Placenta and Reproductive Medicine

REVIEW ARTICLE

Association between human papillomavirus infection and non-cancerous reproductive health outcomes: An umbrella review

Youping Deng[1,*], Lang Wu[2,3], Jingjing Zhu[1,2]

[1]Department of Quantitative Health Sciences, John A. Burns School of Medicine, University of Hawaii at Manoa, Honolulu, HI 96813, USA

[2]Department of Interdisciplinary Oncology and Department of Genetics, LSU-LCMC Health Cancer Center, School of Medicine, Louisiana State University Health Sciences Center, New Orleans, LA 70112, USA

[3]Epidemiology and Population Health Program, School of Public Health, LSU-Health Sciences Center, New Orleans, LA 70112, USA

ABSTRACT

Human papillomavirus (HPV) infection is well established as a cause of multiple cancers; however, its association with non-cancerous reproductive health outcomes remains uncertain. This umbrella review aimed to comprehensively evaluate the strength and credibility of evidence linking HPV infection to non-cancerous reproductive outcomes based on published systematic reviews and meta-analyses. We systematically searched PubMed, Embase, and Web of Science from inception to March 2024 for systematic reviews and meta-analyses of observational studies examining associations between HPV infection, including specific genotypes, and non-cancerous reproductive health outcomes. The credibility of evidence was assessed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework, and methodological quality was evaluated using A Measurement Tool to Assess Systematic Reviews (AMSTAR). This review was not prospectively registered, which is acknowledged as a limitation. A total of 36 meta-analyses from 11 articles were included. According to AMSTAR, all studies were of moderate to high methodological quality. Our associations were supported by suggestive evidence, indicating that HPV infection, especially with high-risk types, was associated with elevated risks of preterm birth, low birth weight, female infertility, and unknown infertility. However, the certainty of evidence was low or very low for relevant outcomes according to GRADE, and most 95% prediction intervals crossed the null. This umbrella review suggests that HPV infection, especially with high-risk genotypes, may contribute to adverse pregnancy outcomes and infertility, but the evidence is of low to very low certainty. These findings highlight the need for further rigorous research to clarify these associations and determine their implications for public health.

Keywords: human papillomavirus, umbrella review, meta-analysis, reproductive health, non-cancerous outcomes, grading of recommendations assessment, development, and evaluation, risk

INTRODUCTION

Human papillomavirus (HPV) is a ubiquitous spherical DNA virus that exclusively infects humans and represents the most prevalent sexually transmitted infection worldwide.[1,2] Among healthy women, particularly those older than 30 years, the global prevalence of HPV infection is estimated at 11.7%.[3] HPV infection is also highly prevalent in men, with more than 31% of men aged ⩾ 15 years infected with at least one genital

***Corresponding Author:**
Youping Deng, Department of Quantitative Health Sciences, John A. Burns School of Medicine, University of Hawaii at Manoa, Honolulu, HI 96813, USA.
Email: dengy@hawaii.edu.cn. https://orcid.org/0000-0002-5951-8213

Received: 7 April 2026; Revised: 15 June 2026; Accepted: 20 June 2026
https://doi.org/10.54844/prm.2026.1201

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs 4.0 International License (https://creativecommons.org/licenses/by-nc-nd/4.0/), which allows others to copy and redistribute the material in any medium or format noncommercially.

HPV genotype and 21% harboring at least one high-risk (oncogenic) type.[4] Accordingly, HPV infection constitutes a major global public health concern.

HPV infection induces abnormal proliferation of epithelial cells in the skin and mucous membranes, leading to a spectrum of conditions ranging from benign lesions and warts to malignancies.[5] Although most early HPV infections are asymptomatic, persistent infection can result in long-term sequelae and increased mortality risk.[4] The probability of viral clearance decreases with prolonged infection duration.[6,7] Mechanistically, HPV interacts with host cell receptors *via* viral proteins to facilitate cellular entry and integration of viral DNA into the host genome, thereby disrupting normal cellular processes.[8] In addition, HPV can evade host immune responses, impair viral clearance, and promote persistent infection.[9]

HPV types are broadly classified as high-risk or low-risk according to their carcinogenic potential.[10,11] Low-risk types, such as HPV-6 and HPV-11, are typically associated with benign lesions (*e.g.*, common, flat, and plantar warts) affecting the genitals, anus, oropharynx, esophageal mucosa, and other sites.[12,13] In contrast, persistent infection with high-risk types, particularly HPV-16 and HPV-18, is strongly associated with multiple cancers,[14] including breast cancer and oesophageal squamous cell carcinoma, as highlighted in a recent umbrella review (UR).[15] However, the relationship between HPV infection and non-cancerous reproductive health outcomes remains unclear and controversial.[16–18] For instance, the 2021 Sexually Transmitted Diseases Treatment Guidelines reported no evidence that HPV infection impairs a woman's ability to conceive or carry a pregnancy to term.[19] In contrast, a 2023 systematic review and meta-analysis found a higher prevalence of high-risk HPV infection among women with pregnancy complications, such as preterm birth (PTB), compared with controls.[20] These inconsistencies underscore the need for a comprehensive evaluation of the available evidence.

UR is a rigorous evidence synthesis approach that systematically re-evaluates and integrates findings from multiple systematic reviews and meta-analyses.[21] This methodology enables a comprehensive and reliable assessment of the strength and credibility of existing evidence, thereby informing clinical practice, research priorities, and policy development.[22] To date, while prior studies have primarily focused on cancer outcomes, no study has comprehensively assessed the association between HPV infection and non-cancerous reproductive health outcomes. Therefore, we conducted an UR to synthesize current evidence from systematic reviews and meta-analyses, with the aim of evaluating the strength and credibility of associations, as well as identifying potential sources of bias and uncertainty in the existing literature.

METHODS

This UR adhered to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) and meta-analyses of observational studies in epidemiology (MOOSE) guidelines (Supplementary Tables 1-2).[23,24] This umbrella review was not prospectively registered in PROSPERO or a similar registry.

