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ORIGINAL RESEARCH

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Causal associations between dietary factors with head and neck cancer: A two-sample Mendelian randomization study

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Abstract

Objective: Although an association exists between dietary habits and head and neck cancer (HNC), the direct cause-and-effect connection remains elusive. Our objective was to investigate the causal associations between dietary factors and the likelihood of developing HNC.

Methods: Genome-wide association study (GWAS) summary statistics for dietary habits were screened from the UK Biobank, the OncoArray Oral Cavity and Oropharyngeal Cancer consortium, and the FinnGen biobank for HNC. A two-sample Mendelian randomization (MR) analysis was utilized to establish causality. The primary method of analysis was inverse variance weighting (IVW).

Results: Clear evidence of an inverse association existed between dried fruit intake and HNC in both cohorts (OncoArray consortium: IVW OR = 0.183; 95% CI, 0.037–0.915; $p = .03864$; FinnGen: IVW OR = 0.281; 95% CI, 0.115–0.688; $p = .00547$). In addition, fresh fruit (IVW-mre OR = 0.066; 95% CI, 0.011–0.413; $p = .00369$), beef (IVW OR = 15.094; 95% CI, 1.950–116.853; $p = .00934$), and lamb/mutton intakes (IVW OR = 5.799; 95% CI, 1.044–32.200; $p = .0448$) were significantly associated with HNC in the OncoArray consortium cohort.

Conclusions: Dried fruit intake may be a protective factor against HNC. The association of fresh fruit and red meat intakes with HNC warrants careful interpretation. Additional studies are necessary to explore potential mechanisms for further evidence.

Level of evidence: III

KEYWORDS
diet, dried fruit, head and neck cancer, Mendelian randomization

Yali Xu, Guangui Chen, and Min Mao contributed equally to this study.

1 | INTRODUCTION

Head and neck cancer (HNC) predominantly originates from the epithelial tissue of the oral cavity, pharynx, and larynx within the upper aerodigestive system. It ranks as the sixth most common cancer (878,348 new cases and 444,347 deaths), accounting for 4.6% of all cancers and 4.5% of all cancer-related deaths worldwide in 2020.[1,2] Major risk factors for head and neck cancer consist of tobacco and alcohol misuse, as well as contracting human papilloma virus (HPV) infections.[3] In spite of the remarkable advancements in therapeutic approaches and betterment of modifiable lifestyle practices (such as quitting smoking, decreasing alcohol consumption, and getting the HPV vaccine), the 5-year overall survival stays below 50% owing to the frequent presence of local recurrences and/or distant metastases.[4] It is imperative to develop novel approaches for the prevention of HNC, with a specific emphasis on addressing easily modifiable high-risk factors. Colditz et al. showed that approximately 30% of cancer cases in the United States are attributed to tobacco use, whereas alcohol consumption contributes to 4% and poor diet is a variable factor in the remaining cases.[5] Islami et al. surveyed publications by the International Agency for Research on Cancer (IARC) and the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) to identify potentially modifiable risk factors for cancer for which exposure occurrence and cancer outcome data were available. The researchers discovered a range in the percentage of all cancer cases linked to inadequate nutrition, starting from 0.3% for low dietary calcium intake to 1.4% for low fruit and vegetable consumption. Interestingly, in cases of HNC, low fruit and vegetable consumption contributed to roughly 30.7% of instances.[6] Another large-scale international collaborative study based on the International Head and Neck Cancer Epidemiology (INHANCE) consortium revealed a significant association between high fruit and vegetable consumption and lower risk of HNC.[7] WCRF/AICR published 10 cancer prevention recommendations, which were updated in the 2018 to reduce the risk of cancer. These latest recommendations included eating a better diet, limiting "fast foods," limiting red and processed meat, cutting down on sugar drinks, and so on.[8] Malcomson et al. performed a study to investigate associations between the 2018 WCRF/AICR score and cancer incidence using the data from the UK Biobank prospective cohort study. The results provided strong evidence that adherence to the 2018 WCRF/AICR Cancer Prevention Recommendations reduces the risk of any cancer as well as the risk of kidney, bladder, ovarian, HNC, esophageal, stomach, liver, and gallbladder cancers.[9] However, a limitation of their study was that because it was an observational study, it only showed that following the WCRF/AICR recommendations is associated with the reduced risk of cancer, but did not demonstrate the cause and effect. Given this, further randomized controlled trials (RCTs) should be planned to investigate the impact of dietary habits on the prevention or management of HNC.

