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# The correlation between vaginal pathogens and high-risk human papilloma virus infection: a meta-analysis of case-control studies

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**Background:** Systematic study on the relationship between vaginal microbiota and high-risk human papillomavirus infection (HR-HPV) is limited. Hence, the aim of this study is to investigate the correlation between vaginal microbiota and HR-HPV infection through a meta-analysis of case-control studies.

**Methods:** Chinese Journal Full-text database, Wanfang database, PubMed database, VIP Chinese Science and Technology Journal database, Web of Science, ScienceDirect, ProQuest, JSTOR, Wiley, and IEEE Xplore were synthetically searched for studies about the correlation between vaginal microbiota and HR-HPV infection. Revman 5.3 software was used to assess the relationship between vaginal microbiota and HPV infection through meta-analysis. Finally, forest map was used to calculate the results and funnel plot was applied to test the publication bias.

**Results:** Fourteen independent studies were admitted in this study, containing a total of 21, 446 women in gynecological outpatients. Compared with HR-HPV negative group, the prevalence of bacterial vaginosis (BV) [odds ratio (OR)=2.45, 95% confidence intervals (CI): 1.83-3.27,  $P<0.00001$ ], *Ureaplasma urealyticum* (UU) (OR=1.38, 95% CI: 1.23-1.54,  $P<0.00001$ ), and *Chlamydia trachomatis* (CT) (OR=3.53, 95% CI: 2.82-4.41,  $P<0.00001$ ) increased in HR-HPV positive group through meta-analysis, while, there was no significant difference in the prevalence of *trichomonal vaginitis* (TV) (OR=1.69, 95% CI: 0.97-2.96,  $P=0.06$ ) and *vulvovaginal candidiasis* (VVC) (OR=0.91, 95% CI: 0.54-1.51,  $P=0.71$ ).

**Conclusions:** Vaginal pathogens are closely related to HR-HPV infection. When BV, UU, and CT are abnormal, the risk of HR-HPV infection is increased.

#### KEYWORDS

HR-HPV, vaginal microbiota, vaginal pathogens, bacterial vaginosis, vaginal infection, meta-analysis

## Introduction

Human papillomavirus (HPV) are a large class of double-stranded DNA viruses that can infect squamous epithelial cells of the human skin layer and mucous membrane (1, 2). On the basis of different carcinogenic risks, HPV types are classified as low-risk (LR-HPV) and high-risk (HR-HPV) (3–5). Persistent infection with HR-HPV has been strongly associated with the development of cervical cancer (6–8). Cervical cancer is the fourth most common cancer among women worldwide, imposing a persistent burden on women's health (9–11). The number of deaths due to cervical cancer is up to 266,000 globally every year, 85% of which are citizens of developing countries (12). It has been reported that continuous infection with HR-HPV for 8 to 24 months can lead to cervical intraepithelial neoplasia, which may progress to cervical cancer after 8 to 12 years (13). In line with the study, most cervical cancers are related to persistent infection with HR-HPV in the cervical mucosa (14–16). Despite the advances in the treatment of cervical cancer, the long-term prognosis of patients with metastatic, persistent, and recurrent cervical cancer still remains unsatisfactory (17, 18). Moreover, the exact risk factors and mechanisms of HPV infection and persistent infection remain unclear. In addition, it is a long process from HR-HPV infection to cervical intraepithelial neoplasia with vaginal microbiota changes (19).

The past decade has revealed a rapid advancement in our understanding of the interplay between vaginal microbiota and HPV infection. It has been reported that vaginal microbiota dysbiosis is associated with HPV infection and that vaginal microbiota dysbiosis contributes to HR-HPV persistent infection and cervical lesions (10, 19, 20). It has been reported that an imbalance of the vaginal microbiota may increase the risk of HPV infection. For example, enhanced diversity of vaginal microbiota combined with decreased relative abundance of *Lactobacillus* spp. is participated with HPV acquisition and persistence (21). At the same time, HPV infection may in turn further disrupt the balance of vaginal microbiota (22). Maintaining a suitable vaginal microbiota environment is crucial for preventing HPV infection and reducing the risk of persistent infection. However, the correlation between HPV infection and vaginal microbiota is still controversial, and there is a lack of sufficient evidence-based medical evidence and support from large-sample clinical data. Meta-analysis is a statistical method for systematic and comprehensive quantitative analysis of multiple existing and independent research results with the same research purpose (23).

Therefore, this study applied the meta-analysis to perform a statistical analysis of the published literature on the correlation between vaginal microbiota and HR-HPV infection, so as to provide theoretical guidance for the prevention and treatment of clinical HPV infection and cervical cancer.