Literature search

We systematically searched PubMed, Embase, and Web of Science from inception to March 2024 without language restrictions. The detailed search strategy is provided in Supplementary Table 3. To ensure completeness, we also manually screened the reference lists of relevant systematic reviews and meta-analyses.

Eligibility criteria

Systematic reviews with meta-analyses of observational studies (cohort, case-control, and cross-sectional) were included if they met the following population, exposure, comparison, outcomes, study (PECOS) design criteria: (1) Population: Individuals with non-cancerous reproductive health outcomes and corresponding controls; (2) Exposure: Infection with HPV or specified genotypes (*e.g.*, HPV-6, HPV-11, or HPV-18); (3) Comparison: Individuals without HPV infection; (4) Outcomes: Risk of any non-cancerous reproductive health outcomes (*e.g.*, asthenospermia, female infertility, low birth weight [LBW]); human immunodeficiency virus (HIV) acquisition was considered within the reproductive health framework because of its strong link with sexual transmission, its frequent co-occurrence with HPV, and its impact on reproductive decision-making and outcomes; (5) Study design: systematic reviews or meta-analyses of observational studies.

Studies were excluded if they met any of the following criteria: (1) Focused on disease prevalence rather than associations, or were randomized controlled trials (RCTs) evaluating HPV vaccine efficacy or safety; (2) Did not report sufficient quantitative data (*e.g.*, effect estimates, 95% confidence intervals [CIs], or sample size); (3) Included fewer than three primary studies in the meta-analysis.[25]

For articles reporting multiple meta-analyses across different reproductive outcomes or HPV types, each analysis was considered separately.[26] When multiple meta-analyses addressed the same research question, the analysis including the largest number of studies was retained for the primary evaluation.[26] This approach minimized duplication of primary studies and reduced

the risk of biased estimates arising from overlapping evidence.[27]

Data extraction

For each eligible study, we extracted the first author, publication year, journal, exposure, comparison, outcomes, number of included studies, study design, number of cases, and total sample size. From each primary study within the included meta-analyses, we additionally extracted the first author, publication year, study design, number of cases, total population, and fully adjusted effect estimates (risk ratio [RR], odds ratio [OR], or hazard ratio [HR]) with corresponding 95% CI. Discrepancies between investigators were resolved through consensus.

Data analysis

To further evaluate the strength of evidence for reported associations, we recalculated summary estimates using data extracted from the original meta-analyses.[28] Adjusted summary effect sizes and corresponding 95% CIs were recomputed using random-effects models, accounting for both within- and between-study heterogeneity.[29] We also calculated 95% prediction intervals (PIs) to quantify the expected range of effects in future studies and to better capture between-study variability.[30,31]

For the largest study in each meta-analysis, the standard error of the effect estimate was calculated.[32] Heterogeneity was assessed using the I^2 statistic, with values > 50% and > 75% indicating substantial and considerable heterogeneity, respectively.[33]

Small-study effects were evaluated using Egger's regression test,[34] with $P < 0.1$ indicating potential bias.[35] We further conducted excess significance testing to compare the observed number of statistically significant studies (O; $P < 0.05$) with the expected number (E).[36] Excess significance bias was defined as $P < 0.1$ or one-sided $P < 0.05$ with O > E.[36] Statistical power for each meta-analysis was estimated using the effect size of the largest study and a non-central *t*-distribution. Agreement between estimates was assessed using the *Kappa* statistic.[37]

Sensitivity analyses were performed to assess the robustness of findings. For meta-analyses excluded due to overlap, we re-evaluated the strength of evidence to determine consistency with the primary analysis.[38] Additionally, for associations showing evidence of small-study effects, we repeated analyses after excluding smaller studies (< 25th percentile) to assess potential changes in evidence strength.[39] All analyses were conducted using Stata version 16 and RStudio version 3.6.2.

Assessment of methodological quality and grading of the evidence

Following established approaches in URs,[22,40,41] the credibility of each meta-analysis was classified as convincing, highly suggestive, suggestive, weak, or non-significant. This classification was based on multiple criteria, including statistical significance in random-effects models, number of cases, heterogeneity, 95% PIs, significance of the largest study, presence of small-study effects, and excess significance bias (Supplementary Table 4).

The methodological quality of included systematic reviews and meta-analyses was assessed using A Measurement Tool to Assess Systematic Reviews (AMSTAR).[42] This validated instrument evaluates methodological rigor across 11 domains, including literature search, study selection, data extraction, statistical analysis, and bias assessment.[42] AMSTAR scores were categorized as high (8-11), moderate (4-7), or low (0-3) quality.[43]

The overall certainty of evidence was further graded using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework.[44] Observational evidence was initially rated as low quality and subsequently downgraded or upgraded based on predefined criteria, including study limitations, inconsistency, indirectness, imprecision, publication bias, magnitude of effect, dose-response relationships, and residual confounding.[45,46]

RESULTS

Literature review

A total of 5784 records were identified through systematic database searches. After removal of duplicates, 3330 records underwent title and abstract screening, and 85 articles were assessed for full-text eligibility. Ultimately, 11 articles comprising 36 meta-analyses were included in this umbrella review (Figure 1). The reasons for exclusion of 30 full-text articles are detailed in Supplementary Table 5.

Credibility and GRADE quality assessments

Genital system diseases

A total of 28 associations evaluated the relationship between HPV infection and genital system diseases, including HIV acquisition ($n = 4$), sperm-related outcomes ($n = 8$), infertility (female, male, and unexplained; $n = 6$), low-grade cervical intraepithelial neoplasia ($n = 3$), high-grade cervical intraepithelial neoplasia ($n = 3$), as well as atypical squamous cells of undetermined significance, teratospermia, asthenospermia, and oligospermia.