Epidemiological or observational studies are limited by a lack of randomization and the potential for reverse causality and/or confounding. In contrast, Mendelian randomization (MR) analysis refers to a novel statistical approach to use genetic variants in observational epidemiology, in the belief that genetic variants are randomly distributed during gamete formation and conception, contributing to a decrease in susceptibility to bias or reversed causality.[10] A study design based on MR analysis allows investigation of many exposures that cannot be assessed in RCTs.[11] Recently, a genome-wide association study by Cole et al. indicated that dietary habits are heritable traits.[12] Currently, MR has successfully identified causal relationships between dietary habits and several diseases, including breast, lung, and endometrial cancer; asthma; and major mental disorders,[13–16] but relevant studies on the causal relationships between dietary factors and HNC risk are lacking.

The aim of this study was to investigate the causal links between dietary factors and HNC risk. We found evidence that consumption of dried fruit may be a protective factor, whereas the evidence regarding the association of fresh fruit and red meat intakes with HNC remained inconclusive. The findings of our study can enhance the comprehension of the risk and protective elements associated with HNC.

2 | MATERIALS AND METHODS

2.1 | Study design

To ensure that an MR study is valid, genetic variants as instrumental variables (IVs) must adhere to the following three assumptions: (1) the IVs need to exhibit a robust connection with exposures; (2) the IVs should not be linked to any confounders; and (3) the IVs should influence the outcome solely by their effect on exposure. The data used in this study were based on published summary statistics of genome-wide association studies (GWASs); consequently, ethical approval was not required.

2.2 | Data sources

The genetic variants of dietary factors in the study and the corresponding number of European individuals were extracted directly from the MRC-IEU UK Biobank OpenGWAS,[17] which included consumption of tea ($N = 447{,}485$), coffee ($N = 428{,}860$), milk ($N = 64{,}943$), yogurt ($N = 64{,}949$), fresh ($N = 446{,}462$), and dried ($N = 421{,}764$) fruit, salad/raw and cooked vegetables ($N = 435{,}435$), beef ($N = 461{,}053$), pork ($N = 460{,}162$), lamb/mutton ($N = 460{,}006$), processed meat ($N = 461{,}981$), oily ($N = 460{,}443$) and non-oily ($N = 460{,}880$) fish, bread ($N = 452{,}236$), cereal ($N = 441{,}640$), and cheese ($N = 451{,}486$). Dietary intakes as exposure factors were acquired by asking about the frequency of dietary intake in the questionnaire. Table S1, Supporting Information shows the specific questions used to assess these dietary habits.

Two GWAS sets of HNC from different cohorts were obtained as outcomes for the current MR analysis to strengthen our results. The GWAS summary data for HNC released by the OncoArray Oral Cavity and Oropharyngeal Cancer consortium contained 2497 cases and 2928 controls in European individuals; 2281 cases and 314,193 controls were included in the FinnGen cohort.[18–20] All data for the

present study are publicly available at https://gwas.mrcieu.ac.uk and https://www.finngen.fi/en/access_results.

