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REVIEW ARTICLE

Gynecology

Trichomonas vaginalis infection is associated with increased risk of cervical carcinogenesis: A systematic review and meta-analysis of 470 000 patients

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Abstract

Background: *Trichomonas vaginalis* infection is the most prevalent non-viral sexually transmitted infection (STI) in women and has been suggested as a risk factor for developing cervical cancer.

Objective: We aimed to investigate the associations between *T. vaginalis* infection and cervical carcinogenesis.

Search Strategy: A comprehensive systematic search was conducted in five databases on 21 October 2021.

Selection Criteria: Studies assessing the relationship between *T. vaginalis* infection, HPV co-infections, cervical dysplasia, and cervical cancer were found eligible.

Data Collection and Analysis: Summary estimates for pooled odds ratios (ORs) and their 95% confidence intervals (CIs) were calculated with a random-effects model. Statistical heterogeneity was measured with I^2 and Cochran's Q tests.

Main Results: The 29 articles included 473 740 women, of whom 8518 were *T. vaginalis*-positive. Our results showed that *T. vaginalis*-infected women had 1.79 times higher odds of being diagnosed with HPV co-infection (95% CI 1.27–2.53; I^2 95%). We also found that *T. vaginalis* infection was associated with high-grade squamous intraepithelial lesion diagnosis (OR 2.34, 95% CI 1.10–4.95; I^2 75%) and cervical cancer (OR 5.23, 95% CI 3.03–9.04; I^2 3%).

Conclusions: Our results showed an association between *T. vaginalis* and cervical carcinogenesis in sexually active women.

KEYWORDS
cervical intraepithelial neoplasia, cervical lesion, cervical precancer, protozoal infection

1 | INTRODUCTION

Cervical cancer is the fourth most commonly diagnosed cancer and the fourth leading cause of cancer-related death in women.[1] Currently, there are effective ways of fighting cervical cancer through immunization, screening, and oncologic treatment.[2] HPV vaccination provides a high level of protection against oncogenic HPV strains and can reduce the burden of cervical cancer. Moreover, cervical smear and HPV tests improve the reliability of cervical cancer screening significantly.[3] In the treatment line of cervical cancer, immunotherapy and target therapy can have an increasing role besides the classical chemotherapeutic regimens.[4] Despite all of these, cervical cancer is still the most frequently diagnosed cancer in developing countries, and the leading cause of cancer-related mortality in emergent nations.[1,2]

The main risk factor of cervical cancer is infection with high-risk HPV types, responsible for various cancer types. Most notably, HPV 16 and HPV 18 types are accountable for 70% of cervical cancers worldwide.[5] After being incorporated into the host cell genome, the virus leads to overexpression of proto-oncogene proteins.[6,7] A persistent HPV infection and the inability of the immune system to clear out the infection in the cervix are key elements of the carcinogenesis.[5] The disruption of the vaginal microbiota performs an essential role in persistent HPV infection, as vaginal dysbiosis occurs, proinflammatory cytokines are increased and immunclearance is reduced.[8] It is well known that other risk factors, including smoking, promiscuity, using oral contraceptive drugs, immunosuppressed state, and sexually transmitted infections (STIs), can also contribute to developing cervical cancer.[7,9–11]

Trichomonas vaginalis, a common cause of STI, causes around 170–190 million infections annually.[12] Infection of the genital tract with these anaerobic protozoa can lead to discomfort by causing odorous discharge, dysuria, itching, and vulvar irritation. However, up to 85% of trichomoniases can be symptomless in women. Moreover, 5%–35% of women can also be reinfected.[13] *Trichomonas vaginalis* can contribute to the development of cervical cancer by causing inflammation, abruption of the cervical epithelium, and influencing the immune system to eliminate HPV. Current evidence on the relationship between *T. vaginalis* infection, cervical dysplasia, and cervical cancer is conflicting. Although several articles report strong associations, other publications do not find *T. vaginalis* to be a risk factor for cervical carcinogenesis.[14–17] Two meta-analyses have been conducted on this topic. The first article, published in 1994, included populations where *T. vaginalis* detection was based only on cytology, which can often underdetect *T. vaginalis*.[18–20] The other meta-analysis focused on cervical dysplasia without differentiating between the different states of cervical lesions and did not investigate the relationship between *T. vaginalis* and HPV.[21]

Hence, on the basis of the available literature, this study aimed to investigate the association between *T. vaginalis* and HPV, cervical dysplasia, and carcinogenesis. We hypothesized that *T. vaginalis* was a risk factor for developing cervical cancer.

2 | MATERIALS AND METHODS

We conducted our systematic review and meta-analysis according to the PRISMA 2020 and MOOSE guidelines (see Figure 1; Tables S1 and S2) while we followed the recommendations of the Cochrane Handbook.[22–24] The pre-study protocol was registered in PROSPERO (CRD42021286097), and we fully adhered to it.

2.1 | Literature search and eligibility criteria

The systematic search was conducted using five major databases on October 20, 2021: MEDLINE (via PubMed), Embase, Cochrane Central Register of Controlled Trials (CENTRAL), Scopus, and Web of Science. We accepted only peer-reviewed articles; therefore, we did not search on ClinicalTrials.gov, nor did our preliminary search find any suitable studies. No filters or restrictions were applied during the search. We used two population, exposure, and outcome (PEO) frameworks to define the eligibility criteria for the articles.[25] All studies reporting sexually active (P_1) or HPV-positive (P_2) women who were screened for *T. vaginalis* infection (E) were deemed eligible. The outcomes of interest (O_1) were HPV positivity, cervical dysplasia, and cervical cancer. In HPV-positive women (P_2), the investigated outcomes (O_2) were cervical dysplasia and cervical cancer. The articles had to include a population of *T. vaginalis*-negative women forming the control group.

Articles were considered where *T. vaginalis* was detected with cytology, wet-mount, culture, or polymerase chain reaction (PCR) methods. Articles were excluded in which *T. vaginalis* was diagnosed on the basis of clinical features or medical history. Studies were suitable if HPV exposure was diagnosed with any nuclear amplification method. Articles where HPV was detected only by cytology were excluded because of the low sensitivity of the method.[26] Cytologic and histopathologic diagnoses were acceptable for cervical intraepithelial neoplasia (CIN) and cancer confirmation. We evaluated the following outcomes in the dysplasia group: atypical squamous cells of undetermined significance (ASCUS), atypical glandular cells, atypical squamous cells for which one could not rule out high-grade squamous intraepithelial lesions (ASC-H), low-grade squamous intraepithelial lesions (LSIL), and high-grade squamous intraepithelial lesions (HSIL). For cytologic samples, the Bethesda classification was required. Articles that proclaimed CIN1–3 diagnoses were divided into LSIL (CIN1) and HSIL (CIN2–3) groups for a more straightforward interpretation.

