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Article

Causal Effects between Gut Flora Significantly Associated with Cervical Cancer and 1400 Metabolites: A Mendelian Randomized Study

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Abstract: Background: Cervical cancer is a life-threatening disease that substantially affects human health. We investigated the association between metabolites, intestinal flora, and cervical cancer through Mendelian analysis to identify metabolic markers for the diagnosis and treatment of cervical cancer. Methods: Using data from the FinnGen Biobank, MiBioGen, and GWAS catalog, we conducted a causal study linking the gut microbiota to cervical cancer. Single nucleotide polymorphisms (SNP) information on gut flora linked to cervical cancer and 1400 metabolites underwent Mendelian analysis. We used inverse variance weighting (IVW), Mendelian Randomization (MR)-Egger, Weighted median (WM), simple mode, and weighted mode for the analysis. Sensitivity analysis included the Cochran Q test, funnel plot, "leave-one-out", and MR-Egger intercept test. Results: Our findings identified four microbial groups with important causal associations with cervicitis: *Pasteurellaceae*, *Veillonellaceae*, *Odoribacter*, and *Bacillales*, which showed a positive correlation with cervical cancer. In addition, *Pasteurellaceae* were positively associated with cervical cancer. In a Mendelian analysis of 1400 blood metabolites, we confirmed 43 metabolites causally linked to *Odoribacter*, with 20 positively and 23 negatively correlated. Among the 38 metabolites, 27 were positively correlated, and 11 were negatively correlated with *Veillonellaceae*. For *Pasteurellaceae*, 44 metabolites were causally associated with 27 positive and 17 negative metabolites. Additionally, 21 metabolites were significantly correlated with *Bacillales*, with 11 positive and 10 negative correlations. The IVW estimates were significant, and the sensitivity analysis revealed no heterogeneity or pleiotropy. Conclusion: Mendelian studies provide robust evidence for the role of specific metabolites in cervical cancer, showing a causal link with the gut flora. These findings could lead to the development of new diagnostic tools and treatments. However, their clinical application remains unclear, and further research is required to confirm and optimize these ideas. Continued exploration can enhance our understanding of cervical and other cancers, aiding in their prevention and treatment.

Keywords: cervical cancer, metabolites, gut microbiota, Mendelian Randomization

1. Introduction

Cervical cancer, one of the most prevalent malignant tumors in women, refers to tumors that grow in the cervical canal and vaginal region of the uterus. Approximately 100,000 people in the US receive treatment for cervical precancerous lesions, 14,000 are diagnosed with cervical cancer, and 4000 die from the disease each year [1]. The most common age group for carcinoma in situ was 30–35 years, whereas that for invasive cervical cancer was 45–55 years.Women of childbearing age are still prone to cervical cancer，despite increased access to vaccination and screening [2]. Studies have demonstrated that there is a reversible precancerous stage in cervical cancer that can persist for many years. The early detection and treatment of cervical cancer are directly correlated

with its incidence rate. Colposcopy, biopsy, Pap smear, and other procedures are currently considered the gold standard for the diagnosis of cervical cancer. Although many studies have highlighted the value of imaging technology for further diagnosis, its application is limited by its significant cost and intrusive nature. Therefore, research and identification of novel biomarkers may be instrumental in the diagnosis and management of cervical cancer [3].

Furthermore, changes in the gut microbiota (GM) of the cervix and toxin release can result in mucosal harm and translocation, leading to diverse inflammations that might modify the metabolome [4]. Research indicates a substantial variance in the species and abundance of intestinal microbiomes between cervical cancer patients and healthy individuals, which could be crucial for diagnosing and managing the condition [5,6]. The causal link between GM and cervical cancer remains insufficiently explored owing to the constraints of conventional observational research.

Alterations in metabolites chiefly pertain to the way biological systems respond to biological occurrences. Such shifts can amplify minor differences in genes and proteins, providing a more precise, perceptive, and instinctual depiction of the physiological and pathological conditions of natural systems [7]. Blood metabolomics is an essential tool for studying several diseases, including endometrial, breast, and colorectal cancers [8–10]. Determining the possible causative association between blood metabolites and cervical cancer, as well as the flora strongly connected with cervical cancer, is challenging to establish due to inevitable confounding factors [11]. Metabolomics has emerged as a prominent field in the exploration of metabolic regulation and cancer. Research in metabolomics offers fresh perspectives on disease development and progression through the direct analysis of alterations in the body's microenvironment, setting the stage for the advancement of creative techniques in both disease prevention and diagnosis. The complex dynamics between metabolic routes may alter the effects of pharmaceuticals. A comprehensive genetic association study involving 1091 blood metabolites and 309 metabolite ratios linked 690 metabolites across 248 distinct sites effectively. Diseases can be effectively targeted by metabolic activity, and this study opens up new avenues for potential therapeutic targets by shedding light on the function of metabolic genes in common disorders and providing important information on their genetic makeup [12]. Metabolomics can also be used to assess the efficacy of cervical cancer treatments. A scientific study pointed out that Radix et Rhizoma can inhibit the growth of cervical cancer cells and promote apoptosis. Despite the potential of small molecules, such as caffeic acid and metformin, to disturb energy equilibrium, the mechanisms underlying their cancer-fighting properties require additional scientific exploration. Therefore, metabolomics is appropriate for assessing the efficacy of treatment for cervical cancer [13]. Metabolites such as short-chain fatty acids, tryptophan (Trp), and bile acids produced by specific GM microbes impact genetic regulation and immune cell metabolism collaboratively regulating individual system homeostasis [14]. Variations in the GM metabolites can lead to the development of various illnesses, including cancer, neurological conditions, gastrointestinal and metabolic diseases, and diseases linked to children. GM metabolites are crucial not only in disease development and progression but also substantially influence disease treatment, anticipated clinical outcomes, prognoses, and the efficacy of immunotherapy and response. This advances our knowledge of numerous illnesses and the purposes for which they are intended. Nevertheless, the exact cause-and-effect connection between cervical cancer, the GM, and its metabolites remains unclear; therefore, this study comprehensively explored this relationship using Mendelian techniques [14]. Mendelian Randomization (MR) serves as a data analysis method employed in epidemiological studies to evaluate underlying etiological hypotheses. This method explores the causal links between exposure elements and outcomes by employing genetic variations known to correlate with exposure factors as variables for evaluation closely.MR studies have many similarities to randomized controlled trials because the odds of passing on any one allele to a single individual are consistent. Since gene variants are often not directly related to other confounders, MR is better at preventing reverse causation and confounders than conventional factors [15]. This study successfully identified intestinal microbiota with significant association with cervical cancer and used TSMR technology to investigate the causal relationship between 1,400 blood metabolites and intestinal microbiota. The findings indicate the presence of numerous carcinogenic microbiota and associated metabolites in the cervical tissues. This study primarily aimed to understand the underlying causes and potential modes of action. The results of this study are expected to lay the foundation for an in-depth examination of the molecular mechanisms underlying the emergence and treatment of cervical cancer. Moreover, this study has the potential to enhance the understanding of cervical cancer's metabolic dynamics, diversify the array of intestinal microbes associated with the condition, investigate the link between these microbes and blood metabolites, unveil a direct causative link to cervical cancer, and set the stage for innovative clinical strategies in its treatment [11].

2. Materials and Methods

2.1. Study Design

Using genetic variation as an instrumental variable, we employed MR analysis to evaluate the causal link between the GM and cervical cancer risk. This technique strengthens the validity of causal inference and reduces the impact of confounding variables. This study investigated the link between 1400 metabolites found in human blood and gut flora closely related to cervical cancer, utilizing MR design analysis of genetic data from both populations. Single nucleotide polymorphisms (SNPs) were used as instrumental variables to eliminate confounders, and the selection criteria were p-value filter $< 1 \times 10^{-5}$. Then, MR Analysis was performed, and a sensitivity analysis was conducted. The design of MR should follow the following three basic assumptions: (1) Correlation hypothesis: close association between genetic variation and exposure factors (GM, 1400 human blood metabolites); (2) Independence hypothesis: no association between genetic variation and confounders (cervical cancer, SNPs corresponding to intestinal flora significantly associated with cervical cancer); (3) Exclude the limiting hypothesis: genetic variation can only play a role through exposure. For the first hypothesis, the strength of each instrumental variable was assessed using statistical methods, such as the F statistic, which is considered a robust instrumental variable if it is greater than the threshold. The second hypothesis was to exclude SNPS from the database that may be associated with all confounders of outcomes to ensure that the IVs studied were not associated with any known confounders. The third hypothesis is that the horizontal pleiotropy of the instrumental variables in this study is assessed using the MR-Egger intercept. Pleiotropy may be present if the MR-Egger intercept is significant and non-zero (Figure 1).

