer risk (13). Moreover, inadequate health education and a lack of awareness about cancer prevention can result in the failure to recognize early symptoms, delaying diagnosis and leading to missed opportunities for effective treatment (14). Compounding these challenges, limited access to high-quality healthcare services hinders preventive measures, early detection, and timely treatment, adversely affecting prognosis (15). The impact of SES on esophageal cancer risk also exhibits regional variability (16). In developing countries, where healthcare systems are often under-resourced and access to care is uneven, the link between low SES and heightened cancer risk is particularly pronounced (17). However, even in developed nations with relatively robust healthcare infrastructures, SES remains a significant determinant of esophageal cancer risk. These findings highlight the urgent need for global strategies to address health inequities driven by socioeconomic disparities and to reduce the burden of esophageal cancer worldwide.

Mendelian randomization (MR) is a sophisticated technique in the field of epidemiology that employs genetic variations as instrumental variables (IVs) to evaluate the causal links between exposure and outcome (18). Because genotypes are randomly assigned during gamete formation, MR functions as a randomized controlled trial, effectively reducing confounding biases and mitigating the influence of reverse causation (19). When examining the effects of SES and modifiable lifestyle factors on cancer risk, MR serves as a powerful analytical tool. For instance, educational attainment—a key proxy for SES—has been strongly associated with cancer risk modulation (20). An MR-based study demonstrated that higher educational attainment significantly reduces the lifetime smoking index, lowering the risk of lower respiratory tract cancers by an impressive 81.7 % (21). Furthermore, the protective effects of education extend to dietary habits, with 10.2 % of its risk reduction mediated through increased vegetable consumption (21). These findings underscore the genetic evidence that education mitigates cancer risk primarily through improved behavioral factors, such as reduced smoking and healthier dietary choices. In conclusion, MR can offer a robust framework for elucidating causal relationships between SES, lifestyle factors, and cancer risk. By providing critical insights into these intricate interactions, MR facilitates the development of targeted prevention strategies, contributing to more effective public health interventions.

To the best of our knowledge, limited research has utilized MR to examine the relationship between socioeconomic status and the risk of esophageal cancer. Therefore, our study seeks to address this gap by employing two-sample bidirectional, multivariable, and mediation MR analyses. Additionally, we explored the mediation effects of nine modifiable lifestyle factors in the connection of socioeconomic status and the risk of esophageal cancer.

MATERIALS AND METHODS

Design of the Mendelian randomization study

This comprehensive MR study, incorporating two-sample bidirectional, multivariable, and mediation analyses, was conducted in adherence to the STROBE-MR guidelines (22). Three key assumptions were upheld in this study: i) the selected IVs were strongly associated with socioeconomic status indicators, such as household income, educational attainment, and the TDI; ii) the IVs were independent of other potential confounders; and iii) the IVs influenced esophageal cancer risk through socioeconomic status (Fig. 1) (23). The inverse variance weighting (IVW) method was employed in establishing the association of socioeconomic status and esophageal cancer risk. Additionally, MR-PRESSO, weighted median, and MR-Egger analyses were utilized to validate the reliability of this study . Mediation analysis further explored the mediation roles of nine modifiable lifestyle factors in the connection of socioeconomic status and esophageal cancer risk. A detailed flowchart of this study is displayed in figure 2.

Socioeconomic status data sources

SES was assessed using three key indicators: i) household income (*n* = 397,751, European population; *n* = 2,060, East Asian population); ii) education (*n* = 461,457, European population; *n* = 1,111, East Asian population); and iii) Townsend deprivation index (TDI) (*n* = 462,464, European population; *n* = 2,698, East Asian population). The SES data sources is provided detailly in supplementary table I.

Esophageal cancer data sources of European and East population

The genome-wide association study (GWAS) data on esophageal cancer risk was obtained from three independent databases, incorporating genetic information from both European and East Asian populations. These included: database 1 (*n* = 476,306, European population), database 2 (*n* = 372,756, European population), and database 3 (*n* = 60,589, East Asian population) (Supplementary Table I).

Nine modifiable lifestyle factors data sources

Additionally, this study incorporated nine modifiable lifestyle factors to further explore the specific associations between socioeconomic status and the risk of esophageal cancer. These factors include body mass index (BMI) (*n* = 407,609), smoking initiation (N = 607,291), alcohol consumption (*n* = 83,626), tea consumption (*n* = 434,171), coffee consumption (*n* = 462,464), processed meat consumption (*n* = 312,220), cooked vegetables consumption (*n* = 435,417), fresh fruit consumption (*n* = 433,186), and mineral and other dietary supplements (*n* = 461,384), with detailed descriptions available in supplementary table II (24-26).