According to GRADE, only one association was rated as

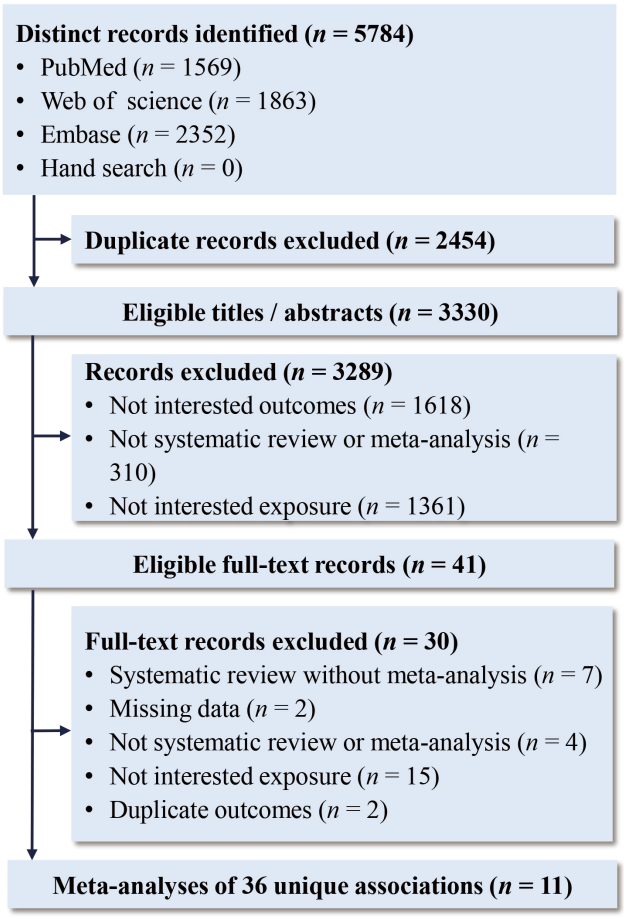

Figure 1. Flowchart of selection of studies for inclusion in umbrella review.

moderate-quality evidence, indicating that HPV infection was associated with an increased risk of male fertility abnormalities compared with HPV-negative controls (OR = 2.98, 95% CI: 1.98-4.48). The remaining 27 associations were graded as low or very low quality (Figure 2; Supplementary Figures 1-3; Supplementary Table 6).

Based on credibility assessment, two associations provided suggestive evidence: high-risk HPV infection was associated with increased risks of female infertility (OR = 2.33, 95% CI: 1.42-3.83) and infertility of unknown origin (OR = 2.96, 95% CI: 1.74-5.05). The remaining associations were classified as weak (n = 17) or non-significant (n = 9) (Figure 2; Supplementary Figures 1-3; Supplementary Table 7).

Pregnancy outcomes

Eight associations examined the relationship between HPV infection and pregnancy outcomes, including intrauterine growth restriction, assisted reproductive technology pregnancy rates, premature rupture of membranes, PTB, preterm premature rupture of membranes, spontaneous abortion, spontaneous PTB, and LBW.

Two associations provided suggestive evidence: HPV infection was associated with increased risks of PTB (OR = 1.50, 95% CI: 1.19-1.88) and LBW (OR = 1.91, 95% CI: 1.33-2.76) (Figure 2; Supplementary Figure 4; Supplementary Table 6).

The remaining associations were supported by weak (n = 4) or no evidence (n = 2). According to GRADE, three associations were rated as low-quality and five as very low-quality evidence (Figure 2; Supplementary Figure 4; Supplementary Table 7).

Characteristics of the included meta-analyses

The 11 included systematic reviews and meta-analyses were published between 2008 and 2023 and comprised 36 associations between HPV infection and non-cancerous reproductive health outcomes. Of these, 28 (77.8%) addressed genital system diseases and 8 (22.2%) focused on pregnancy outcomes.

Overall, 27 associations (75.0%) examined HPV infection status (overall, low-risk, high-risk, or combined), whereas 9 (25.0%) evaluated persistent versus non-persistent infection. The median number of primary studies per meta-analysis was 6 (range: 2-18), with a median sample size of 2637 participants (range: 441-336,391) and 603 cases (range: 72-7765). Five associations included more than 1000 cases (Supplementary Table 8).

Summary findings of the included meta-analyses

The summary results of the 36 associations are shown in Supplementary Tables 7 and 9. Based on random effects models, 25 (69.4%) of the 36 associations demonstrated positive associations between HPV infection and risk of non-cancerous reproductive health outcomes ($P < 0.05$). Among them, 18 associations (50.0%) met a more stringent significance threshold ($P < 10^{-3}$), and 10 (27.8%) reached $P < 10^{-6}$.

Regarding heterogeneity, 18 associations (50.0%) showed low heterogeneity ($I^2 < 50\%$), 9 (25.0%) showed high heterogeneity (I^2 = 50%-75%), and 9 (25.0%) reported very high heterogeneity ($I^2 > 75\%$). When 95% PIs were evaluated to assess the uncertainty of summary effects, 8 (22.2%) associations excluded the null value. In addition, we observed a small study effect for 3 associations (8.3%) and an excess significance bias for 11 associations (30.6%).

Quality assessment of included meta-analyses

According to AMSTAR criteria, 3 articles (27.3%) were rated as high quality (scores: 8-11), and 8 (72.7%) as moderate quality (scores: 4-7; Supplementary Table 10).

