

Risk of cervical cancer and high-grade lesions in vulnerable women a systematic review and meta-analysis

Received: 7 March 2025

Accepted: 6 February 2026

Published online: 02 March 2026

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Cervical cancer is largely preventable, yet causes around 300,000 deaths annually, disproportionately affecting vulnerable women. In here, we aim to estimate the risk of high-grade cervical lesions and cervical cancer among vulnerable populations in high- and upper-middle-income countries. We conduct a systematic review and meta-analysis of studies published up to February 2024 (from 2004 for HIV) across four databases. Risk of bias is assessed using the Newcastle–Ottawa Scale. We include women with low socioeconomic status, migrants, prisoners, sex workers, women with substance use disorders, mental illness, and living with HIV. The primary outcome is the pooled risk of cervical cancer and high-grade lesions; the secondary outcome is subgroup-specific risk. The analysis focuses on biologically defined females, with sex determined by author reporting. In this work, based on 127 studies, we show that vulnerable women face higher risks of cervical cancer (RR2.78; 95%CI 2.32–3.32) and high-grade lesions (RR 2.5; 95%CI 2.05–3.04), with high heterogeneity supporting equity-focused prevention strategies.

Cervical cancer (CC) remains a major global public health concern, with over 600,000 new cases diagnosed annually¹. Even in high- and upper-middle-income countries (HICs and UMICs), where screening and HPV vaccination have significantly reduced CC incidence and mortality, these benefits are not equitably distributed^{2–4}. Evidence shows a persistent social gradient in CC outcomes^{5–8}, with certain subgroups—such as women living with HIV (WLWH), socio-economically disadvantaged individuals, women with disabilities, and migrants—facing significantly higher risks of high-grade cervical lesions (HGL) and CC^{6,9–11}.

These disparities result from a complex interplay of factors, including lower cervical screening uptake, delayed diagnoses, and a higher burden of persistent HPV infection in affected groups^{12–14}. Limited awareness of HPV, negative attitudes toward screening, and various cultural and systemic barriers further restrict access to care^{15–17}. Together, these challenges hinder progress toward the equity-focused targets set by the World Health Organisation (WHO) in its global strategy for cervical cancer elimination¹⁸.

However, the concept of “vulnerability” is still not clearly defined in the literature, and there are no standardised criteria for identifying at-risk populations in different settings. While individual studies have reported increased cervical disease burden in various subgroups^{6,9–11}, few have applied rigorous meta-analytic methods to quantify risk across diverse vulnerable populations in high-income (HICs) and upper-middle-income (UMICs) countries. This limits the generalisability of findings and the development of evidence-based policies.

Filling this gap is essential. In most high-resource settings, cervical cancer prevention strategies tailored to vulnerable women are underdeveloped or lacking¹⁹. Policymakers lack a comprehensive synthesis of the burden of high-grade lesions and cervical cancer in these populations. A robust systematic review and meta-analysis could generate the evidence needed to guide targeted interventions and public health priorities. Adopting an inclusive definition of vulnerability and conducting subgroup analyses would help identify the most

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at-risk populations, enabling equity-oriented, country-specific prevention strategies.

This review adopts the WHO's conceptual framework on social determinants of health to define vulnerability. It sees health inequities as shaped by structural and intermediary determinants within social, economic, and political systems²⁰. In this context, vulnerability refers to greater barriers in accessing, using, and receiving quality cervical cancer prevention, screening, and treatment due to disadvantaged social positions and systemic exclusion. We focus on socioeconomically disadvantaged women (e.g., those in deprived areas or with low education/income), female sex workers (FSW), migrants, female prisoners, women living with HIV (WLWH), and women with mental illness or substance use disorders (alcohol, drugs, or both).

In this work, we synthesise existing evidence on the risk of cervical cancer and high-grade lesions (CIN2+, CIN3+, carcinoma in situ, and HSIL) among vulnerable women in high- and upper-middle-income countries. Through a systematic review and meta-analysis, we quantify the relative risk faced by these populations compared to the general female population. By pooling risk estimates from a diverse range of studies, we seek to provide a clearer picture of the inequities that exist beyond basic resource limitations and to support the design of more targeted, equity-driven prevention and control strategies.