Selected IVs

The selected IVs were utilized to ensure a robust association with socioeconomic status indicators, including household income, educational attainment, and the TDI. For the European population, IVs with a *p*-value $< 5 \times 10^{-8}$ were deemed significant and included in the analysis (27). Due to the limited number of IVs available for the East Asian population, the selection threshold was relaxed to a *p*-value $< 1 \times 10^{-5}$ (28). Additionally, IVs were filtered to minimize linkage disequilibrium (LD) with an $R^2 < 0.001$ and were required to have a physical distance of $\geq$ 10,000 kb to reduce the risk of LD-related biases (29).

To further enhance the validity of the instruments, an F-statistic threshold ($F > 10$) was applied to minimize the weak instruments biases (30). All selected IVs were screened using the PhenoScanner database (http://www.phenoscanner.medschl.cam.ac.uk/) to identify and exclude those associated with potential confounding factors (31). Any single nucleotide polymorphism (SNP) linked to esophageal cancer risk or confounders was removed. A detailed list of the IVs employed in this MR study is provided in supplementary table IV.

Statistical analysis

All analyses were conducted using R software (Version 4.4.1). MR analyses were performed utilizing the "TwoSampleMR" (Version 0.6.8) R package. To minimize the risk of type I errors, a Bonferroni-corrected significance threshold was applied, with *p*-values < 0.017 (0.05/3) considered statistically significant (32). P-values ranging from 0.017 to 0.05 were interpreted as indicative of a potential association, warranting further investigation. P-values exceeding 0.05 were deemed to indicate no statistically significant relationship between the exposures and outcomes. Meanwhile, to mitigate the potential influence of sample overlap on the study results, we employed specialized tool (https://sb452.shinyapps.io/overlap/) to evaluate the extent of overlap between the exposure and outcome datasets (33). All analyses were performed using two-sided hypothesis testing.

RESULTS

Two-sample bidirectional MR study

The primary findings of the two-sample MR analysis, with socioeconomic status and esophageal cancer risk, are summarized in table I and figure 3. The results demonstrated a significant connection of household income and the risk of esophageal cancer, with higher household income consistently linked to a reduced risk of esophageal cancer across three independent databases (Database 1: OR = 0.286, 95 % CI: 0.083-0.982, p = 0.047; Database 2: OR = 0.700, 95 % CI: 0.578-0.996, p = 0.037; Database 3: OR = 0.776, 95 % CI: 0.387-0.934, p = 0.045). To enhance robustness, we integrated findings from the three databases using meta-analysis, which corroborated the inverse association between household income and esophageal cancer risk (OR = 0.698, 95 % CI: 0.556-0.876, p = 0.002). However, no significant relationship was identified of other socioeconomic indicators, such as educational attainment or the TDI, and esophageal cancer risk.

To address potential reverse causality, reverse MR analysis was performed to assess whether esophageal cancer risk influences socioeconomic status. These analyses revealed no evidence of a reverse causal relationship between esophageal cancer risk and socioeconomic factors. The detailed results of the reverse MR analysis are provided in supplementary table V. Furthermore, sample overlap rate, as presented in supplementary table III, was less than 10 %, exerting a negligible impact on the study outcomes.

Sensitivity analysis

Initially, we computed the F-statistics for all IVs, all of which exceeded a threshold of 10. This indicates that the IVs employed in this study are robust and are not subject to the risk of weak instrument bias

(Supplementary Table IV). To further validate the robustness of the finding (both for the forward and reverse analyses), we used a series of comprehensive sensitivity tests. These included heterogeneity assessments, pleiotropy tests, and MR-PRESSO approach. The results demonstrated no evidence of heterogeneity or horizontal pleiotropy within the analyses, supporting the validity of the MR assumptions.

Moreover, we assessed the statistical power for each individual analysis, all of which exhibited power values exceeding 0.9, providing additional assurance regarding the dependability of this study. The results of sensitivity analyses and power calculations are presented in supplementary tables VI and VII.

Multivariable MR study

This study employed multivariable MR analysis to explore the association of nine modifiable lifestyle factors on the connection of household income and esophageal cancer risk. These findings indicated that after adjusting for these factors (such as BMI, tea consumption, coffee consumption, processed meat consumption, cooked vegetables consumption, and fresh fruit consumption), the association between household income and esophageal cancer risk was no longer statistically significant (Supplementary Table VIII). This suggests that the observed link between household income and esophageal cancer risk is likely mediated by these modifiable lifestyle factors.