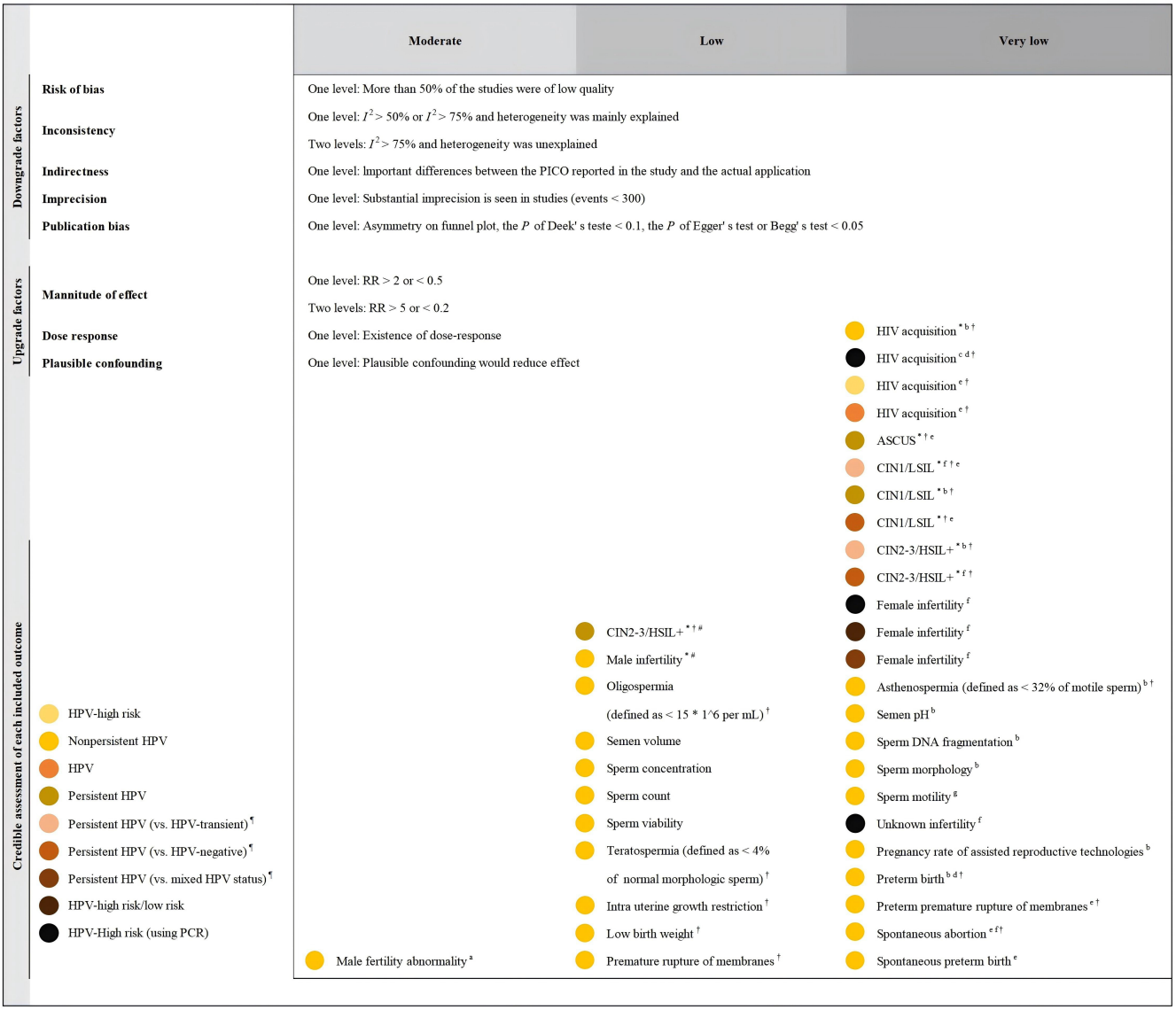

Figure 2. GRADE of included meta-analyses evaluating the associations between HPV infection and risk of reproductive health and pregnancy outcomes. [a] Upgraded by only one level for magnitude of effect: combined effect size > 2. [b] Downgraded by one level for inconsistency: substantial heterogeneity is seen between studies (I^2 > 50%). [c] Downgraded by one level for risk of bias: > 50% of studies in this comparison were from studies at high risk of bias. [d] Downgraded by one level for publication bias: asymmetry on funnel plot, the *P* of Egger's test or Begg's test < 0.05. [e] Downgraded by one level for imprecision: substantial imprecision is seen in studies (events < 300 or total population size < 400). [f] Downgraded by only one level for inconsistency: substantial heterogeneity is seen between studies (I^2 > 75%), whereas heterogeneity was mainly explained. [g] Downgraded by two levels for inconsistency: substantial heterogeneity is seen between studies (I^2 > 75%), whereas heterogeneity was unexplained. * Studies do not conduct methodological quality assessment. † Studies do not carry out corresponding analyses or show corresponding results, so the results recalculated in this UR are used to assess the certainty of evidence. # Studies do not evaluate the risk of bias, so they cannot be downgraded or upgraded based on the factors above. ¶ Other than these studies, the other studies are all HPV positive status compared with HPV negative status. ASCUS, atypical squamous cells of undetermined significance; CI, confidence interval; CIN, cervical intraepithelial neoplasia; CIN1, low-grade cervical intraepithelial neoplasia; CIN2-3, high-grade cervical intraepithelial neoplasia; DNA, deoxyribonucleic acid; ELISA, enzyme linked immunosorbent assay; FFT, fresh frozen tissue; HIV, human immunodeficiency virus; HPV, human papillomavirus; HSIL+, high-grade squamous intraepithelial lesions; LSIL, low-grade squamous intraepithelial lesions; PCR, polymerase chain reaction; PET, paraffin-embedded tissue.

Common methodological limitations included failure to incorporate grey literature in the search strategy, absence of a list of excluded studies, and lack of assessment of study quality or its impact on the overall findings.

Sensitivity analyses

Seven associations were excluded due to overlapping data. The direction and statistical significance of these associations were largely consistent with the main findings (Supplementary Table 11).

Three associations demonstrated evidence of small-study effects. Sensitivity analyses excluding smaller studies (< 25th percentile) did not materially alter the results (Supplementary Table 12).

For associations excluded from quantitative synthesis due to insufficient data, qualitative summaries indicated findings consistent with the primary analysis (Supplementary Table 13).