## Methods

### Literature screening

We systematically searched for vaginal microbiota and HR-HPV infection in the Chinese Journal Full-text database, Wanfang database, PubMed database, VIP Chinese Science and Technology Journal database, Web Of Science, ScienceDirect, ProQuest, JSTOR, Wiley, and IEEE Xplore, without any language limitation. We also searched the reference in the original literature, combining subject words and free words.

The search terms were composed of the following themes: “HR-HPV,” “HPV,” “TAVR,” “high-risk human papilloma virus,” “human papilloma virus,” and so forth. We also searched the following themes: “vaginal microbiota,” “kysthitis,” “vaginal cleanliness,” “bacterial vaginosis,” “trichomonal vaginitis,” “vulvovaginal candidiasis,” “Pondus Hydrogenii,” and so forth. We adopted the search strategy of subject term + free term and adjusted the search strategy according to the database. The specific search strategy is [HR-HPV (Title/Abstract) OR HPV (Title/Abstract)] OR [high-risk human papilloma virus (Title/Abstract)] OR [human papilloma virus (Title/Abstract)] AND [vaginal microbiota (Title/Abstract)] OR [kysthitis (Title/Abstract)] OR [vaginal cleanliness (Title/Abstract)] OR [bacterial vaginosis (Title/Abstract)] OR [BV (Title/Abstract)] OR [trichomonal vaginitis (Title/Abstract)] OR [TV(Title/Abstract)] OR [vulvovaginal candidiasis (Title/Abstract)] OR [VVC(Title/Abstract)] OR [ureaplasma urealyticum (Title/Abstract)] OR [chlamydia trachomatis (Title/Abstract)].

### Inclusion and exclusion criteria

The following criteria were performed for the inclusion of eligible literature: (1) Published studies on the association between vaginal microbiota and HPV infection where Chinese

literature was published in core journals, (2) the study sample size was in accordance with the research standards and the statistical methods were reasonable, and (3) the research methods of all literatures were similar. (4) For replicated studies, one of them was used; (5) there was no languages variety. The following criteria were utilized for the exclusion of improper literature: (1) review articles, duplicate literature, and unpublished literature; (2) relevant specific data could not be obtained; and (3) the group was inconsistent with the inclusion criteria of this study design.

The design of the included study also should combine the following criteria: (1) the type of study was a case-control study. Patients in the case group had a definite diagnosis of HR-HPV positive, and patients in the control group had a definite diagnosis of HR-HPV negative. (2) HR-HPV included HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68 (24). (3) There was no restriction on the testing of HR-HPV, and it could include single-base extension, polymerase chain reaction (PCR)—reverse dot hybridization, hybrid capture-chemiluminescence method, enzyme-linked immunosorbent assay (ELISA), *in-situ* hybridization, matrix Assisted Laser Desorption Ionization Time-of-flight mass spectrometry (MALDI-TOFMS), and so on. (4) The research data encompassed the HPV-positive group, the HPV-negative group, bacterial vaginosis (BV), *trichomonal vaginitis* (TV), *vulvovaginal candidiasis* (VVC), *Ureaplasma urealyticum* (UU), and *Chlamydia trachomatis* (CT). (5) Diagnostic criteria for vaginal microbiota dysbiosis (25): the diagnostic methods for BV were rapid BV kit, gram staining smear, or Nugent (score  $\geq 7$ ). The diagnostic methods of VVC were fungal culture, gram staining smear showing false mycelia and spores, or smear microscopy. The TV diagnosis method was that trichomonas vaginalis was microscopically observed in 0.9% sodium chloride injection. For the UU susceptibility test, cervical secretions were cultured in the microbial chamber, and UU routine detection and UU susceptibility identification were carried out in strict accordance with the operating instructions of the kit. CT was detected by real-time fluorescent polymerase chain reaction (PCR), RNA real-time fluorescent nucleic acid isothermal amplification, transcription-mediated nucleic acid isothermal amplification enzyme-linked immunosorbent assay, direct immunofluorescence assay or rapid immunochromatographic assay.

