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*Original Article*

# Genetic estimation of correlations between circulating glutamine and cancer

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**Abstract:** The controversy regarding the causal relationship between circulating glutamine and cancer risk remains unresolved. Here, we aim to assess the causal impact of glutamine on the risk of six prevalent cancer types and their respective subtypes including breast, lung, ovarian, thyroid, prostate, and endometrial cancers. A Mendelian randomization (MR) analysis was conducted to evaluate the causal effect of circulating glutamine on cancers risk. Data on circulating glutamine were extracted from the UK Biobank (UKB), comprising 114,750 European patients. To ensure the validity of our findings, we employed several analytical approaches, such as inverse variance weighting, weighted median, weighted mode test, MR-Egger regression, and MR-PRESSO method. Both univariable and multivariable MR analyses were conducted. Additionally, we employed a large-scale summary-level study on circulating glutamine involving 24,925 European participants for validation purposes. Our MR analysis reveals a causal association between circulating glutamine and thyroid cancer in both the UKB cohort (IVW: OR = 0.667, 95% CI [0.541-0.822], $P = 1.52\times10^{-4}$) and the validated cohort (IVW: OR = 0.577, 95% CI [0.421-0.790], $P = 6.14\times10^{-4}$). Sensitivity analysis, including multivariable MR analyses, consistently supports this finding ($P < 0.05$), affirming the reliability and robustness of our study. Our findings indicate an inverse correlation between circulating glutamine and the incidence of thyroid cancer in European populations. However, further research encompassing diverse ancestries is necessary to validate this causal relationship.

**Keywords:** Circulating glutamine, cancer, Mendelian randomization, GWAS, UK Biobank, genetics

## Introduction

Glutamine, as an essential and versatile nutrient, is a key component of metabolism and exerts a significant influence on human health [1]. However, the research on the involvement of glutamine in tumorigenesis through observational studies remains limited. Several studies have demonstrated the potential of glutamine to facilitate the progression of tumor cells, as it serves as a critical metabolite promoting cellular proliferation [2-4]. However, recent studies have found that increasing glutamine levels can boost the antitumor immune response [5], because glutamine is an important raw material in the metabolism of immune cells and inflammatory T-cell responses [6-9]. Previous studies have provided conflicting or insufficient evidence regarding the association between glutamine and cancers. This highlights the need for a thorough analysis to systematically evaluate the associations between glutamine and the incidence of cancer. Furthermore, estimating the causal relationship between glutamine and cancer incidence remains challenging due to potential unmeasured confounding factors in observational studies.

Mendelian randomization (MR) analysis, as a new epidemiological method, has been widely applied to investigate the causal effect between risk factors and diseases [10, 11]. This approach can strengthen casual inference by extracting genetic variants to represent an exposure. The MR approach is less likely to be affected by potential unmeasured confounding factors or reverse causality compared to observational studies. This is because MR, similar to randomized controlled trials, benefits from the random distribution of genetic variants at conception, which serves as a standardization mechanism [12-14].

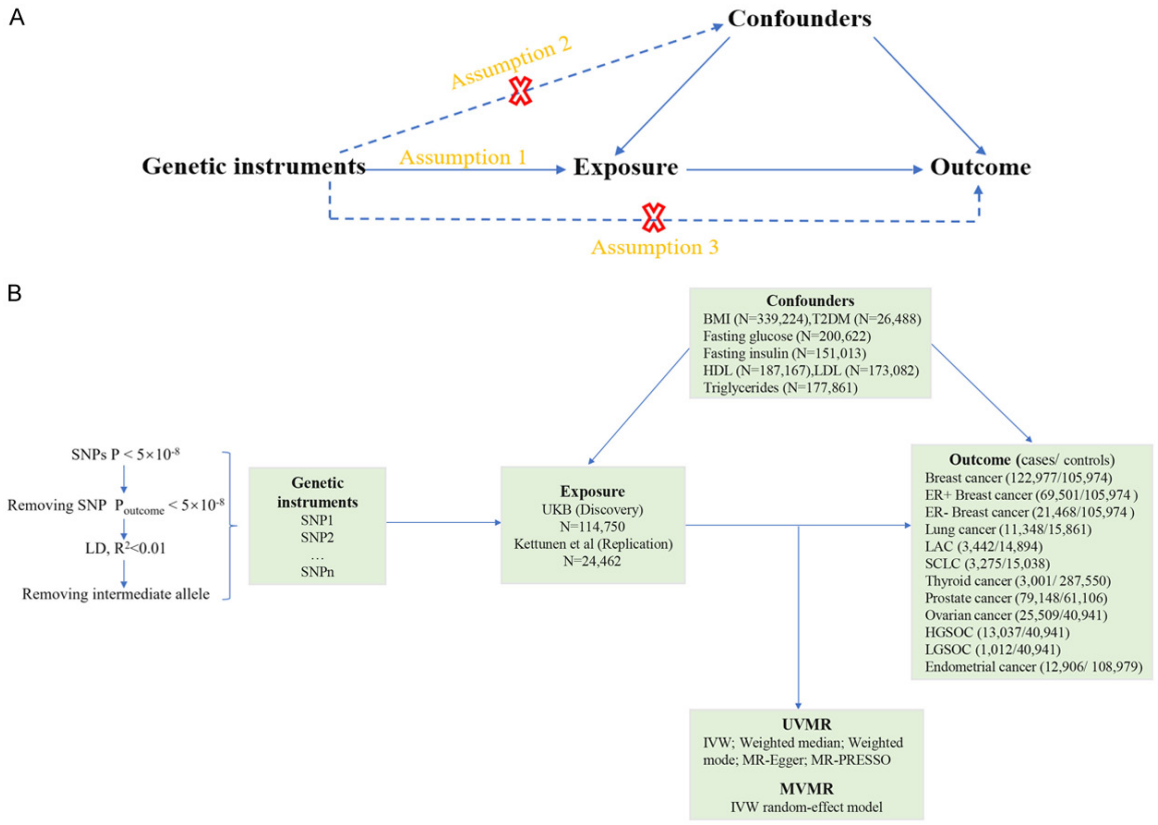


**Figure 1.** Schematic overview of the study design. A. Basic assumptions of Mendelian randomization: Assumption 1, the genetic instruments have strong relationships with the exposure; assumption 2, the genetic instruments should not be associated with potential confounders; and assumption 3, the genetic instruments should affect the risk of outcome only through exposure and not through other alternative pathways. B. Main design of this study: Independent SNPs for glutamine were identified as instrumental variables, whereas summary statistics of gene-glutamine associations were retrieved separately from the GWAS performed by Kettunen et al. and UK Biobank. LD, linkage disequilibrium; SNP, single nucleotide polymorphism; IVW, inverse-variance weighted; PRESSO, pleiotropy residual sum and outlier; BMI, body mass index; T2DM, type 2 diabetes; LAC, lung adenocarcinoma; SCLC, squamous cell lung cancer; HGSOC, high-grade serous ovarian cancer; LGSOC, low-grade serous ovarian cancer; UVMR, Univariable Mendelian randomization; MVMR, Multivariable Mendelian randomization.

To investigate the causal effects of circulating glutamine on six common cancers and their subtypes, we conducted a MR study. We utilized the genome-wide association study (GWAS) summary statistics of circulating glutamine from the UK Biobank and another large-scale study, analyzing them separately. Moreover, we accounted for potential confounding factors by adjusting the results for body mass index (BMI), lipidemic traits, and type 2 diabetes mellitus (T2DM), which have known genetic associations with circulating glutamine.

## Materials and methods

### *Study design*

Two-sample MR was applied in this study, and the schematic overview of the study design and data sources are detailed in **Figure 1A** and **1B**. The genetic instruments used in this MR must follow the three basic assumptions: (1) The genetic instruments have strong relationships with the exposure. (2) The genetic instruments have no associations with any confounder that may affect exposure or outcome. (3) The genetic instruments cannot affect the outcome directly [15]. We first performed a series of univariable MR (UVMR) to explore the relationship between circulating glutamine and cancers. Given the known relationships between glutamine, cancers, and some metabolism factors [16-18], we then performed multivariable MR (MVMR) analyses using metabolism-associated genetic variants to examine the direct effects of glutamine on cancer risk. The direct effect was the effect of the exposure on the

**Table 1.** Details of data source included in the study

| Traits | Data source | Cases/Controls | PMID | Ancestry |
|---|---|---|---|---|
| Exposures | | | | |
| Glutamine (Discovery set) | UKB | 114,750 | - | 100% European |
| Glutamine (Replicated set) | Kettunen et al. | 24,462 | 27005778 | 100% European |
| Outcomes | | | | |
| Breast cancer | BCAC | 122,977/105,974 | 29059683 | 100% European |
| ER+ breast cancer | BCAC | 69,501/105,974 | 29059683 | 100% European |
| ER- breast cancer | BCAC | 21,468/105,974 | 29059683 | 100% European |
| Lung Cancer | ILCCO | 11,348/15,861 | 24880342 | 100% European |
| LAC | ILCCO | 3,442/14,894 | 24880342 | 100% European |
| SCLC | ILCCO | 3,275/15,038 | 24880342 | 100% European |
| Thyroid cancer | Gudmundsson et al. | 3,001/287,550 | 28195142 | 100% European |
| Prostate cancer | PRACTICAL | 79,148/61,106 | 29892016 | 100% European |
| Ovarian cancer | OCAC | 25,509/40,941 | 28346442 | 100% European |
| HGSOC | OCAC | 13,037/40,941 | 28346442 | 100% European |
| LGSOC | OCAC | 1,012/40,941 | 28346442 | 100% European |
| Endometrial cancer | O'Mara TA et al. | 12,906/108,979 | 30093612 | 100% European |
| Possible mediators/confounders (MVMR) | | | | |
| BMI | GIANT | 339,224 | 25673413 | 95% European |
| T2DM | DIAGRAM | 26,488/83,964 | 24509480 | 70% European |
| Fasting glucose | MAGIC | 200,622 | 34059833 | 70% European |
| Fasting insulin | MAGIC | 151,013 | 34059833 | 70% European |
| HDL | GLGC | 187,167 | 24097068 | 90% European |
| LDL | GLGC | 173,082 | 24097068 | 90% European |
| Triglycerides | GLGC | 177,861 | 24097068 | 90% European |

outcome only via one path (direct). Moreover, we replicated our findings with another independent dataset of circulating glutamine to investigate the robustness. The same replicated method was applied in some other MR analyses [19, 20].