Results

Study selection

Our systematic search, yielded 11540 citations, of which, 138 fully published studies met our eligibility criteria. Data were extractable from 127 of them (see Supplementary Fig. 21 for the PRISMA flow diagram and supplementary Data 2 for the list of excluded studies).

For cervical cancer (CC) and high-grade lesions (HGL), 92% and 79% of the included studies, respectively, were conducted in high-income countries. Most studies reporting on CC originated from Europe and Central Asia (42%) and North America (31%). A similar pattern was observed for HGL, with 33% of studies originating from Europe and Central Asia and 29% from North America (see Table 1).

The quantitative analysis included studies of WLWH ($n=59$), migrants ($n=22$), Female sex workers (FSW, $n=7$), women with substance use disorders ($n=9$), women of low socioeconomic status ($n=7$), prisoners ($n=7$), and women with mental illness ($n=16$).

For both cervical cancer (CC) and high-grade lesions (HGL), the majority of included studies were cohort studies, accounting for 90% ($n=95$) and 60% ($n=25$), respectively. These were followed by cross-sectional studies, representing 7% ($n=8$) of CC studies and 33% ($n=14$) of HGL studies. Case-control studies were the least common, comprising 3% ($n=3$) of CC studies and 7% ($n=3$) of HGL studies.

Study characteristics

A detailed description of the characteristics of the included study by group is available in the supplementary material (Supplementary table 2 and 3).

For the comparative meta-analysis, we found considerable significant heterogeneity for all outcomes and subgroups, except for HGL with both women with substance use disorder ($p=0.22$, $I^2=34\%$) and prisoners ($p=0.46$, $I^2=0\%$).

Definitions of exposure varied within vulnerability groups. In women with substance use disorder group ($n=9$), six studies focused exclusively on alcohol use disorders, one reported on drug but excluded alcohol use disorders and tobacco use, one included any type of substance abuse, and one did not define drug use disorders.

Of studies on migrants ($n=22$), four focused on migrants from developed countries, four on migrants from developing countries, and 14 did not specify country of origin.

For the women of low socioeconomic status, definitions varied within studies. These were based on family income ($n=2$), educational level ($n=1$), living in economically deprived areas ($n=5$), and remote/

rural areas ($n=4$). Some papers reported more than one definition. Due to the use of different definitions or outcomes, some studies contributed multiple comparisons, resulting in more than one entry per study in the analysis. A full description of the eligible studies stratified by vulnerable groups and their definitions of exposure are available in supplementary Data 4.

Primary outcome

We conducted a pooled risk analysis of CC using data from 127 studies, comparing seven vulnerable groups to a control population. Vulnerable women had significantly higher risk of CC (RR 2.78; 95%CI: 2.32–3.32; 106 studies) with high heterogeneity among studies ($I^2=98.3\%$) (Fig. 1). The same pattern was found with HGL (RR 2.5; 95% CI 2.05–3.04; 42 studies) with a significant heterogeneity ($I^2=99.6\%$) (Fig. 2).

Secondary outcome: Risk of CC and HGL by vulnerability

In the subgroup analysis, we found overall pooled risk of CC was significantly higher for women with substance use disorder (RR 2.75; 95% CI: 2.02–3.74; $I^2=78.6\%$, 8 studies), WLWH (RR 5.02; 95%CI: 4.05–6.21; $I^2=90.4\%$, 50 studies), migrants (RR 1.43 95% CI: 1.01–2.03; $I^2=98\%$, 20 studies), women with mental illness (RR 1.37; 95% CI: 1.04–1.80; $I^2=94.1\%$, 14 studies), prisoners (RR 3.01; 95%CI: 1.67–5.43; $I^2=52.9\%$, 5 studies), women of low socioeconomic status (RR 1.12; 95% CI 1.01–1.23; $I^2=84.9\%$, 6 studies) and FSW (RR 50.51; 95%CI: 2.72–937.35, with only 1 study) (Fig. 1).