## Screening method and quality evaluation of the study

Research screening steps: The literature was preliminarily screened based on the title and abstract of the research. Then, the literature was ultimately obtained by reading the full text and conducting further screening in strict accordance with the inclusion design. Quality evaluation methods: The Newcastle-Ottawa-Scale (NOS) scoring standard (including selection, comparability, and exposure) was utilized to independently assess the quality of the selected literature. The total score of NOS was 9

points, and the literature quality was regarded as high when the score was  $\geq 7$ . Quality control of literature screening: two researchers were responsible for formulating the search strategy, conducting literature retrieval, screening the literature, and evaluating the literature quality. In case of disagreement between the two, a third party would make the decision. Finally, the data included in the study would be collated and extracted. Data entry: The data of the included study were extracted by two researchers and collected into a pre-standardized data table. All data were revised by a third researcher to ensure data accuracy.

## Statistical analysis

The meta-analysis was performed by RevMan 5.3. The Z-test was applied to analyze the heterogeneity among the studies. When there was no heterogeneity among the studies ( $P > 0.1$  and  $I^2 < 50\%$ ), the fixed effects model (FEM) was utilized. When statistical heterogeneity existed between studies and the source of heterogeneity could not be eliminated, the random effects model (REM) was adopted. Sensitivity was analyzed by successive exclusion of individual studies and recalculation of their combined effect sizes.

## Results

### Literature screening situation

Ultimately, 88 works of English literatures were obtained. On the basis of the titles and abstracts of the literatures, duplicate literatures were further screened and eliminated, and a total of 30 literatures were selected. After reading the full text of the 30 literatures, 14 English literatures were finally included. A total of 21,446 women in gynecological outpatients underwent HPV and vaginal microbiota testing. The steps of the literature search are shown in Figure 1.

### Basic features of the 14 studies

The quality evaluation of the 14 included literatures (26–39) was all  $\geq 7$  points. The basic characteristics of the fourteen studies were shown in Table 1.

### The combined results of the study

The 14 studies included in this study were combined. The prevalence of BV, TV, UU, and CT in the HR-HPV-positive group was 19.34%, 3.57%, 7.5%, 49.3%, and 6.02%, respectively. The prevalence of BV, TV, VVC, UU, and CT in the HR-HPV-negative group was 10.58%, 1.75%, 4.29%, 40.3%, and 2.98%, respectively.