Mediation MR study

Building on these findings, we proceeded with mediation analyses to further dissect the causal pathway. The findings demonstrated that BMI serves as a mediator in the connection of household income and esophageal cancer risk (OR = 0.914, 95 % CI: 0.841-0.992, p = 0.031), with mediation role accounting for 27.23 % of the observed association. The detailed results of these mediation analyses are provided in table II.

DISCUSSION

In this comprehensive MR study, we investigated the association between socioeconomic status (including household income, educational attainment, and TDI) and esophageal cancer risk. These findings unvealed a significant association of household income and esophageal cancer risk. Moreover, BMI was identified as a crucial mediator in this association, offering valuable insights into the mechanisms by which household income influences esophageal cancer risk.

SES is widely served as a critical factor of individual health (34). Disparities in access to healthcare services and health education across SES levels significantly influence the risk of chronic conditions including cardiovascular diseases and some cancer (35). Numerous MR studies have uncovered the association of SES and some diseases, uncovering associations of conditions such as asthma, Alzheimer's disease, obesity, anxiety, lung cancer, and etc. (36,37). Consistent with these findings, our study observed that people with higher income levels exhibit a lower esophageal cancer risk, compared to people with lower income levels. However, we found no evidence of a correlation between educational attainment or TDI and esophageal cancer risk, highlighting the need for further investigation through larger-scale observational studies to explore potential associations.

In addition to SES, modifiable lifestyle factors also influence cancer risk (38). Previous research has demonstrated a link between SES and overweight status, while Zhan et al. identified an association between BMI and esophageal cancer risk (39). Our findings align with these observations. Using multivariable MR and mediation MR analyses, we determined that BMI mediates the connection of household income and the risk of esophageal cancer, suggesting a valuable avenue for future research. However, we did not identify other modifiable lifestyle factors as mediators of this relationship. This result warrants further validation and interpretation through larger-scale studies to refine our understanding of the complex interactions of SES, lifestyle, and cancer risk.

This MR study has several notable strengths. Firstly, the databases for socioeconomic status and the risk of esophageal cancer were derived from both European and East Asian populations, thereby minimizing potential biases associated with population-specific differences (33). Secondly, the use of Bonferroni-corrected analyses helped mitigate the risk of type I errors, ensuring robust statistical inferences (32). Thirdly, the connection of socioeconomic status and the risk of esophageal cancer found in this study was validated by other databases and population, which can enhance the generalizability of the research results. Lastly, this study is the first to establish a connection of socioeconomic status and the risk of esophageal cancer, providing novel insights into this association.

There are still some limitations in our study. First, these results may not be generalizable to other ethnic groups, although our analysis incorporated data from European and East Asian populations. Future studies should aim to utilize more diverse populations to achieve a deeper understanding of the connection of socioeconomic status and esophageal cancer risk. Second, as this study relies on population-level data, it does not delve into the underlying biological mechanisms. Further experimental investigations are warranted to uncover the pathways or processes that mediate this association.

In conclusion, this comprehensive MR study elucidated the association of socioeconomic status and the risk of esophageal cancer through MR analyses. We uncovered a significant connection of household income and esophageal cancer risk, with BMI identified as a key mediator in this pathway. These results underscore the importance of targeting low-income populations in public health initiatives aimed at reducing esophageal cancer risk, while emphasizing weight management as a pivotal strategy for mitigating related disease burdens.