*Data sources*

We used the circulating glutamine GWAS summary statistics from two independent studies, and all summary datasets can be downloaded from the MRC IEU OpenGWAS (https://gwas.mrcieu.ac.uk/). The discovery set of circulating glutamines was from the UK Biobank (UKB), and the GWAS was conducted in 114,750 European individuals (study ID "met-d-Gln"). The replicated set was derived from 14 European cohorts from Finland (53%), Netherlands (22%), Estonia 3884 (16%), Germany (7%), and Poland (2%), which included 24,925 participants reported by Kettunen et al. (study ID "met-c-860") [21]. Human blood metabolites were quantified using a high-throughput NMR metabolomics platform in this study.

We excluded cancer outcome data that overlapped with the exposed population in order to mitigate potential bias arising from the overlap. Our study ultimately encompassed six prevalent types of cancer. The GWAS summary statistics for cancer can be accessed from public databases such as MRC IEU OpenGWAS and Decode datasets (https://www.decode.com/). **Table 1** provides an overview of the data sources used for different traits examined in our study. The GWAS summary data for breast, ovarian, lung, and pancreatic cancer were obtained from BCAC (Breast Cancer Association Consortium) [22], OCAC (Ovarian Cancer Association Consortium) [23], ILCCO (International Lung Cancer Consortium) [24], and PanScan (Pancreatic Cancer Cohort Consortium) [25], respectively. Gudmundsson et al. conducted a GWAS of thyroid cancer that included 3,001 European cases and 287,550 controls [26]. The summary dataset for endometrial cancer in the GWAS analysis consisted of 12,906 studies published by O'Mara TA et al. [27].

We conducted MVMR analysis, adjusting for several metabolic factors, to investigate potential mediators and mitigate the impact of confounders on our results. The GWAS summary dataset of BMI and T2DM were obtained from GIANT (Genetic Investigation of ANthropometric Traits) [28] and DIAGRAM (Diabetes Genetics Replication and Meta-analysis) [29] consortium, respectively. The GWAS summary statistics of fasting glucose and fasting insulin were obtained from MAGIC (Meta-Analyses of Glucose and Insulin-related traits Consortium) [30]. The data source of lipidemic traits was obtained from the Global Lipids Genetics Consortium (GLGC), including high-density lipoprotein-cholesterol (HDL), LDL, and triglycerides [31].

Ethical approval was gained in all original studies. Details of the data sources included in the study can be found in **Table 1**.

*Genetic instrument selection*

The genetic instruments significantly associated with the exposure were retrieved using a threshold of $P < 5\times10^{-8}$, and any SNPs that were associated with the outcome were excluded. To ensure statistical independence, SNPs with a linkage disequilibrium (LD) $R^2 > 0.01$ were pruned. Additionally, we excluded palindromic SNPs with intermediate allele frequencies and calculated the F parameter to assess the strength of the instruments. SNPs with an F value less than 10 were removed due to lower statistical power. $R^2$ was used to estimate the ability of genetic instruments to explain the exposure. We conducted power calculations based on the $R^2$ of the genetic instruments and outcome sample sizes using the Online sample size and power calculator for Mendelian randomization. We used a type I error of 0.5% and computed the statistical power to examine odds ratios (ORs) at four effect sizes (0.60, 0.70, 0.80, and 0.90). The results of the power analysis from two databases are presented in Supplementary Tables 1 and 2.

*Statistical analysis*

The inverse-variance weighted (IVW) method was employed as the primary analysis in our study. We calculated Cochran's Q to assess heterogeneity among instruments. In the presence of significant heterogeneity, we utilized the IVW-random effect model to elucidate the association between exposure and outcome. Alternatively, if no significant heterogeneity was detected, we employed the IVW-fixed effect model. In addition, a series of sensitivity analyses were conducted as supplements to the IVW method. The weighted median method can provide a causal estimate even when less than 50% of the weight of the genetic instruments is invalid [32]. Weighted mode regression assesses the causal effect reliable if there are most valid SNPs [33]. The MR-Egger intercept analysis, based on the Instrument Strength Independent of Direct Effect (InSIDE), can be utilized to evaluate pleiotropy. In this MR study, the *P*-value for the MR-Egger intercept was employed to detect the presence of directional pleiotropy [34]. The MR pleiotropy residual sum and outlier (MR-PRESSO) test can correct horizontal pleiotropy using outlier removal and evaluate significant differences before and after outlier removal [35]. To account for multiple testing, a Bonferroni-corrected threshold of $P < 0.0042$ ($\alpha = 0.05/12$) was applied. Associations with $P < 0.0042$ were considered significant, and associations with $P \geq 0.0042$ and $< 0.05$ were considered suggestive.

We also conducted MVMR with more exposures, such as BMI, diabetes, and lipidemic traits, which may increase the incidence of cancer and may be related to circulating glutamine. A multivariable random-effects IVW model, adjusted for metabolism factors, was employed to evaluate the potential reduction in the effects of liability to circulating glutamine on the outcome.

All statistical analyses were performed based on the TwoSampleMR, MRPRESSO, and MVMR packages in R version 4.1.0.

## Results

*Discovery results in the UKB consortium*

In the UKB circulating glutamine GWAS, we discovered 55 independent genetic instruments for circulating glutamine, which collectively accounted for approximately 44.0% of the phenotypic variation in glutamine. The F statistics for instruments in the UKB vary from 29.7 to 369.4. The results of genetically predicted circulating glutamine on all cancer risks can be

**Table 2.** Mendelian randomization estimates between glutamine and cancer risk

| | SNPs | IVW | | Weighted median | | Weighted mode | | MR-Egger | |
|---|---|---|---|---|---|---|---|---|---|
| | | OR (95% CI) | *P* | OR (95% CI) | *P* | OR (95% CI) | *P* | OR (95% CI) | *P* |
| UKB | | | | | | | | | |
| Breast cancer | 39 | 1.048 (0.947-1.159) | 0.364 | 1.061 (0.965-1.166) | 0.221 | 1.059 (0.946-1.187) | 0.326 | 1.012 (0.823-1.243) | 0.911 |
| ER+ breast cancer | 40 | 1.048 (0.928-1.182) | 0.451 | 1.101 (0.979-1.238) | 0.108 | 1.045 (0.899-1.214) | 0.570 | 1.035 (0.809-1.324) | 0.785 |
| ER- breast cancer | 39 | 1.034 (0.928-1.152) | 0.539 | 1.114 (0.930-1.335) | 0.240 | 1.136 (0.905-1.425) | 0.278 | 1.149 (0.889-1.484) | 0.294 |
| Lung Cancer | 46 | 0.938 (0.832-1.057) | 0.290 | 0.859 (0.716-1.029) | 0.099 | 0.902 (0.765-1.064) | 0.228 | 0.872 (0.715-1.063) | 0.182 |
| LAC | 46 | 1.023 (0.854-1.226) | 0.802 | 0.997 (0.764-1.301) | 0.984 | 0.992 (0.776-1.268) | 0.948 | 1.000 (0.735-1.359) | 0.998 |
| SCLC | 46 | 0.945 (0.785-1.137) | 0.548 | 0.828 (0.626-1.098) | 0.191 | 0.869 (0.666-1.133) | 0.305 | 0.910 (0.665-1.242) | 0.556 |
| Thyroid cancer | 44 | 0.667 (0.541-0.822) | $1.52\times10^{-4}$ | 0.624 (0.462-0.842) | $2.02\times10^{-3}$ | 0.618 (0.461-0.829) | $2.54\times10^{-3}$ | 0.585 (0.425-0.805) | $2.05\times10^{-3}$ |
| Prostate cancer | 54 | 0.968 (0.895-1.044) | 0.403 | 0.934 (0.863-1.011) | 0.089 | 0.943 (0.868-1.025) | 0.174 | 0.915 (0.816-1.027) | 0.136 |
| Ovarian cancer | 40 | 0.996 (0.881-1.127) | 0.949 | 1.102 (0.918-1.611) | 0.298 | 1.097 (0.900-1.338) | 0.365 | 1.233 (0.943-1.611) | 0.123 |
| HGSOC | 40 | 1.023 (0.884-1.185) | 0.760 | 1.111 (0.886-1.392) | 0.362 | 1.194 (0.873-1.634) | 0.274 | 1.137 (0.843-1.532) | 0.406 |
| LGSOC | 40 | 1.022 (0.656-1.592) | 0.226 | 1.454 (0.695-3.042) | 0.321 | 1.975 (0.637-6.126) | 0.246 | 1.389 (0.549-3.514) | 0.492 |
| Endometrial cancer | 55 | 1.066 (0.968-1.174) | 0.191 | 0.934 (0.811-1.075) | 0.340 | 1.013 (0.859-1.196) | 0.878 | 1.005 (0.855-1.182) | 0.948 |
| Kettunen *et al.* | | | | | | | | | |
| Breast cancer | 3 | 0.957 (0.845-1.083) | 0.486 | 1.040 (0.854-1.265) | 0.618 | 1.106 (0.886-1.381) | 0.468 | 0.197 (0.002-20.55) | 0.618 |
| ER+ breast cancer | 3 | 0.988 (0.853-1.146) | 0.876 | 0.932 (0.764-1.137) | 0.485 | 0.890 (0.687-1.154) | 0.472 | 0.196 (0.027-1.404) | 0.352 |
| ER- breast cancer | 3 | 1.055 (0.843-1.319) | 0.640 | 1.132 (0.835-1.535) | 0.424 | 1.257 (0.836-1.889) | 0.387 | 0.934 (0.001-83.78) | 0.988 |
| Lung Cancer | 5 | 0.886 (0.739-1.060) | 0.186 | 0.853 (0.698-1.041) | 0.117 | 0.826 (0.671-1.017) | 0.146 | 0.734 (0.516-1.045) | 0.185 |
| LAC | 5 | 1.055 (0.806-1.382) | 0.653 | 0.989 (0.731-1.338) | 0.942 | 0.975 (0.713-1.514) | 0.881 | 0.963 (0.524-1.769) | 0.910 |
| SCLC | 5 | 0.875 (0.660-1.159) | 0.351 | 0.811 (0.591-1.113) | 0.195 | 0.745 (0.518-1.072) | 0.188 | 0.613 (0.351-1.069) | 0.183 |
| Thyroid cancer | 5 | 0.577 (0.421-0.790) | $6.14\times10^{-4}$ | 0.531 (0.374-0.752) | $3.72\times10^{-4}$ | 0.522 (0.362-0.752) | 0.025 | 0.389 (0.212-0.715) | 0.017 |
| Prostate cancer | 5 | 0.906 (0.784-1.046) | 0.178 | 0.927 (0.844-1.018) | 0.113 | 0.937 (0.843-1.041) | 0.293 | 0.990 (0.735-1.335) | 0.953 |
| Ovarian cancer | 3 | 1.044 (0.806-1.352) | 0.747 | 1.076 (0.793-1.460) | 0.639 | 1.102 (0.769-1.580) | 0.649 | 0.350 (0.011-10.83) | 0.656 |
| HGSOC | 3 | 0.129 (0.930-1.537) | 0.439 | 1.118 (0.732-1.7070 | 0.606 | 1.118 (0.620-2.013) | 0.745 | 0.015 (0.001-1.035) | 0.295 |
| LGSOC | 3 | 0.760 (0.077-7.460) | 0.814 | 1.772 (0.443-7.076) | 0.418 | 2.525 (0.563-1.131) | 0.350 | 1.669 (0.372-7.471) | 0.314 |
| Endometrial cancer | 5 | 0.995 (0.858-1.153) | 0.943 | 0.950 (0.803-1.123) | 0.547 | 0.908 (0.764-1.080) | 0.337 | 0.787 (0.585-1.058) | 0.211 |