DISCUSSION

This UR comprehensively synthesizes and critically appraises evidence from 11 articles encompassing 36 associations derived from systematic reviews and meta-analyses examining the relationship between HPV infection, including specific genotypes, and non-cancerous reproductive health outcomes. Four associations were supported by suggestive evidence, indicating increased risks of PTB, LBW, female infertility, and infertility of unknown origin. Critically, the certainty of evidence according to GRADE was low or very low for all these suggestive associations, and most 95% prediction intervals crossed the null, indicating that the true effects remain uncertain and might be null in some populations. Therefore, these results should be interpreted with caution and do not prove causation.

Our findings indicate that HPV infection is associated with an increased risk of adverse pregnancy outcomes, particularly PTB and LBW, both supported by suggestive evidence. Specifically, HPV infection was associated with a higher risk of PTB (OR= 1.50, 95% CI: 1.19-1.88), consistent with previous studies. For instance, a meta-analysis of seven cohort studies reported that HPV infection may influence maternal physiology and increase the risk of PTB (OR = 1.81, 95% CI: 1.25-2.62).[47] Similarly, a large retrospective population-based register study (1999-2016) including 400,583 women found that HPV infection shortly before or during pregnancy was associated with an elevated risk of PTB (OR = 1.19, 95% CI: 1.01-1.42).[48] However, it is important to note that the association between HPV and PTB may be confounded by prior cervical treatments, such as loop electrosurgical excision procedure (LEEP) or conization, which are themselves independent risk factors for PTB. Most primary studies did not adequately adjust for these procedures, potentially biasing the observed associations. Future research should distinguish between untreated HPV infection, persistent infection, and post-treatment status to clarify the independent effect of HPV. Evidence also suggests that specific high-risk genotypes may confer greater risk. In the HERITAGE prospective cohort study of 1052 pregnant women, persistent HPV-16/18 infection was associated with a substantially increased risk of PTB (OR = 3.72, 95% CI: 1.47-9.39).[49] Together, these findings support the hypothesis that HPV infection, particularly with high-risk genotypes, may contribute to the risk of PTB.

PTB and LBW frequently co-occur, as shortened gestational duration is a major determinant of reduced birth weight.[50] Consistent with this relationship, our umbrella review also identified a suggestive association between HPV infection and increased risk of LBW (OR = 1.91, 95% CI: 1.33-2.76). This aligns with prior evidence indicating that HPV infection during pregnancy may adversely affect maternal and neonatal outcomes, including LBW, premature rupture of membranes, spontaneous abortion, and fetal death.[51]

The biological mechanisms underlying these associations remain incompletely understood but are likely multifactorial. HPV oncoproteins E6 and E7 may disrupt placental development and function by impairing trophoblast invasion and promoting apoptosis, thereby compromising placental integrity.[52] Such dysfunction may reduce nutrient and oxygen transfer, contributing to intrauterine growth restriction and LBW. In addition, HPV infection may ascend into the amniotic cavity, triggering inflammatory responses characterized by elevated cytokine levels.[53] Increased production of pro-inflammatory mediators, including interleukin-6 and tumor necrosis factor-α, may further disrupt placental function and promote pathways leading to PTB and premature rupture of membranes.[54–56] Nevertheless, the substantial heterogeneity and the fact that the 95% PIs for these outcomes cross 1.0 indicate that the associations are not consistently observed and may be non-significant in different contexts. The low or very low GRADE certainty further underscores that these findings remain tentative. Therefore, they should not be used to justify changes in clinical screening practices; instead, they highlight the need for additional prospective studies with standardized HPV exposure definitions.

Despite these findings, the results should be interpreted with caution. Substantial heterogeneity was observed, and prediction intervals often included the null value, indicating limited generalizability and potential variability across populations and study settings. From a clinical and public health perspective, these findings underscore the need for future research to investigate whether HPV prevention and monitoring strategies among women of reproductive age could clarify the observed associations. Specifically, well-designed prospective studies are warranted to evaluate whether standardized HPV assessment (including timing of infection, persistence, and prior cervical treatment history) or preventive interventions—such as vaccination—are associated with reduced risks of adverse pregnancy outcomes and infertility. Until such evidence becomes available, no changes to current clinical screening or vaccination guidelines are warranted.

Our UR also identified a suggestive association between high-risk HPV infection and increased risk of female infertility (OR = 2.33, 95% CI: 1.42-3.83). This finding is consistent with previous evidence. A nationwide population-based cohort study reported a higher risk of infertility among women with prior HPV infection, particularly those aged 26-35 years.[57] Similarly, a case-control study involving 190 participants (95 infertile and 95 fertile women) found that HPV was the most prevalent viral agent among infertile women and was significantly associated with infertility (OR = 7.02, 95% CI: 1.52-32.3).[58]

Several biological mechanisms may explain this association. First, high-risk HPV infection can lead to cervical intraepithelial neoplasia, which may result in cervical stenosis or obstruction, thereby impairing sperm transport and fertilization.[59] In addition, HPV-induced chronic cervicitis may alter cervical mucus properties and disrupt sperm-mucus interactions, further compromising fertility. Second, high-risk HPV infection has been implicated in tubal factor infertility. Viral oncoproteins E6 and E7 may disrupt cell cycle regulation and induce epithelial abnormalities in the fallopian tubes, potentially leading to tubal damage or occlusion.[60] Furthermore, HPV-associated chronic endometritis and endometrial inflammation may impair endometrial receptivity and hinder embryo implantation.[61]

Meanwhile, our UR also identified a moderate-quality association between HPV infection and male fertility abnormality (OR = 2.98, 95% CI = 1.98-4.48), although this finding requires confirmation in larger, well-controlled studies. Given that HPV is commonly transmitted through sexual contact, evaluation of male partners—even when asymptomatic—may be important in the context of infertility assessment and management.[62] However, these results should be interpreted cautiously due to substantial heterogeneity and the inclusion of the null value within the 95% prediction interval, suggesting limited robustness and potential variability across studies. Further well-designed studies are needed to clarify these associations. Again, the result for female infertility should be interpreted with caution because of high heterogeneity and the 95% PI including the null. The evidence does not establish that HPV infection causes infertility; rather, it signals an association that requires further validation, especially in well-controlled prospective studies.