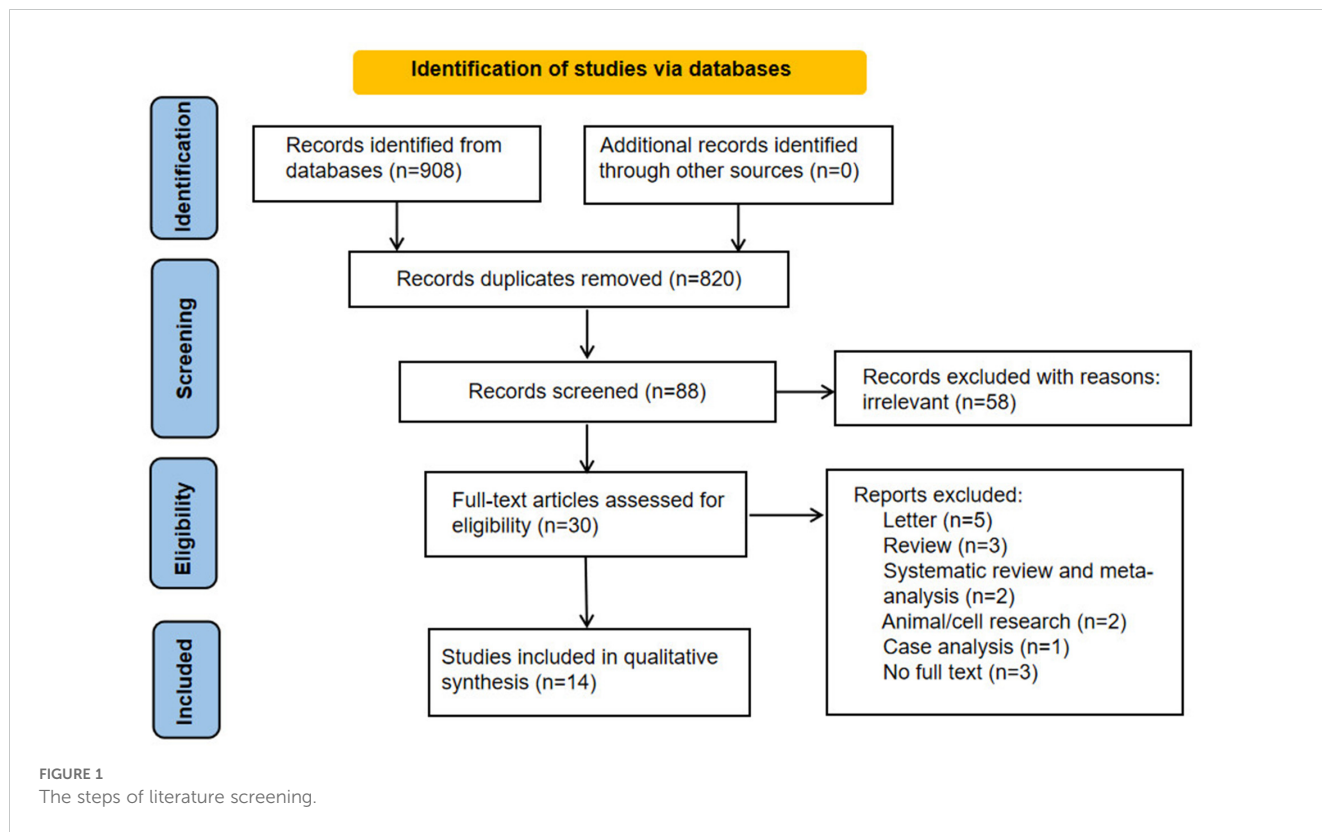


TABLE 1 Basic characteristics of 14 included studies.

The first author	Year	Object of study	Number of cases	BV	TV	VVC	UU	CT	Quality evaluation (point)
Lv PP (34)	2019	HR-HPV <sup>+</sup>	254	52	8	NR	39	40	8
		HR-HPV <sup>-</sup>	572	40	1	NR	49	23	
Zhang D (38)	2017	HR-HPV <sup>+</sup>	76	18	3	2	29	4	8
		HR-HPV <sup>-</sup>	877	82	13	33	309	17	
Liu JH (31)	2016	HR-HPV <sup>+</sup>	1452	94	55	NR	845	78	7
		HR-HPV <sup>-</sup>	2838	66	93	NR	1460	48	
Xu CY (37)	2012	HR-HPV <sup>+</sup>	622	107	9	7	NR	NR	8
		HR-HPV <sup>-</sup>	5590	446	53	98	NR	NR	
Verteramo R (36)	2009	HR-HPV <sup>+</sup>	266	23	3	32	96	37	8
		HR-HPV <sup>-</sup>	591	31	7	80	147	32	
da Silva CS (27)	2004	HR-HPV <sup>+</sup>	26	14	NR	5	NR	9	8
		HR-HPV <sup>-</sup>	26	4	NR	6	NR	2	
Murta EF (35)	2000	HR-HPV <sup>+</sup>	390	NR	7	47	NR	NR	8
		HR-HPV <sup>-</sup>	396	NR	9	88	NR	NR	
Lu H (33)	2015	HR-HPV <sup>+</sup>	1738	270	NR	NR	NR	43	7
		HR-HPV <sup>-</sup>	1764	54	NR	NR	NR	5	
Huang J (29)	2023	HR-HPV <sup>+</sup>	416	147	44	34	NR	NR	7
		HR-HPV <sup>-</sup>	911	190	31	32	NR	NR	

(Continued)

TABLE 1 Continued

The first author	Year	Object of study	Number of cases	BV	TV	VVC	UU	CT	Quality evaluation (point)
Lin WY (30)	2022	HR-HPV <sup>+</sup>	138	68	0	18	NR	NR	8
		HR-HPV <sup>-</sup>	310	120	4	36	NR	NR	
Bommana S (26)	2024	HR-HPV <sup>+</sup>	41	NR	NR	NR	NR	21	7
		HR-HPV <sup>-</sup>	217	NR	NR	NR	NR	78	
Dong BH (28)	2022	HR-HPV <sup>+</sup>	270	106	NR	NR	NR	NR	7
		HR-HPV <sup>-</sup>	550	200	NR	NR	NR	NR	
Liu YJ (32)	2023	HR-HPV <sup>+</sup>	271	163	NR	NR	NR	NR	7
		HR-HPV <sup>-</sup>	744	330	NR	NR	NR	NR	
Zhang Z (39)	2021	HR-HPV <sup>+</sup>	80	23	NR	NR	NR	NR	8
		HR-HPV <sup>-</sup>	20	2	NR	NR	NR	NR	

The symbol "+" means positive and the symbol "-" means negative. BV, bacterial vaginosis; TV, trichomonal vaginitis; VVC, vulvovaginal candidiasis; UU, *Ureaplasma urealyticum*; CT, *Chlamydia trachomatis*; NR, none reported.