REFERENCES

1. Waters JK, Reznik SI. Update on Management of Squamous Cell Esophageal Cancer. Curr Oncol Rep 2022;24(3):375-85. DOI: 10.1007/s11912-021-01153-4
2. Zhu H, Ma X, Ye T, Wang H, Wang Z, Liu Q, Zhao K. Esophageal cancer in China: Practice and research in the new era. Int J Cancer 2023;152(9):1741-51. DOI: 10.1002/ijc.34301
3. Li H, Teng Y, Yan X, Cao M, Yang F, He S, et al. Profiles and Findings of Population-Based Esophageal Cancer Screening With Endoscopy in China: Systematic Review and Meta-analysis. JMIR Public Health Surveill 2023;9:e45360. DOI: 10.2196/45360
4. Yang CS, Chen XL. Research on esophageal cancer: With personal perspectives from studies in China and Kenya. Int J Cancer 2021;149(2):264-76. DOI: 10.1002/ijc.33421
5. Tong X, Jin M, Wang L, Zhang D, Yin Y, Shen Q. Prognostic biomarkers for immunotherapy in esophageal cancer. Front Immunol 2024;15:1420399. DOI: 10.3389/fimmu.2024.1420399
6. Ghosh NR, Jones LA. Dietary risk factors for esophageal cancer based on World Health Organization regions. Nutrition 2022;95:111552. DOI: 10.1016/j.nut.2021.111552
7. Huang FL, Yu SJ. Esophageal cancer: Risk factors, genetic association, and treatment. Asian J Surg 2018;41(3):210-5. DOI: 10.1016/j.asjsur.2016.10.005
8. Smyth EC, Lagergren J, Fitzgerald RC, Lordick F, Shah MA, Lagergren P, et al. Oesophageal cancer. Nature reviews Disease primers 2017;3:17048.
9. Deboever N, Jones CM, Yamashita K, Ajani JA, Hofstetter WL. Advances in diagnosis and management of cancer of the esophagus. BMJ 2024;385:e074962. DOI: 10.1136/bmj-2023-074962

10. Li S, He Y, Liu J, Chen K, Yang Y, Tao K, et al. An umbrella review of socioeconomic status and cancer. Nat Commun 2024;15(1):9993. DOI: 10.1038/s41467-024-54444-2
11. Abnet CC, Arnold M, Wei WQ. Epidemiology of Esophageal Squamous Cell Carcinoma. Gastroenterology 2018;154(2):360-73. DOI: 10.1053/j.gastro.2017.08.023. Erratum in: Gastroenterology 2018;155(4):1281. DOI: 10.1053/j.gastro.2018.09.048
12. Delman AM, Ammann AM, Turner KM, Vaysburg DM, Van Haren RM. A narrative review of socioeconomic disparities in the treatment of esophageal cancer. J Thorac Dis 2021;13(6):3801-8. DOI: 10.21037/jtd-20-3095
13. Sardana RK, Chhikara N, Tanwar B, Panghal A. Dietary impact on esophageal cancer in humans: a review. Food Funct 2018;9(4):1967-77. DOI: 10.1039/c7fo01908d
14. Williams J, Allen L, Wickramasinghe K, Mikkelsen B, Roberts N, Townsend N. A systematic review of associations between non-communicable diseases and socioeconomic status within low- and lower-middle-income countries. J Glob Health 2018;8(2):020409. DOI: 10.7189/jogh.08.020409
15. Kaphingst KA, Peterson E, Zhao J, Gaysynsky A, Elrick A, Hong SJ, et al. Cancer communication research in the era of genomics and precision medicine: a scoping review. Genet Med 2019;21(8):1691-8. DOI: 10.1038/s41436-018-0402-0
16. Sommer I, Griebler U, Mahlknecht P, Thaler K, Bouskill K, Gartlehner G, et al. Socioeconomic inequalities in non-communicable diseases and their risk factors: an overview of systematic reviews. BMC Public Health 2015;15:914. DOI: 10.1186/s12889-015-2227-y

17. Pohl SA, Nelson BA, Patwary TR, Amanuel S, Benz EJ Jr, Lathan CS. Evolution of community outreach and engagement at National Cancer Institute-Designated Cancer Centers, an evolving journey. CA Cancer J Clin 2024;74(4):383-96. DOI: 10.3322/caac.21841
18. Sekula P, Del Greco M F, Pattaro C, Köttgen A. Mendelian Randomization as an Approach to Assess Causality Using Observational Data. J Am Soc Nephrol 2016;27(11):3253-65. DOI: 10.1681/ASN.2016010098
19. Yang Y, Chen B, Zheng C, Zeng H, Zhou J, Chen Y, Su Q, Wang J, Wang J, Wang Y, Wang H, Jin R, Bo Z, Chen G, Wang Y. Association of glucose-lowering drug target and risk of gastrointestinal cancer: a mendelian randomization study. Cell Biosci 2024;14(1):36. DOI: 10.1186/s13578-024-01214-8
20. Goding Sauer A, Siegel RL, Jemal A, Fedewa SA. Current Prevalence of Major Cancer Risk Factors and Screening Test Use in the United States: Disparities by Education and Race/Ethnicity. Cancer Epidemiol Biomarkers Prev 2019;28(4):629-42. DOI: 10.1158/1055-9965.EPI-18-1169
21. Zagkos L, Schwinges A, Amin HA, Dovey T, Drenos F. Exploring the contribution of lifestyle to the impact of education on the risk of cancer through Mendelian randomization analysis. Sci Rep 2024;14(1):6074. DOI: 10.1038/s41598-024-54259-7
22. Skrivankova VW, Richmond RC, Woolf BAR, Yarmolinsky J, Davies NM, Swanson SA, et al. Strengthening the Reporting of Observational Studies in Epidemiology Using Mendelian Randomization: The STROBE-MR Statement. JAMA 2021;326(16):1614-21. DOI: 10.1001/jama.2021.18236
23. Gibson MJ, Spiga F, Campbell A, Khouja JN, Richmond RC,