2.3 | Selection of IVs

To choose appropriate IVs, we included single-nucleotide polymorphisms (SNPs) at the genome-wide significance level (p < 5e-8) and used strict cutoff values (r^2 < 0.001; region size = 10,000 kb) to filter out SNPs exhibiting linkage disequilibrium. For milk and yogurt intake, we chose a relaxed threshold (p < 1e-5; r^2 < 0.01; region size = 5000 kb) because of the absence of eligible SNPs under the strict cutoff values. F statistics were calculated to validate the strength of individual SNPs. An F value >10 is commonly accepted as the threshold for a strong correlation. If the F value was <10, the SNP was excluded, and estimation of the causal effect using inverse variance weighting (IVW) was repeated after filtering. To fulfill the requirements of the second and third assumptions, we used PhenoScanner (www.phenoscanner.medschl.cam.ac.uk) to remove IVs that were associated with other confounding characteristics in previous GWAS, such as smoking and alcohol behavior, squamous cell carcinoma, and other. Additionally, we eliminated SNPs that showed significant correlations with several dietary patterns to mitigate potential pleiotropy across SNPs. To maintain uniformity in the SNPs used as IVs across the different analyses, we refrained from missing variants with proxies. Prior to performing the MR analysis, we undertook data-harmonization steps to ensure that the impact of a specific SNP on both exposure and outcome corresponded to the same allele.

2.4 | Statistical analysis

In line with the instructions for MR, IVW was selected as the optimal analysis method to determine the causal link between dietary habits and HNC. The heterogeneity of the IVW model was assessed using Cochran's Q test, and evidence of heterogeneity was considered at a p-value less than .05. In the case of heterogeneity, a multiplicative random-effects (mre) IVW model was applied. The intercept from the MR-Egger test was used to assess pleiotropy.[21,22] The odds ratios (ORs) were transformed with effect estimates (equivalent to beta coefficients), and the results are presented with 95% confidence intervals (CIs). To display the outcomes, we generated leave-one-out, scatter, and forest plots. All MR analyses were conducted using the TwoSampleMR (version 0.5.6) package in R (version 3.4.2). Significance was determined at a p-value of less than .05.

3 | RESULTS

3.1 | SNP selection and validation

The F-statistics values for milk intake were all below 10 (OncoArray consortium: 3.994–5.023; FinnGen biobank: 3.994–5.970). Therefore, milk intake was excluded from subsequent MR analysis. Table S1 presents the specific characteristics of the IVs associated with 17 dietary factors. In this study, a causal relationship was identified for four factors including dried fresh intake, fresh fruit intake, beef intake, and lamb/mutton intake (IVW p < .05).

3.2 | Causal correlations between dietary intake and HNC in the GWAS statistics from the OncoArray consortium

We found that fresh fruit intake was related to a reduced likelihood of developing HNC (IVW-mre OR = 0.066; 95% CI, 0.011–0.413; p = .00369) (Figure 1). The results from the Cochran's Q test revealed heterogeneity between the IVs for fresh fruit intake (p = .04587), indicating that the estimation of fixed-effects IVW may be biased; a mre IVW model was thus applied. No horizontal pleiotropy was detected in the MR-Egger intercept test (p > .05). Dried fruit intake was inversely associated with HNC risk (IVW OR = 0.183; 95% CI, 0.037–0.915; p = .03864) (Figure 1). Heterogeneity and pleiotropy tests confirmed the strength of the MR results (p > .05). Leave-one-out, scatter, and forest plots showing the association between dried fruit intake with HNC were generated (Figure 2A–C). Overall, the MR analysis showed consistent and robust results for dried fruit intake. The IVW analysis revealed that beef (IVW OR = 15.094; 95% CI, 1.950–116.853; p = .00934) and lamb/mutton (IVW OR = 5.799; 95% CI, 1.044–32.200; p = .0448) intakes were related to an increased risk of HNC (Figure 1). The MR-Egger regression showed absence of horizontal pleiotropy (p > .05). No associations were observed for other dietary factors in the IVW analysis. In the sensitivity analysis, mild-to-moderate heterogeneity was recorded for certain exposures, including fresh fruit, processed meat, pork, oily fish, and cereal intake; nevertheless, there was no evidence of pleiotropic effects that were statistically significant (p > .05) as indicated in Table S2.