SNP, single nucleotide polymorphisms; IVW, inverse variance weighted; MR-PRESSO, MR-pleiotropy residual sum and outlier; OR, odds ratio; CI, confidence interval; LAC, lung adenocarcinoma; SCLC, squamous cell lung cancer; HGSOC, High grade serous ovarian cancer; LGSOC, Low grade serous ovarian cancer.

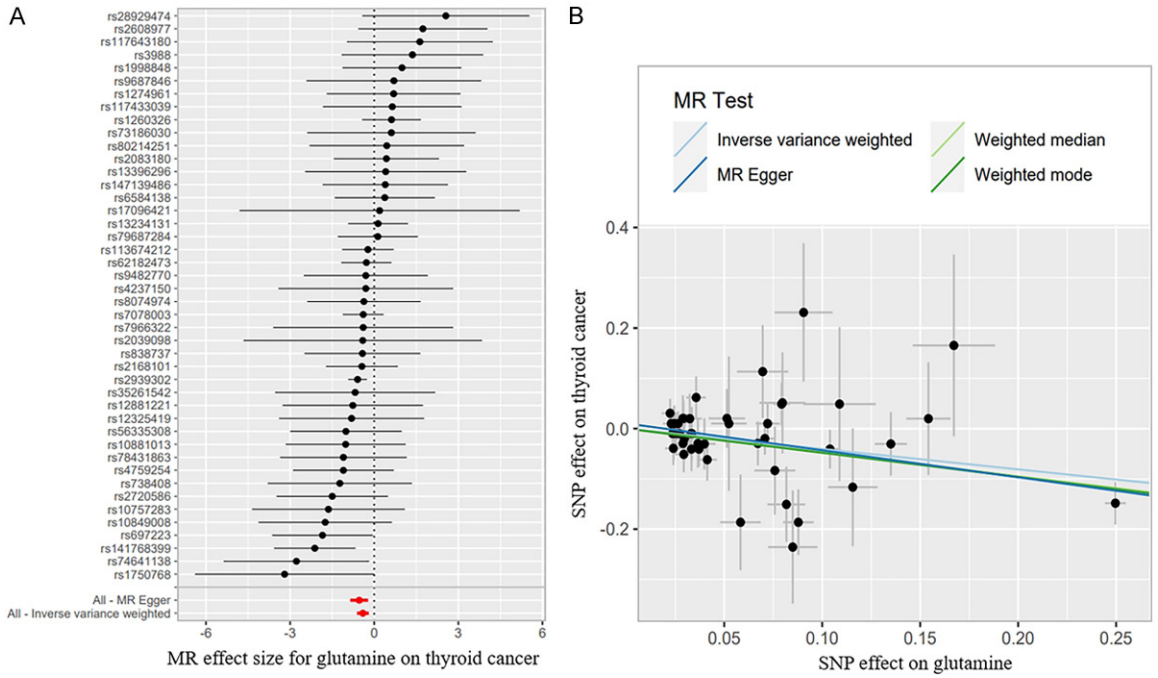


**Figure 2.** MR analyses from glutamine to thyroid cancer in UKB dataset. A. Forest plots: the red points showed the combined causal estimate using all SNPs together in a single instrument, using two different methods (MR-Egger and IVW). B. Scatter plots: X axes represent the genetic instruments - glutamine associations in UKB and Y axes represent genetic instruments - thyroid cancer associations. Black dots denote to the genetic instruments included in the primary MR analyses. Light blue: Inverse variance weighted; light green: Weighted Median; blue: MR Egger; green: Weighted mode.

found in **Table 2**. We observed a potential decrease in the risk of thyroid cancer associated with circulating glutamine. However, in both the IVW method and sensitivity analysis, we did not find any evidence of an association between glutamine and the risk of breast, lung, prostate, ovarian, or endometrial cancer. The forest plots and scatter plots can be found in Supplementary Figures 1, 2, 3, 4.

The lower levels of circulating glutamine may be associated with an increased risk of thyroid cancer (IVW: OR = 0.667, 95% CI [0.541-0.822], P = $1.52\times10^{-4}$). The fixed model of the IVW method was applied because we did not examine the strong heterogeneity. The sensitivity analysis continues to support the IVW result (weighted median: OR = 0.624, 95% CI [0.462-0.842], P = $2.02\times10^{-3}$; weighted mode: OR = 0.618, 95% CI [0.461-0.829], P = $2.54\times10^{-3}$; MR-Egger: OR = 0.585, 95% CI [0.425-0.805], P = $2.05\times10^{-3}$). The forest plots and scatter plots for thyroid cancer outcomes in discovery practice were shown in **Figure 2A** and **2B**. There was no horizontal pleiotropy or outliers in thyroid cancer in this stage (Supplementary Tables 3, 4).

*Replicated results in the Kettunen et al. study*

We also identified 5 independent genetic instruments for circulating glutamine, and the explained variance was approximately 8.3% in the replicated stage. The F statistics ranged from 44.9 to 166.6. In the Kettunen et al. dataset, we successfully replicated the MR results of thyroid cancer outcome, and no causal effect of glutamine on other cancer types was found in this part (**Table 2**). The forest plots and scatter plots for cancer outcomes can be found in Supplementary Figures 5, 6, 7, 8.

The lower levels of circulating glutamine may be associated with an increased risk of thyroid cancer (IVW: OR = 0.577, 95% CI [0.421-0.790], P = $6.14\times10^{-4}$). The fixed model of the IVW method was utilized due to the absence of heterogeneity. Furthermore, the results of the sensitivity analysis suggested that a genetic predisposition to lower levels of circulating glutamine may decrease the risk of thyroid cancer

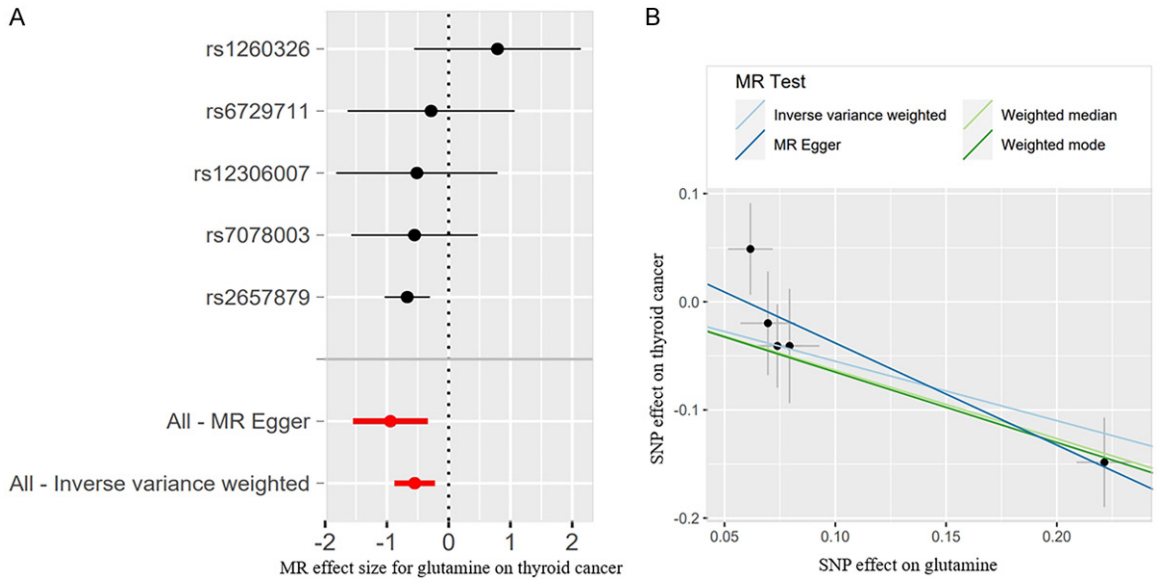


**Figure 3.** MR analyses from glutamine to thyroid cancer in Kettunen et al. dataset. A. Forest plots: the red points showed the combined causal estimate using all SNPs together in a single instrument, using two different methods (MR-Egger and IVW). B. Scatter plots: X axes represent the genetic instruments - glutamine associations in Kettunen et al. and Y axes represent genetic instruments - thyroid cancer associations. Black dots denote to the genetic instruments included in the primary MR analyses. Light blue: Inverse variance weighted; light green: Weighted Median; blue: MR Egger; green: Weighted mode.