Munafò MR. Reporting and methodological quality of studies that use Mendelian randomisation in UK Biobank: a meta-epidemiological study. BMJ Evid Based Med 2023;28(2):103-10. DOI: 10.1136/bmjebm-2022-112006

24. Mbatchou J, Barnard L, Backman J, Marcketta A, Kosmicki JA, Ziyatdinov A, et al. Computationally efficient whole-genome regression for quantitative and binary traits. Nat Genet 2021;53(7):1097-103. DOI: 10.1038/s41588-021-00870-7
25. Liu M, Jiang Y, Wedow R, Li Y, Brazel DM, Chen F, et al. Association studies of up to 1.2 million individuals yield new insights into the genetic etiology of tobacco and alcohol use. Nat Genet 2019;51(2):237-44. DOI: 10.1038/s41588-018-0307-5
26. Pirastu N, McDonnell C, Grzeszkowiak EJ, Mounier N, Imamura F, Merino J, et al. Using genetic variation to disentangle the complex relationship between food intake and health outcomes. PLoS Genet 2022;18(6):e1010162. DOI: 10.1371/journal.pgen.1010162
27. Bowden J, Holmes MV. Meta-analysis and Mendelian randomization: A review. Res Synth Methods 2019;10(4):486-96. DOI: 10.1002/jrsm.1346
28. Dudbridge F. Polygenic Mendelian Randomization. Cold Spring Harb Perspect Med 2021;11(2):a039586. DOI: 10.1101/cshperspect.a039586
29. Boef AG, Dekkers OM, le Cessie S. Mendelian randomization studies: a review of the approaches used and the quality of reporting. Int J Epidemiol 2015;44(2):496-511. DOI: 10.1093/ije/dyv071
30. Burgess S, Thompson SG; CRP CHD Genetics Collaboration. Avoiding bias from weak instruments in Mendelian

randomization studies. Int J Epidemiol 2011;40(3):755-64. DOI: 10.1093/ije/dyr036

31. Kamat MA, Blackshaw JA, Young R, Surendran P, Burgess S, Danesh J, et al. PhenoScanner V2: an expanded tool for searching human genotype-phenotype associations. Bioinformatics 2019;35(22):4851-3. DOI: 10.1093/bioinformatics/btz469

32. Sedgwick P. Multiple hypothesis testing and Bonferroni's correction. BMJ 2014;349:g6284. DOI: 10.1136/bmj.g6284

33. Burgess S, Davies NM, Thompson SG. Bias due to participant overlap in two-sample Mendelian randomization. Genet Epidemiol 2016;40(7):597-608. DOI: 10.1002/gepi.21998

34. Allen L, Williams J, Townsend N, Mikkelsen B, Roberts N, Foster C, et al. Socioeconomic status and non-communicable disease behavioural risk factors in low-income and lower-middle-income countries: a systematic review. Lancet Glob Health 2017;5(3):e277-89. DOI: 10.1016/S2214-109X(17)30058-X

35. Schultz WM, Kelli HM, Lisko JC, Varghese T, Shen J, Sandesara P, et al. Socioeconomic Status and Cardiovascular Outcomes: Challenges and Interventions. Circulation 2018;137(20):2166-78. DOI: 10.1161/CIRCULATIONAHA.117.029652

36. Peng L, Wen WP. Socioeconomic status and asthma: A bidirectional Mendelian randomization study. World Allergy Organ J 2023;16(6):100790. DOI: 10.1016/j.waojou.2023.100790

37. Geng C, Meng K, Tang Y. Identifying the mediating role of inflammation on the relationship between socioeconomic status and Alzheimer's disease: a Mendelian randomization analysis and mediation analysis. J Neurol 2024;271(5):2484-93. DOI:

10.1007/s00415-023-12176-1

38. Marino P, Mininni M, Deiana G, Marino G, Divella R, Bochicchio I, et al. Healthy Lifestyle and Cancer Risk: Modifiable Risk Factors to Prevent Cancer. Nutrients 2024;16(6):800. DOI: 10.3390/nu16060800