### Correlation between vaginal microecosystem and HR-HPV infection

#### BV and HR-HPV

The combined OR of BV and HR-HPV infection was 2.45 (95% CI: 1.83–3.27). The HR-HPV-positive group had a higher prevalence of BV, the difference being statistically significant ( $Z = 6.07, P < 0.00001$ ), as shown in Figure 2A.

#### TV and HR-HPV

The combined OR of TV and HR-HPV infection was 1.69 (95% CI: 0.97–2.96). There was no significant difference in TV prevalence between the HR-HPV positive and the negative ( $Z = 1.86, P = 0.06$ ), as shown in Figure 2B.

#### VVC and HR-HPV

The combined OR of VVC and HR-HPV infection was 0.91 (95% CI: 0.54–1.51). There was no significant difference in VVC prevalence between the HR-HPV positive and the negative ( $Z = 0.37, P = 0.71$ ), as shown in Figure 3A.

#### UU and HR-HPV

The combined OR of UU and HR-HPV infection was 1.38 (95% CI: 1.23–1.54). The HR-HPV-positive group had a higher prevalence of UU, the difference being statistically significant ( $Z = 5.63, P < 0.00001$ ), as shown in Figure 3B.

#### CT and HR-HPV

The combined OR of CT and HR-HPV infection was 3.53 (95% CI: 2.82–4.41). The HR-HPV-positive group had a higher prevalence of CT ( $Z = 11.06, P < 0.00001$ ), as shown in Figure 3C.

### Bias risk assessment

The funnel plot was shown in Figure 4, which reveals that some studies intersect or are outside the funnel slope, indicating that

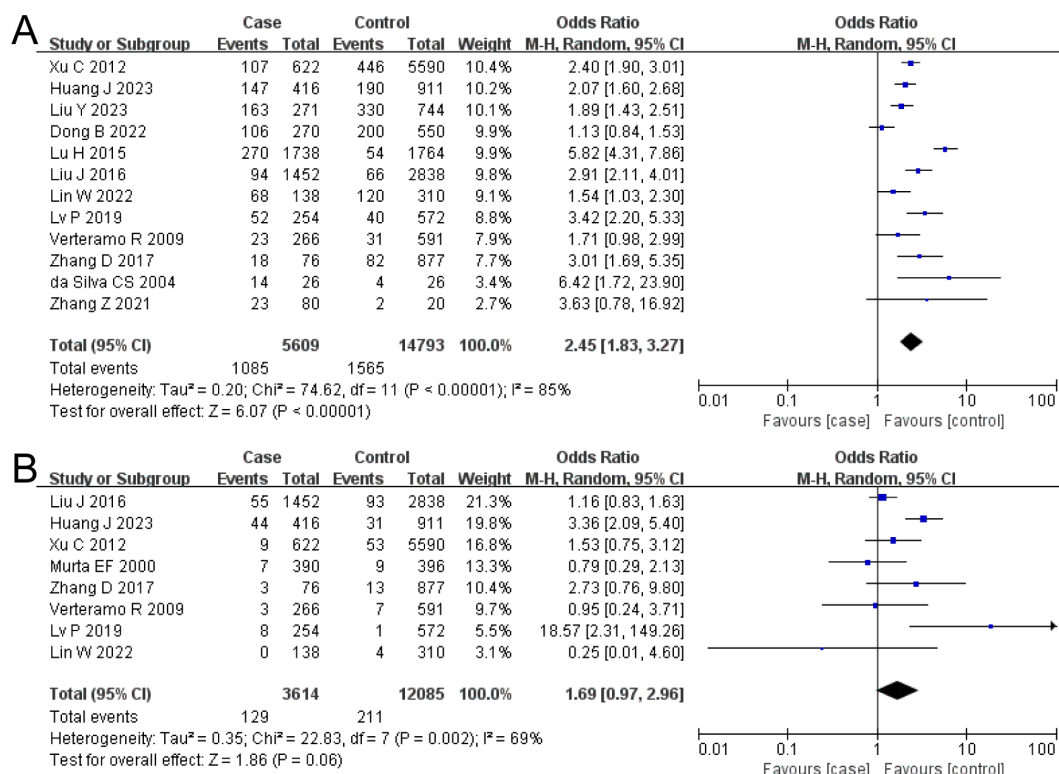
these studies may have the risk of bias, which might be related to the small number of studies included in this study.