Observational studies, such as cross-sectional, case–control, and cohort analyses, were accepted. Abstracts were excluded in our review. Non-English language articles were translated for possible evaluation.

2.2 | Search strategy

During the systematic search, we used the following main concepts: "trichomonas", "human papillomavirus", "cervical intraepithelial

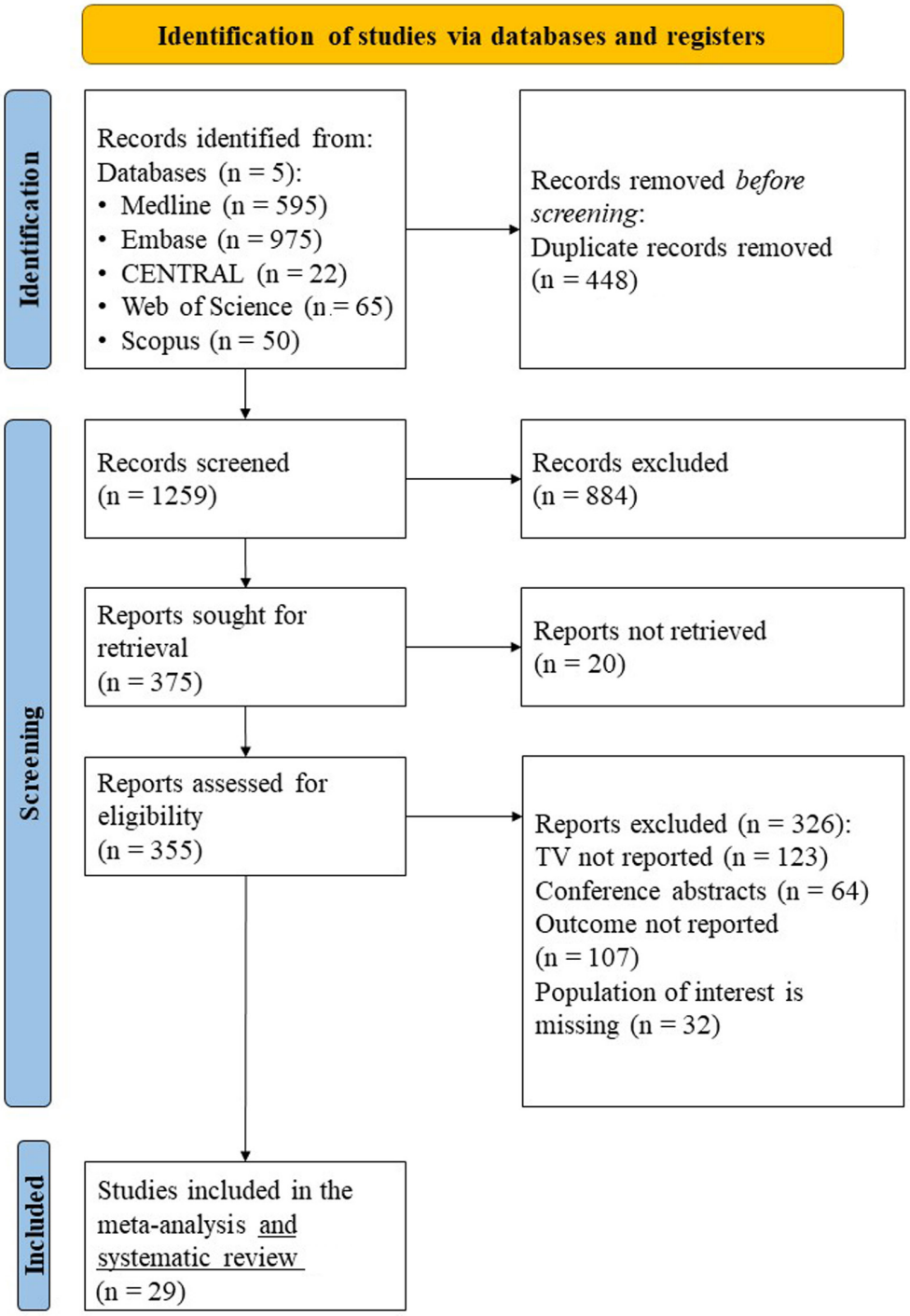


FIGURE 1 PRISMA 2020 flowchart representing the study selection process.

neoplasia", and "cervical cancer". The whole search key can be found in Supporting Information.

2.3 | Study selection and data collection

A reference management program (ENDNOTE X9) was used to select the articles. First, a duplicate removal was performed, then, two independent reviewers (BH, EH) carried out a title and abstract selection and then full-text selection. Cohen's κ coefficient measured the degree of agreement.[27] A third independent investigator (ZSH) agreed on debated articles. If we could not find an article, or data were missing, we contacted the authors.

Two independent reviewers (BH, EH) extracted variables from the eligible studies into a pre-defined Microsoft EXCEL spreadsheet (Windows 11 Pro). The following variables were collected from each article: first author, publication year, digital object identifier, study design, study type, demography (age, sample size), country,

centers, the detection method of *T. vaginalis*, HPV, and cytologic/histologic lesions. Where possible, data regarding the outcomes were extracted in two-by-two tables. Otherwise, we collected the unadjusted odds ratios (ORs). In order to handle confounding factors, when possible, we collected adjusted ORs, and the variables for these results were adjusted. In case of any disagreement, a consensus was reached involving a third investigator (ZSH).

2.4 | Risk of bias and quality assessment of the included articles

To critically assess the outcome data, we performed a risk of bias assessment with the help of the Quality in Prognostic Studies (QUIPS) tool.[28] The QUIPS tool includes six domains: study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding, and statistical analysis reporting. In each domain, four classifications can be given: not applicable, low risk, moderate risk, and high risk of bias. To grade the level of evidence of our findings, we implemented the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) approach. The Summary of Findings table was prepared by using the GradePro tool.[29] Both QUIPS and GRADE were performed by two independent reviewers (BH, EH), and in case of disagreement, a third investigator resolved the dispute (ZSH).