(weighted median: OR = 0.531, 95% CI [0.374-0.752], P = $3.72\times10^{-4}$; weighted mode: OR = 0.522, 95% CI [0.362-0.752], P = 0.025; MR-Egger: OR = 0.389, 95% CI [0.212-0.715], P = 0.017). The forest plots and scatter plots for thyroid cancer outcomes in the replicated set were shown in **Figure 3A** and **3B**. No horizontal pleiotropy or outliers were examined in the thyroid cancer outcome in this part (Supplementary Tables 3, 4).

*Multivariable MR analyses*

MVMR analysis was conducted to incorporate additional exposures such as BMI, diabetes, and lipidemic traits, as these factors have been shown to potentially exacerbate the severity of thyroid cancer and could be associated with circulating glutamine phenotypes. The independent causal effects of glutamine and thyroid cancer remained significant with adjustment of each of the seven confounders individually (**Figure 4A** and **4B**; Supplementary Table 5). The effect sizes of MVMR were consistent with the univariable MR in both UKB consortium (controlling for BMI: OR = 0.663, P = $1.24\times10^{-3}$; controlling for T2DM: OR = 0.626, P = $1.99\times10^{-5}$; controlling for fasting glucose: OR = 0.721, P = $4.91\times10^{-3}$; controlling for fasting insulin: OR = 0.695, P = $4.69\times10^{-4}$; controlling for HDL: OR = 0.681, P = $2.17\times10^{-3}$; controlling for LDL: OR = 0.664, P = $3.16\times10^{-3}$; controlling for triglycerides: OR = 0.662, P = $9.55\times10^{-4}$) (**Figure 4A**) and replicated sets (controlling for BMI: OR = 0.599, P = $2.17\times10^{-3}$; controlling for T2DM: OR = 0.568, P = $9.71\times10^{-4}$; controlling for fasting glucose: OR = 0.570, P = $4.99\times10^{-4}$; controlling for fasting insulin: OR = 0.610, P = $2.06\times10^{-3}$; controlling for HDL: OR = 0.660, P = $8.38\times10^{-3}$; controlling for LDL: OR = 0.545, P = $8.49\times10^{-4}$; controlling for triglycerides: OR = 0.624, P = $3.34\times10^{-3}$) (**Figure 4B**).

## Discussions

Glutamine is an abundant and versatile nutrient involved in a variety of functional roles in the body, including signaling in cancer cells [36]. However, the role it plays in tumors is not clear. To our knowledge, this is the first MR study to explore whether increased levels of circulating glutamine affect cancer incidence. We found that genetically predicted circulating glutamine levels were not related to cancer risk, except for a protective association between glutamine levels and thyroid cancer.

First, we found instrument variants representing the exposure (circulating glutamine) from a

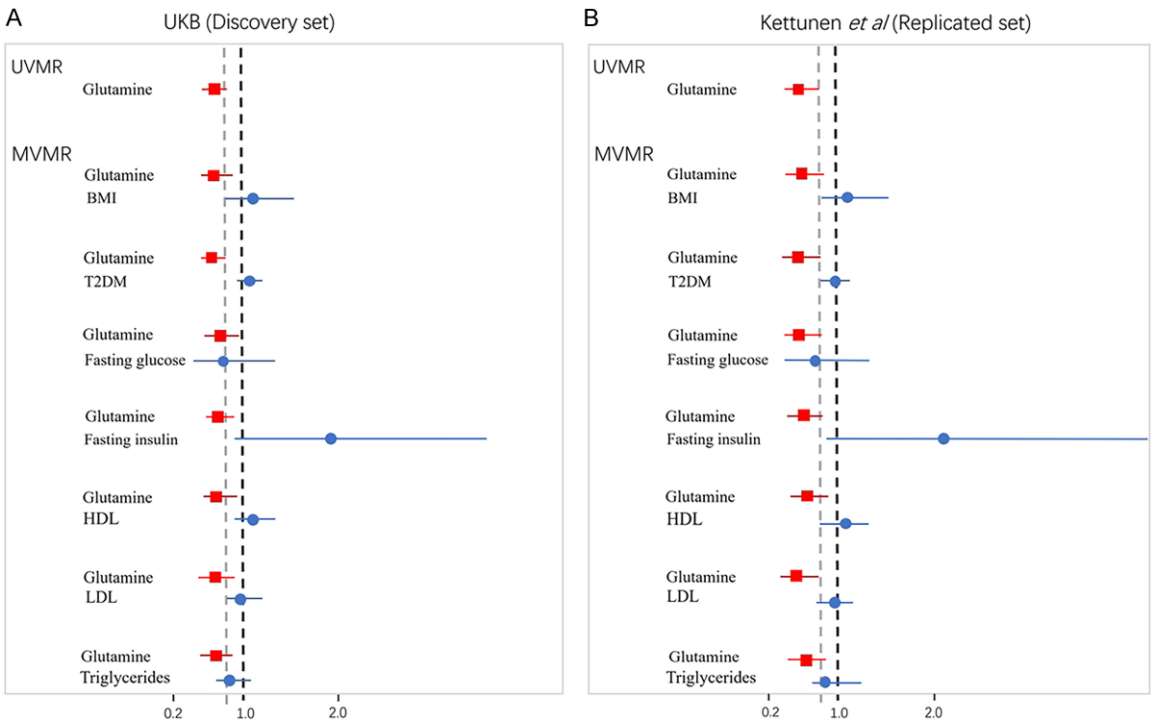


**Figure 4.** UVMR and MVMR MR analyses of glutamine and thyroid cancer in different datasets. A. UKB dataset (Discovery set). B. Kettunen et al. dataset (Replication set). Red plots (bars) represent OR (95% CI) of IVW for the risk of thyroid cancer associated with each 1 - SD increase of glutamine after unadjusted (UVMR) or adjusted (MVMR) for confounding factors. Blue plots (bars) represent OR (95% CI) of IVW for the risk of thyroid cancer associated with each 1 - SD increase of risk factors after adjusted (MVMR) for glutamine. MVMR, multivariable Mendelian randomization; UVMR, univariable Mendelian randomization; BMI, body mass index; T2DM, type 2 diabetes.

large-scale UKB cohort that included 114,750 European individuals, and those instrument variants have shown an inverse association with circulating glutamine to thyroid cancer based on the main IVW method and all other sensitivity analyses. Second, we successfully replicated the MR results after extracting some instrument variants representing the exposure from another separate large-scale study. The statistical power for both UKB and replicated exposure was 100%. There was no heterogeneity, and horizontal pleiotropy and outliers were examined when thyroid cancer was the outcome. We also performed MVMR to assess the causal relationship between circulating glutamine and thyroid cancer with adjustments for BMI, T2DM, fasting glucose, fasting insulin, HDL, LDL, and triglycerides. The MVMR results indicated that the causal association between glutamine and thyroid cancer risk was robust, and it was unlikely to be affected by confounders.

Many previous studies have suggested that glutamine promotes the development and progression of cancer because of the involvement of glutamine in cancer metabolism [37-39]. This theory seems reasonable, but some studies found that higher levels of glutamine in rats did not promote tumor growth [40, 41]. Some recent studies have found that there is strong heterogeneity in the glutamine requirements of different tumor cell lines [42, 43], such as luminal-type cells [44], and a panel of lung cancer cell lines tends to be glutamine-independent [45]. The reasons for the difference between cancers were that different types of cells have distinct ways of utilizing nutrients and generating energy, thus resulting in distinct nutrient needs. Such cell type-specific metabolic differences are associated with many biological processes and force the symbiosis between different cells and organisms.

Taken together, we have reason to believe that circulating glutamine could reduce thyroid incidence, although we did not find observational studies to support our view. Indeed, very few publications address the issue of how glutamine participates in thyroid tumorigenesis, and

the mechanism is still not well understood [46]. Although some experimental studies have confirmed higher levels of glutamine in thyroid cancer tissue than in normal tissue [47, 48], this does not support glutamine as the cause of thyroid cancer. For example, some cancer cells can use micropinocytosis to engulf extracellular proteins, which can degrade in lysosomes to release glutamine [49-51]; in this case, glutamine is an outcome rather than an etiology. Some studies have suggested that glutamine may reduce cancer rates. *Mari* et al. reported that glutamine can slow melanoma tumor growth by suppressing epigenetically activated oncogenic pathways [52]. They also found that although glutamine increased several tricarboxylic acid intermediates, it was not utilized for proliferation and progression in melanoma tumors directly [52]. Moreover, recent studies have shown that increasing glutamine levels can boost the antitumor immune response [5], because glutamine is an important raw material in the metabolism of immune cells and inflammatory T-cell responses [6-9]. In addition, some studies have found that glutamine metabolism can inhibit the progression of cancer by promoting autophagy in tumors [53, 54]. The experimental mechanism described above may explain how glutamine reduces the incidence of thyroid cancer, but previous studies on glutamine and thyroid cancer are very few, and more research is needed to explore and support our view in the future.

There are some strengths in our MR study. First, genetically instrumented circulating glutamine can rule out potential confounding factors. Second, we obtained gene-exposure associations from two independent GWASs (UKB and Kettunen et al. study), including large sample sizes. The effect from two exposure data sources and a range of sensitivity analysis tests, including MVMR, all point to the same conclusion. Third, there are no overlap samples between exposure and outcome, which suggests that any relationships in the exposures are unlikely to be replicated with the clinical outcomes.

This study still has some limitations. First, the GWASs utilized in our study were all from individuals of European descent. The "population bottleneck" theory suggests that different populations may lead to differential genetic variants [55]. Thus, the results might not be replicated in other ethics of the world. Further study of other population GWAS datasets should be conducted to confirm the findings. Second, we cannot examine whether the effects of circulating glutamine on cancers vary by age or sex because of the limitations of datasets. Stratified MR analysis should be conducted in the future. Third, strong heterogeneity was observed when the outcomes were breast and prostate cancer, and it could not be eliminated even though we took steps to exclude outliers. We applied the random-model IVW method as the main result to minimize the effect of heterogeneity.

