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The causal associations of 25(OH)D and its metabolites with oropharyngeal cancer risk: A Mendelian randomization study

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ADMINISTRATIVE INFORMATION

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 19 September 2024 and was last updated on 19 September 2024.

INTRODUCTION

Review question / Objective Our primary objective was to evaluate the causal impact of 25-hydroxyvitamin D and 25-hydroxyvitamin D (25(OH)D) metabolites, including 25(OH)D3 and its epimeric counterpart (C3-epi-25(OH)D3), on susceptibility to OPC through the utilization of Mendelian randomization (MR) methodology.

Condition being studied Previous studies have posited distinctive correlations of 25-hydroxyvitamin D (25(OH)D) metabolites, specifically 25 hydroxyvitamin D, with health conditions and cancer, the precise causal direction of this association in oropharyngeal cancer (OPC) is unknown.

METHODS

Participant or population We screened the PubMed investigating GWAS data association with 25 hydroxyvitamin D were used for the European population, North America, and South America. For the rest of the literatures, we read the full-text to assess the eligibility. In addition, we also manually searched related references by literature for other potential related articles.

Intervention Following the removal of single-nucleotide polymorphisms (SNPs) with linkage disequilibrium r2 < 0.001, a clumping distance of 10,000 kb, and an F-statistic threshold of F < 10, SNPs ($p < 5 \times 10-8$) were incorporated into the analysis for the Vit D set.

Comparator Not applicable.

Study designs to be included Following the removal of single-nucleotide polymorphisms (SNPs) with linkage disequilibrium r2 < 0.001, a

clumping distance of 10,000 kb, and an F-statistic threshold of F < 10.

Eligibility criteria SNPs (p < 5 × 10−8) were incorporated; Excluded were single-nucleotide polymorphisms (SNPs) with linkage disequilibrium r2 < 0.001, a clumping distance of 10,000 kb, and an F-statistic threshold of F < 10.

Information sources We screened the PubMed investigating GWAS data association with 25 hydroxyvitamin D were used for the European population, North America, and South America. For the rest of the literatures, we read the full-text to assess the eligibility. In addition, we also manually searched related references by literature for other potential related articles.

Main outcome(s) The paper revealed evidence suggesting a decreased causal impact of 25(OH)D3 on OPC risk within the European population (weighted median (WM) OR = 0.47, 95% CI = 0.24-0.91, P = 0.03). Only one of the 21 MR analyses was significant. The IVW results indicated significance, but subsequent leave-one-out analyses showed instability in the negative results. Notably, the results turned positive after the exclusion of rs9304669 (OR = 0.51, 0.28-0.91, P = 0.02), while the other results remained negative. Sensitivity analysis outcomes exhibited stability, with no observed heterogeneity or pleiotropy.

Quality assessment / Risk of bias analysis This approach involved the selection of relevant SNPs for identifying the risk factors associated with OPC. Subsequently, we calculated SNP-specific Wald estimates (obtained by dividing the SNP result estimate by the SNP exposure estimate) and applied the IVW method to conduct a meta-analysis of these estimates. This allowed us to derive an estimate of the impact of these risk factors on OPC risk.

Strategy of data synthesis MR analysis was performed using data from patients with OPC from Europe, North America, and South America using genetic variations robustly related to C3-epi-25 (OH) D3, 25 (OH) D, and 25 (OH) D3. The primary analytical approach involved inverse-variance weighting (IVW) as the main method for two-sample MR analysis, and five other methods (weighted median (WM), MR-Egger, and Cochran's Q) were concurrently employed as sensitivity analyses to test and adjust for pleiotropy.

Subgroup analysis None.

Sensitivity analysis we performed additional analyses using weighted median (WM) and MR-Egger methods to appraise the potential of imbalanced-level horizontal pleiotropy, which are also mentioned in detail elsewhere14. In short, the WM specifies that at least 50% of the weights in the assay come from effective tools15.
Even if the mutation is invalid, MR-Egger provides credible effect calculations, which can also adjust and test for directional pleiotropy16. To further evaluate the stability of the results, (1) we scrutinized the potential existence of ineffective instrumental variables, particularly in cases of horizontal pleiotropy, to assess heterogeneity between individual genetic variable quantity using Cochran's Q statistic, (2) the Egger intercept test was utilized as a tool for detecting pleiotropy, and (3) scatter plots and leave-one-out tests were used to investigate whether the IVW method was influenced by specific SNPs.To further support our analysis, we performed sensitivity analyses employing MR-Egger and the weighted median approach. These methodologies were instrumental in detecting instances of horizontal or uncorrelated pleiotropy, where genetic variants impact both the exposure (Vit D set) and the outcome (OPC) through distinct mechanisms. Correlated pleiotropy, on the other hand, represents a situation that can engender spurious associations in Mendelian randomization. In such cases, genetic variants influence both the exposure and the outcome via shared heritable factors. It is imperative to consider the possibility of correlated pleiotropy within the instruments related to the Vit D set, as its detection is crucial to prevent false-positive results.

Country(ies) involved China (School and Hospital of Stomatology,Wenzhou Medical University).

Keywords Oropharyngeal cancer; Mendelian randomization; 25(OH)D; 25(OH)D3;C3-epi-25(OH)D3.

Contributions of each author

Author 1 - YaoHui Yu - Y.H.Y wrote the main manuscript text. Y.H.Y prepared figures and tables. All authors reviewed the manuscript.
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