HGL risk was found to be significantly higher among all groups: women with substance use disorder (RR 2.31; 1.09–4.89; $I^2=34\%$, 3 studies); WLWH (RR 2.88; 2.11–3.93; $I^2=95.1\%$, 18 studies); migrants (RR 1.68; 1.36 –2.06; $I^2=80.9\%$, 5 studies); women of low socioeconomic status (RR 1.33; 1.11–1.60; $I^2=99.6\%$, 3 studies); FSW (RR 4.04; 95% CI 2.54–6.4; $I^2=54.2\%$, 7 studies) and prisoners (RR 2.77; 2.41–3.17; $I^2=0\%$, 4 studies). Only two studies were included for women with mental illness (RR 4.47; 95%CI: 1.13; 17.62; $I^2=100\%$) (Fig. 2).

A summary of the main results by outcome and vulnerability group is provided in Supplementary Table 4 and the detailed forest plots by vulnerability in Supplementary figs. 1–14.

Subgroup analysis

The overall conclusions of the analysis were not significantly affected by income level, publication date, risk of bias or study design. The data are available in Fig. 3 and Fig. 4.

Publication bias and risk of bias assessment

Where applicable we generated funnel plots, which revealed substantial publication bias among our primary and secondary outcomes (Supplementary figs. 15–20). We also found an overall high risk of bias in 44% of the included studies, a moderate risk in 42%, and a low risk in only 14%. The risk of bias was low to moderate in over 50% of the studies in the following three groups: women of low socioeconomic status (50%); women with substance use disorder (67%); and women with a mental illness (56%) (Supplementary Data 4). Common methodological weaknesses included insufficient observation periods and inadequate reporting on loss to follow-up.

Discussion

Our systematic review and meta-analysis included 127 studies. Our findings indicate that the pooled relative risks of cervical cancer and high-grade cervical lesions are significantly higher in all of the groups studied than in the general population. The highest risks for CC were observed among women living with HIV (WLWH), incarcerated women, and those with substance use disorders, with relative risks three to five times higher than in the general population. For high-grade cervical lesions, the highest risks were observed among female

Table 1 | Description of Included studies for Cervical Cancer and High-Grade lesions

	Cervical Cancer (N = 106)	High-Grade Lesions (N = 42)
OECD classification		
High income	97 (92%)	33 (79%)
Upper middle income	9 (8%)	9 (21%)
Group		
Female Sex Workers	1 (1%)	7 (17%)
Migrants	20 (19%)	5 (12%)
Prisoners	5 (5%)	4 (9%)
Women Living With HIV (WLWH)	51 (48%)	18 (43%)
Women with low Socio-economic Status	6 (6%)	3 (7%)
Women with Mental Illness	15 (14%)	2 (5%)
Women with substance use disorder	8 (7%)	3 (7%)
Region		
East Asia & Pacific	16 (15%)	9 (21%)
Europe & Central Asia	45 (42%)	14 (33%)
Latin America & Caribbean	5 (5%)	2 (5%)
Middle East & North Africa	4 (4%)	1 (2%)
North America	33 (31%)	12 (29%)
Sub-Saharan Africa	3 (3%)	4 (10%)
Study design I		
Ecological	6 (6%)	3 (7%)
Individual	100 (94%)	39 (93%)
Study design II		
Case-control	3 (3%)	3 (7%)
Cohort	95 (90%)	25 (60%)
Cross-sectional	8 (7%)	14 (33%)

The total number of studies presented in the descriptive tables exceeds the number of unique studies shown in the PRISMA flow diagram ($n = 127$), as some studies reported on both cervical cancer and high-grade lesions and were therefore included in both columns.

sex workers, WLWH and incarcerated women, with relative risks three to four times higher. These results imply that the transition from precancerous lesions to invasive cancer may be influenced not only by biological factors, but also by substantial disparities in access to screening, prompt diagnosis, follow-up care, and treatment.