## Conclusions

In summary, this is the first MR study exploring causal inferences between circulating glutamine concentrations and the risk of multiple cancers based on a European population. This MR study suggests that circulating glutamine can reduce the risk of thyroid cancer but not other types of cancers. Nevertheless, further studies should be conducted to confirm our findings as well as to examine the causality associations across ancestries, and further investigations into the underlying mechanisms are necessary.

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## Disclosure of conflict of interest

None.

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**Supplementary Table 1.** Power calculation for UKB

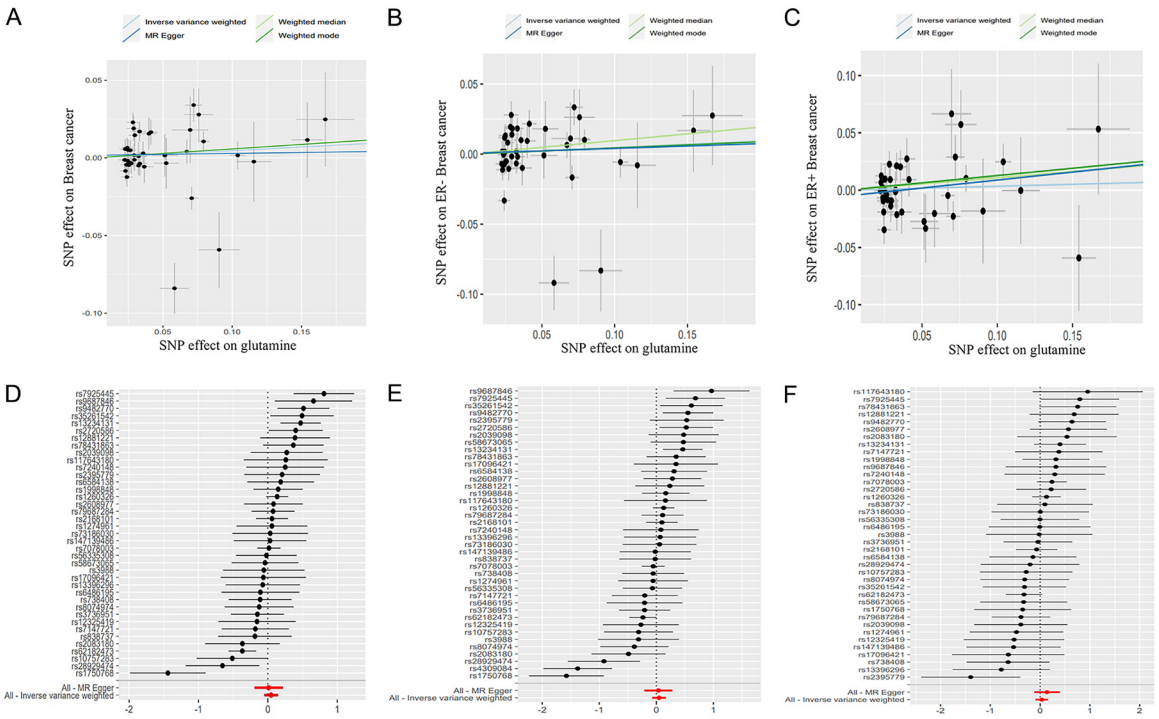
| Cancer | Cases/Controls | $R^2$ (%) | Power (%) | | | |
|---|---|---|---|---|---|---|
| | | | OR = 0.9 | OR = 0.8 | OR = 0.7 | OR = 0.6 |
| Breast cancer | 122,977/105,974 | 44.0 | 100 | 100 | 100 | 100 |
| ER+ breast cancer | 69,501/105,974 | 44.0 | 100 | 100 | 100 | 100 |
| ER- breast cancer | 21,468/105,974 | 44.0 | 100 | 100 | 100 | 100 |
| Lung Cancer | 11,348/15,861 | 44.0 | 100 | 100 | 100 | 100 |
| LAC | 3,442/14,894 | 44.0 | 95.4 | 100 | 100 | 100 |
| SCLC | 3,275/15,038 | 44.0 | 95.2 | 100 | 100 | 100 |
| Thyroid cancer | 3,001/287,550 | 44.0 | 96.7 | 100 | 100 | 100 |
| Prostate cancer | 79,148/61,106 | 44.0 | 100 | 100 | 100 | 100 |
| Ovarian cancer | 25,509/40,941 | 44.0 | 100 | 100 | 100 | 100 |
| HGSOC | 13,037/40,941 | 44.0 | 100 | 100 | 100 | 100 |
| LGSOC | 1,012/40,941 | 44.0 | 58.1 | 99.6 | 100 | 100 |
| Endometrial cancer | 12,906/108,979 | 44.0 | 100 | 100 | 100 | 100 |

LAC, lung adenocarcinoma; SCLC, squamous cell lung cancer; HGSOC, High grade serous ovarian cancer; LGSOC, Low grade serous ovarian cancer.

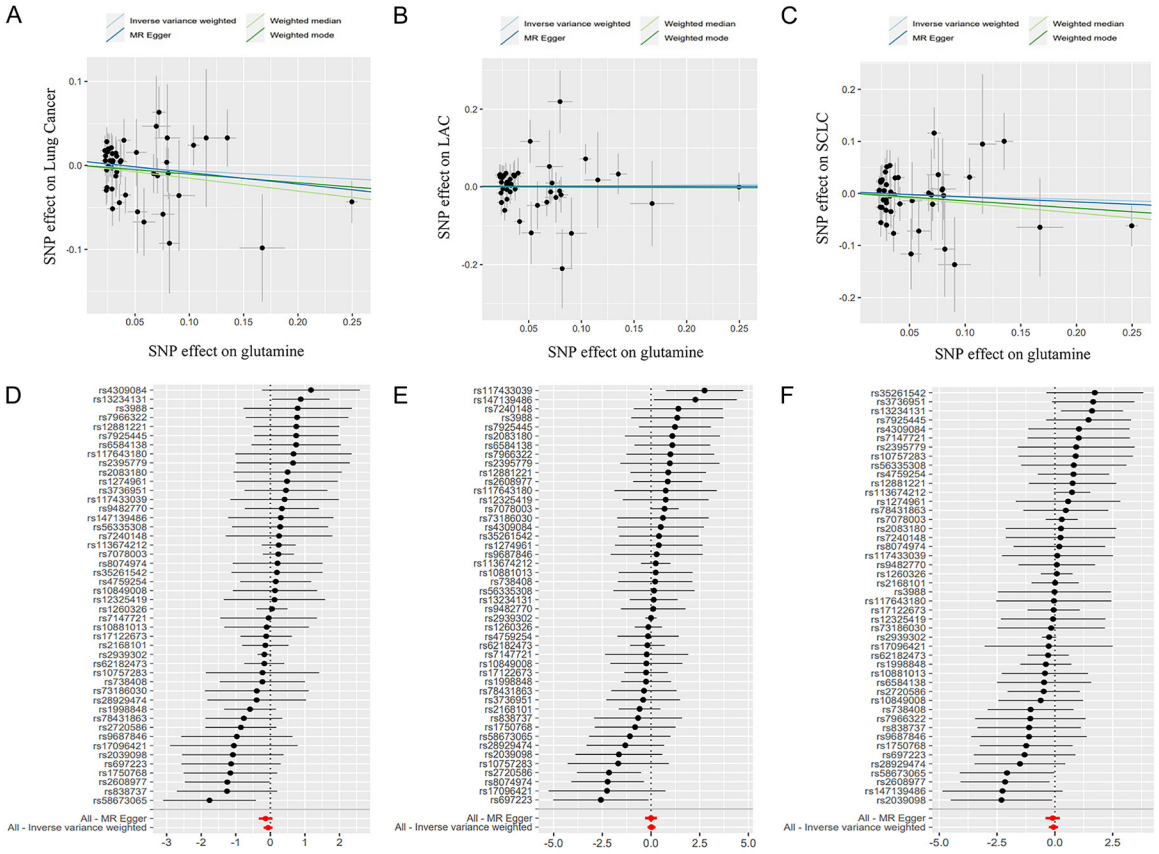
**Supplementary Table 2.** Power calculation for Kettunen *et al.*

| Cancer | Cases/Controls | $R^2$ (%) | Power (%) | | | |
|---|---|---|---|---|---|---|
| | | | OR = 0.9 | OR = 0.8 | OR = 0.7 | OR = 0.6 |
| Breast cancer | 122,977/105,974 | 8.3 | 100 | 100 | 100 | 100 |
| ER+ breast cancer | 69,501/105,974 | 8.3 | 100 | 100 | 100 | 100 |
| ER- breast cancer | 21,468/105,974 | 8.3 | 98.2 | 100 | 100 | 100 |
| Lung Cancer | 11,348/15,861 | 8.3 | 100 | 100 | 100 | 100 |
| LAC | 3,442/14,894 | 8.3 | 34.9 | 91.5 | 100 | 100 |
| SCLC | 3,275/15,038 | 8.3 | 34.6 | 91.2 | 100 | 100 |
| Thyroid cancer | 3,001/287,550 | 8.3 | 37.5 | 93.5 | 100 | 100 |
| Prostate cancer | 79,148/61,106 | 8.3 | 100 | 100 | 100 | 100 |
| Ovarian cancer | 25,509/40,941 | 8.3 | 96.2 | 100 | 100 | 100 |
| HGSOC | 13,037/40,941 | 8.3 | 85.1 | 100 | 100 | 100 |
| LGSOC | 1,012/40,941 | 8.3 | 15.3 | 50.8 | 88.6 | 99.5 |
| Endometrial cancer | 12,906/108,979 | 8.3 | 99.9 | 100 | 100 | 100 |