2.5 | Synthesis methods

During data synthesis, both qualitative and quantitative assessments were carried out. The R programming language was used for statistical data analysis (R Core Team, 2022; R version 4.2). The minimum number of studies for performing the quantitative synthesis was three. Forest plots were used to visualize individual studies and overall results. Subgroup analyses were performed based on the detection method of *T. vaginalis* and the country of origin of the article. Sensitivity analyses were carried out for four outcomes.

Where possible, we estimated pooled ORs with 95% confidence intervals (CIs) with a random-effects model, using the tel-Haenszel method with the metabin function from meta v5.50 package, and we applied the Paule-Mandel method to estimate the between-study variance.[30–32] Statistical significance was substantiated for a result when $P < 0.05$. I^2 and Cochran's Q tests were used to measure statistical heterogeneity, where $P < 0.1$ indicated significant heterogeneity.[28] A general interpretation of the heterogeneity values is as follows: 0%–40% possibly not important heterogeneity; 30%–60% moderate heterogeneity; 50%–90% substantial heterogeneity; and 75%–100% considerable heterogeneity. Beside I^2, we also reported the prediction intervals (i.e. the expected range of effects of future studies) of the pooled estimates if the minimum study number was reached.[33]

The inspection of funnel plots and an Egger's test were used to assess publication bias when a minimum of 10 articles were available for one outcome.

3 | RESULTS

3.1 | Search and selection

Our comprehensive search identified 1707 articles. After duplicate removal, 1259 publications were screened based on title and abstract. During the full-text selection, 355 articles were screened, resulting in 29 eligible studies for the quantitative and qualitative data syntheses. Cohen's κ was 0.9 for title and abstract selection; and 0.85 for full-text selection. Despite contacting authors for non-retriveble articles, we received only a few responses.

3.2 | Basic characteristics of included studies

The eligible articles were published between 2009 and 2021, with 11 publications from Asia, five from Europe, seven from South America, five from Africa, and one from North America. According to study type, we found 22 cross-sectional, five case–control, and one prospective cohort study.

As for demographics, the mean age of women was 37.57 years. In 15 articles, *T. vaginalis* was detected with PCR, in eight with wet-mount, in four with cytology and in two with cultures and wet-mount. All the studies assessed the exposure and the outcome at the same time.

Altogether 473 740 women were included in our meta-analysis. Of them, 8518 patients had *T. vaginalis* infection in the exposure group. Baseline characteristics of the eligible studies are detailed in Table 1.

3.3 | Quantitative and qualitative analysis

The association between *T. vaginalis* and HPV infections

Twenty-four studies including 7291 women in the *T. vaginalis*-infected group and 452 161 in the control group reported an association between *T. vaginalis* and HPV infections.[14,16,17,34–54] Our results showed that *T. vaginalis*-positive women were 1.79 times more likely to be diagnosed with an HPV co-infection (95% CI 1.27–2.53; I^2 95%; Figure 2) compared with *T. vaginalis*-negative women.

When a *T. vaginalis* infection was confirmed with the wet-mount method, the odds of detecting a co-infection with HPV were slightly higher, by the odds of 2.29 (95% CI 1.23–4.28; I^2 97%). The results from the subgroups based on region showed that *T. vaginalis*-positive women from Asia had the highest chance for HPV co-infection (OR 2.05, 95% CI 1.08–3.88; I^2 97%; see Figure S1). A sensitivity analysis (leave-one-out method) did not recognize any influential study (see Figure S2).

In one article,[54] a multivariate analysis showed 2.29 odds (95% CI1.46–3.60) for the diagnosis of HPV in the case of *T. vaginalis*

TABLE 1 Basic characteristics of included studies.

Author, year	Study type	Region	Number of patients	Mean age, y	Diagnosis of *Trichomonas vaginalis*	Diagnosis of HPV	Diagnosis of cervical lesion	Cervical lesion-related outcomes
Verteramo et al., 2009[34]	Cross-sectional	Europe	860	32.7	Culture and wet-mount	PCR	NA	NA
Noel et al., 2010[35]	Case–control	Europe	507	<30–50[a]	Cytology	HCII	NA	NA
Depuydt et al., 2010[36]	Cross-sectional	Europe	62 944	42	PCR	PCR	NA	NA
Caiyan et al., 2012[37]	Cross-sectional	Asia	6339	39.2	Wet-mount	HCII	Histology	LSIL, HSIL
Donders et al., 2013[16]	Cross-sectional	Europe	63 251	NA	PCR	PCR	Cytology	ASCUS, LSIL, HSIL
Mendoza et al., 2013[38]	Cross-sectional	South America	181	30[b]	Culture and wet-mount	PCR	NA	NA
Paesi et al., 2013[39]	Cross-sectional	South America	208	13–69[a]	Cytology	PCR	NA	NA
Lazenby et al., 2014[14]	Cross-sectional	Africa	324	38	PCR	HCII	Cytology/histology	LSIL, HSIL
Liu et al., 2015[40]	Cross-sectional	Asia	429	39	Wet-mount	PCR	NA	NA
Casillas-Vega et al., 2016[41]	Cross-sectional	South America	662	31	PCR	PCR	NA	NA
Camporiondo et al., 2016[42]	Cross-sectional	Europe	309	49[b]	PCR	PCR	NA	NA
Dey et al., 2016[55]	Cross-sectional	Asia	7962	NA	Cytology	NA	Cytology	ASCUS, LSIL, HSIL
de Abreau et al., 2016[57]	Cross-sectional	South America	685	40.3	PCR	NA	Cytology/histology	HSIL
Kim et al., 2016[43]	Case–control	Asia	1000	NA	PCR	PCR	Cytology	ASCUS, ASC-H LSIL, HSIL
Amorim et al., 2017[56]	Case–control	South America	132	38.2	PCR	NA	Cytology/histology	LSIL, HSIL
Costa-Lira et al., 2017[44]	Cross-sectional	South America	180	16–50[a]	PCR	PCR	—	NA
Ghosh et al., 2017[17]	Case–control	Asia	483	30–60[a]	Wet-mount	HCII	Histology	LSIL, HSIL, CA
Al-Awadhi et al., 2018[15]	Cross-sectional	Asia	8836	NA	Cytology	NA	Cytology	ASCUS, LSIL, HSIL
Lockhart et al., 2019[45]	Prospective cohort	Africa	344	18–49[a]	PCR	PCR	NA	NA
Ferre et al., 2019[46]	Cross-sectional	Africa	320	25	PCR	PCR	NA	NA
Lv et al., 2019[47]	Cross-sectional	Asia	826	38.5	Wet-mount	PCR	NA	NA
Cunha et al., 2020[48]	Cross-sectional	South America	353	39.7	PCR	PCR	NA	NA
Wang et al., 2020[49]	Cross-sectional	Asia	4449	43.6	Wet-mount	PCR	NA	NA
Yang et al., 2020[50]	Cross-sectional	Asia	310 545	>30	Wet-mount	PCR	NA	NA
Zheng et al., 2020[51]	Case–control	Asia	532	42.2	Wet-mount	PCR	Histology	LSIL, HSIL, CA
Gupta et al., 2020[58]	Case–control	Asia	168	21–65[a]	Wet-mount	NA	Histology	CA
Taku et al., 2021[52]	Cross-sectional	Africa	205	45[b]	PCR	PCR	NA	NA
Jary et al., 2021[53]	Cross-sectional	Africa	144	37	PCR	PCR	NA	NA
Belfort, 2021[54]	Cross-sectional	South America	562	30–49[c]	PCR	PCR	NA	NA