To our knowledge, this is the first UR to comprehensively evaluate the hierarchy and credibility of evidence linking HPV infection to non-cancerous reproductive health outcomes, including adverse pregnancy outcomes, infertility, HIV coinfection, and cervical precancerous lesions. We applied rigorous and standardized criteria to assess methodological quality, strength of epidemiological evidence, and GRADE ratings. Overall, the included studies were of moderate to high methodological quality. Sensitivity analyses of excluded, overlapping meta-analyses addressing similar research questions demonstrated largely consistent findings, supporting the robustness of our results. By integrating evidence across a broad range of studies, this umbrella review provides a valuable evidence-based foundation to inform clinical practice and public health policy.

However, several limitations should be considered. First, this UR was not prospectively registered in PROSPERO or a similar registry. Although we strictly adhered to PRISMA and MOOSE guidelines and defined our protocol a priori, the lack of registration may increase the risk of selective reporting bias and should be considered when interpreting the findings. Second, as this review is based on observational studies, it is inherently subject to biases typical of such designs, including selection bias and residual confounding. Although many included studies adjusted for known confounders, unmeasured or incompletely measured factors, may still influence the observed associations. In particular, the timing of HPV infection (preconception, early *vs.* late pregnancy, persistent infection, or history of treated lesions) was not consistently differentiated across primary studies. This exposure heterogeneity may obscure distinct risk profiles and represents a critical gap in the literature. For pregnancy outcomes, insufficient adjustment for prior cervical excisional procedures in most primary studies could have biased the estimates. While some primary studies accounted for these variables,[48,63] heterogeneity in data quality and adjustment methods remains, which may contribute to residual bias and partially explain the generally low GRADE ratings. Nonetheless, given the ethical and practical challenges of conducting randomized controlled trials in this context, observational evidence represents the best available source of data. Third, substantial statistical heterogeneity was observed across several meta-analyses. This may reflect variability in study populations, exposure definitions, outcome classification, and study design. In particular, misclassification of non-cancerous reproductive outcomes in registry-based studies and differences in population characteristics may have contributed to both overestimation and underestimation of associations.[64] Fourth, the reliability of our findings depends on the quality of the included meta-analyses and their underlying primary studies. Although we verified extracted data against original studies, detailed evaluation of each primary study was beyond the scope of this review. Finally, some recently published primary studies may not have been captured;[65,66] however, comparisons with overlapping meta-analyses suggest that their omission is unlikely to

materially affect the overall conclusions.

CONCLUSIONS

This UR synthesized the existing evidence on the association between HPV infection and the risk of non-cancerous reproductive health outcomes. Our UR has provided evidence indicating that HPV or high-risk HPV infection was associated with an elevated risk of PTB, LBW, female infertility, and unknown infertility. However, the certainty of this evidence is low or very low, and most prediction intervals include the null value. These findings should not be interpreted as proof of a causal relationship. Given the limitations, this review does not support altering current clinical screening or vaccination guidelines. Instead, it identifies critical research priorities, including the need for studies that distinguish HPV exposure timing, account for cervical treatment history, and evaluate whether preventive interventions can ultimately mitigate these reproductive risks. Future larger prospective cohort studies, as well as experimental models to validate biological plausibility and potential causal mechanisms, are needed to verify these associations.

DECLARATIONS

Supplementary information

Supplementary materials are only available at the official site of the journal (www.hksmp.com).

Acknowledgement

We acknowledge the researchers who conducted the original studies and the meta-analyses that were included in this review for their valuable contributions to advancing knowledge in this field.

Author contributions

Deng YP, Zhu JJ: Conceptualization, Design. Deng YP, Wu L, Zhu JJ: Conduction, Investigation, Data analysis, Interpretation, Manuscript development, Revision. All authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.

Source of funding

None.

Ethical approval

Not applicable.

Informed consent

Not applicable.

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Use of large language models, AI and machine learning tools

No artificial intelligence (AI) tools or large language models (LLMs) were used in the design, conduct, analysis, or writing of this study.

Data availability statement

All related data are included in this review.