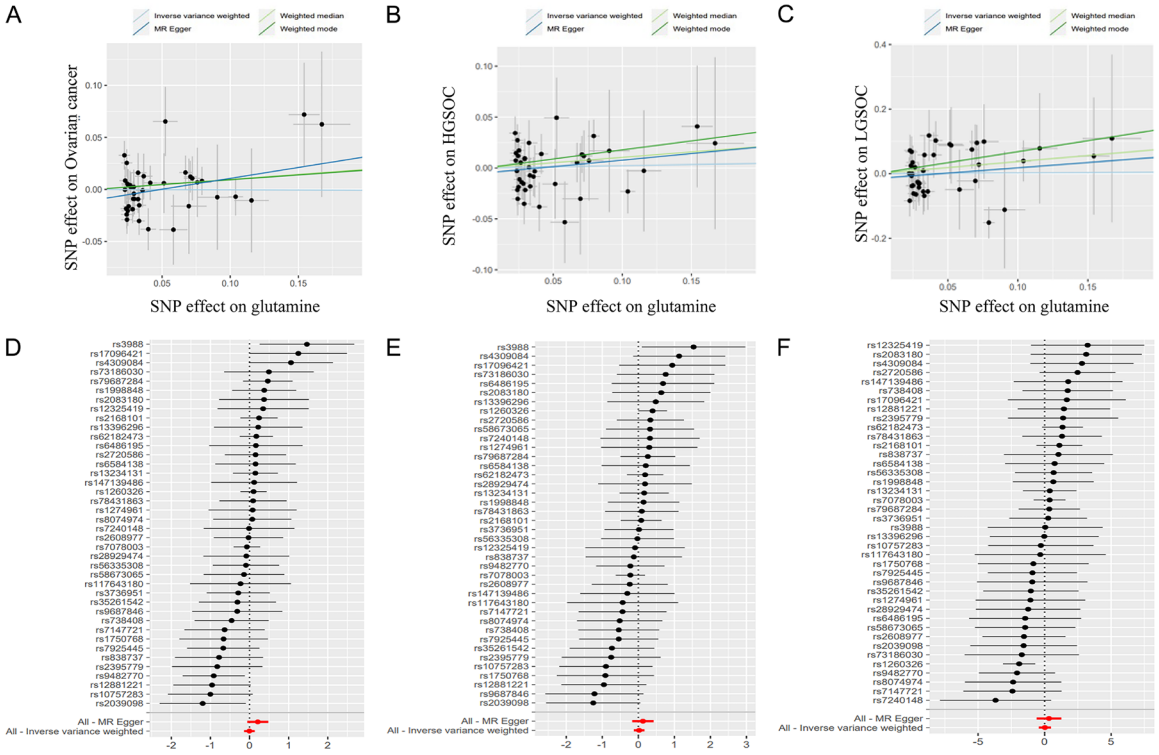
LAC, lung adenocarcinoma; SCLC, squamous cell lung cancer; HGSOC, High grade serous ovarian cancer; LGSOC, Low grade serous ovarian cancer.



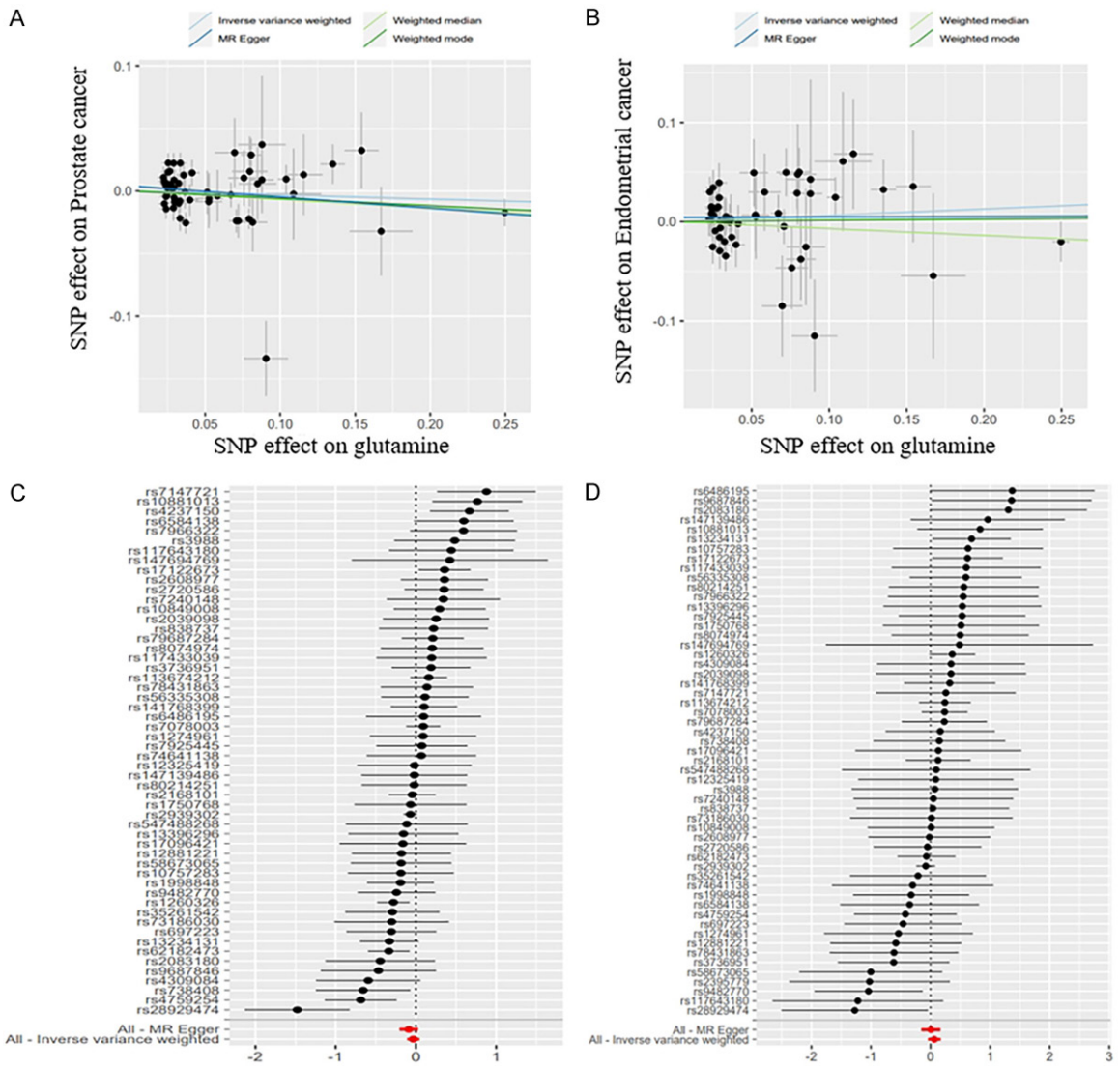

**Supplementary Figure 1.** Scatter plots for MR analysis of the causal effect of glutamine on breast cancer based on UKB. A. Breast cancer. B. ER+ breast cancer. C. ER- breast cancer. Forest plots of instrumental variable Wald ratios and causal effect assessments of the relationship between glutamine and the risk of breast cancer based on UKB. D. Breast cancer. E. ER+ breast cancer. F. ER- breast cancer.



**Supplementary Figure 2.** Scatter plots for MR analysis of the causal effect of glutamine on lung cancer based on UKB. A. Lung cancer. B. LAC. C. SCLC. Forest plots of instrumental variable Wald ratios and causal effect assessments of the relationship between glutamine and the risk of lung cancer based on UKB. D. Lung cancer. E. LAC. F. SCLC. LAC, lung adenocarcinoma; SCLC, squamous cell lung cancer.




**Supplementary Figure 3.** Scatter plots for MR analysis of the causal effect of glutamine on ovarian cancer based on UKB. A. Ovarian cancer. B. HGSOC. C. LGSOC. Forest plots of instrumental variable Wald ratios and causal effect assessments of the relationship between glutamine and the risk of ovarian cancer based on UKB. D. Ovarian cancer. E. HGSOC. F. LGSOC. HGSOC, High-grade serous ovarian cancer; LGSOC, low-grade serous ovarian cancer.




**Supplementary Figure 4.** Scatter plots for MR analysis of the causal effect of glutamine on prostate cancer (A) and endometrial cancer (B) based on UKB. Forest plots of instrumental variable Wald ratios and causal effect assessments of the relationship between glutamine and the risk of prostate cancer (C) and endometrial cancer (D) based on UKB.