3.3 | Causal correlations between dietary intake and HNC in the GWAS statistics from the FinnGen biobank

We replicated the diet–HNC association using GWAS data for HNC outcomes from the FinnGen consortium R10 release. Accordingly, we found that dried fruit intake was inversely associated with HNC risk (IVW OR = 0.281; 95% CI, 0.115–0.688; p = .00547) (Figure 3). In the sensitivity analyses, no evidence of heterogeneity or directional pleiotropy for dried fruit intake was detected (p > .05). The credibility and reliability of the MR results were further confirmed through the leave-one-out examination. Leave-one-out, scatter, and forest plots were illustrated to describe the association between dried fruit intake with HNC (Figure 2D–F). In addition, we found that fresh fruit intake was weakly positively associated with HNC risk using GWAS datasets from the FinnGen study (IVW OR = 0.365; 95% CI,

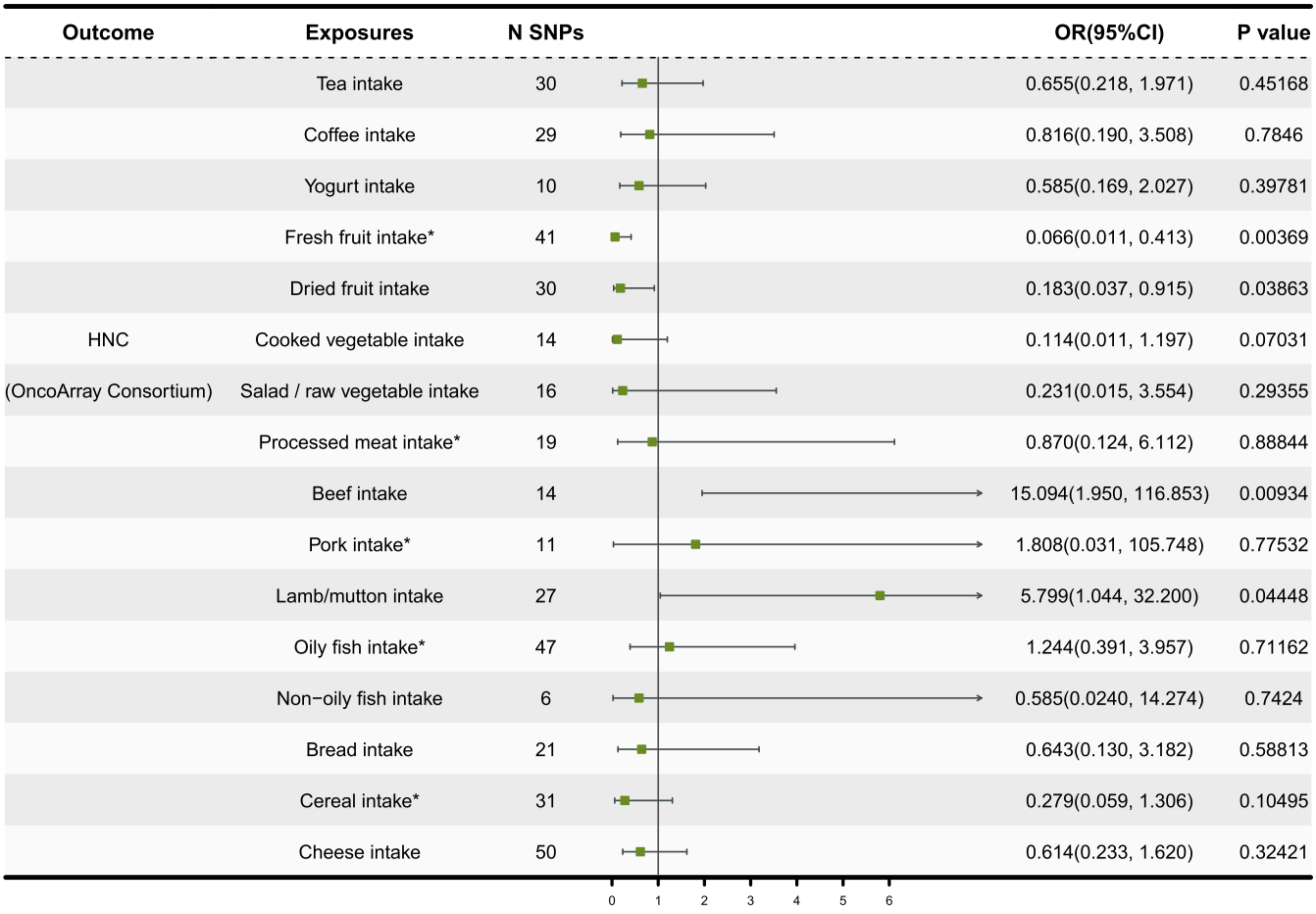

FIGURE 1 Forest plot showing the results of the MR analysis to assess associations between dietary intake and HNC using GWAS statistics from the OncoArray Oral Cavity and Oropharyngeal Cancer consortium. GWAS, genome-wide association study; HNC, head and neck cancer; MR, Mendelian randomization; OR, odds ratio; SNP, single-nucleotide polymorphisms; 95% CI, 95% confidence interval.

0.122–1.092), but the significance was dampened ($p = .07141$). The findings on the correlation between genetically predicted beef and lamb/mutton consumption and heightened HNC risk could not be confirmed in the FinnGen dataset (IVW $p > .05$). There was no significant evidence of a link between other genetically predicted dietary factors and HNC. In the sensitivity analysis, mild heterogeneity was observed for cooked vegetable intake, whereas no evidence of directional pleiotropy was detected in the MR-Egger regression analysis with the exception of processed meat and pork intake, as shown in Table S2.