REFERENCES

1. Pańczyszyn A, Boniewska-Bernacka E, Głąb G. Telomeres and Telomerase During Human Papillomavirus-Induced Carcinogenesis. *Mol Diagn Ther*. 2018;22(4):421-430.
2. Bouvard V, Baan R, Straif K, *et al*. A review of human carcinogens--Part B: biological agents. *Lancet Oncol*. 2009;10(4):321-322.
3. Bruni L, Diaz M, Castellsagué X, Ferrer E, Bosch FX, de Sanjosé S. Cervical human papillomavirus prevalence in 5 continents: meta-analysis of 1 million women with normal cytological findings. *J Infect Dis*. 2010;202(12):1789-1799.
4. Bruni L, Albero G, Rowley J, *et al*. Global and regional estimates of genital human papillomavirus prevalence among men: a systematic review and meta-analysis. *Lancet Glob Health*. 2023;11(9):e1345-e1362.
5. zur Hausen H. Papillomaviruses and cancer: from basic studies to clinical application. *Nat Rev Cancer*. 2002;2(5):342-350.
6. Ho GY, Bierman R, Beardsley L, Chang CJ, Burk RD. Natural history of cervicovaginal papillomavirus infection in young women. *N Engl J Med*. 1998;338(7):423-428.
7. Schiffman M, Herrero R, Desalle R, *et al*. The carcinogenicity of human papillomavirus types reflects viral evolution. *Virology*. 2005;337(1):76-84.
8. Gammoh N, Grm HS, Massimi P, Banks L. Regulation of human papillomavirus type 16 E7 activity through direct protein interaction with the E2 transcriptional activator. *J Virol*. 2006;80(4):1787-1797.
9. Bhat P, Mattarollo SR, Gosmann C, Frazer IH, Leggatt GR. Regulation of immune responses to HPVinfection and during HPV-directed immunotherapy. *Immunol Rev*. 2011;239(1):85-98.
10. Egawa N, Egawa K, Griffin H, Doorbar J. Human Papillomaviruses; Epithelial Tropisms, and the Development of Neoplasia. *Viruses*. 2015;7(7):3863-3890.
11. Zandberg DP, Bhargava R, Badin S, Cullen KJ. The role of human papillomavirus in nongenital cancers. *CA Cancer J Clin*. 2013;63(1):57-81.
12. Taliercio S, Cespedes M, Born H, *et al*. Adult-onset recurrent respiratory papillomatosis: a review of disease pathogenesis and implications for patient counseling. *JAMA Otolaryngol Head Neck Surg*. 2015;141(1):78-83.
13. Dunne EF, Park IU. HPV and HPV-associated diseases. *Infect Dis Clin N Am*. 2013;27(4):765-778.
14. Kataja V, Syrjnen K, Syrjanen S, *et al*. Prospective follow-up of genital HPV infections: Survival analysis of the HPV typing data. *Eur J Epidemiol*. 1990;6(1):9-14.
15. Cao F, Li YZ, Zhang DY, *et al*. Human papillomavirus infection and the risk of cancer at specific sites other than anogenital tract and oropharyngeal region: an umbrella review. *EBioMedicine*. 2024;104:105155.
16. Yuan S, Qiu Y, Xu Y, Wang H. Human papillomavirus infection and female infertility: a systematic review and meta-analysis. *Reprod BioMed Online*. 2020;40(2):229-237.
17. D'Costa J, Saranath D, Dedhia P, Sanghvi V, Mehta AR. Detection of HPV-16 genome in human oral cancers and potentially malignant