**Supplementary Table 3.** Original results of heterogeneity and horizontal pleiotropy analyses

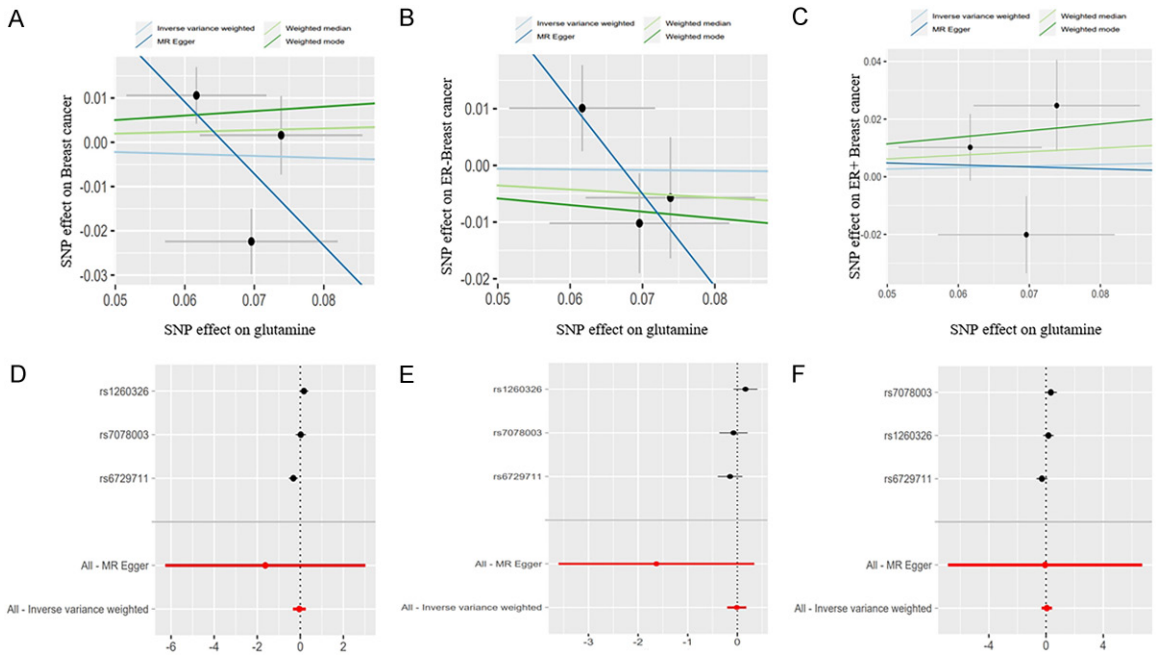
| Outcomes | UKB | | | | Kettunen *et al.* | | | |
|---|---|---|---|---|---|---|---|---|
| | $P_{(Heterogeneity)}$ | $P_{(Pleiotropy)}$ | $P_{(Global\ test)}$ | Outliers | $P_{(Heterogeneity)}$ | $P_{(Pleiotropy)}$ | $P_{(Global\ test)}$ | Outliers |
| Breast cancer | < 0.001 | 0.704 | < 0.001 | 3 | 0.003 | 0.625 | < 0.001 | 2 |
| ER+ breast cancer | < 0.001 | 0.913 | < 0.001 | 2 | 0.185 | 0.353 | 0.331 | 0 |
| ER- breast cancer | 0.065 | 0.361 | 0.069 | 0 | 0.073 | 0.978 | 0.255 | 0 |
| Lung Cancer | 0.206 | 0.349 | 0.213 | 0 | 0.549 | 0.312 | 0.512 | 0 |
| LAC | 0.146 | 0.844 | 0.178 | 0 | 0.372 | 0.752 | 0.526 | 0 |
| SCLC | 0.204 | 0.757 | 0.201 | 0 | 0.265 | 0.241 | 0.334 | 0 |
| Thyroid cancer | 0.423 | 0.290 | 0.351 | 0 | 0.358 | 0.235 | 0.502 | 0 |
| Prostate cancer | < 0.001 | 0.208 | < 0.001 | 1 | 0.011 | 0.543 | 0.128 | 0 |
| Ovarian cancer | 0.152 | 0.080 | 0.244 | 0 | 0.781 | 0.644 | 0.894 | 0 |
| HGSOC | 0.451 | 0.432 | 0.555 | 0 | 0.109 | 0.287 | 0.190 | 0 |
| LGSOC | 0.341 | 0.460 | 0.228 | 0 | 0.002 | 0.309 | 0.054 | 0 |
| Endometrial cancer | 0.159 | 0.500 | 0.129 | 0 | 0.148 | 0.168 | 0.337 | 0 |

$P_{(Heterogeneity)}$, *p* value of Cochrane's Q value in heterogeneity test; $P_{(Pleiotropy)}$, the *P* value for the intercept in the MR-Egger regression was used present the pleiotropy (P < 0.05); $P_{(Global\ test)}$, the *P* value for the global test in the MR-PRESSO; LAC, lung adenocarcinoma; SCLC, squamous cell lung cancer; HGSOC, High grade serous ovarian cancer; LGSOC, Low grade serous ovarian cancer.

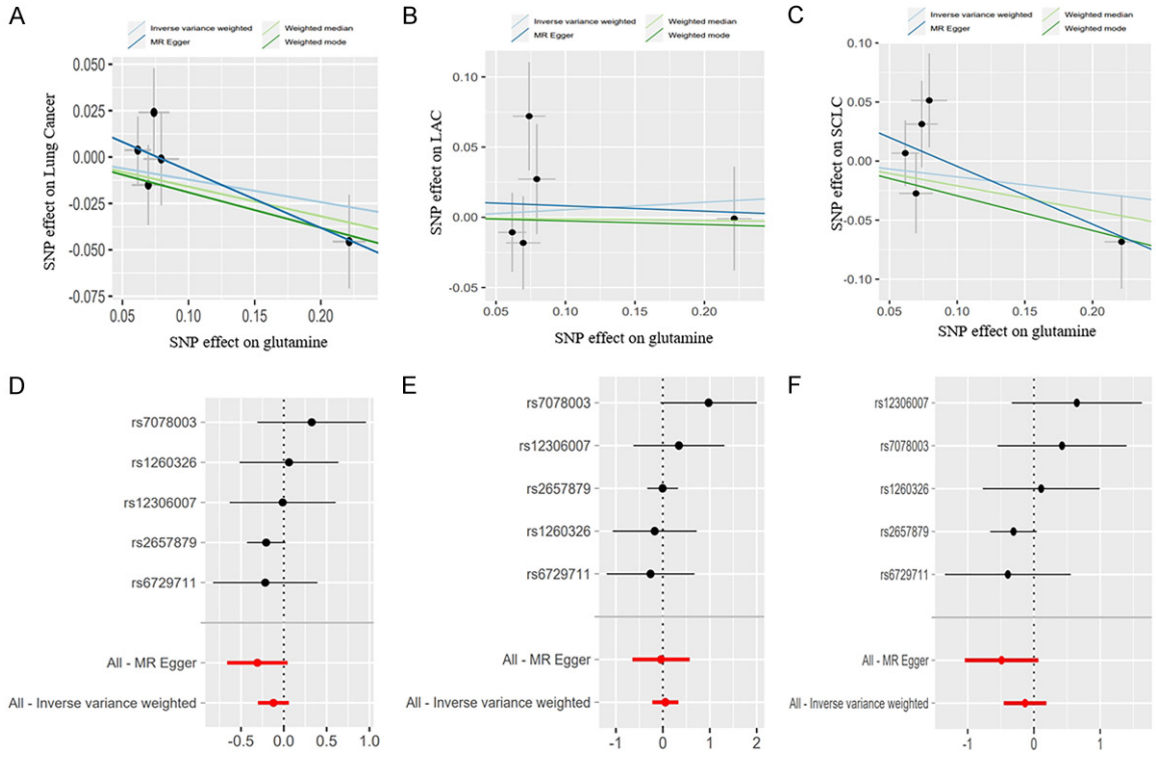
**Supplementary Table 4.** The results of the MR-PRESSO analysis

| Outcome | $P_{(Heterogeneity)}$ | Outliers | $P'_{(Heterogeneity)}$ | MR-PRESSO | |
|---|---|---|---|---|---|
| | | | | OR (95% CI) | *P* |
| UKB | | | | | |
| Breast cancer | < 0.001 | rs62182473 rs1750768 rs7925445 | 0.045 | 1.076 (0.985-1.056) | 0.056 |
| ER+ breast cancer | < 0.001 | rs1750768 rs4309084 | 0.003 | 1.089 (0.989-1.200) | 0.083 |
| ER- breast cancer | 0.065 | 0 | 0.065 | 1.034 (0.928-1.152) | 0.539 |
| Lung Cancer | 0.206 | 0 | 0.206 | 0.938 (0.832-1.057) | 0.290 |
| LAC | 0.146 | 0 | 0.146 | 1.023 (0.854-1.226) | 0.802 |
| SCLC | 0.204 | 0 | 0.204 | 0.945 (0.785-1.137) | 0.548 |
| Thyroid cancer | 0.423 | 0 | 0.423 | 0.667 (0.541-0.822) | $1.52\times10^{-4}$ |
| Prostate cancer | < 0.001 | rs28929474 | 0.001 | 0.977 (0.911-1.048) | 0.517 |
| Ovarian cancer | 0.152 | 0 | 0.152 | 0.996 (0.881-1.127) | 0.949 |
| HGSOC | 0.451 | 0 | 0.451 | 1.023 (0.884-1.185) | 0.760 |
| LGSOC | 0.341 | 0 | 0.341 | 1.022 (0.656-1.592) | 0.226 |
| Endometrial cancer | 0.159 | 0 | 0.159 | 1.066 (0.968-1.174) | 0.191 |
| Kettunen *et al.* | | | | | |
| Breast cancer | 0.003 | rs1260326 rs6729711 | - | 1.022 (0.807-1.294) | 0.857 |
| ER+ breast cancer | 0.185 | 0 | 0.185 | 0.988 (0.853-1.146) | 0.876 |
| ER- breast cancer | 0.073 | 0 | 0.073 | 1.055 (0.843-1.319) | 0.640 |
| Lung Cancer | 0.549 | 0 | 0.549 | 0.886 (0.739-1.060) | 0.186 |
| LAC | 0.372 | 0 | 0.372 | 1.055 (0.806-1.382) | 0.653 |
| SCLC | 0.358 | 0 | 0.358 | 0.875 (0.660-1.159) | 0.351 |
| Thyroid cancer | 0.358 | 0 | 0.358 | 0.577 (0.421-0.790) | $6.14\times10^{-4}$ |
| Prostate cancer | 0.011 | 0 | 0.011 | 0.906 (0.784-1.046) | 0.178 |
| Ovarian cancer | 0.781 | 0 | 0.781 | 1.044 (0.806-1.352) | 0.747 |
| HGSOC | 0.109 | 0 | 0.109 | 0.129 (0.930-1.537) | 0.439 |
| LGSOC | 0.002 | 0 | 0.002 | 0.760 (0.077-7.460) | 0.814 |
| Endometrial cancer | 0.148 | 0 | 0.148 | 0.995 (0.858-1.153) | 0.943 |