4 | DISCUSSION

In the present study, we used GWAS summary data from different cohorts to conduct a two-sample MR analysis to examine the causal relationships between 17 different dietary factors and HNC risk. Four candidate dietary factors have been pinpointed as potentially linked to HNC. Strong associations were noted between the consumption of dried fruits and a lowered likelihood of developing HNC in the European population. Fresh fruit, beef, and lamb/mutton intake showed causal associations with HNC in the OncoArray consortium dataset, but convincing causal effects on HNC risk were not replicated in the data from the FinnGen biobank. The variations in the two GWAS sets observed in our studies may be attributed to the confounded factors by hidden population structures and the different HNC subtypes. Due to the variations found in the two GWAS datasets, our results for fresh fruit, beef, and lamb/mutton consumption should be interpreted cautiously. Based on current knowledge, this is the first MR comprehensive exploration of the causal association between dietary factors and HNC.

The correlation between nutrition and cancer risk has been a topic of research for many years. Previous studies have indicated that a diet rich in fruits, vegetables, whole grains, and fiber, while low in animal products and refined carbohydrates, could diminish the risk of post-menopausal breast cancer; the association was nearly consistent in colorectal cancer.[23] A review by Rodríguez-Molinero indicated that foods such as fruits, vegetables, curcumin, and green tea can reduce the risk of oral cancer, whereas a diet rich in red meat and fried foods can enhance the risk.[24] Maino Vieytes et al. constructed a multivariable binary logistic regression model and found that promoting the consumption of a diet abundant in fruits, vegetables, wholegrains, low-fat dairy, legumes, and nuts, with a minimal intake of red and