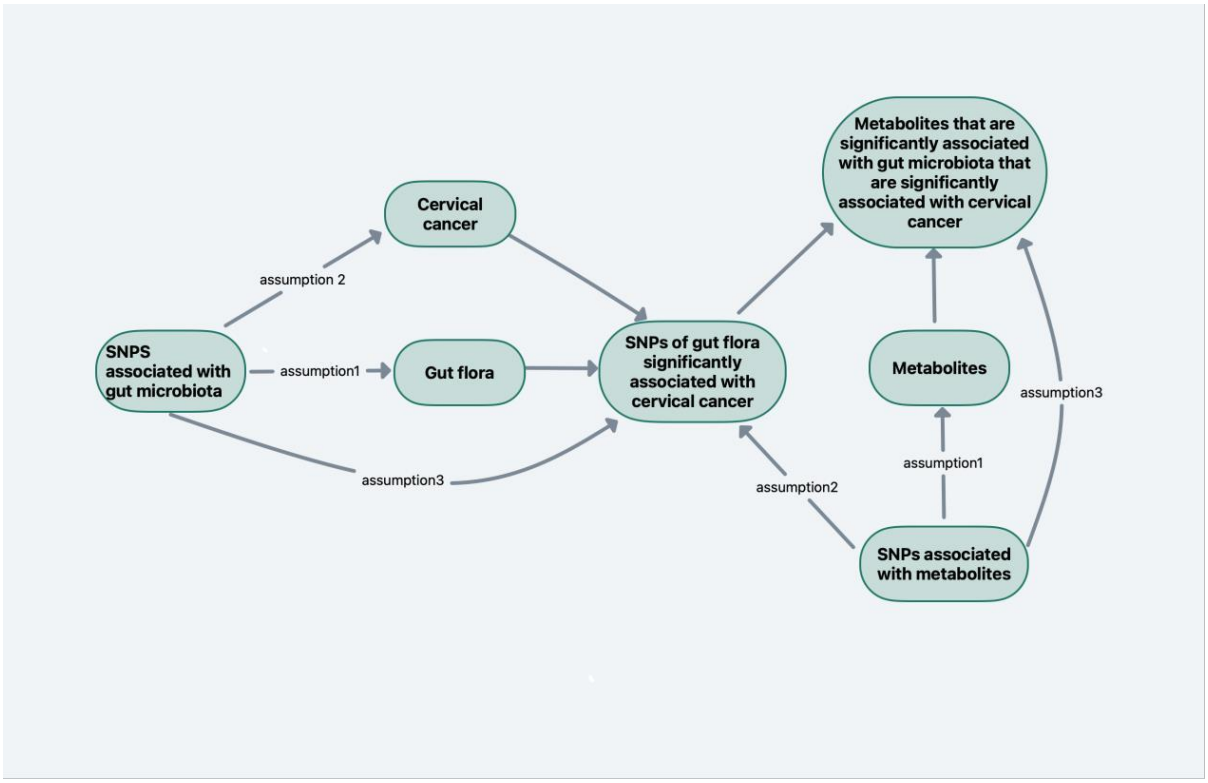


Figure 1. Schematic representation of MR research: Hypothesis 1 suggests a strong link between genetic diversity and exposure. Hypothesis 2 posits that genetic variation operates independently of interfering elements. Hypothesis 3 suggests that genetic diversity influences the results solely via exposure.

2.2. Data Source

This item, which contains 211 intestinal flora data downloads, is located at https://biogen.gcc.rugs.nl (accessed on 21 February 2025). A total of 18,340 participants in 24 cohorts from the US, Canada, Israel, South Korea, and the UK had their genotyping data examined by the MiBioGen International Consortium. Under strict quality control, a large-scale, multi-ancestor, genome-wide analysis was conducted to determine the relationship between genetic diversity in human genes and the gut microbiome [16]. Cervical cancer data were obtained from the FinnGen database, which used GWAS genotyping to generate near-complete genomic variation data for

500,000 participants. The sample consists of two entities: (1) legacy samples (approximately 200,000 prospecting), mainly collected by THL (National Institute for Health and Welfare), and (2) approximately 300,000 expected samples. The FinnGen project started in August 2017 and was split into two phases: FinnGen 1 (years 1–3) and FinnGen 2 (years 4–6). This comprised 182,927 healthy individuals and 388 patients with cervical cancer. All participants in the original study provided informed consent [17]. Shin et al. gathered data from the KORA dataset (n = 1768) and the TwinsUK dataset (1052 people and 250 metabolites) to conduct an in-depth study of metabolites. Previous studies have incorporated 529 metabolites among 7824 European adults 5002. TwinsUK individuals were newly described in this dataset. In the two cohorts included in this work, 486 metabolites were available for genetic investigation, and a genome-wide analysis of over 2.1 million SNPs was conducted initially [18]. 1400 blood metabolites Numbers for GCST90027001-GCST90028000/ GCST90027857GCST90027446-GCST90027857, Data are available on https://www.ebi.ac.uk/gwas/ (accessed on 21 February 2025) [17].

2.3. Selection of Instrument Variables

The linkage disequilibrium test was then run, and upon removal of the linkage disequilibrium, dlump kb = 500, clump_ r2 = 0.1 was set. The F statistic was determined, and SNPS (weak instrumental variables) with F < 10 were eliminated to eliminate the bias caused by inferior instruments. To exclude genetic variation SNPS that were significantly correlated with exposure factors, screening, and correlation analysis were performed on the intestinal microbiome data acquired from MiBioGen. Pvalflter < 1×10^{-5} was the selection criterion for strong, favorable exposure findings. The intestinal microbiome data downloaded from MiBioGen were screened, and correlation analysis was conducted to screen for genetic variation SNPS strongly related to exposure factors. The selection criteria for strong positive exposure results was pvalflter < 1×10^{-5}. Uniform selection criteria were set for the genetic variation of 1400 metabolites. A strict threshold was selected in the MR analysis ($p < 1 \times 10^{-8}$), and a significant strong positive exposure result was obtained. Further analysis of linkage unbalances if the clump_ r2 parameter is <0.1 and the distance between SNPS is less than 500 kb, it is considered that a linkage unbalance exists [19]. The F statistic is calculated, and weak instrumental variables with F < 10 are removed. A series of sensitivity analyses were performed to evaluate the pleiotropy of the MR results; however, there may still be a small number of confounding SNP confounders ($p < 1 \times 10^{-5}$), and SNPs significantly associated with confounders were excluded.

2.4. Mendelian Analysis

This study employed five MR analysis methods, the principal one being random effects inverse variance weighted (IVW), which was based on the three hypotheses of MR and the idea of a randomized experiment, taking the inverse of the variance and weighting the estimate, using genetic variation to explore the causal relationship between observed exposure factors and outcomes; and the analysis method of evaluating the relationship between metabolites that cause SNPS (shared with metabolites) corresponding to intestinal flora significantly associated with cervical cancer [20]. We additionally used MR-Egger, Weighted median (WM), simple mode, and weighted mode as supplements to assess the outcome and exposure components. The IVW approach may introduce bias into the analysis of genetic pleiotropy and effect results due to some unidentified confounding factors. Among these, MR-Egger regression may be more suitable when there is significant heterogeneity, pleiotropy, and $p < 0.05$. When half of the weights in the MR analysis were invalid, the WM technique was used to assess the causal effects. In preliminary studies, simple models are typically used to evaluate the direct link between two variables. It is a basic statistical model without complicated adjustments or variables. The weight of the weighted model is typically determined by the reliability of the data, and weighting processing allows the contributions of various factors to be more accurately represented [21]. Sensitivity analysis of heterogeneity and pleiotropy was also performed, including Cochran's Q test, funnel plot, and "leave-one-out" analysis. The Cochran Q value was used to evaluate the heterogeneity of the analysis. There may be variations in the instrumental variables (IV, usually SNP) from various analysis platforms, including experiments and populations, which will ultimately impact the outcomes.

In this study, outliers were identified using a scatter plot. The result is regarded as heterogeneity between the heterogeneous exposure factor and the outcome causal effect if the *p*-value is less than 0.05. The impact of heterogeneity did not need to be considered in the study results because SNPS with *p* values larger than 0.05 were chosen. MR-PRESSO was then employed to identify horizontal gene pleiotropy [11]. "Leave-one-out" analysis is a technique used to assess how deleting an SNP may affect the outcome. The RforMac program (version 4.3.1) was used for all studies. Data plotting and statistical analyses were performed using the "TwoSampleMR" and "MR-PRESSO" packages.