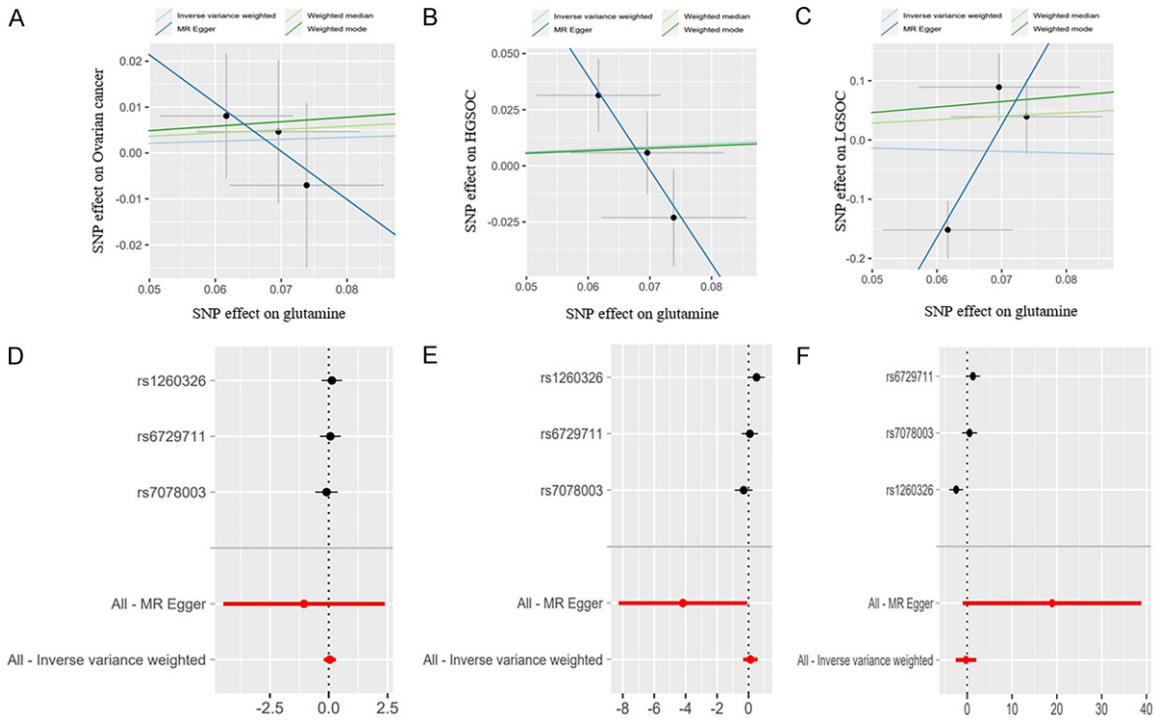
$P_{(Heterogeneity)}$, *p* value of Cochrane's Q value in heterogeneity test before MR-PRESSO; $P_{(Global\ test)}$, the *P* value for the global test in the MR-PRESSO; $P'_{(Heterogeneity)}$, *p* value of Cochrane's Q value in heterogeneity test after removing outliers; LAC, lung adenocarcinoma; SCLC, squamous cell lung cancer; HGSOC, High grade serous ovarian cancer; LGSOC, Low grade serous ovarian cancer.



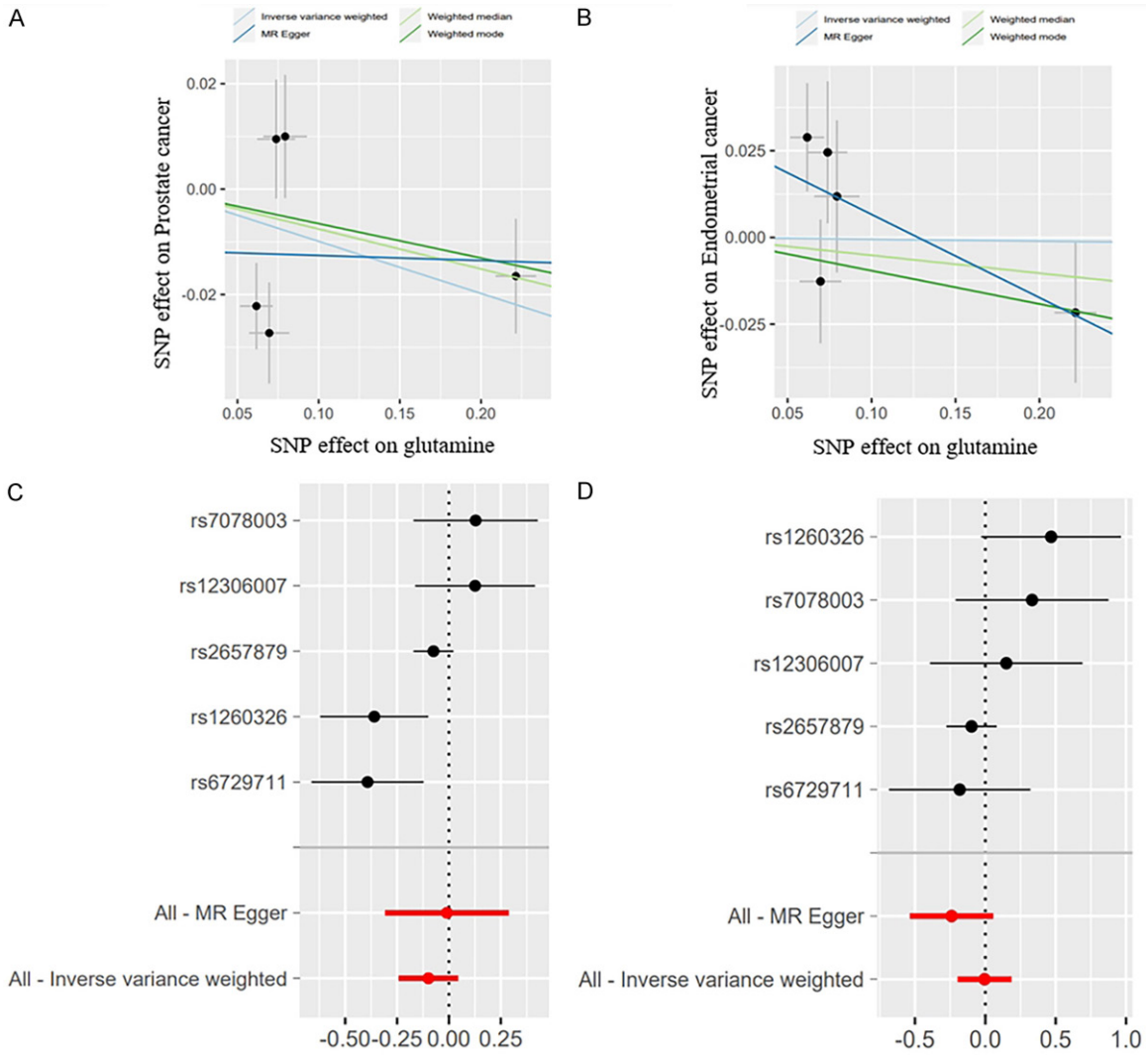

**Supplementary Figure 5.** Scatter plots for MR analysis of the causal effect of glutamine on breast cancer based on Kettunen et al. A. Breast cancer. B. ER+ breast cancer. C. ER- breast cancer. Forest plots of instrumental variable Wald ratios and causal effect assessments of the relationship between glutamine and the risk of breast cancer based on Kettunen et al. D. Breast cancer. E. ER+ breast cancer. F. ER- breast cancer.




**Supplementary Figure 6.** Scatter plots for MR analysis of the causal effect of glutamine on lung cancer based on Kettunen et al. A. Lung cancer. B. LAC. C. SCLC. Forest plots of instrumental variable Wald ratios and causal effect assessments of the relationship between glutamine and the risk of lung cancer based on Kettunen et al. D. Lung cancer. E. LAC. F. SCLC. LAC, lung adenocarcinoma; SCLC, squamous cell lung cancer.




**Supplementary Figure 7.** Scatter plots for MR analysis of the causal effect of glutamine on ovarian cancer based on Kettunen et al. A. Ovarian cancer. B. HGSOC. C. LGSOC. Forest plots of instrumental variable Wald ratios and causal effect assessments of the relationship between glutamine and the risk of ovarian cancer based on Kettunen et al. D. Ovarian cancer. E. HGSOC. F. LGSOC. HGSOC, High-grade serous ovarian cancer; LGSOC, low-grade serous ovarian cancer.




**Supplementary Figure 8.** Scatter plots for MR analysis of the causal effect of glutamine on prostate cancer (A) and endometrial cancer (B) based on the study by Kettunen et al. Forest plots of instrumental variable Wald ratios and causal effect assessments of the relationship between glutamine and the risk of prostate cancer (C) and endometrial cancer (D) based on the study by Kettunen et al.

**Supplementary Table 5.** MVMR estimates between glutamine and thyroid cancer risk

| Models | Outcomes | UKB | | Kettunen *et al*. | |
|---|---|---|---|---|---|
| | | OR (95% CI) | *P* | OR (95% CI) | *P* |
| Glutamine+BMI | Glutamine | 0.663 (0.517-0.851) | $1.24\times10^{-3}$ | 0.599 (0.431-0.831) | $2.17\times10^{-3}$ |
| | BMI | 1.082 (0.772-1.515) | 0.644 | 1.094 (0.788-1.519) | 0.601 |
| Glutamine+T2DM | Glutamine | 0.626 (0.505-0.776) | $1.99\times10^{-5}$ | 0.568 (0.406-0.795) | $9.71\times10^{-4}$ |
| | T2DM | 0.626 (0.899-1.160) | 0.750 | 0.961 (0.827-1.117) | 0.600 |
| Glutamine+Fasting glucose | Glutamine | 0.721 (0.574-0.916) | $4.91\times10^{-3}$ | 0.570 (0.415-0.782) | $4.99\times10^{-4}$ |
| | Fasting glucose | 0.761 (0.437-1.322) | 0.333 | 0.744 (0.417-1.326) | 0.316 |
| Glutamine+Fasting insulin | Glutamine | 0.695 (0.567-0.852) | $4.69\times10^{-4}$ | 0.610 (0.445-0.835) | $2.06\times10^{-3}$ |
| | Fasting insulin | 1.962 (0.890-4.328) | 0.095 | 2.178 (0.898-5.282) | 0.085 |
| Glutamine+HDL | Glutamine | 0.681 (0.532-0.870) | $2.17\times10^{-3}$ | 0.660 (0.484-0.899) | $8.38\times10^{-3}$ |
| | HDL | 1.071 (0.879-1.304) | 0.497 | 1.069 (0.802-1.308) | 0.521 |
| Glutamine+LDL | Glutamine | 0.664 (0.505-0.871) | $3.16\times10^{-3}$ | 0.545 (0.381-0.778) | $8.49\times10^{-4}$ |
| | LDL | 0.964 (0.800-1.161) | 0.697 | 0.962 (0.798-1.160) | 0.686 |
| Glutamine+Triglycerides | Glutamine | 0.662 (0.519-0.846) | $9.55\times10^{-4}$ | 0.624 (0.455-0.855) | $3.34\times10^{-3}$ |
| | Triglycerides | 0.822 (0.660-1.048) | 0.118 | 0.844 (0.747-1.187) | 0.170 |