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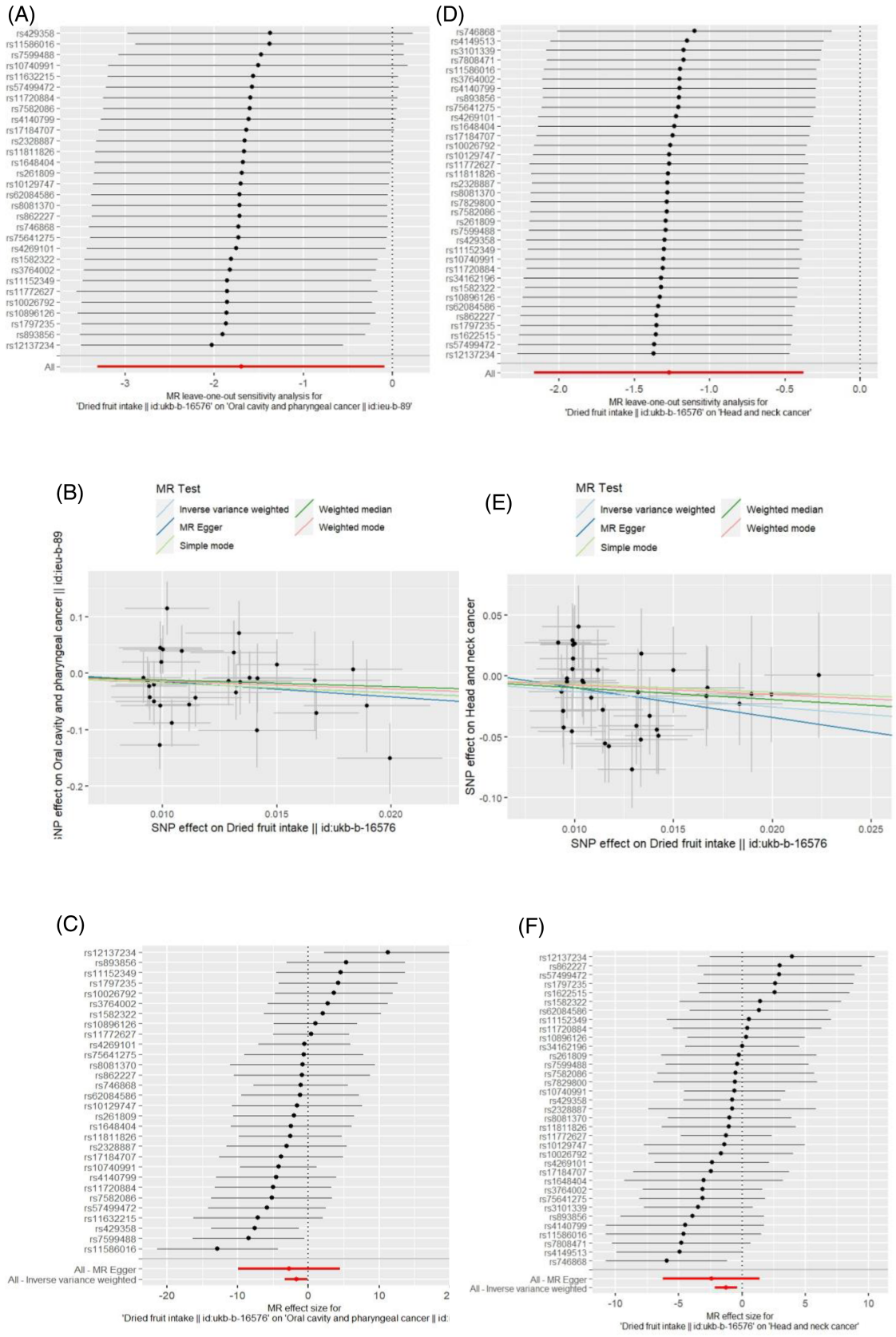

FIGURE 2 Analyses of genetically predicted dried fruit intake and HNC. (A–C) Leave-one-out, scatter, and forest plots, respectively, using GWAS statistics from the OncoArray Oral Cavity and Oropharyngeal Cancer consortium. (D–F) Leave-one-out, scatter, and forest plots, respectively, using GWAS statistics from the FinnGen biobank. GWAS, genome-wide association study.