39. Zhan ZQ, Chen YZ, Huang ZM, Luo YH, Zeng JJ, Wang Y, et al. Metabolic syndrome, its components, and gastrointestinal cancer risk: a meta-analysis of 31 prospective cohorts and Mendelian randomization study. J Gastroenterol Hepatol 2024;39(4):630-41. DOI: 10.1111/jgh.16477

Table I. Association of socioeconomic status and esophageal cancer

Exposure (socioeconomic status)	**Outcome (esophageal cancer)**	**Method**	**OR (95 % CI)**	***p*-value**
Household Income	Database 1	IVW	0.286 (0.083, 0.982)	0.047
		WM	0.751 (0.456, 0.942)	0.039
		MR Egger	0.167 (0.042, 0.654)	0.036
	Database 2	IVW	0.700 (0.578, 0.996)	0.037
		WM	0.999 (0.997, 1.002)	0.622
		MR Egger	0.995 (0.987, 1.003)	0.241
	Database 3	IVW	0.776 (0.387, 0.934)	0.045
		WM	0.871 (0.582, 1.299)	0.490
		MR Egger	0.910 (0.243, 3.401)	0.892
	Combined	Meta-analysis	0.698 (0.556, 0.876)	0.002
Education	Database 1	IVW	0.965 (0.903, 1.032)	0.299
		WM	0.951 (0.862, 1.049)	0.313
		MR Egger	0.875 (0.653, 1.172)	0.371

	Database 2	IVW	1.003 (0.996, 1.008)	0.600
		WM	0.986 (0.868, 1.112)	0.523
		MR Egger	0.999 (0.998, 1.002)	0.096
	Database 3	IVW	0.960 (0.793, 1.162)	0.677
		WM	1.107 (0.897, 1.367)	0.343
		MR Egger	0.719 (0.422, 1.225)	0.244
	Combined	Meta-analysis	1.003 (0.997, 1.009)	0.385
Townsend Deprivation Index	Database 1	IVW	1.505 (0.435, 5.205)	0.518
		WM	0.785 (0.144, 4.265)	0.779
		MR Egger	2.034 (0.808, 6.286)	0.373
	Database 2	IVW	1.002 (0.998, 1.006)	0.336
		WM	1.003 (0.997, 1.008)	0.348
		MR Egger	1.013 (0.986, 1.040)	0.372
	Database 3	IVW	1.072 (0.897, 1.280)	0.445
		WM	1.027 (0.808, 1.306)	0.827

		MR Egger	0.845 (0.511, 1.396)	0.532
	Combined	Meta-analysis	1.002 (0.998, 1.006)	0.317

Table II. Mediation effect of modifiable lifestyle factors on household income and esophageal cancer

Mediation factors	**OR (95 % CI)**	**Proportion of mediation effect**	***p*-value**
Body mass index	0.914 (0.841, 0.992)	27.23 %	0.031
Tea consumption	1.006 (0.093, 10.818)	4.42 %	0.996
Coffee consumption	1.066 (0.477, 4.592)	5.14 %	0.991
Processed meat consumption	1.038 (0.219, 8.836)	2.971 %	0.999
Cooked vegetables consumption	1.387 (0.152, 6.557)	26.144 %	0.968
Fresh fruit consumption	1.100 (0.126, 9.610)	7.595 %	0.932