The women in the vulnerable groups that we focused on faced multiple challenges, including low vaccination coverage and low participation in screening programmes. Low resources, drug consumption and HIV infection act together to increase the risk of HGL and cancer in these populations. For instance, a Canadian study found a high prevalence of HIV infection (11.5%) and mental illness (57%) among female sex workers²¹. Thus, when interpreting these results, researchers should carefully consider intersectionality of different risk factors.

Another key finding of our analysis was the identification of two broad population groups with different levels of vulnerability to high-grade lesions (HGL) and cervical cancer (CC). The first group faces a substantially elevated risk—more than twice that of the general population—and includes women living with HIV, individuals with substance use disorders, sex workers, and incarcerated women. These individuals often experience multiple vulnerabilities; for instance, a concurrent HIV infection, unstable housing and substance use can collectively increase the likelihood of persistent HPV infection, unprotected sex and having a high number of sexual partners²².

The second group of vulnerability exhibits a more moderate increase in risk, with relative risks ranging from 1.12 to 1.43, and

includes migrant women, women of low socioeconomic status, and those with mental health disorders. However, these populations are heterogeneous. For instance, migrant women from high-HPV-prevalence regions differ significantly from those from settings with restrictive sexual norms—differences that may cancel out in aggregate data. Likewise, socioeconomic disadvantage is often measured using composite indices, which may obscure critical individual-level variation. The risk profiles of women with mental health disorders also vary widely depending on disorder severity and treatment.

To address this complexity, we structured our analysis around these two overarching categories, enabling a more precise examination of the underlying mechanisms and context-specific vulnerabilities.

Sex workers with HIV and substance use disorders accumulate common risk factors, including early initiation of sexual activity, many sexual partners, and higher exposure to persistent human papillomavirus (HPV) infection^{23–25}. Unprotected sex increases risk for co-infection with HIV²⁶, which can increase immune suppression and increase the likelihood HPV will persist and progress to HGL²⁷. We believe this is why women who belong to these groups had 2- to 5-fold higher risk of HGL and CC than the general population. Our findings align with two prior meta-analysis that reported a 3- to 5-fold increase^{9,28}.

Prisoners face risks 2-fold higher for HGL and 3-fold higher for CC. Contributing factors include poverty, migration, prostitution, alcohol and drug abuse, increased risk of HIV infection²⁹, and lack of organised screening and follow-up in prison settings^{30,31}. Notably, loss to follow-up upon release exacerbates this challenge^{32,33}. A systematic review of a similar population reported that all 21 of the included studies described higher prevalence of dysplasia in prison population than in control groups³¹. Another meta-analysis showed a 5-fold increase in cervical lesions and a 100-fold increase in CC prevalence³⁴.

Both migrants and socio-economic status are heterogeneous variously defined, so risk assessments must consider context and definitions.

Migrants were at higher risk of HGL (RR 1.68 ;1.36–2.06), which may have been attributable to higher prevalence of HPV infections in their country of origin, low vaccination coverage, and lower adherence to screening³⁵. Women who immigrated after becoming sexually active¹¹ and women from countries with high HPV prevalence, such as eastern Europe and western Africa, may be especially at risk³⁶. However, CC among migrants was significant but more heterogeneous (RR 1.43; 1.01–2.03). Some studies suggest that risk decreases the longer migrants remain in their host country and could be higher for women who were older when they migrated^{37,38}. Country of origin also plays a pivotal role in shaping risk patterns. Women who migrated from more societies where cultural and religious norms—such as prohibitions against premarital sex or multiple sexual partners—may be less exposed to HPV infection, and thus may be at lower risk of developing CC^{37,39}. For example, a study from Australia compared infection-related cancer patterns in migrants and found similar stomach and liver cancer trends, but CC incidence varied by country of origin; rates were lowest among women from North Africa (IRR 0.42;0.23-0.77) and the Middle East (IRR 0.63; 0.49-0.81)⁴⁰. A Swedish study also found significantly lower risk for women from these regions (HR 0.31; 0.24-0.39)⁴¹.