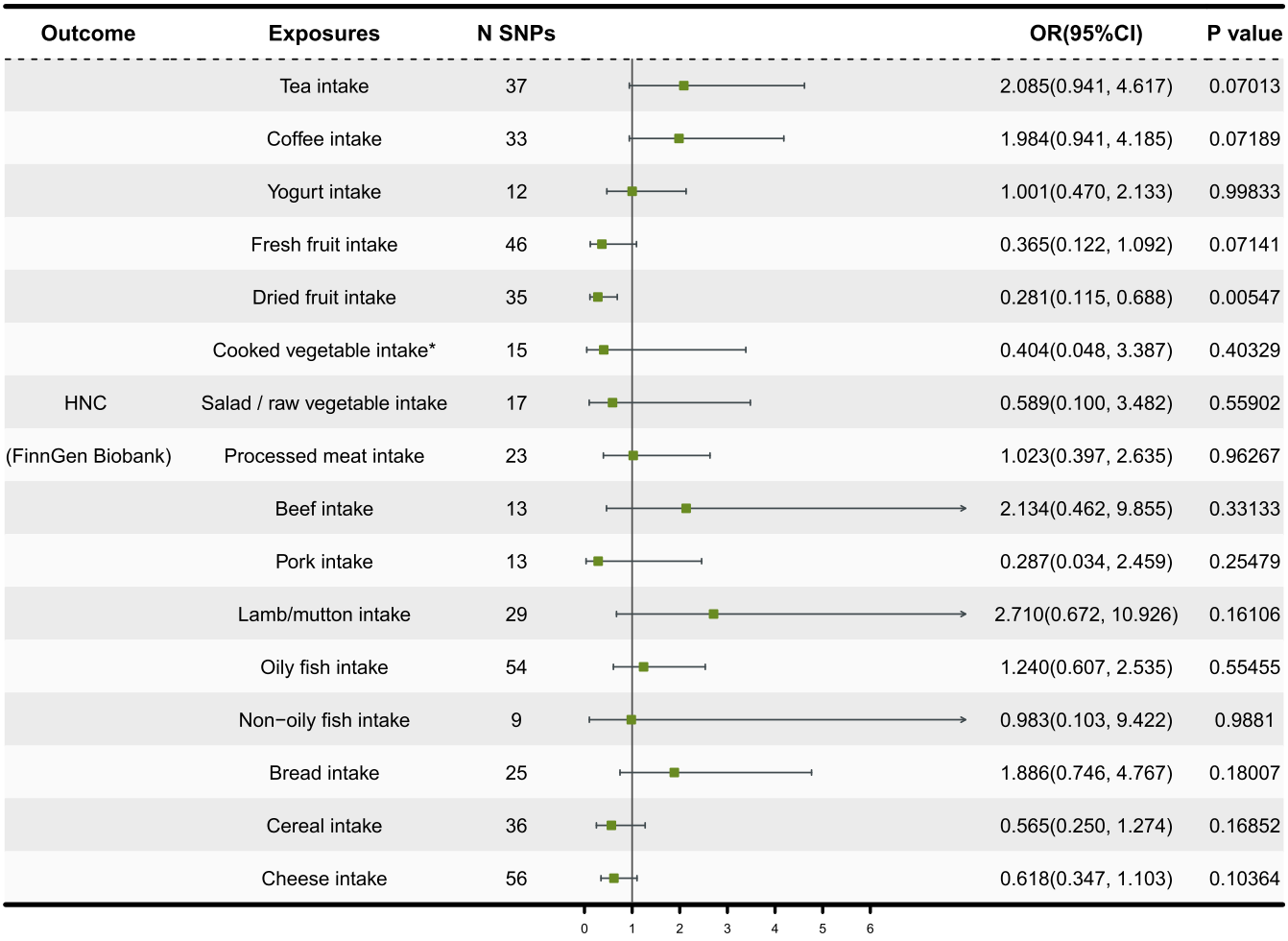

FIGURE 3 Forest plot showing MR results to assess associations between dietary intake and HNC using GWAS statistics from the FinnGen biobank. GWAS, genome-wide association study; HNC, head and neck cancer; MR, Mendelian randomization; OR, odds ratio; SNP, single-nucleotide polymorphisms; 95% CI, 95% confidence interval.

processed meat and sodium, may potentially reduce the overall symptom load for patients who have recently been diagnosed with head and neck squamous cell carcinoma.[25] According to WCRF, high consumption of fruits, vegetables, and wholegrains as well as low intake of red and processed meat can decrease the likelihood of cancer development.[26] A diet rich in vegetables and fruits is believed to be beneficial due to the presence of various bioactive compounds, such as carotenoids, flavonoids, polyphenols, and vitamins, which can act collectively to boost anti-cancer activity. This encompasses the amplification of anti-oxidative capacity, inhibition of signal-transducing pathways, promotion of cell proliferation and oncogene expression, as well as induction of cell-cycle arrest.[27–29] However, Hurtado-Barroso et al. performed a meta-analysis of five cohort studies reporting on the associations between vegetable and fruit intake with cancer recurrence, mortality, and all-cause mortality in patients with cancer, unveiling contrasting results. The results suggested an inverse association between total vegetable consumption before diagnosis and overall mortality (hazard ratio [HR] 0.75; 95% CI, 0.65–0.87) in patients with HNC, but no association was detected between all-cause mortality and fruit consumption assessed before diagnosis.[30] The discrepancies in results may stem from the varying research methodologies and approaches utilized in evaluating dietary patterns. In our study, dried fruit intake was associated with a decreased risk of HNC in the GWAS datasets from both the OncoArray consortium and the FinnGen biobank. Fresh fruit intake showed a protective effect in HNC in the GWAS datasets from the OncoArray consortium, but no significant effect in those from the FinnGen biobank. Therefore, it is important to interpret with caution the conflicting data concerning the consumption of fresh fruits.