3. Result

3.1. Examination of the Strong Association between Intestinal Microbiota and Cervical Cancer

Figure 2 displays the MR-IVW study of 211 GM species and cervical cancer risk. Four gut microbiome groups out of the 211 bacterial groups showed a strong causal connection with cervicitis. Cervical cancer is linked to the *Pasteurellaceae*, *Veillonellaceae*, *Odoribacter*, and *Bacillales* families, in that order.

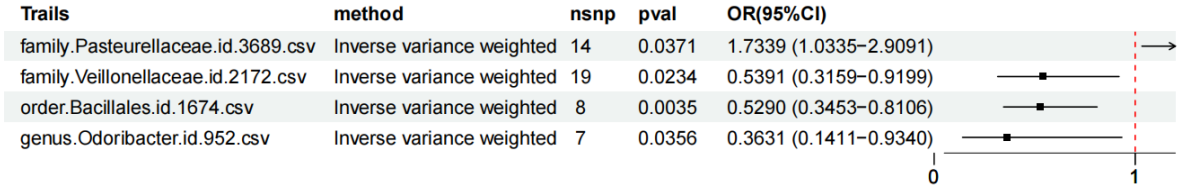


Figure 2. The forest map shows the causal relationship between intestinal flora and cervical cancer; the analytical method used was IVW.

Pasteurellaceae (IVW OR = 1.73, 95% confidence interval (CI) 1.03–2.91, $p = 0.004$) was the microbiota that showed a positive correlation, indicating that the microbiota in the human gut increases the risk of cervical cancer. WM analysis further confirmed the above results *Pasteurellaceae* (OR = 1.92, 95% CI 0.92–4.01, $p = 0.083$). The causal assessment analyzed by MR-Egger also showed that the above bacterial groups had a consistent correlation with cervical cancer (OR = 1.45, 95% CI 0.46–4.63, $p = 0.540$), but it was not significant (Figure 2).

The other three groups consisted of *Odoribacter* (IVW OR = 0.36, 95% CI 0.14–0.93, IVW OR = 0.54, 95% CI 0.34–1.00, $p = 0.023$) and *Veillonellaceae* (IVW OR = 0.54, 95% CI 0.34–1.00, $p = 0.023$). Periodontitis had a negative causal influence on *Bacillales* (IVW OR = 0.53, 95% CI 0.35–0.81, $p = 0.003$), suggesting that *Bacillales* tended to lower the risk of periodontitis through causality. IVW analysis was compatible with other MR analyses (WM and MR-Egger, Simple mode, weighted mode) (Figure 3A–H).

Gene pleiotropy and data heterogeneity analyses were performed to assess whether there was any bias in the results. In the pleiotropy study, the MR-Egger intercept term suggested a low chance of pleiotropy. The microflora of all three PMR-PRESSO models was found to be $p > 0.05$, according to the results. A single SNP did not indicate a causal link between gut flora and cervical cancer, according to the results of the "leave-one-out" test. The investigation demonstrated a consistent causal link between cervical cancer and the families *Pasteurellaceae*, *Veillonellaceae*, *Odoribacter*, and *Bacillales* (Figure 3I–L). Second, the funnel plot was used to visually detect no significant bias in the study (Figure 3M–P). These microbial communities may continue to play therapeutic and curative roles after the development of cervical cancer.

3.2. Correlation Analysis between Intestinal Flora Significantly Associated with Cervical Cancer and 1400 Metabolites

Of the 1400 blood metabolites, our results in the second Mendelian analysis confirmed a causal relationship between 43 metabolites and the *Odoribacter* taxa (Figure 4), of which 20 metabolites were positively correlated, including 1–stearoyl–GPI, pregnenediol disulfate (OR ≥ 1, $p < 0.05$), and 23 metabolites were negatively correlated, including pyridoxate, stachydrine (OR less than 1, $p < 0.05$). Thirty-eight metabolites were associated with acetic acid in *Veillonellaceae*, of which 27 were positively correlated, including docosadioate and 1H–indole–7–acetic acid (OR ≥ 1, $p < 0.05$), and 11 metabolites were negatively correlated with it, including propionylcarnitine and 1–oleoyl–2–docosahexaenoyl–GPC (OR < 1, $p < 0.05$). A total of 44 metabolites were causally associated with *Pasteurellaceae* flora, of which 27 were positively associated, including 3–hydroxypyridine sulfate, 1,2,3–benzenetriol sulfate (OR ≥ 1, $p < 0.05$), and 17 metabolites were negatively correlated with it, including ascorbic acid 3–sulfate, beta–hydroxyisovalerate (OR less than 1, $p < 0.05$). In addition, 21 metabolites were significantly correlated with *Bacillales*, among which 11 metabolites were positively correlated with *Bacillales*, such as 1–palmitoyl–2–dihomo–linolenoyl–GPC, 2–stearoyl–GPE (OR ≥ 1, $p < 0.05$), and 10 metabolites were negatively correlated with *Bacillales*, including taurine X−12849 (OR less than 1, $p < 0.05$). We identified a genetic inclination towards metabolites using the IVW method (Figure 5A–D). Alternative techniques such as WM and MR-Egger, simple mode, and weighted mode were employed to eliminate the impact of additional variables on the outcomes. Blood metabolites were significantly associated with the intestinal flora of cervical cancer, and a causal association between intestinal flora and metabolites linked to cervical cancer was

established. In addition to the WM approach, the scatter plot also reinforced the connection between intestinal flora and metabolites (Figure 5E–H).

Sensitivity analysis was used to assess potential bias in establishing the significance of estimates by MR analysis using PIVW < 0.05 and was examined using multiple effects and heterogeneity tests. The "leave-one-out" technique confirmed the steady causal relationship between gut flora and its metabolites, which were strongly linked to cervical cancer (Figure 5I–L). *p* values and I^2 indicate a partial causal relationship and heterogeneity, respectively. The intercept term in the MR-Egger method indicates the level of risk associated with horizontal pleiotropy. We screened for a PMR-PRESSO value greater than 0.05 to minimize the impact of pleiotropy (Figure 5M–P). Various plots, including scatter plots, "leave-one-out" plots, funnel plots, and forest plots, demonstrated that the estimations adhered to all assumptions.

