Journal of Translational Medicine

LETTER TO THE EDITOR Open Access

Gender factor cannot be ignored in two-sample Mendelian randomization studies

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Dear Editor,

I read Lin Zhou et al.'s study [1] with great interest. Their study used Mendelian randomization (MR) to assess the relationship between Metabolic Syndrome (MetS) and 10 types of tumors (lung cancer, thyroid cancer, breast cancer, gastric cancer, hepatic cancer, colorectal cancer, oesophagus cancer, kidney cancer, bladder cancer, and prostate cancer) in populations of European ancestry. Their results demonstrate that MetS may increase the risk of hepatocellular carcinoma, and MetS was not causally associated with cancers at other sites. As the components of the MetS, waist circumference may increase the risk of lung and oesophageal cancers and decrease the risk of prostate cancer; hypertension may reduce the risk of Hepatic cancer. This article is the study with the most tumor types included so far. It is undoubtedly valuable and will receive widespread attention. The advantage of MR analysis is that it can effectively avoid interference of potential confounding and reverse causality effects. However, this analytical method is subject to important limitations and assumptions, and improper use may lead to erroneous conclusions. There, there are some methodological issues that need to be reconsidered in this study.

First and foremost, gender-specific phenomena in exposure and outcomes in two-sample MR may mislead the causal inference. The major assumptions of Two-sample MR are that exposure and outcome cohorts should be independent and non-overlapping and should be representative of the same population [2]. This means similar age and sex distribution and the same ethnic group. Prostate cancer and breast cancer are hormone-dependent and sex-specific cancer. Although the gender of the samples is not disclosed in the basic information of the dataset used in this study, there is no doubt that GWAS of prostate cancer (ID: ebi-a-GCST90018905, IEU Open GWAS Database) was assessed only in men, and GWAS of breast cancer (ID: ebi-a-GCST90018799, IEU Open GWAS Database) was assessed in almost all women. But GWAS of MetS was assessed involved both men and women. This means that SNPs for MetS are non-sex specific. This error also existed in an MR study of Alzheimer's disease (including men and women) and cancer (including prostate cancer, breast cancer, and endometrial cancer) [3].

Second, definition of MetS. In the past few decades, different institutions and countries have defined MetS, and the revision and update of the diagnostic criteria for MetS have never stopped. The prevalence of MetS varies according to different definition [4]. Disclosing the diagnostic criteria of MetS in this study will help us better understand the causality between MetS and cancers. At the same time, it is a valuable task to conduct subgroup analysis based on the main manifestations of MetS patients, such as hypertension or hyperglycemia. In addition, authors also assessed the relationship between the components of the MetS (waist circumference, hypertension, fasting blood glucose, high-density lipoprotein cholesterol, and triglycerides) and 10 types of tumors. Readers need to note that hypertension here is independent and represents meeting the diagnostic criteria for

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hypertension, which is not equivalent to hypertension in MetS.

Third, population and databases. The study performed in populations of European ancestry. The findings may not necessarily apply to other ethnic groups with different genetic backgrounds and dietary habits. In addition, GWAS of exposure and outcome were from a single cohort. Supplementing the analysis with other research cohorts can reduce bias from relying on a single cohort.

In conclusion, this is the first MR study to comprehensively explore MetS and various cancers. These findings strengthen the evidence base for public health policies relating to MetS and cancers. We raise some concerns for improvement in the study to help further refine related research programme in the future.

Acknowledgements
Not applicable.

Author contributions
Manuscript writing: Yuanyuan Shao, Fuding Lu. Conception, design, review and editing: Zhiguo Zhu. All authors read and approved the final manuscript.

Funding
This research was funded by China Postdoctoral Science Foundation (2023M731309), Guangdong Basic and Applied Basic Research Foundation (2020A1515110946), PhD Research Foundation of Affiliated Hospital of Jining Medical University (2022-BS-001), Research Fund for Academician LinHe New Medicine (JYHL2022FMS09) and Jining Key Research and Development Foundation (2023YXNS023).

Data availability
Not applicable.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Received: 9 August 2024 / Accepted: 12 August 2024
Published online: 28 August 2024

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