Abbreviations: ASC-H, atypical squamous cells for which one cannot rule out high-grade squamous intraepithelial lesions; ASCUS, atypical squamous cells of undetermined significance; CA, cervical cancer; HCII, Hybrid capture II; HSIL, high-grade squamous intraepithelial lesions; LSIL, low-grade squamous intraepithelial lesions; NA, not available; PCR, polymerase chain reaction.

[a]Minimum–maximum age values.

[b]Median age value.

[c]In this age range, 48.40% of patients were included.

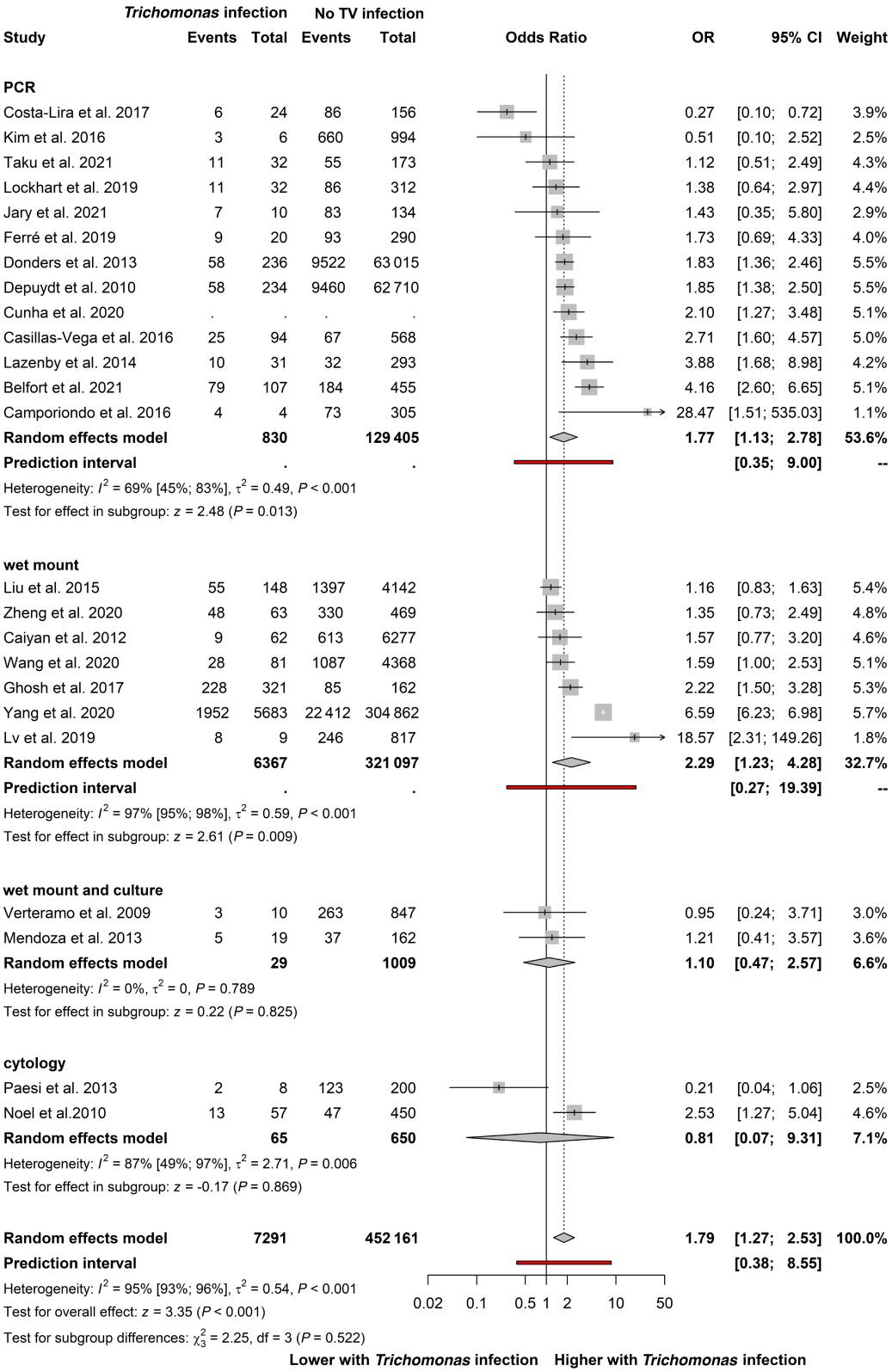


FIGURE 2 Forest plot of studies representing that *Trichomonas vaginalis* infection was associated with HPV co-infection. CI, confidence interval; OR, odds ratio; PCR, polymerase chain reaction; TV, *Trichomonas vaginalis*.

detection. A second study[14] found even higher chances for HPV-co-infection (OR 4.10, 95% CI 1.70–9.80, see Table S3).

The association between *T. vaginalis* and cervical dysplasia

For the ASCUS outcome, five studies evaluated 1493 women in the exposure group and 75 135 women in the control group.[15,16,43,54,55] Women who were *T. vaginalis*-positive had a 2.3 times higher chance for ASCUS diagnosis (95% CI 1.63–3.26; I^2 52%, see Figure S3) compared with women who did not have a *T. vaginalis* infection. A subgroup analysis based on the screening method showed that when *T. vaginalis* was detected with PCR, this association was even stronger (OR 2.91; 95% CI 1.95–4.35; I^2 0%;). Articles from South America and Europe found almost threefold increased odds for the diagnosis of ASCUS (Belfort et al.[54]: OR 2.99, 95% CI 1.06–8.43; Donders et al.[16]: OR 2.94, 95% CI 1.88–4.57, respectively; see Figure S4). When the leave-one-out analysis was carried out, the exclusion of Al-Awadhi et al.[15] from ASCUS resulted in a higher association (OR 2.79, 95% CI 2.21–3.53; I^2 0%; see Figure S5).