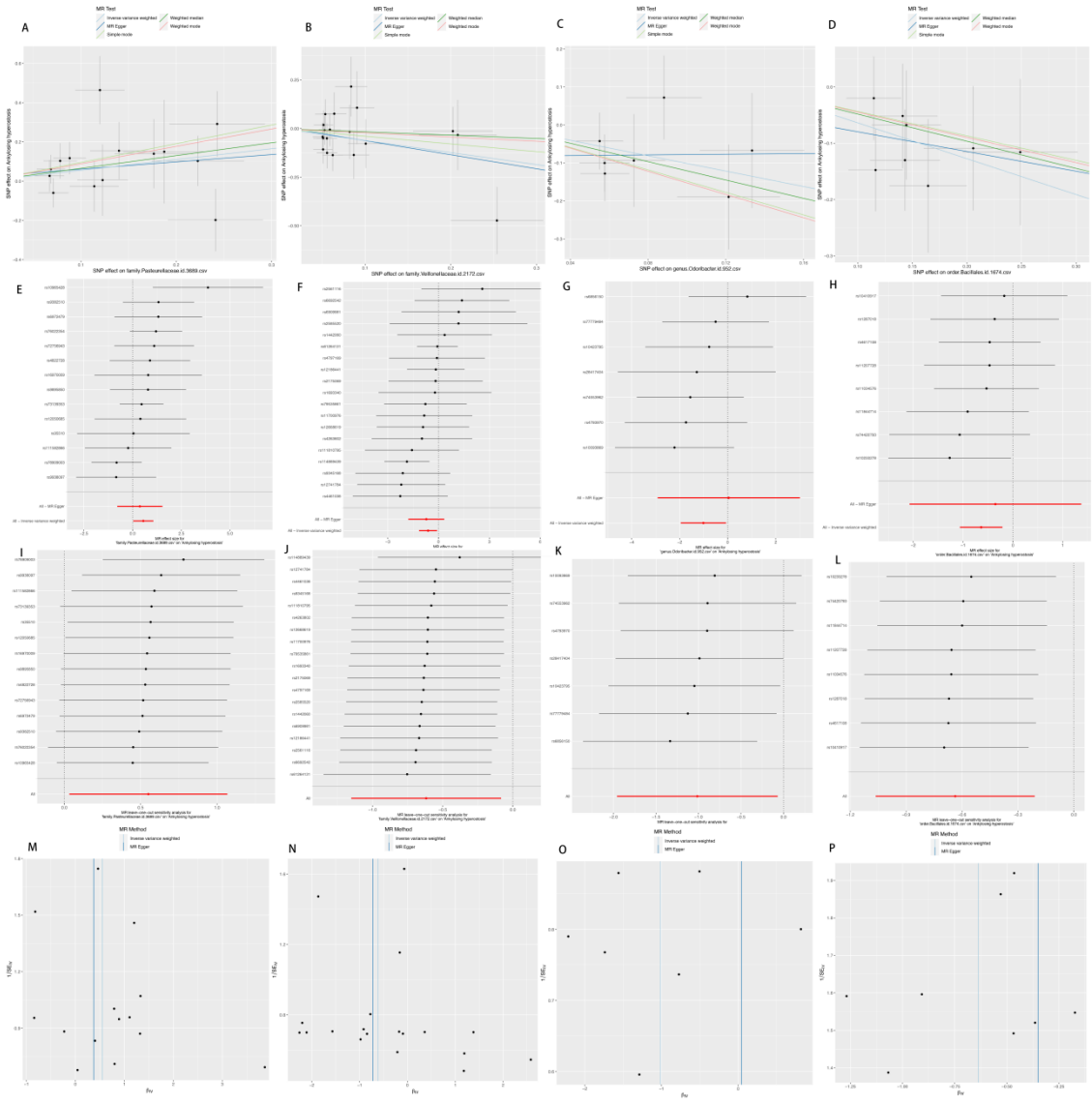
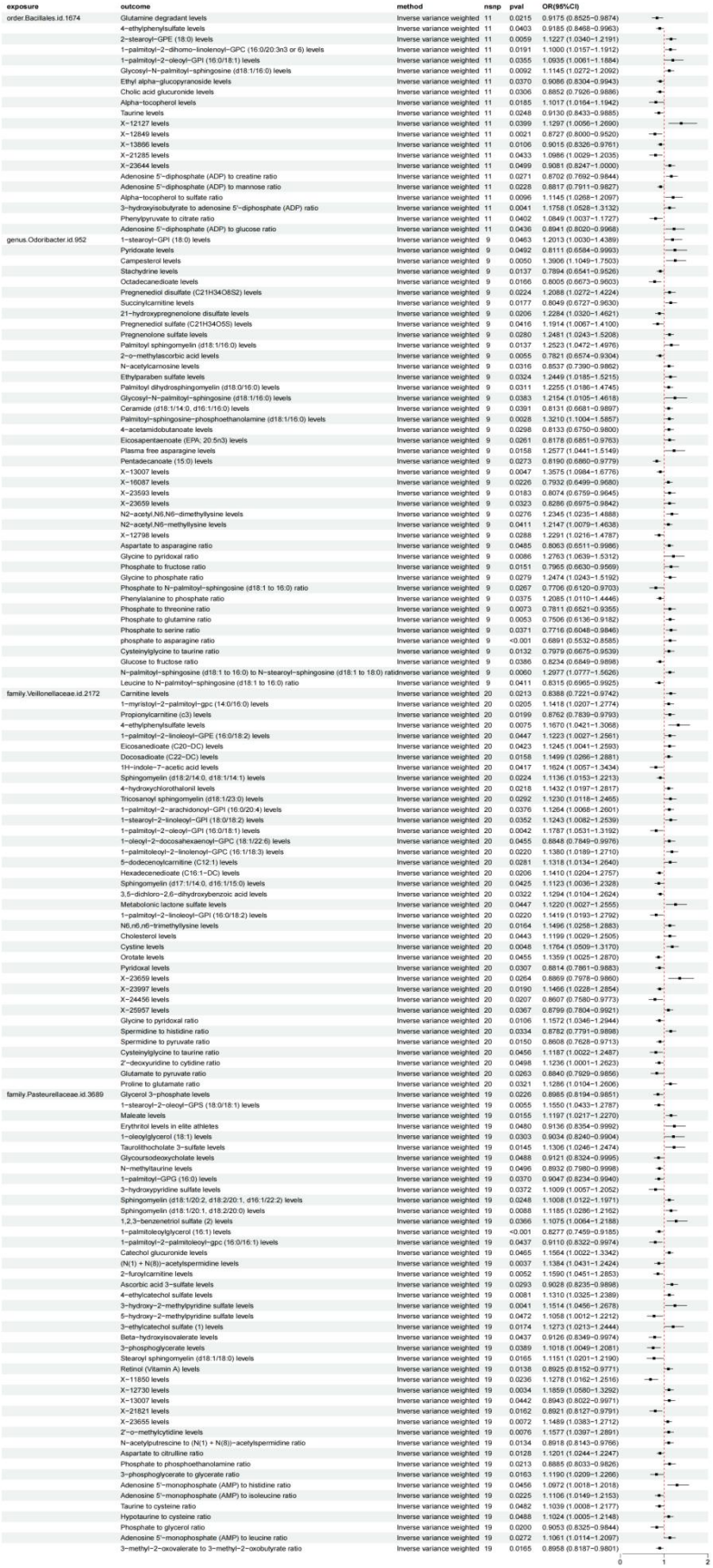


Figure 3. Risk and sensitivity analyses of gut flora were significantly associated with cervical cancer. (**A**–**D**): Scatter plot of four types of gut flora associated with cervical cancer risk. (**E**–**H**): Forest map of the four types of gut flora associated with cervical cancer risk. (**I**–**L**): Four types of gut flora associated with cervical cancer risk were mapped using the "leave-one-out" method. (**M**–**P**): Funnel plot for sensitivity analysis of four types of gut flora associated with cervical cancer risk.