Dried fruit is a nutrient-concentrated form of fresh fruit with lower moisture content and comprises numerous bioactive elements. The beneficial health effects of the compounds found in dried fruits are likely related to their strong antioxidant and anti-inflammatory properties, and ability to regulate estrogen metabolites.[31,32] As far as we know, the European Food Safety Authority has only endorsed one health claim regarding the beneficial effect of dried fruits on gastrointestinal health. A meta-analysis carried out by Mossine et al. showed that dried fruit may be associated with lower cancer incidence or

mortality, particularly cancers of the digestive system.[33] Our study found a genetically predicted relationship between dried fruit intake and HNC, but not between vegetable intake and HNC. Additional in vivo and extended RCTs are essential to analyze the influence of consuming fruits and vegetables on the occurrence of HNC.

Processed meat has been categorized as "carcinogenic for humans" and red meat as "probably carcinogenic" by the IARC.[34] Recently, numerous studies have suggested detrimental associations between the consumption of red and processed meat and various cancer outcomes.[35] An umbrella review identified 72 meta-analyses with 20 unique outcomes for red meat, and the results showed that red meat consumption was associated with a higher chance of mortality related to cancer in general. Specifically, red meat consumption had a detrimental effect on nasopharyngeal carcinoma (relative risk [RR] 1.35; 95% CI, 1.21–1.51), but no significant association was evident with oral cavity and oropharynx carcinoma.[36] Our results indicate a possible positive association between beef and lamb/mutton intake with HNC. Despite the contradictory conclusions from different cohorts, the association between red meat (beef and lamb/mutton) intake with HNC should also be considered. To address this contentious matter, more carefully designed studies with larger sample sizes are required, together with a more robust selection of SNPs. In addition, consumption of processed meat did not appear to influence HNC significantly, and we detected subtle horizontal pleiotropy among IVs related to processed meat exposure in the FinnGen biobank. However, completely excluding the influence of potential directional pleiotropy is difficult in any MR study due to the uncontrolled and residual confounding effects of selected IVs.

To improve the precision of our MR analysis, we conducted a sensitivity test and intercept and leave-one-out analyses. Even with these measures in place, it is important to acknowledge certain limitations. Initially, the study only included individuals of European descent, potentially limiting the generalizability of the results to a broader range of populations. Second, the *F*-statistics indicated that the IVs used in this study satisfied the first assumption for selected IVs (*F*-statistics values >10); however, a considerable portion of the *F*-statistics values were lower than 100, which may affect the accuracy of the consequences. Third, although we took control measures, IVs may still have unmeasurable confounding effects and may affect the outcome. Notwithstanding these limitations, to our knowledge, this is the most comprehensive MR study to assess the causal role of dietary habits regarding HNC risk. Future well-planned cohort studies are necessary to corroborate our findings.

5 | CONCLUSIONS

Our MR study provided clear evidence that dried fruit intake plays a causal role in lowering the likelihood of developing HNC. However, the association of fresh fruit, beef, and lamb/mutton intakes with HNC risk needs more cautious interpretation. Further research is necessary to confirm our findings and explore the underlying mechanisms. The findings of our research may assist clinicians in enhancing their health education for patients with HNC and motivate patients to alter their dietary patterns.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The OpenGWAS Database is a database of publicly available datasets. The University of Helsinki is the organization responsible for the FinnGen Project.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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