### Discussion

Once HPV infection, it escapes or avoids host immune response (40, 41). During epithelial cell differentiation, HPV infection results in cell growth and increases virus-mediated immune escape ability (42, 43). On the other hand, it can cause specific interference with innate and adaptive immunity through its own concealment, thereby causing persistent infection in the host (7). Previous studies have confirmed that persistent HR-HPV infection can lead to the development of cervical cancer (7, 44). Compared to normal vaginal flora, Bacteroidetes and Fusobacteria increased in HR-HPV-infected group (45). Moreover, it has been reported that BV, TV, and VVC were significantly correlated with HR-HPV infection (6). For instance, women with persistent HR-HPV had a prevalence of BV of 11%, while women who cleared their HR-HPV only had 5% (46). However, not all findings support this correlation. Therefore, it is necessary to systematically evaluate the correlation between vaginal microbiota and HR-HPV infection using evidence-based medicine methods.

Our meta-analysis results indicated that the prevalence of BV, UU, and CT was significantly higher in HR-HPV-positive patients than that in HR-HPV-negative patients, while the prevalence of VVC and TV had no significant difference. Our results suggested that BV, UU, and CT are risk factors for HR-HPV infection, while VVC and TV have no significant correlation with HR-HPV infection. The results of the bias risk assessment showed that each funnel plot had good symmetry and the risk of bias was considered to be small, indicating that the conclusions of this study had certain stability and reliability.

There are various kinds of female vaginal microflora, which are symbiotic and antagonistic with each other and in a state of dynamic equilibrium under normal conditions. Abnormalities in the reproductive tract system's anatomical structure, local



**FIGURE 2**  
The risk association between bacterial vaginosis (BV) or trichomonal vaginitis (TV) and high-risk human papillomavirus infection (HR-HPV) infection. (A) BV; (B) TV.

immunity, microbial flora, endocrine, and other factors can cause microbial flora imbalance (47). The normal vaginal microecological state (48) is as follows: the dominant bacteria of the vagina is *Lactobacillus*, the concentration of bacteria is grades II to III, the diversity is grades II to III, the pH value is 3.8 to 4.5, the leucocyte esterase is negative, and the *Lactobacillus* function is normal (normal secretion of H<sub>2</sub>O<sub>2</sub>). Once the vaginal microbiota is unbalanced, various types of vaginitis, such as BV and TV, will occur (49). BV is a mixed endogenous infection caused by a significant reduction in the vaginal production of hydrogen peroxide-producing *Lactobacillus* and the proliferation of *Gardnerella* and anaerobic bacteria. It has been reported that there is a significant correlation between BV and HR-HPV infection (50), and our study has also confirmed this result. *Lactobacillus* spp. are thought to confer protection against HPV infection (51, 52). BV is a proinflammatory genital condition characterized by high vaginal bacterial diversity and a paucity of *Lactobacillus* spp. (53). Moreover, the increase of mucin-degrading enzyme in vaginal fluid may destroy the glial layer on the surface of cervical epithelial cells, thus making the body more vulnerable to virus invasion (54). BV may also lead to a decrease in the secretion of secreted leukocyte protease inhibitor in the vagina, thereby weakening the body's ability to inhibit the virus (30); simultaneously, it may reduce the secretion of IL-1β and other cytokines in the cervical epithelium, thus disrupting the immune balance of the body and making the body easily infected with HR-

HPV (55, 56). TV is a type of lower genital tract inflammation caused by *Trichomonas vaginalis* infection. *Trichomonas* consumes glycogen in vaginal epithelial cells and competitively inhibits the growth of *Lactobacillus*, resulting in an increased vaginal pH and frequent co-infection with BV (57). This inflammation was once regarded as the cause of cervical cancer, which may cause degeneration and necrosis of the cervical epithelium, causing damage to the barrier function of the cervical epithelium, thereby triggering an immune response and releasing inflammatory factors, creating favorable conditions for the reproduction of other pathogenic microorganisms, thereby promoting the persistent infection of HPV, and ultimately promoting the occurrence of cervical lesions (58). Some scholars believe that TV has a certain correlation with HPV infection. They found that the HPV-16 infection rate of TV patients was 6.5 times that of TV-negative patients (59). The reason maybe that the patient was infected with TV after the vaginal mucosa congestion and edema, the vaginal and cervical mucosa were damaged. The conclusions of the meta-analysis of BV and TV in this study were consistent with the majority of published studies (60). However, there was no significant correlation between VVC and HR-HPV infection in our study, which reveals different results compared with previous studies. This needs to be further studied in future research. Vaccination against HPV can prevent HPV infection, thereby preventing diseases associated with HPV infection, such as cervical cancer, anal cancer, vulvar cancer, and vaginal cancer.