Two studies investigated atypical glandular cells and *T. vaginalis* infection in sexually active women. Neither found an association between *T. vaginalis* positivity and atypical glandular cells (Donders et al.[16]: OR 1.33, 95% CI 0.08–21.40; Al-Awadhi et al.[15]: OR 1.55, 95% CI 0.46–5.41).

Altogether there were 10 eligible studies concerning LSIL, investigating 1740 women in the *T. vaginalis* group and 82 362 in the control group.[14–17,37,43,51,54–56]

When examining the association between *T. vaginalis* and LSIL, we found that women who were infected with *T. vaginalis* had almost twofold odds of having LSIL (OR 1.92, 95% CI 0.78–4.77; I^2 91%; see Figure S6), compared with women who were not *T. vaginalis*-infected. However, the findings were statistically not significant. When *T. vaginalis* was detected with PCR, women had higher odds of having an LSIL diagnosis (OR 3.66, 95% CI 1.51–8.86; I^2 69%). Regarding the analysis of regional differences, we detected a ninefold chance for LSIL when *T. vaginalis* was present in women from South America (OR 9.36, 95% CI 2.34–37.36; I^2 63%; Figure S7). When the leave-one-out analysis was carried out, the exclusion of the study by Al-Awadhi et al.[15] resulted in a higher association between *T. vaginalis* and LSIL detection (OR 2.79; 95% CI 1.61–4.82; I^2 65%). Furthermore, when the article by Amorim et al.[56] was excluded, we found an OR of 1.51 (95% CI 0.65–3.55; I^2 95%; see Figure S8).

Regarding a relationship between *T. vaginalis* and ASC-H, we could not find any association (OR 1.78, 95% CI 0.21–15.12; see Figure S9).[16,43,54]

Eleven studies assessed 1796 women in the exposure group and 80 276 women in the control group for the association between *T. vaginalis* infection and HSIL.[14–17,37,43,51,54–57] Patients diagnosed with *T. vaginalis* infection had 2.34 times higher odds of having an HSIL diagnosis (95% CI 1.10–4.95; I^2 75%; Figure 3) than women who were not diagnosed with *T. vaginalis*. According to the *T. vaginalis* detection method, women diagnosed with PCR had higher odds of receiving an HSIL result (OR 3.81, 95% CI 1.23–11.78; I^2 81%). The subgroup analysis of the origins of the articles displayed sixfold odds in South America (OR 6.52, 95% CI 0.74–57.75; I^2 92%), although the findings were statistically not significant. One study from Europe found high odds for HSIL when *T. vaginalis* was present (Donders et al.[16]: OR 3.14, 95% CI 1.49–6.78; see Figure S10). When the leave-one-out analysis was carried out, the exclusion of the article by Al-Awadhi et al.[15] from HSIL resulted in an OR of 2.87 (95% CI 1.43–5.75; I^2 67%). In addition, when the article by Amorim et al.[56] was excluded, the OR changed to 1.72 (95% CI 1.01–2.91; I^2 42%; see Figure S11).

One paper[54] performed a multivariate analysis (see Table S3).

The association between *T. vaginalis* and cervical cancer

Three articles were quantitatively analyzed, with 219 women in the *T. vaginalis*-positive group and 397 women in the control group.[17,51,58] Women who were *T. vaginalis*-positive had 5.24 times higher odds of having cervical cancer (OR 5.23, 95% CI 3.03–9.04; I^2 3%; Figure 4) compared with *T. vaginalis*-negative women.

Association between *T. vaginalis*, cervical lesions, and cervical cancer in the HPV-positive population

We found four articles for the quantitative synthesis regarding the HPV-positive population when evaluating the association between *T. vaginalis* infection and cervical lesions.[17,50,51,57]

For LSIL, three articles were analyzed, assessing 1932 women in the exposure group and 20 033 in the control group.[17,50,51] *Trichomonas vaginalis*-positive women had 2.81 higher odds for LSIL diagnosis than women who were not *T. vaginalis* infected (95% CI 2.37–3.33; I^2 0%; see Figure 5).

In total, there were 1921 women in the exposure group and 20 750 women in the control group for HSIL.[17,50,51,57] Patients who were diagnosed with *T. vaginalis* had more than twofold odds of having HSIL compared with women who were not diagnosed with *T. vaginalis* (OR 2.36, 95% CI 1.79–3.11; I^2 10%; see Figure 5).

Three studies examined cervical cancer, with 1811 women in the exposure group and 19 331 in the control group.[17,50,51] We found that women who were *T. vaginalis*-positive had increased odds of being diagnosed with cervical cancer compared with women who were not *T. vaginalis*-positive (OR 3.09, 95% CI 1.66–5.77; I^2 45%; see Figure 5).

3.4 | Risk of bias assessment and quality of evidence

The results of the risk of bias assessment are presented for every outcome. For the *T. vaginalis*-HPV co-infection outcome, seven articles demonstrated "a moderate risk for study confounding bias",