Women with low socio-economic status had a modestly elevated risk of both HGL (RR 1.33; 1.11–1.6) and CC (1.12; 1.01–1.23), possibly because studies classified cancer differently. The technique used can also fail to effectively detect cancer lesions as reported by Prummel et al. for Pap tests²⁹ which could lead to underdiagnoses of CC^{42,43}.

A second explanation of this result may be attributable to the study setting, where the comparison group already faces significant socioeconomic challenges as found in Luce's et al. study carried in the French West Indies⁴⁴. A third explanation is that these women constitute a highly heterogeneous group in the studies we included. The

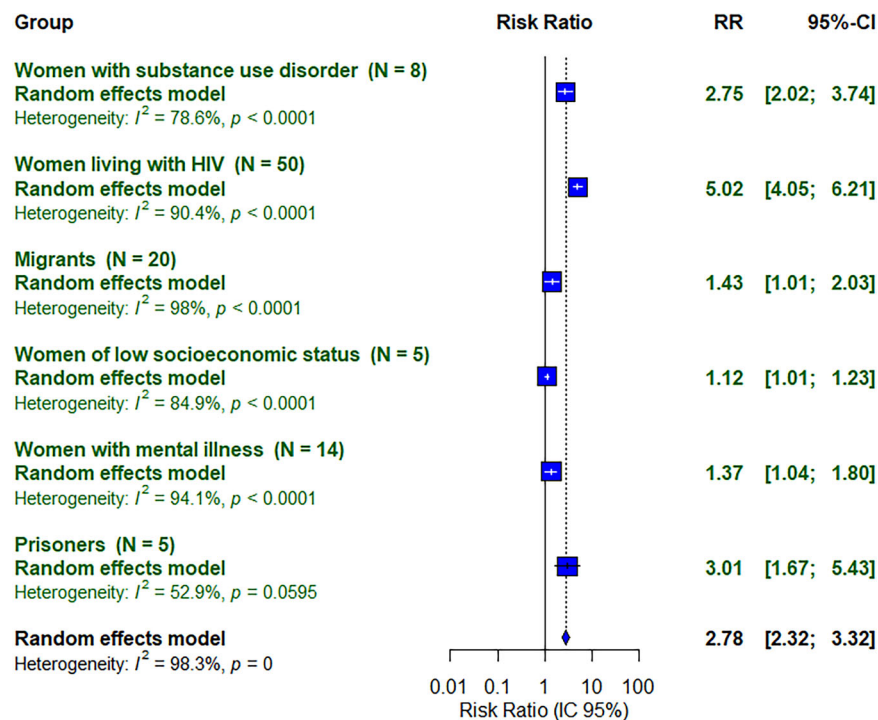


Fig. 1 | Pooled risk of cervical cancer among vulnerable women in high and upper-middle countries. The figure illustrates subgroup-specific and pooled relative risks (RRs) of cervical cancer with corresponding 95% confidence intervals, estimated using a random-effects model (inverse-variance method). A total of 106 unique studies were included; some contributed to multiple vulnerability groups.

Among these, 85 studies reported crude data, representing a total of 15,077,522 participants. The overall effect was statistically significant ($p < 0.0001$). All tests were two-sided, and no adjustment was made for multiple comparisons. Between-study heterogeneity was assessed using Higgins' I^2 statistic, where $I^2 > 75\%$ indicates considerable heterogeneity.

definition of low socioeconomic status can vary from individual, e.g., women with low household income or low educational attainment, to collective, e.g., women who live in areas far from health services or who are generally disadvantaged, and these differences may dilute or mask the true effect. For example, a nationwide study in Denmark found higher risk for women with the lowest income (IRR 1.17; 1.07–1.28) and lower risk for those who lived in rural areas (IRR 0.87; 0.77–0.99)⁴⁵.

Women with mental illness showed a moderate but significant increase in CC risk (RR 1.37; 1.04–1.8), although findings across studies were inconsistent. The meta-analysis by Wotten et al.⁴⁶, reported a similar result (OR = 1.35 [1.2–1.5]). Variability may result from different definitions and severity levels of mental illness; decreased risk could result from reduced sexual activity⁴⁷. Conversely, increased risk may result from higher prevalence of HPV infection, lower adherence to primary and secondary prevention^{48–50}, or to smoking or alcohol use^{51–53}.