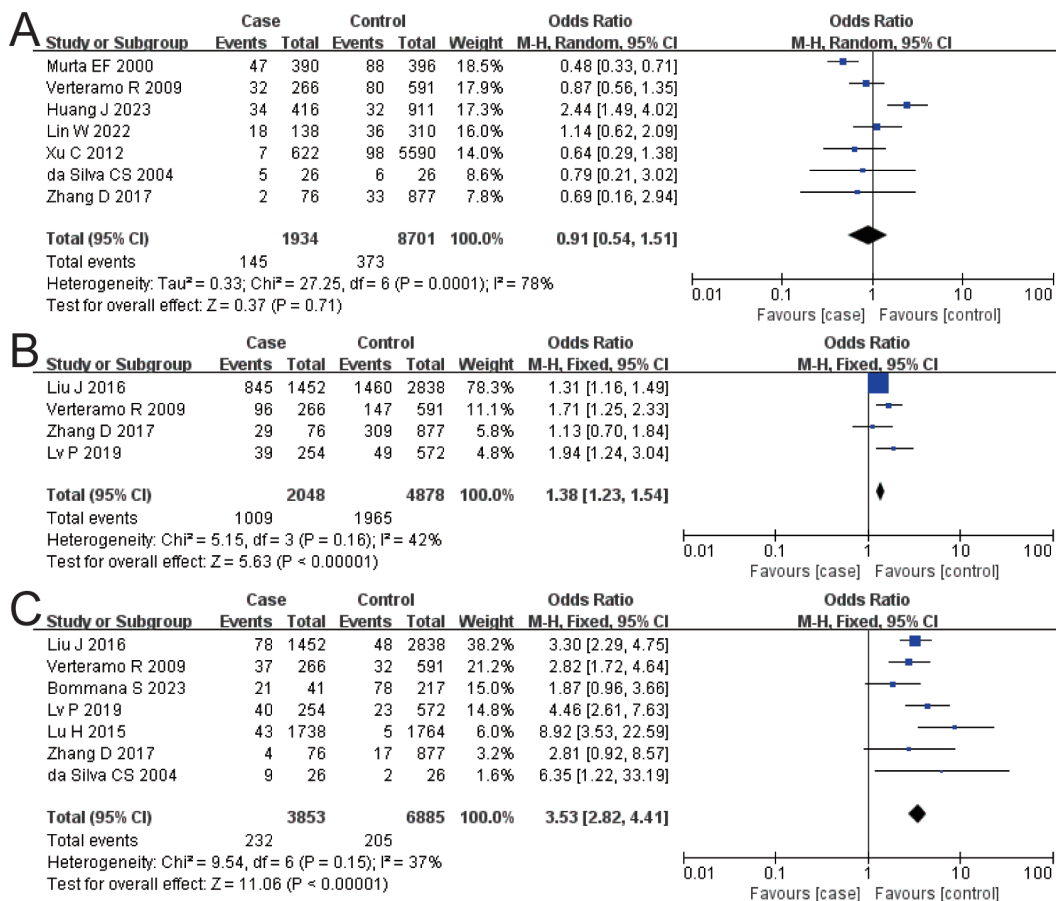


FIGURE 3 The risk association between vulvovaginal candidiasis (VVC), *Ureaplasma urealyticum* (UU), *Chlamydia trachomatis* (CT), and high-risk human papillomavirus infection (HR-HPV) infection. (A) VVC; (B) UU; (C) CT.