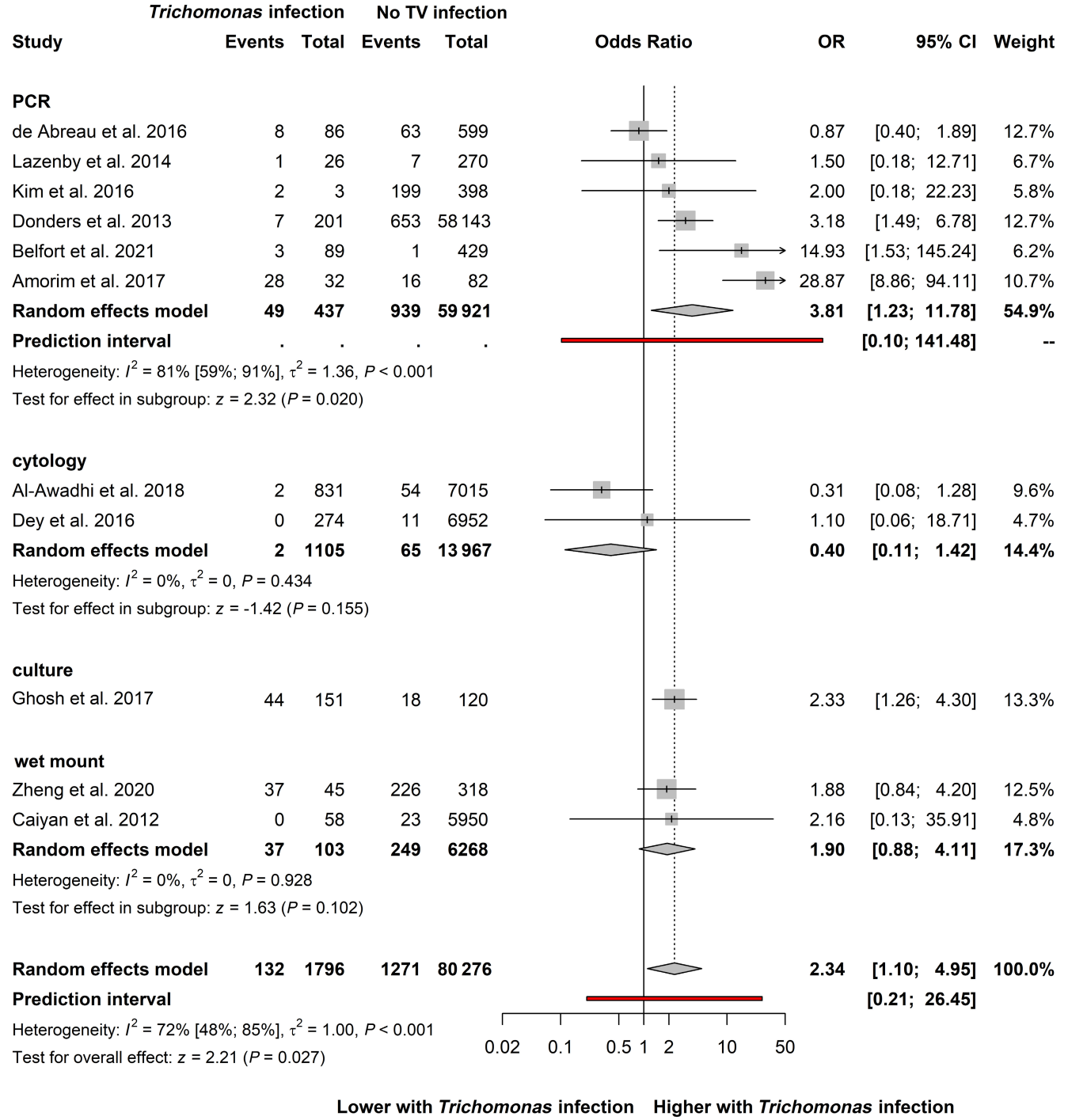


FIGURE 3 Forest plot of studies representing that *Trichomonas vaginalis* infection was associated with high-grade squamous intraepithelial lesions. CI, confidence interval; HSIL, high-grade squamous intraepithelial lesions; OR, odds ratio; PCR, polymerase chain reaction; TV, *Trichomonas vaginalis*.

and three articles demonstrated "a high risk of bias". In the study participation domain we detected a high risk of bias in three articles. In the cervical dysplasia groups, the risk of bias was low. In the study confounding domain, we found one article to be at a high risk of bias in ASCUS and two articles of a high risk of bias in the LSIL and HSIL groups. In the cervical cancer group, we found one article in the confounding domain of the study at a high risk of bias. (see Figures S12–S22).

Our Summary of Findings included six outcomes for the first PEO and three for the second PEO (see Tables S3 and S4). The quality of evidence was "low" for six outcomes and "very low" for three outcomes.

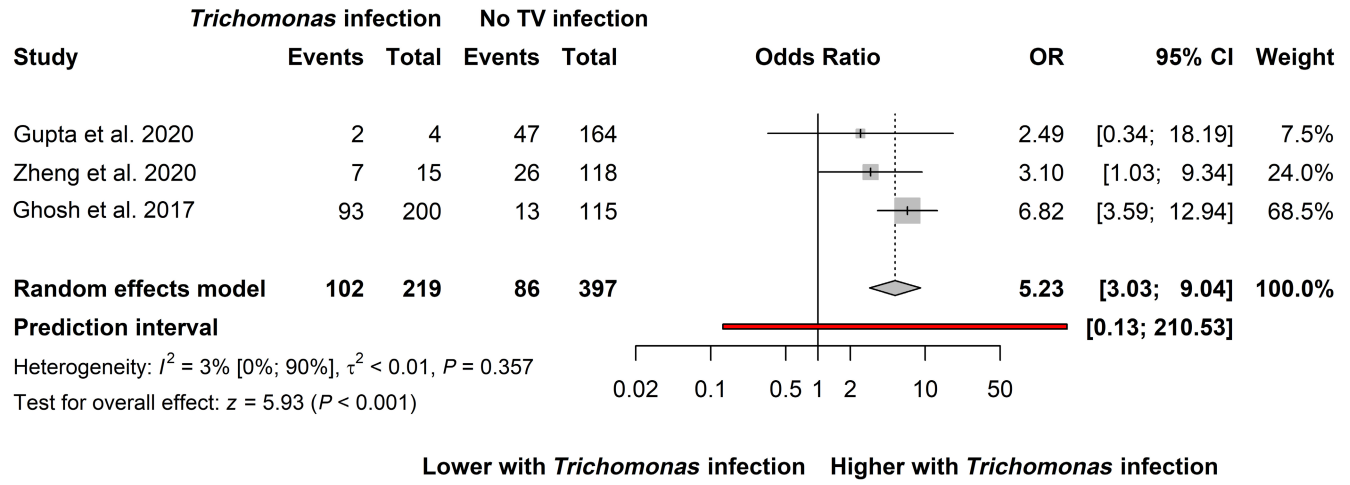


FIGURE 4 Forest plot of studies representing that *Trichomonas vaginalis* infection was associated with cervical cancer. CI, confidence interval; OR, odds ratio; TV, *Trichomonas vaginalis*.

3.5 | Publication bias and heterogeneity

We performed the Egger test and a funnel plot to assess publication bias in the *T. vaginalis*-HPV co-infection, *T. vaginalis*-LSIL, and *T. vaginalis*-HSIL groups. In all three cases, the funnel plots showed some asymmetry. Even on the basis of Egger test, we did not find a significant publication bias as the *P* values were greater than 0.1 (see Figures S23–S25).