To our knowledge, this is the first analysis including a wide definition of vulnerable groups.

The data we present have limitations. The first is that, although we calculated a pooled global estimate of the RR, there was considerable statistical heterogeneity across the studies, as was reported in a previous paper that focused on women living with HIV⁹. In registry linkage studies, data on lifestyle and behavioural variables was rarely collected, so key confounders such as smoking and sexual behaviour may have been omitted^{23,24}.

To explore the substantial heterogeneity across studies, we conducted subgroup analyses by country income level, study design, and risk of bias. These factors did not appear to influence the main results. However, subgroup analyses have notable limitations: high between-study heterogeneity may reduce precision and obscure true differences, while non-significant results may reflect low statistical power⁵⁴.

In the absence of formal power calculations, the impact of these moderators cannot be reliably assessed. Moreover, as these are observational analyses, causal inferences cannot be drawn and confounding by unmeasured variables remains possible⁵⁴.

Heterogeneity may also stem from within-group variations, such as country of origin among migrant women, mental illness subtype, or definitions of social deprivation. Future analyses will examine specific factors—including country-specific HPV prevalence, age, duration of migration, and type of mental illness—to better understand risk variations within vulnerable populations.

Definitions of cervical lesions according to cytological and histological classifications and also methods for measuring them varied across studies, which may have impacted the robustness of our findings.

Our analysis revealed substantial publication bias, as indicated by the asymmetry of the funnel plot. This bias may have led to an overestimation of the pooled effect sizes, highlighting the importance of interpreting the findings with caution.

Of the eleven studies not considered in the quantitative synthesis, nine lacked either a pooled effect estimate or sufficient crude numbers. These included three studies on women living with HIV (out of 59 included), three studies on migrant populations (out of 22 included), one study on mental illness (out of 16 included) and two studies on prisoners (out of 7 included). While excluding these studies may have resulted in the loss of some potentially relevant information, the small number of studies and the substantial representation of these groups in the meta-analysis suggest that the overall results are unlikely to have been significantly impacted.

Future research should prioritise developing a more nuanced understanding of cervical cancer risk within and across different vulnerable groups. Comparative assessments of sociodemographic strata are essential for exploring intra-group differences, uncovering hidden