exposure	outcome	method	nsnp	pval	OR(95%CI)
order.Bacillales.id.1674	Glutamine degradant levels	Inverse variance weighted	11	0.0215	0.9175 (0.8525−0.9874)
	4−ethylphenylsulfate levels	Inverse variance weighted	11	0.0403	0.9185 (0.8468−0.9963)
	2−stearoyl−GPE (18:0) levels	Inverse variance weighted	11	0.0059	1.1227 (1.0340−1.2191)
	1−palmitoyl−2−dihomo−linolenoyl−GPC (16:0/20:3n3 or 6) levels	Inverse variance weighted	11	0.0191	1.1000 (1.0157−1.1912)
	1−palmitoyl−2−oleoyl−GPI (16:0/18:1) levels	Inverse variance weighted	11	0.0355	1.0935 (1.0061−1.1884)
	Glycosyl−N−palmitoyl−sphingosine (d18:1/16:0) levels	Inverse variance weighted	11	0.0092	1.1145 (1.0272−1.2092)
	Ethyl alpha−glucopyranoside levels	Inverse variance weighted	11	0.0370	0.9086 (0.8304−0.9943)
	Cholic acid glucuronide levels	Inverse variance weighted	11	0.0306	0.8852 (0.7926−0.9886)
	Alpha−tocopherol levels	Inverse variance weighted	11	0.0185	1.1017 (1.0164−1.1942)
	Taurine levels	Inverse variance weighted	11	0.0248	0.9130 (0.8433−0.9885)
	X−12127 levels	Inverse variance weighted	11	0.0399	1.1297 (1.0056−1.2690)
	X−12849 levels	Inverse variance weighted	11	0.0021	0.8727 (0.8000−0.9520)
	X−13866 levels	Inverse variance weighted	11	0.0106	0.9015 (0.8326−0.9761)
	X−21285 levels	Inverse variance weighted	11	0.0433	1.0986 (1.0029−1.2035)
	X−23644 levels	Inverse variance weighted	11	0.0499	0.9081 (0.8247−1.0000)
	Adenosine 5'−diphosphate (ADP) to creatine ratio	Inverse variance weighted	11	0.0271	0.8702 (0.7692−0.9844)
	Adenosine 5'−diphosphate (ADP) to mannose ratio	Inverse variance weighted	11	0.0228	0.8817 (0.7911−0.9827)
	Alpha−tocopherol to sulfate ratio	Inverse variance weighted	11	0.0096	1.1145 (1.0268−1.2097)
	3−hydroxyisobutyrate to adenosine 5'−diphosphate (ADP) ratio	Inverse variance weighted	11	0.0041	1.1758 (1.0528−1.3132)
	Phenylpyruvate to citrate ratio	Inverse variance weighted	11	0.0402	1.0849 (1.0037−1.1727)
	Adenosine 5'−diphosphate (ADP) to glucose ratio	Inverse variance weighted	11	0.0436	0.8941 (0.8020−0.9968)
genus.Odoribacter.id.952	1−stearoyl−GPI (18:0) levels	Inverse variance weighted	9	0.0463	1.2013 (1.0030−1.4389)
	Pyridoxate levels	Inverse variance weighted	9	0.0492	0.8111 (0.6584−0.9993)
	Campesterol levels	Inverse variance weighted	9	0.0050	1.3906 (1.1049−1.7503)
	Stachydrine levels	Inverse variance weighted	9	0.0137	0.7894 (0.6541−0.9526)
	Octadecanedioate levels	Inverse variance weighted	9	0.0166	0.8005 (0.6673−0.9603)
	Pregnenediol disulfate (C21H34O8S2) levels	Inverse variance weighted	9	0.0224	1.2088 (1.0272−1.4224)
	Succinylcarnitine levels	Inverse variance weighted	9	0.0177	0.8049 (0.6727−0.9630)
	21−hydroxypregnenolone disulfate levels	Inverse variance weighted	9	0.0206	1.2284 (1.0320−1.4621)
	Pregnenediol sulfate (C21H34O5S) levels	Inverse variance weighted	9	0.0416	1.1914 (1.0067−1.4100)
	Pregnenolone sulfate levels	Inverse variance weighted	9	0.0280	1.2481 (1.0243−1.5208)
	Palmitoyl sphingomyelin (d18:1/16:0) levels	Inverse variance weighted	9	0.0137	1.2523 (1.0472−1.4976)
	2−o−methylascorbic acid levels	Inverse variance weighted	9	0.0055	0.7821 (0.6574−0.9304)
	N−acetylcarnosine levels	Inverse variance weighted	9	0.0316	0.8537 (0.7390−0.9862)
	Ethylparaben sulfate levels	Inverse variance weighted	9	0.0324	1.2449 (1.0185−1.5215)
	Palmitoyl dihydrosphingomyelin (d18:0/16:0) levels	Inverse variance weighted	9	0.0311	1.2255 (1.0186−1.4745)
	Glycosyl−N−palmitoyl−sphingosine (d18:1/16:0) levels	Inverse variance weighted	9	0.0383	1.2154 (1.0105−1.4618)
	Ceramide (d18:1/14:0, d16:1/16:0) levels	Inverse variance weighted	9	0.0391	0.8131 (0.6681−0.9897)
	Palmitoyl−sphingosine−phosphoethanolamine (d18:1/16:0) levels	Inverse variance weighted	9	0.0028	1.3210 (1.1004−1.5857)
	4−acetamidobutanoate levels	Inverse variance weighted	9	0.0298	0.8133 (0.6750−0.9800)
	Eicosapentaenoate (EPA; 20:5n3) levels	Inverse variance weighted	9	0.0261	0.8178 (0.6851−0.9763)
	Plasma free asparagine levels	Inverse variance weighted	9	0.0158	1.2577 (1.0441−1.5149)
	Pentadecanoate (15:0) levels	Inverse variance weighted	9	0.0273	0.8190 (0.6860−0.9779)
	X−13007 levels	Inverse variance weighted	9	0.0047	1.3575 (1.0984−1.6776)
	X−16087 levels	Inverse variance weighted	9	0.0226	0.7932 (0.6499−0.9680)
	X−23593 levels	Inverse variance weighted	9	0.0183	0.8074 (0.6759−0.9645)
	X−23659 levels	Inverse variance weighted	9	0.0323	0.8286 (0.6975−0.9842)
	N2−acetyl,N6,N6−dimethyllysine levels	Inverse variance weighted	9	0.0276	1.2345 (1.0235−1.4888)
	N2−acetyl,N6−methyllysine levels	Inverse variance weighted	9	0.0411	1.2147 (1.0079−1.4638)
	X−12798 levels	Inverse variance weighted	9	0.0288	1.2291 (1.0216−1.4787)
	Aspartate to asparagine ratio	Inverse variance weighted	9	0.0485	0.8063 (0.6511−0.9986)
	Glycine to pyridoxal ratio	Inverse variance weighted	9	0.0086	1.2763 (1.0639−1.5312)
	Phosphate to fructose ratio	Inverse variance weighted	9	0.0151	0.7965 (0.6630−0.9569)
	Glycine to phosphate ratio	Inverse variance weighted	9	0.0279	1.2474 (1.0243−1.5192)
	Phosphate to N−palmitoyl−sphingosine (d18:1 to 16:0) ratio	Inverse variance weighted	9	0.0267	0.7706 (0.6120−0.9703)
	Phenylalanine to phosphate ratio	Inverse variance weighted	9	0.0375	1.2085 (1.0110−1.4446)
	Phosphate to threonine ratio	Inverse variance weighted	9	0.0073	0.7811 (0.6521−0.9355)
	Phosphate to glutamine ratio	Inverse variance weighted	9	0.0053	0.7506 (0.6136−0.9182)
	Phosphate to serine ratio	Inverse variance weighted	9	0.0371	0.7716 (0.6048−0.9846)
	phosphate to asparagine ratio	Inverse variance weighted	9	<0.001	0.6891 (0.5532−0.8585)
	Cysteinylglycine to taurine ratio	Inverse variance weighted	9	0.0132	0.7979 (0.6675−0.9539)
	Glucose to fructose ratio	Inverse variance weighted	9	0.0366	0.8234 (0.6849−0.9898)
	N−palmitoyl−sphingosine (d18:1 to 16:0) to N−stearoyl−sphingosine (d18:1 to 18:0) ratidnverse variance weighted		9	0.0060	1.2977 (1.0777−1.5626)
	Leucine to N−palmitoyl−sphingosine (d18:1 to 16:0) ratio	Inverse variance weighted	9	0.0411	0.8315 (0.6965−0.9925)
family.Veillonellaceae.id.2172	Carnitine levels	Inverse variance weighted	20	0.0213	0.8388 (0.7221−0.9742)
	1−myristoyl−2−palmitoyl−gpc (14:0/16:0) levels	Inverse variance weighted	20	0.0205	1.1418 (1.0207−1.2774)
	Propionylcarnitine (c3) levels	Inverse variance weighted	20	0.0199	0.8762 (0.7839−0.9793)
	4−ethylphenylsulfate levels	Inverse variance weighted	20	0.0075	1.1670 (1.0421−1.3068)
	1−palmitoyl−2−linoleoyl−GPE (16:0/18:2) levels	Inverse variance weighted	20	0.0447	1.1223 (1.0027−1.2561)
	Eicosanedioate (C20−DC) levels	Inverse variance weighted	20	0.0423	1.1245 (1.0041−1.2593)
	Docosadioate (C22−DC) levels	Inverse variance weighted	20	0.0158	1.1499 (1.0266−1.2881)
	1H−indole−7−acetic acid levels	Inverse variance weighted	20	0.0417	1.1624 (1.0057−1.3434)
	Sphingomyelin (d18:2/14:0, d18:1/14:1) levels	Inverse variance weighted	20	0.0224	1.1136 (1.0153−1.2213)