4 | DISCUSSION

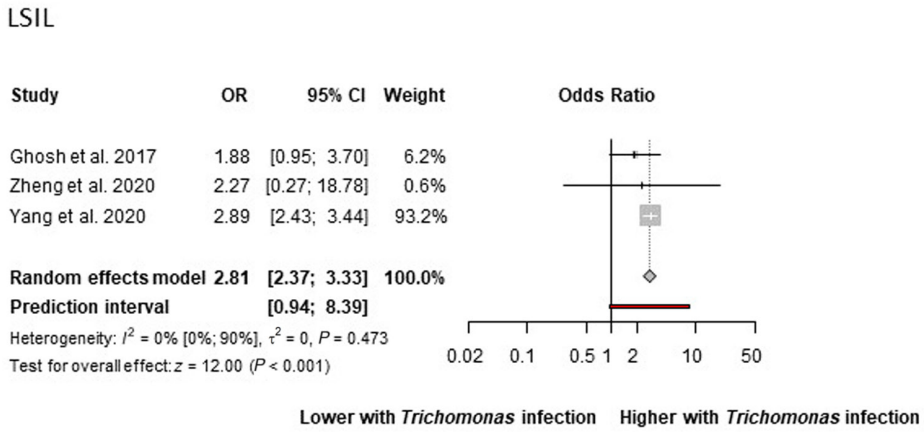
Our study, which included nearly half a million women from population-based studies, showed a positive association between *T. vaginalis* and cervical carcinogenesis. First, we investigated the association between *T. vaginalis* and HPV. We found that women with a *T. vaginalis* infection had higher odds of being diagnosed with a concomitant HPV infection than women who were *T. vaginalis*-negative. In the relation between *T. vaginalis* and cervical dysplasia, a significant association was found. When we evaluated the relationship between *T. vaginalis* and cervical cancer, we also found a statistically significant association resulting in higher odds of developing cervical cancer among women infected with *T. vaginalis*. Regarding our second clinical question in the HPV-positive population, we found a positive association between *T. vaginalis*, LSIL, HSIL, and cervical cancer.

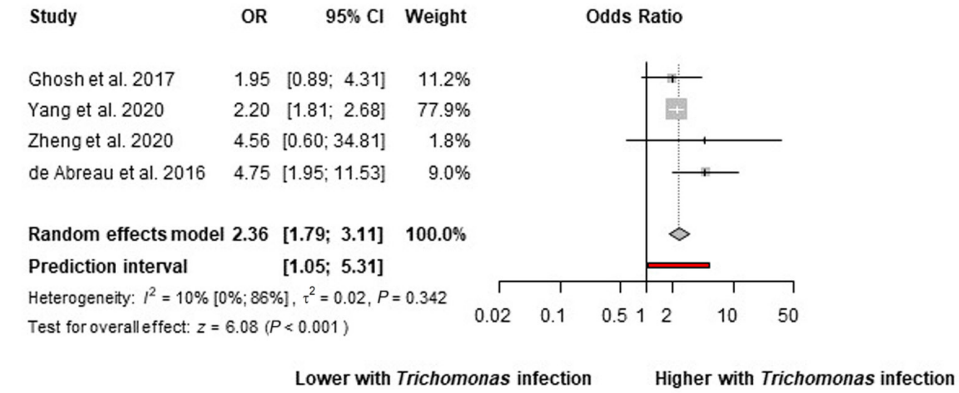
As for strengths, our study is the first meta-analysis to investigate the relationship between *T. vaginalis*, HPV, and cervical lesions in detail. As a result of the large sample size in the assessed articles, we could include nearly half a million patients in the analysis. Moreover, most of the studies carried a low risk of bias.

However, the results need to be interpreted together with the limitations. First, as none of the studies followed up the *T. vaginalis*-infected population, and all participants were screened for *T. vaginalis*, HPV, and cervical carcinogenesis simultaneously, we do not know how *T. vaginalis* can contribute to the development of the outcomes. Second, as many studies did not perform multivariate analyses, we could not calculate pooled adjusted ORs. The inadequate control of confounders may lead to an underestimation or overestimation of the analyzed associations. Third, it is not clear whether *T. vaginalis* infection causes the cervical environment to be more susceptible to HPV infection and to the subsequent CIN, or whether cervical dysplasia makes the environment more attractive to *T. vaginalis* infection.[59] Fourth, in the diagnosis of cervical lesions, some studies used cytology, which is subjective, and it is a diagnostic method that is difficult to replicate.[60] Fifth, according to the GRADE assessment, the quality of evidence was low in six and very low in three outcomes. Sixth, not all HPVs are oncogenic though in the *T. vaginalis*-HPV association, 10 studies included non-oncogenic HPV strains in their investigation too.

The association between *T. vaginalis* and HPV showed that STIs often coexist because of similar behavioral risk factors such as young age, a high number of sexual partners, and unprotected intercourse.[16,61] Therefore, we cannot conclude that *T. vaginalis* infection affects HPV acquisition because both infections can be concomitantly present. The etiology of cervical cancer and most CIN are attributable to high-risk HPV types.[5] Therefore, HPV could be a confounding factor for our cervix-related outcomes. However, if we only investigate the HPV-positive population, we could observe an even more increased association between *T. vaginalis* cervical dysplasia and cancer.

In contrast, not all HPV types carry the same oncogenic risk as HPV 16 and HPV 18, which cause around 70% of all cervical cancers worldwide.[5] Therefore, HPV positivity in women does not represent a homogeneous population from an oncogenic point of view. Some prospective studies suggest that the likelihood of a persistent HPV infection increases in the presence of concomitant *T. vaginalis* infection.[45,62] Behind this observation there is a presumption of how *T. vaginalis* can alter HPV clearance. *Trichomonas vaginalis* can cause micro-lesions in the cervical epithelium,





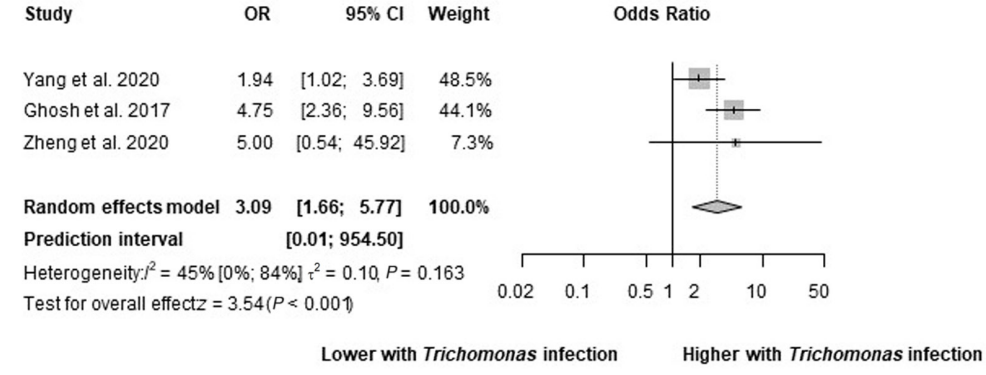


FIGURE 5 Forest plot of studies representing that *Trichomonas vaginalis* was associated with low-grade squamous intraepithelial lesions, high-grade squamous intraepithelial lesions, and cervical cancer in the HPV-positive population. CI, confidence interval; HSIL, high-grade squamous intraepithelial lesions; LSIL, low-grade squamous intraepithelial lesions.