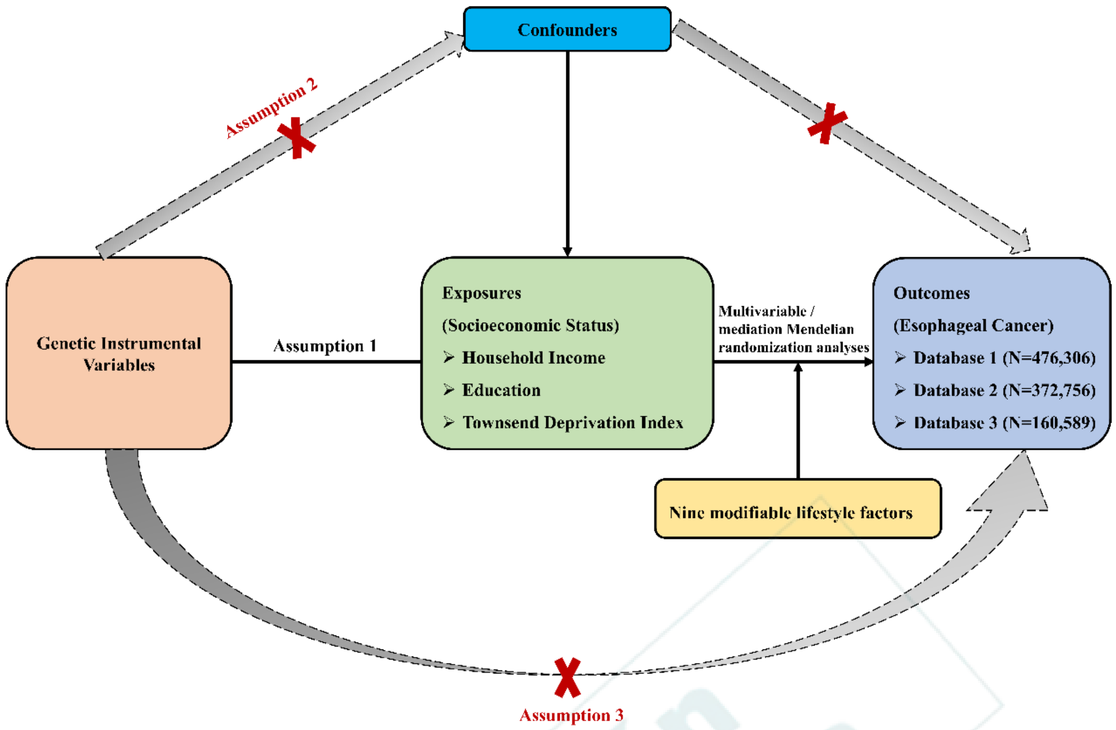

Figure 1. Directed acyclic graph of this comprehensive Mendelian randomization study.

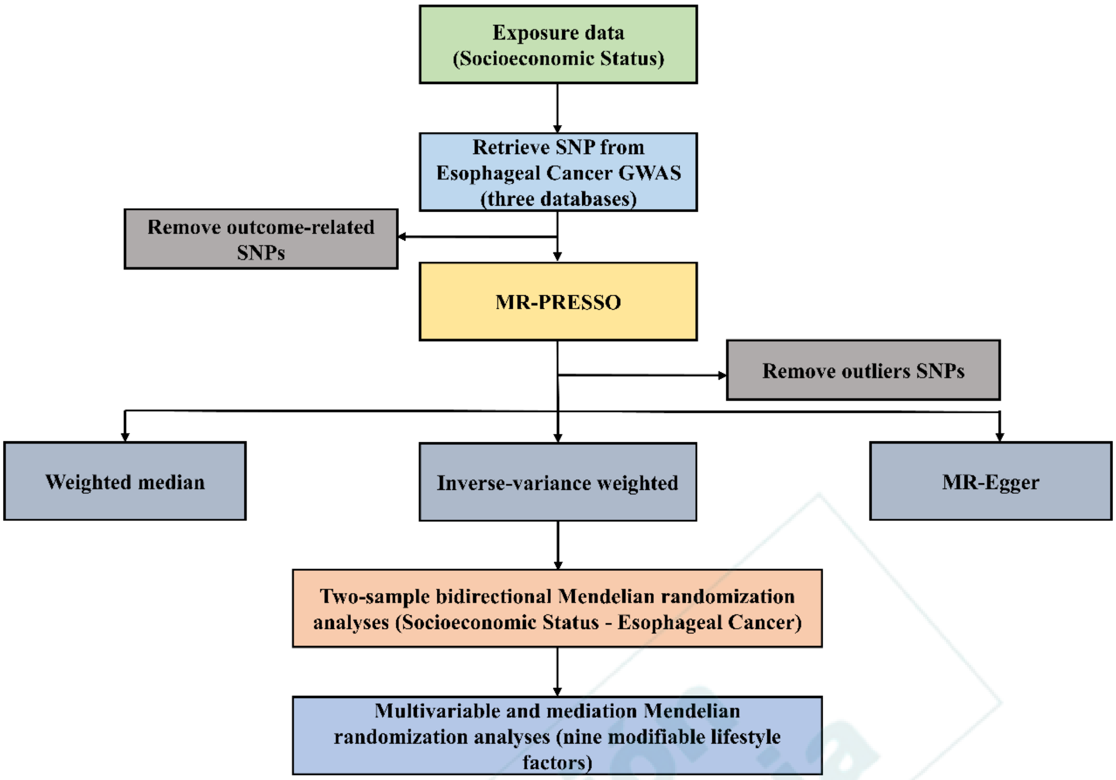

Figure 2. The flowchart of this comprehensive Mendelian randomization study (GWAS: genome-wide association studies; MR-PRESSO: MR Pleiotropy RESidual Sum and Outlier; SNP: single nucleotide polymorphisms).