	4−hydroxychlorothalonil levels	Inverse variance weighted	20	0.0218	1.1432 (1.0197−1.2817)
	Tricosanoyl sphingomyelin (d18:1/23:0) levels	Inverse variance weighted	20	0.0292	1.1230 (1.0118−1.2465)
	1−palmitoyl−2−arachidonoyl−GPI (16:0/20:4) levels	Inverse variance weighted	20	0.0376	1.1264 (1.0068−1.2601)
	1−stearoyl−2−linoleoyl−GPI (18:0/18:2) levels	Inverse variance weighted	20	0.0352	1.1243 (1.0082−1.2539)
	1−palmitoyl−2−oleoyl−GPI (16:0/18:1) levels	Inverse variance weighted	20	0.0042	1.1787 (1.0531−1.3192)
	1−oleoyl−2−docosahexaenoyl−GPC (18:1/22:6) levels	Inverse variance weighted	20	0.0455	0.8848 (0.7849−0.9976)
	1−palmitoleoyl−2−linolenoyl−GPC (16:1/18:3) levels	Inverse variance weighted	20	0.0220	1.1380 (1.0189−1.2710)
	5−dodecenoylcarnitine (C12:1) levels	Inverse variance weighted	20	0.0281	1.1318 (1.0134−1.2640)
	Hexadecenedioate (C16:1−DC) levels	Inverse variance weighted	20	0.0206	1.1410 (1.0204−1.2757)
	Sphingomyelin (d17:1/14:0, d16:1/15:0) levels	Inverse variance weighted	20	0.0425	1.1123 (1.0036−1.2328)
	3,5−dichloro−2,6−dihydroxybenzoic acid levels	Inverse variance weighted	20	0.0322	1.1294 (1.0104−1.2624)
	Metabolonic lactone sulfate levels	Inverse variance weighted	20	0.0447	1.1220 (1.0027−1.2555)
	1−palmitoyl−2−linoleoyl−GPI (16:0/18:2) levels	Inverse variance weighted	20	0.0220	1.1419 (1.0193−1.2792)
	N6,n6,n6−trimethyllysine levels	Inverse variance weighted	20	0.0164	1.1496 (1.0258−1.2883)
	Cholesterol levels	Inverse variance weighted	20	0.0443	1.1199 (1.0029−1.2505)
	Cystine levels	Inverse variance weighted	20	0.0048	1.1764 (1.0509−1.3170)
	Orotate levels	Inverse variance weighted	20	0.0455	1.1359 (1.0025−1.2870)
	Pyridoxal levels	Inverse variance weighted	20	0.0307	0.8814 (0.7861−0.9883)
	X−23659 levels	Inverse variance weighted	20	0.0264	0.8869 (0.7978−0.9860)
	X−23997 levels	Inverse variance weighted	20	0.0190	1.1466 (1.0228−1.2854)
	X−24456 levels	Inverse variance weighted	20	0.0207	0.8607 (0.7580−0.9773)
	X−25957 levels	Inverse variance weighted	20	0.0367	0.8799 (0.7804−0.9921)
	Glycine to pyridoxal ratio	Inverse variance weighted	20	0.0106	1.1572 (1.0346−1.2944)
	Spermidine to histidine ratio	Inverse variance weighted	20	0.0334	0.8782 (0.7791−0.9898)
	Spermidine to pyruvate ratio	Inverse variance weighted	20	0.0150	0.8608 (0.7628−0.9713)
	Cysteinylglycine to taurine ratio	Inverse variance weighted	20	0.0456	1.1187 (1.0022−1.2487)
	2'−deoxyuridine to cytidine ratio	Inverse variance weighted	20	0.0498	1.1236 (1.0001−1.2623)
	Glutamate to pyruvate ratio	Inverse variance weighted	20	0.0263	0.8840 (0.7929−0.9856)
	Proline to glutamate ratio	Inverse variance weighted	20	0.0321	1.1286 (1.0104−1.2606)
family.Pasteurellaceae.id.3689	Glycerol 3−phosphate levels	Inverse variance weighted	19	0.0226	0.8985 (0.8194−0.9851)
	1−stearoyl−2−oleoyl−GPS (18:0/18:1) levels	Inverse variance weighted	19	0.0055	1.1550 (1.0433−1.2787)
	Maleate levels	Inverse variance weighted	19	0.0155	1.1197 (1.0217−1.2270)
	Erythritol levels in elite athletes	Inverse variance weighted	19	0.0480	0.9136 (0.8354−0.9992)
	1−oleoylglycerol (18:1) levels	Inverse variance weighted	19	0.0303	0.9034 (0.8240−0.9904)
	Taurolithocholate 3−sulfate levels	Inverse variance weighted	19	0.0145	1.1306 (1.0246−1.2474)
	Glycoursodeoxycholate levels	Inverse variance weighted	19	0.0488	0.9121 (0.8324−0.9995)
	N−methyltaurine levels	Inverse variance weighted	19	0.0496	0.8932 (0.7980−0.9998)
	1−palmitoyl−GPG (16:0) levels	Inverse variance weighted	19	0.0370	0.9047 (0.8234−0.9940)
	3−hydroxypyridine sulfate levels	Inverse variance weighted	19	0.0372	1.1009 (1.0057−1.2052)
	Sphingomyelin (d18:1/20:2, d18:2/20:1, d16:1/22:2) levels	Inverse variance weighted	19	0.0248	1.1008 (1.0122−1.1971)
	Sphingomyelin (d18:1/20:1, d18:2/20:0) levels	Inverse variance weighted	19	0.0088	1.1185 (1.0286−1.2162)
	1,2,3−benzenetriol sulfate (2) levels	Inverse variance weighted	19	0.0366	1.1075 (1.0064−1.2188)
	1−palmitoleoylglycerol (16:1) levels	Inverse variance weighted	19	<0.001	0.8277 (0.7459−0.9185)
	1−palmitoyl−2−palmitoleoyl−gpc (16:0/16:1) levels	Inverse variance weighted	19	0.0437	0.9110 (0.8322−0.9974)
	Catechol glucuronide levels	Inverse variance weighted	19	0.0465	1.1564 (1.0022−1.3342)
	(N(1) + N(8))−acetylspermidine levels	Inverse variance weighted	19	0.0037	1.1384 (1.0431−1.2424)
	2−furoylcarnitine levels	Inverse variance weighted	19	0.0052	1.1590 (1.0451−1.2853)
	Ascorbic acid 3−sulfate levels	Inverse variance weighted	19	0.0293	0.9028 (0.8235−0.9898)
	4−ethylcatechol sulfate levels	Inverse variance weighted	19	0.0081	1.1310 (1.0325−1.2389)
	3−hydroxy−2−methylpyridine sulfate levels	Inverse variance weighted	19	0.0041	1.1514 (1.0456−1.2678)
	5−hydroxy−2−methylpyridine sulfate levels	Inverse variance weighted	19	0.0472	1.1058 (1.0012−1.2212)
	3−ethylcatechol sulfate (1) levels	Inverse variance weighted	19	0.0174	1.1273 (1.0213−1.2444)
	Beta−hydroxyisovalerate levels	Inverse variance weighted	19	0.0437	0.9126 (0.8349−0.9974)
	3−phosphoglycerate levels	Inverse variance weighted	19	0.0389	1.1018 (1.0049−1.2081)
	Stearoyl sphingomyelin (d18:1/18:0) levels	Inverse variance weighted	19	0.0165	1.1151 (1.0201−1.2190)
	Retinol (Vitamin A) levels	Inverse variance weighted	19	0.0138	0.8925 (0.8152−0.9771)
	X−11850 levels	Inverse variance weighted	19	0.0236	1.1278 (1.0162−1.2516)
	X−12730 levels	Inverse variance weighted	19	0.0034	1.1859 (1.0580−1.3292)
	X−13007 levels	Inverse variance weighted	19	0.0442	0.8943 (0.8022−0.9971)
	X−21821 levels	Inverse variance weighted	19	0.0162	0.8921 (0.8127−0.9791)
	X−23655 levels	Inverse variance weighted	19	0.0072	1.1489 (1.0383−1.2712)
	2'−o−methylcytidine levels	Inverse variance weighted	19	0.0076	1.1577 (1.0397−1.2891)
	N−acetylputrescine to (N(1) + N(8))−acetylspermidine ratio	Inverse variance weighted	19	0.0134	0.8918 (0.8143−0.9766)
	Aspartate to citrulline ratio	Inverse variance weighted	19	0.0128	1.1201 (1.0244−1.2247)
	Phosphate to phosphoethanolamine ratio	Inverse variance weighted	19	0.0213	0.8885 (0.8033−0.9826)
	3−phosphoglycerate to glycerate ratio	Inverse variance weighted	19	0.0163	1.1190 (1.0209−1.2266)
	Adenosine 5'−monophosphate (AMP) to histidine ratio	Inverse variance weighted	19	0.0456	1.0972 (1.0018−1.2018)
	Adenosine 5'−monophosphate (AMP) to isoleucine ratio	Inverse variance weighted	19	0.0225	1.1106 (1.0149−1.2153)
	Taurine to cysteine ratio	Inverse variance weighted	19	0.0482	1.1039 (1.0008−1.2177)
	Hypotaurine to cysteine ratio	Inverse variance weighted	19	0.0488	1.1024 (1.0005−1.2148)
	Phosphate to glycerol ratio	Inverse variance weighted	19	0.0200	0.9053 (0.8325−0.9844)
	Adenosine 5'−monophosphate (AMP) to leucine ratio	Inverse variance weighted	19	0.0272	1.1061 (1.0114−1.2097)
	3−methyl−2−oxovalerate to 3−methyl−2−oxobutyrate ratio	Inverse variance weighted	19	0.0165	0.8958 (0.8187−0.9801)