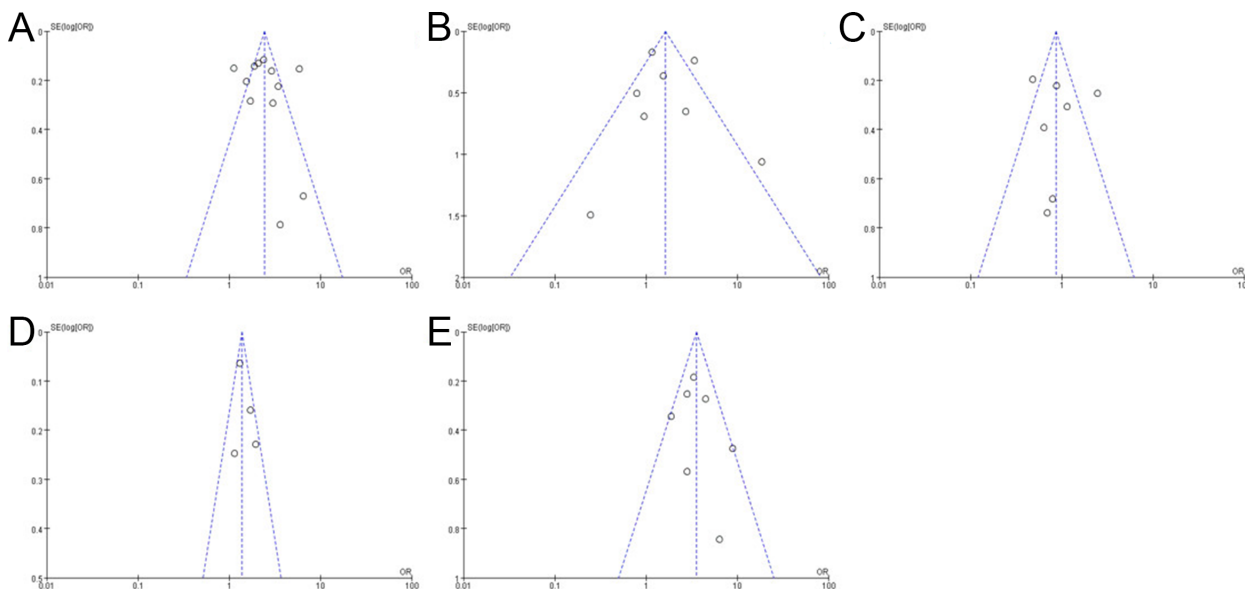


FIGURE 4 Funnel plot shows bacterial vaginosis (BV) risk (A), trichomonal vaginitis (TV) risk (B), vulvovaginal candidiasis (VVC) risk (C), *Ureaplasma urealyticum* (UU) risk (D), and *Chlamydia trachomatis* (CT) risk (E).

Nevertheless, it cannot prevent all types of vaginitis. HPV is a virus that can cause a variety of diseases, the most common of which is cervical cancer (61). HPV vaccines can assist people in preventing HPV infection, thereby reducing the risk of developing diseases related to HPV infection. However, vaginitis is caused by microorganisms such as bacteria and fungi, and the HPV vaccine is unable to prevent infection by these microorganisms. However, considering the findings of this study that BV and abnormal vaginal pH are associated with HR-HPV infection and that HR-HPV infection may promote the occurrence of BV and abnormal vaginal pH. Therefore, we believe that vaccination against HPV may reduce the occurrence of BV and abnormal vaginal pH. The HPV vaccine has a significant potential impact on vaginal microbiota and the prevention of HPV infection. In terms of preventing HPV infection, the HPV vaccine establishes a defense line against HPV virus invasion for the human body by inducing the body to produce specific antibodies (62). This greatly reduces the risk of HPV infection. The effect is more obvious, especially for those who have not had sexual intercourse or have infrequent sexual intercourse. In the long term, it can significantly reduce the incidence of malignant diseases such as cervical cancer and anal cancer caused by persistent HPV infection (63). For vaginal microbiota, HPV infection may lead to vaginal flora imbalance and destroy the microecological balance (64). After vaccination with HPV vaccine, the possibility of HPV infection is reduced, which helps maintain the normal microbial community in the vagina (63). A healthy vaginal microbiota can enhance the self-cleaning ability of the vagina and resist the invasion of pathogens. In addition, a stable microecological environment is also conducive to maintaining the normal physiological functions of the female reproductive system and reducing the occurrence of diseases such as vaginitis and cervicitis.

## Conclusion

Vaginal pathogens are closely related to HR-HPV infection. BV, UU, and CT are high-risk factors for HR-HPV infection. Patients with high-risk factors should be vigilant, and timely preventive interventions should be taken to reduce the risk of HR-HPV infection. This study is an update meta-analysis of the research on the correlation between vaginal microbiota and HR-HPV infection. The risk of research bias was low, and the conclusions were stable and reliable to a certain extent, which could guide the clinical prevention, control, and treatment of HR-HPV. However, due to the limited number of studies included in this study, the risk of research bias could not be disregarded. In addition, incomplete data reporting of some vaginal pathogens may affect the comprehensiveness and accuracy of the detection results. Therefore, in subsequent studies, we need to further increase the inclusion of studies and improve data collection and analysis to enhance the reliability of the results of this study.

## Data availability statement

Publicly available datasets were analyzed in this study. Manuscript contains all data.

## Author contributions

JY: Writing – review & editing, Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Writing – original draft. XL: Data curation, Writing – original draft. SL: Data curation, Writing – review & editing. MZ: Writing – original draft, Writing – review & editing. LH: Conceptualization, Supervision, Writing – review & editing.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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