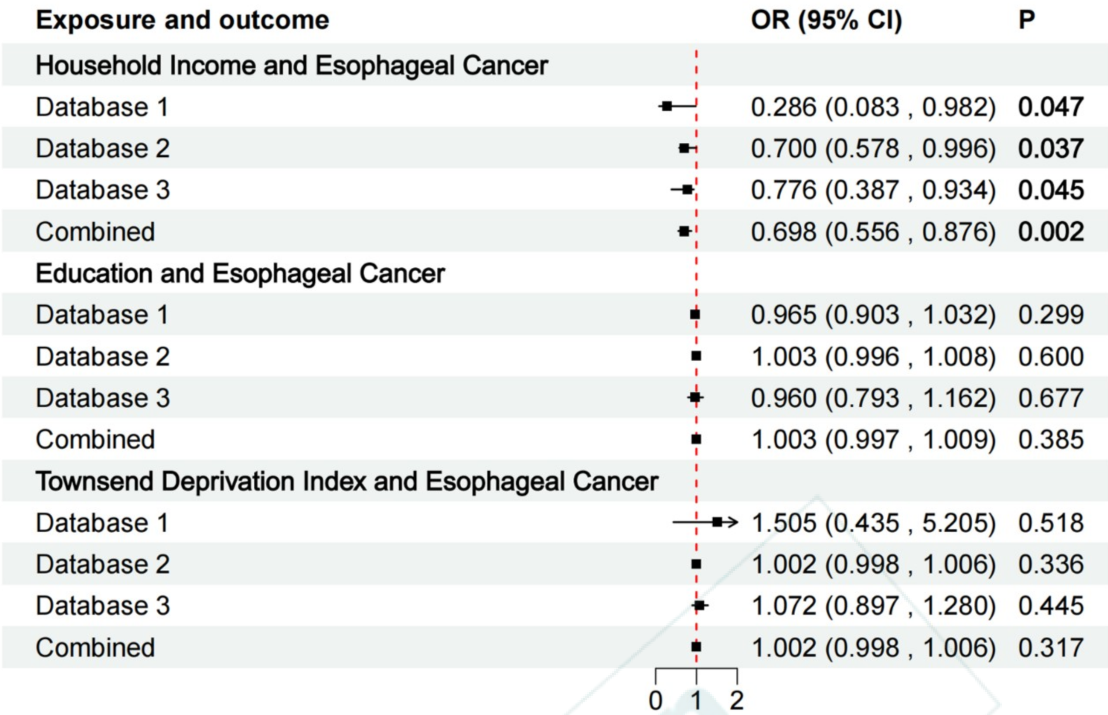

Figure 3. Association of socioeconomic status and Esophageal Cancer risk (95 % CI: 95 % confidence interval; OR: odds ratio).

Supplementary Tables

Supplementary Table I | Details of GWAS summary data (exposure and outcome databases). **Abbreviations:** PMID: Pubmed ID.

Supplementary Table II | Details of Modifiable Lifestyle Factors databases. **Abbreviations:** PMID: Pubmed ID.

Supplementary Table III | Sample overlap between the exposure databases and outcome databases.

Supplementary Table IV | Characteristics of SNPs extracted from exposure data (Socioeconomic Status database). **Abbreviations:** Chr: chromosome; EA: effect Allele; EAF: effect allele frequency; OA: other Allele; SE: standard error.

Supplementary Table V | Association of Esophageal Cancer risk and Socioeconomic Status. **Abbreviations:** 95% CI: 95% confidence interval; IVW: inverse-variance weighted; OR: odds ratio; WM: weighted median.

Supplementary Table VI | Sensitivity and power analyses on the association of Socioeconomic Status and Esophageal Cancer risk. **Abbreviations:** MR-PRESSO: MR Pleiotropy RESidual Sum and Outlier.

Supplementary Table VII | Sensitivity and power analyses on the association of Esophageal Cancer risk and Socioeconomic Status. **Abbreviations:** MR-PRESSO: MR Pleiotropy RESidual Sum and Outlier.

Supplementary Table VIII | Effects of Socioeconomic Status on Esophageal Cancer risk after regulating nine Modifiable Lifestyle Factors by multivariate Mendelian randomization analysis. **Abbreviations:** 95% CI: 95% confidence interval; BMI: body mass index; IV: instrumental variables; IVW: inverse-variance weighted; OR: odds ratio.