lesions from India. *Oral Oncol*. 1998;34(5):413-420.
18. Pérez-González A, Cachay E, Ocampo A, Poveda E. Update on the Epidemiological Features and Clinical Implications of Human Papillomavirus Infection (HPV) and Human Immunodeficiency Virus (HIV) Coinfection. *Microorganisms*. 2022;10(5):1047.
19. Workowski KA, Bachmann LH, Chan PA, *et al*. Sexually Transmitted Infections Treatment Guidelines, 2021. *MMWR Recomm Rep*. 2021;70(4):1-187.
20. Ardekani A, Sepidarkish M, Mollalo A, *et al*. Worldwide prevalence of human papillomavirus among pregnant women: A systematic review and meta-analysis. *Rev Med Virol*. 2023;33(1):e2374.
21. Ioannidis J. Next-generation systematic reviews: prospective meta-analysis, individual-level data, networks and umbrella reviews. *Br J Sports Med*. 2017;51(20):1456-1458.
22. Ioannidis JP. Integration of evidence from multiple meta-analyses: a primer on umbrella reviews, treatment networks and multiple treatments meta-analyses. *CMAJ*. 2009;181(8):488-493.
23. Shamseer L, Moher D, Clarke M, *et al*. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ*. 2015;350:g7647.
24. Stroup DF, Berlin JA, Morton SC, *et al*. Meta-analysis of observational studies in epidemiology: A proposal for reporting. *JAMA*. 2000;283(15):2008-2012.
25. Lane MM, Gamage E, Du S, *et al*. Ultra-processed food exposure and adverse health outcomes: umbrella review of epidemiological meta-analyses. *BMJ*. 2024;384:e077310.
26. Veronese N, Solmi M, Caruso MG, *et al*. Dietary fiber and health outcomes: an umbrella review of systematic reviews and meta-analyses. *Am J Clin Nutr*. 2018;107(3):436-444.
27. Park JH, Eisenhut M, van der Vliet HJ, Shin JI. Statistical controversies in clinical research: overlap and errors in the meta-analyses of microRNA genetic association studies in cancers. *Ann Oncol*. 2017;28(6):1169-1182.
28. Aromataris E, Fernandez R, Godfrey CM, Holly C, Khalil H, Tungpunkom P. Summarizing systematic reviews: methodological development, conduct and reporting of an umbrella review approach. *Int J Evid Based Healthc*. 2015;13(3):132-140.
29. Lau J, Ioannidis JP, Schmid CH. Quantitative synthesis in systematic reviews. *Ann Intern Med*. 1997;127(9):820-826.
30. Graham PL, Moran JL. Robust meta-analytic conclusions mandate the provision of prediction intervals in meta-analysis summaries. *J Clin Epidemiol*. 2012;65(5):503-510.
31. Riley RD, Higgins JP, Deeks JJ. Interpretation of random effects meta-analyses. *BMJ*. 2011;342:d549.
32. Sun H, Gong TT, Xia Y, *et al*. Diet and ovarian cancer risk: An umbrella review of systematic reviews and meta-analyses of cohort studies. *Clin Nutr*. 2021;40(4):1682-1690.
33. Stoll R, Faucounau N. [Deficiencies of the müllerian ducts induced by norethindrone in the female chick embryo]. *C R Seances Soc Biol Fil*. 1987;181(3):300-306.
34. Sterne JA, Sutton AJ, Ioannidis JP, *et al*. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *BMJ*. 2011;343:d4002.
35. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ Br Med J*. 1997;315(7109):629-634. http://www.jstor.org/stable/25175671. Accessed 22 June 2026.
36. Ioannidis JP, Trikalinos TA. An exploratory test for an excess of significant findings. *Clin Trials*. 2007;4(3):245-253.
37. Kundel HL, Polansky M. Measurement of observer agreement. *Radiology*. 2003;228(2):303-308.
38. Kalliala I, Markozannes G, Gunter MJ, *et al*. Obesity and gynaecological and obstetric conditions: umbrella review of the literature. *BMJ*. 2017;359:j4511.
39. Dechartres A, Altman DG, Trinquart L, Boutron I, Ravaud P. Association between analytic strategy and estimates of treatment outcomes in meta-analyses. *JAMA*. 2014;312(6):623-630.
40. Bellou V, Belbasis L, Tzoulaki I, Evangelou E, Ioannidis JP. Environmental risk factors and Parkinson's disease: An umbrella review of meta-analyses. *Parkinsonism Relat Disord*. 2016;23:1-9.
41. Li X, Meng X, Timofeeva M, *et al*. Serum uric acid levels and multiple health outcomes: umbrella review of evidence from observational studies, randomised controlled trials, and Mendelian randomisation studies. *BMJ*. 2017;357:j2376.
42. Shea BJ, Grimshaw JM, Wells GA, *et al*. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. *BMC Med Res Methodol*. 2007;7:10.
43. Shea BJ, Hamel C, Wells GA, *et al*. AMSTAR is a reliable and valid measurement tool to assess the methodological quality of systematic reviews. *J Clin Epidemiol*. 2009;62(10):1013-1020.
44. Guyatt G, Oxman AD, Akl EA, *et al*. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol*. 2011;64(4):383-394.
45. Guyatt GH, Oxman AD, Vist GE, *et al*. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336(7650):924-926.
46. Tan J, Li L, Huang X, *et al*. Associations between gastro-oesophageal reflux disease and a range of diseases: an umbrella review of systematic reviews and meta-analyses. *BMJ Open*. 2020;10(12):e038450.
47. Wu D, Chen L, Zhen J, Jin X. Systematic review and meta-analysis on influence of human papillomavirus infection during pregnancy on premature rupture of membranes and premature delivery. *Ann Palliat Med*. 2021;10(10):10735-10743.
48. Wiik J, Nilsson S, Kärrberg C, Strander B, Jacobsson B, Sengpiel V. Associations of treated and untreated human papillomavirus infection with preterm delivery and neonatal mortality: A Swedish population-based study. *PLoS Med*. 2021;18(5):e1003641.
49. Niyibizi J, Mayrand MH, Audibert F, *et al*. Association Between Human Papillomavirus Infection Among Pregnant Women and Preterm Birth. *JAMA Netw Open*. 2021;4(9):e2125308.
50. Ohuma EO, Moller AB, Bradley E, *et al*. National, regional, and global estimates of preterm birth in 2020,with trends from 2010: a systematic analysis. *Lancet*. 2023;402(10409):1261-1271.
51. Condrat CE, Filip L, Gherghe M, Cretoiu D, Suciu N. Maternal HPV Infection: Effects on Pregnancy Outcome. *Viruses*. 2021;13(12):2455.
52. Gomez LM, Ma Y, Ho C, McGrath CM, Nelson DB, Parry S. Placental infection with human papillomavirus is associated with spontaneous preterm delivery. *Hum Reprod*. 2008;23(3):709-715.
53. Kwon JY, Romero R, Mor G. New insights into the relationship between viral infection and pregnancy complications. *Am J Reprod Immunol*. 2014;71(5):387-390.
54. Kusanovic JP, Romero R, Chaiworapongsa T, *et al*. Amniotic fluid sTREM-1 in normal pregnancy, spontaneous parturition at term and preterm, and intra-amniotic infection/inflammation. *J Matern Fetal Neonatal Med*. 2010;23(1):34-47.
55. Chang Y, Li W, Shen Y, Li S, Chen X. Association between interleukin-6 and preterm birth: a meta-analysis. *Ann Med*. 2023;55(2):2284384.
56. Romero R, Gómez R, Chaiworapongsa T, Conoscenti G, Kim JC, Kim YM. The role of infection in preterm labour and delivery. *Paediatr Perinat Epidemiol*. 2001;15 Suppl 2:41-56.
57. Hsu LC, Tsui KH, Wei JC, Yip HT, Hung YM, Chang R. Female Human Papillomavirus Infection Associated with Increased Risk of Infertility: A Nationwide Population-Based Cohort Study. *Int J Environ Res Public Healh*. 2020;17(18):6505.
58. Pebdeni PH, Saffari F, Mollaei HR, *et al*. Increased Risk of Infertility in Women Infected with Human Papillomavirus. *J Reprod Infertil*. 2023;24(3):188-197.
59. Ang KK, Harris J, Wheeler R, *et al*. Human papillomavirus and survival of patients with oropharyngeal cancer. *N Engl J Med*. 2010;363(1):24-35.
60. Pal A, Kundu R. Human Papillomavirus E6 and E7: The Cervical Cancer Hallmarks and Targets for Therapy. *Front Microbiol*.

2020;10:3116.

61. Kombe Kombe AJ, Li B, Zahid A, *et al*. Epidemiology and Burden of Human Papillomavirus and Related Diseases, Molecular Pathogenesis, and Vaccine Evaluation. *Front Public Health*. 2020;8:552028.
62. Lundqvist M, Westin C, Lundkvist Ö, *et al*. Cytologic screening and human *Papilloma* virus test in women undergoing artificial fertilization. *Acta Obstet Gynecol Scand*. 2002;81(10):949-953.
63. Khayargoli P, Mayrand MH, Niyibizi J, *et al*. Association between Human Papillomavirus 16 Viral Load in Pregnancy and Preterm Birth. *Viruses*. 2024;16(2):298.
64. Bray F, Parkin DM. Evaluation of data quality in the cancer registry: principles and methods. Part I: comparability, validity and timeliness. *Eur J Cancer*. 2009;45(5):747-755.
65. Bi D, Wei S, Luo X, Luo X, Tang X. Management for persistent HPV infection and cervical lesions among women infected with HIV: a retrospective observational cohort study. *Virol J*. 2024;21(1):133.
66. Agyare Gyane F, Modey E, Maya E, *et al*. Prevalence and risk factors associated with high-risk human papillomavirus infection among women living with HIV (WLWH) at a tertiary health facility in *Accra*, Ghana. *PLoS One*. 2024;19(5):e0303535.