Figure 4。 Forest maps showed a causal relationship between gut flora and metabolites significantly associated with cervical cancer. The analytical method was IVW.

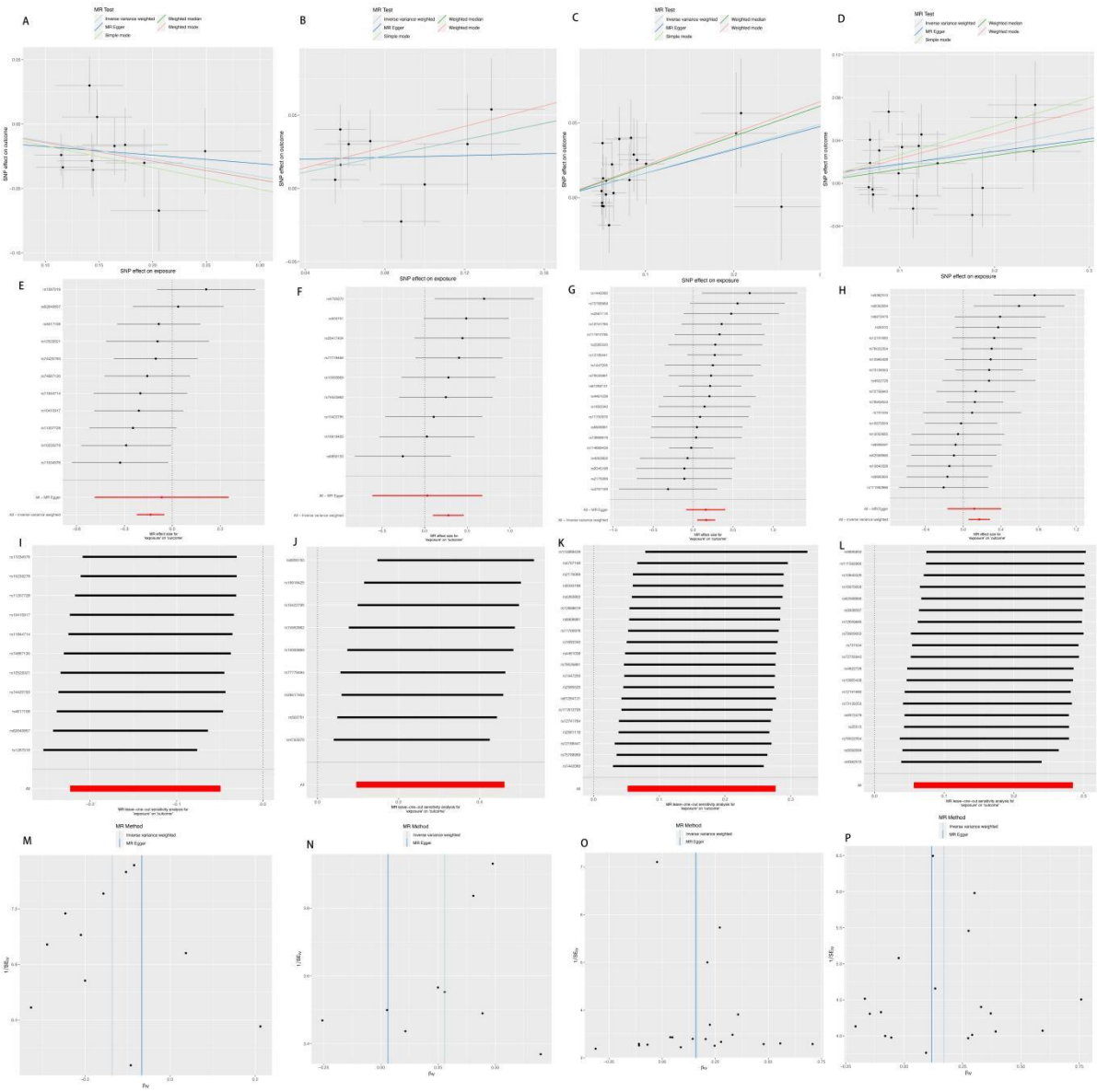


Figure 5. The metabolites with the most significant relationships with the four bacterial groups were selected as representatives. (**A**–**D**): Scatter plots of four types of gut microbiota strongly associated with cervical cancer and metabolite risk. (**E**–**H**): Forest map of the four types of gut flora strongly associated with cervical cancer and metabolite risk. (**I**–**L**): Four types of gut microbiota closely associated with cervical cancer and metabolite risk were mapped using the "leave-one-out" method. (**M**–**P**): Funnel plot for sensitivity analysis of metabolite risk associated with four types of gut microbiota strongly associated with cervical cancer.

4. Discussion

Research indicates that blood metabolites and GM are crucial for the development of cervical cancer. Novel methods have been developed to observe these microbiota and alterations in metabolites and metabolic pathways to evaluate tumor advancement and forecast prognosis. Future studies should investigate the impact of microbiome-related metabolites on cervical cancer and determine whether closely linked microbiome-related interventions can enhance the efficacy of preclinical models in terms of treatment response.

This study utilized two Mendelian approaches to explore the causal link between GM and cervical cancer, as well as the causal connection between metabolites linked to GM and cervical cancer. Our research addresses the question of whether metabolites associated with the gut microbiome play a role in the diagnosis and treatment of cervical cancer.

The cervical and vaginal microbiomes collaborate with the nearby microenvironment to maintain tissue equilibrium. The deep and detailed interplay between vaginal tract epithelial cells and the neighboring stroma plays a vital role. Irregular ecological stability can result in an imbalance, triggering a range of pathological responses, including the decline of epithelial walls, unusual cellular growth, instability in the genome, onset of

new angiogenesis, persistent inflammation, and disturbance in metabolic activities. The foremost in this list are cancer types and various illnesses linked to infections of the reproductive system. An imbalance in the vaginal ecosystem may result from elevated levels of proinflammatory cytokines and chemokines linked to a greater variety of pathogenic microorganisms, leading to increased immune cell recruitment and intensification of the inflammatory reaction, potentially promoting cancer development [22]. Multiple studies have suggested a potential connection between cervical cancer and the GM, investigating the presence of a direct causal relationship. Intestinal flora could be a novel focus for the prevention, treatment, and management of cervical cancer in the long run [4]. We used data from FinnGen and MiBioGen in our MR analysis and identified a definite causative relationship between four bacterial taxa (*Pasteurellaceae*, *Veillonellaceae*, *Odoribacter*, and *Bacillales*) and cervical cancer.

Furthermore, a few of these bacteria have been discovered, and more research is needed on their harmful mechanisms. According to our research, specific gut microorganisms may play a role in the pathogenesis of cervical cancer and may be employed in diagnostic and therapeutic analyses. This may assist in identifying women at a higher risk of developing cervical cancer and facilitate early detection of the disease. Pasteurella multocida toxin (PMT) is a potent mitogen that impedes apoptosis and is a potential carcinogen. PMT alters and activates three of the four heterotrimeric G-protein families, all of which may play a role in carcinogenesis. They have a close relationship with the invasion, growth, and metastasis of cancer cells. PMT activates genes associated with primordial cancer. They are linked to the proliferation of cancer cells, and tumor stem cells may play a role in this regulatory process. Known to be a highly effective mitotic medium that can cause resting cells to reenter the cell cycle, undergo the S phase, and undergo mitosis. This action inhibits and triggers the proliferation of multiple fused resting cells. This study provides detailed evidence that these bacteria contribute to the development of cervical cancer, consistent with the findings of a previous study [23]. Regarding the incidence of cervical cancer, *Veillonellaceae*, *Odoribacter*, and *Bacillales* had opposite effects. Research has indicated that the *Veillonellaceae* family may have a pathogenic effect by interfering with specific extraskeletal processes linked to vitamin D, primarily immune system activities [24]. Studies have indicated that the risk of hepatocellular carcinoma (HCC) and cirrhosis may decrease [25]. This study found that *Bacillales*, *Odoribacter*, and *Veillonellaceae* could lower the incidence of cervical cancer. Although there has not been sufficient academic support for research on how these bacteria affect cervical cancer, our MR study can be verified from a genetics perspective to avoid these issues, obtain strong evidence, maximize the exclusion of potential interfering factors, and draw more precise conclusions.