decrease the protective mucus layer of the vagina, and induce proinflammatory cytokines through immune response, which can facilitate the spread of an HPV infection into the basal layer of the cervical epithelium and induce persistent HPV infection.[7,63,64] As persistent HPV infection occurs, the probability of cervical dysplasia increases, promoting cervical carcinogenesis.[65] Coexistence

of different genital infections, *Chlamydia trachomatis*, and bacterial vaginosis can also induce persistent HPV infection, resulting in cervical dysplasia progression.[66,67]

When assessing ASCUS, we found a significant association with *T. vaginalis* infection. A Belgian study also found that women diagnosed with ASCUS had been HPV-negative but *T. vaginalis*-positive in a few cases, suggesting that *T. vaginalis* could also lead to ASCUS.[16] In the cervical dysplasia group, we found the highest odds for cervical lesions when *T. vaginalis* was detected with PCR, probably because this method was the most sensitive for *T. vaginalis* detection.[19] In the *T. vaginalis* and cervical dysplasia group, we found higher odds in the ASCUS and LSIL groups in South America, although we had only one article in the ASCUS group. The prevalence of *T. vaginalis* is deeply connected to socioeconomic variables, sexual behaviors, and access to health care. Without surveillance programs, the actual epidemiologic state of *T. vaginalis* is unknown. However, countries where the populations have higher incomes generally have a lower prevalence of *T. vaginalis*, and countries where the populations have lower incomes generally have a higher prevalence.[13] In the sensitivity analysis, two articles could have altered our results. One of the outliers[15] led to a lower association between *T. vaginalis* and cervical dysplasia. In this study, *T. vaginalis* was diagnosed with cytology, which is not a reference standard detection of *T. vaginalis*.[19] The other article[56] came from an area of Brazil where poverty rate was high, and cervical cancer was the second most common cancer.[3] These findings can explain the high ORs we experienced in the *T. vaginalis* and cervical dysplasia group.

Lipophosphoglycan (LPG), a virulence factor found on the surface of *T. vaginalis*, can induce immunologic reactions depending on the type of LPG. In reaction to these LPG particles, the host epithelial cells can secrete proinflammatory cytokines, interleukin-8 and macrophage inflammatory protein 3α, which induce the inflammation of the cervix and the vagina. At the same time, other LPGs found on *T. vaginalis* can decrease the level of proinflammatory cytokines and evade immune reactions. This is in line with the clinical finding that *T. vaginalis* can often be asymptomatic or can cause persistent infection.[64]

Inflammation of the cervix has been associated with an increased risk of CIN in one study.[7] Another article found elevated levels of interleukin-6 and interleukin-8 in CIN and cervical cancer.[68] Generally, inflammation is considered a risk factor for developing many cancer types.[69] One study investigated the microbial component of the vagina in cervical cancer patients and non-cervical cancer patients, assuming that cervical cancer disrupts the vaginal microbiota and makes it attractive to infectious diseases. *Trichomonas vaginalis* is possibly less of a cofactor than a consequence of cervical cancer.[70] The intact state of the vaginal microbiome with *Lactobacillus* species is essential for protection against STIs. The abruption of this complex microbiome increases the probability of genital infections due to decreased defensive barriers.[71] One study proved the proinflammatory synergism between vaginal dysbiosis and *T. vaginalis*; moreover, it suggested a surface biofilm that makes them more resistant to antibiotic treatment.[72] Overall, STIs and vaginal infections have been considered possible cofactors in the development of CIN and cervical cancer. In one meta-analysis, *Chlamydia trachomatis* was found to be associated with cervical cancer, whereas another meta-analysis also found an association between bacterial vaginosis and cervical lesions.[61,67] Our findings also support the idea that STIs and vaginal infections might act as cofactors in the development of cervical cancer.

We believe that more studies are needed to control the confounding factors; therefore, the true effect of *T. vaginalis* on cervical carcinogenesis could be estimated in a more reliable way. Second, we recommend that clinicians who treat women in their practice always consider HPV infection and cervical lesions when diagnosing *T. vaginalis* infection. Even though we cannot conclude a causative relationship between *T. vaginalis* and cervical carcinogenesis, *T. vaginalis* is associated with HPV infection, cervical lesions, and cervical cancer, so a follow up of patients after the *T. vaginalis* diagnosis might be beneficial. Many countries have implemented HPV-based cervical cancer screening programs, which means a greater detection rate in HPV strains.[73] According to our study, *T. vaginalis* and HPV are associated; therefore, in the case of an HPV diagnosis, the screening and treatment of *T. vaginalis* are advisable because of its potential carcinogenic effect on the cervix.

In conclusion, our results showed that *T. vaginalis* infection might increase the odds of cervical lesions and cancer development in sexually active women. We advise clinicians to evaluate HPV and cervical dysplasia in the case of a *T. vaginalis* diagnosis.

AUTHOR CONTRIBUTIONS

Balázs Hamar contributed to conceptualization, project administration, and writing the original draft; Brigitta Teutsch and Péter Hegyi contributed to conceptualization, project administration, methodology, and writing—review & editing; Eszter Hoffmann and Zsombor Hunka contributed to data curation and writing–review & editing; Alex Váradi contributed to data curation, formal analysis, visualization, and writing–review & editing; Nándor Ács and Zsolt Melczer contributed to conceptualization, supervision, and writing—review & editing; and Péter Nyirády, Balázs Lintner, and Réka Juhász Hermánné contributed to conceptualization, and writing—review & editing. All authors certify that they have participated sufficiently in the work, including the concept, design, analysis, writing, and/or revision of the manuscript, to take public responsibility for the content of the work.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data sets used in this study can be found in the full-text articles included in the systematic review and meta-analysis.

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SUPPORTING INFORMATION

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

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