The field of metabolic control in cancer has progressively attracted public attention, paralleling the rising fame of metabolomics. Metabolomics is an emerging field that has significantly advanced in biotechnology, farming, and healthcare. Exploring metabolomics provides a fresh perspective for preventing and diagnosing diseases and helps us intuitively identify alterations in the body's microenvironment. Understanding how metabolites contribute to the development and advancement of diseases is profound. Numerous blood metabolites were found to have a significant connection to cervical cancer risk in a MR study focused on the effects of these metabolites on mouth cancer.

In combination with metabolomics and genomic data, our systematic MR study provides clues to aid in the search for potential biomarkers of cervical cancer. Of the 1400 blood metabolites, our data revealed cause-and-effect correlations between 43 metabolites and the *Odoribacter* group, of which 20 metabolites were positively and 23 were negatively correlated. Of the 38 metabolites, 11 were negatively correlated, and 27 were positively correlated with the abundance of *Veillonellaceae*. A total of 44 metabolites were causally associated with *Pasteurellaceae* flora, of which 27 were positively, and 17 were negatively associated. In addition, 21 metabolites were substantially linked to *Bacillales*; of these, 10 metabolites were negatively correlated, and 11 were positively correlated with *Bacillales*. Seven of the 146 metabolites were unidentified. This study employed existing GWAS data with MR methods to further explore the causal connection between gut flora and blood metabolites that are highly related to cervical cancer. We performed an in-depth sensitivity analysis to uncover the many factors affecting the results, thereby improving confidence in our findings.

Numerous studies have been conducted on the compounds most strongly linked to the *Odoribacter* microbiome, particularly their various functions in cancer treatment. There was a strong negative correlation between the proline and glutamate ratios. While the conversion link between glutamine and proline has been extensively studied in the past, recent research has revealed that pro-oncogenes, cellular myeloma oncogenes, enhanced glutamine usage, and the glutamate pathway can all generate proline. Furthermore, collagen that is high in proline can be a good site for storing proline. The first stage in the synthesis of glutamine is the activation of the gamma carbon of glutamate by ATP, which results in the production of G-glutamylphosphate. P5C synthase is the first enzyme to catalyze the synthesis of proline from glutamate and initiates this step [26].

This study found a good correlation between campesterol and the suppression of *Odoribacter* microflora in cervical cancer, while other researchers have only shown that campesterol has anticancer properties. The primary function of campesterol in people's diets is to reduce the absorption of cholesterol in the stomach, thereby easing the accumulation of low-density lipoprotein in the blood and heart-related issues. Studies have indicated that consumption of meals rich in plant sterols can reduce the incidence of cancer by 20%. Sterol biosynthesis regulates the production of phytosterols, which can impact the growth of hormone-dependent endocrine cancers by improving the immune system's detection of cancer and generating antitumor effects. Furthermore, plant sterols can directly prevent tumor growth by delaying cell cycle progression and triggering apoptosis [27].

The study details taurine, glutamine degradator, and additional metabolic elements inversely related to *Bacillales*. Studies have focused on taurine's possible role (SLC6A6 transporter) in cancer progression and explored the therapeutic advantages of its inhibitors. Research indicates a potential link between excessive expression of this protein and colon or breast cancer. Ongoing clinical tests for a ligand involved in the SLC6A6 transporter are currently in their initial stages. Drugs targeting cancer may find a biological site in the SLC6A6 transporter [28]. Glutamine is known for its critical role in nutrition and is predominantly used to repair tissue damage after radiation and chemotherapy. The Food and Drug Administration has approved an oral form of glutamine for use as an adjuvant to cancer treatment. There is evidence that oral glutamine can successfully reduce discomfort in patients with cancer and enhance and/or preserve their quality of life. These advantages also reduce the possibility of mucous membrane disorders, such as pharyngitis, stomatitis, and mucositis. Topical or oral administration of this amino acid seems to be the best way to support mucosal healing during and after cancer therapy [29]. *Veillonellaceae* and carnitine have an inverse relationship, and it is believed that the carnitine system (CS) can effectively stimulate the metabolic response in cancer cells. Essentially, every element of this mechanism participates in the two-way movement of acyl groups from the cytosol to the mitochondria, which is crucial for regulating the metabolic transformation of glucose and fatty acids. Additionally, it maintains strong connections with various biological functions, such as tumor spread, programmed cell death, diversification, and cellular growth. Consequently, managing CS is crucial for epigenetic and enzymatic functions, opening novel treatment pathways for cancer prevention and control in humans [30].

Orotate, a metabolite closely linked to *Veillonellaceae*, has been of great value and relevance, with its diverse effects on cancer noted in past research. Orotate-rich goat milk could protect against type 2 diabetes, Alzheimer disease, and cancer [31]. Retinol, also known as vitamin A, is associated with the microbial community of *Pasteurellaceae*. The combination of retinol and its derivatives influences cellular growth, differentiation, and death. Their significant physiological functions extend to several biological processes. Various scientific fields have recently focused on the role of retinol-associated signaling (CRBP-1) in cancer progression. Reductions in CRBP-1 are associated with a higher probability of developing cancerous features in breast, ovarian, and nasopharyngeal cancers. Reactivating CRBP-1 increases the responsiveness to retinol and decreases the incidence of ovarian cancer [32].

These findings have far-reaching consequences for public health and therapeutic practices. Our findings underscore the significance of gut microbial communities and metabolites in cervical cancer development, offering novel insights for the development of prevention and treatment strategies based on microbial and metabolite regulation. Treatment for cervical cancer must consider genetic variations because of the connection between these factors and the disease. Clinical experts are now focusing on metabolites as a valuable early diagnostic tool due to data indicating an increase in the incidence of cervical cancer. This study is the first to conduct an extensive, systematic MR analysis of the GM metabolites closely linked to cervical cancer. It is essential to evaluate their correlation with cervical cancer risk. Significant alterations were also observed in certain groups of patients with cancer and healthy individuals. Our team undertook an in-depth analysis of different key intestinal flora groups to discern their variations in serum metabolites. Our extensive efforts in this field aim to contribute modestly to the creation and advancement of novel diagnostic and treatment methods. Our MR study utilized a substantial quantity of GWAS data for research purposes. During this procedure, novel techniques and tactics are employed, along with sensitivity analysis, to lower the rate of error detection and diminish the incidence of false positives. By employing a comparably extensive sample size, we can efficiently eliminate nonessential interfering elements, thus improving the precision of the statistics and leading to more precise statistical deductions.

Throughout this research, it is essential to acknowledge the existence of multiple limitations. Furthermore, the lack of sufficient proof linking cancer occurrence to age means that we cannot dismiss the potential impact of factors such as sex, ethnicity, and socioeconomic status on human health. The GWAS data, mainly obtained from Europe, especially from white Europeans, could have limited the scope of our findings across diverse ethnic groups. Consequently, the breadth of ethnicities and regions is not reflected in our research. Our investigation also delved into the possible risks linked to the illness, examining different factors that might influence these evaluations. In

the supplementary findings, seven metabolites were categorized as either undefined or partially characterized. Numerous recognized biomarkers play a role in every aspect of clinical decision-making, including cancer diagnosis, prognosis evaluation, and treatment. Clinical attention may be drawn to these possible risk factors; however, the impact of plasma metabolite concentrations linked to cervical cancer on the diagnosis and prognosis of patients with cervical cancer remains unclear. Therefore, further research is urgently needed to identify more effective associations between serum metabolites and cervical cancer.

5. Conclusions

This study conclusively demonstrated the role of gut microbiota-related blood metabolites in cervical cancer, underscoring the risks or protective effects of various metabolites. These findings may be instrumental in developing novel treatments and approaches for cervical cancer. It is concluded that metabolite changes caused by intestinal microecological imbalances can result in cancer, based on evidence from GWAS and cervical cancer. Despite the significant potential of these findings, further research is required to confirm and optimize these ideas. Consequently, we will examine this topic thoroughly and broadly. This study provides an essential step for the clinic, which we will learn more about in the future.

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Author Contributions

The conception and design of the study, acquisition of data, or analysis and interpretation of data: C.X., Y.X. Drafting the article or revising it critically for important intellectual content: C.X. Final approval of the version to be submitted: G.W. All authors have read and agreed to the published version of the manuscript.

Institutional Review Board Statement

This study employed publicly available data from the GWAS and FinnGen Database, which are de-identified and do not contain any personal information. Consequently, specific ethical approval and informed consent were not required for this research. All data were accessed and analyzed in strict accordance with the terms of use of the respective databases.

Data Availability Statement

The datasets generated and/or analyzed during the current study are publicly available.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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