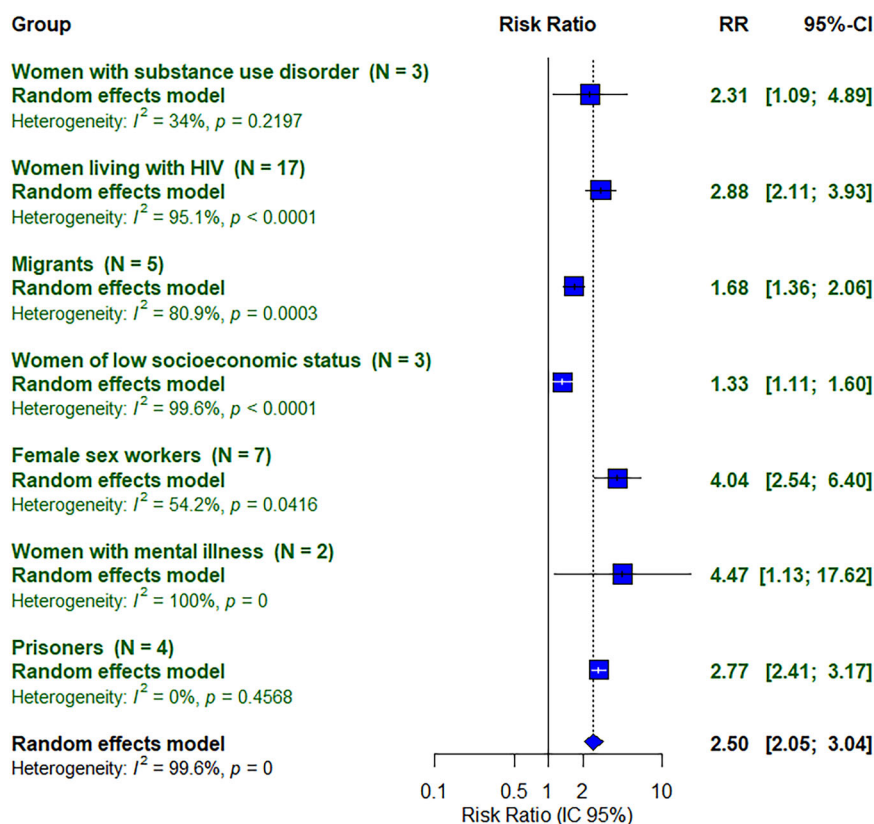


Fig. 2 | Pooled risk of high-grade lesions among vulnerable women in high and upper-middle countries. WLWH: Women living with HIV, FSW: Female Sex Workers. The figure illustrates subgroup-specific and pooled relative risks (RRs) of high-grade lesions with corresponding 95% confidence intervals, estimated using a random-effects model (inverse-variance method). A total of 42 unique studies were included, some contributed to multiple vulnerability groups. Among these, 35

reported crude data, representing a total of 4,702,900 participants. The overall effect was statistically significant ($p < 0.0001$). All tests were two-sided, and no adjustment was made for multiple comparisons. Between-study heterogeneity was assessed using Higgins' I^2 statistic, where $I^2 > 75\%$ indicates considerable heterogeneity.

layers of vulnerability, accounting for heterogeneity in outcomes and guiding more precise and equitable policy interventions.

The WHO highlights two core pillars for cervical cancer control: primary prevention via HPV vaccination and secondary prevention through screening, both requiring context-specific implementation. Ensuring vaccine affordability and expanding eligible age groups has proven effective and safe⁵⁵, and may improve coverage in underserved populations. Similarly, access to screening can be increased through self-sampling kits, mobile units, community health workers, and patient navigators, with encouraging results^{56–62}. Nonetheless, these measures alone are insufficient to achieve the WHO's 90-70-90 targets.

To achieve meaningful impact, a multidisciplinary and culturally sensitive approach is required. This includes community-based education, addressing women's preferences and barriers to care, and tailoring interventions to local contexts. As loss to follow-up in cervical screening can result in clinically significant lesions being missed, proactive measures such as phone reminders or facilitated consultations may be essential to ensure timely follow-up, particularly among vulnerable women^{63,64}.

Innovative strategies, such as the HPV-Faster approach—which combines simultaneous vaccination and screening with cost-effectiveness evaluation—offer a promising path forward⁶⁵. Such initiatives may enhance reach and sustainability, particularly among hard-to-reach populations.

From a policy standpoint, our findings highlight the urgent need for prevention strategies that are tailored to specific populations. Generating evidence, particularly through meta-analyses, is essential to inform policy. The CBIG-SCREEN policy survey of 22 European

countries found that, while 90% of respondents recognised underserved groups in their screening programmes, over 70% had not implemented targeted strategies to address these disparities¹⁹. The recent introduction of health system assessment tools by the International Agency for Research on Cancer offers a solid foundation on which to design and implement effective cervical cancer control programmes that are appropriate for the local context and tailored to vulnerable groups⁶⁶.

Vulnerable groups are at higher risk of developing both HGL lesions and CC, highlighting the importance of tailoring interventions to meet their needs. Where multiple disadvantages intersect, the social determinants of health must be addressed by, for example, introducing a Social Vulnerability Index (SVI) into screening programmes to aid policymakers and researchers in identifying and serving vulnerable populations more effectively⁶⁷.

Method

This systematic review and meta-analysis follows the Cochrane Handbook and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines⁶⁸, based on the full search protocol published in Prospero (ID: CRD42024535331)⁶⁹.

Eligibility criteria

We included any English-language epidemiological studies (cohort, case-control and cross-sectional) of cervical high-grade lesions (HGL) or cancer among vulnerable women conducted in upper-middle and high-income countries, as classified by the OECD (Supplementary Data 1). We included studies with a comparison group—either reporting

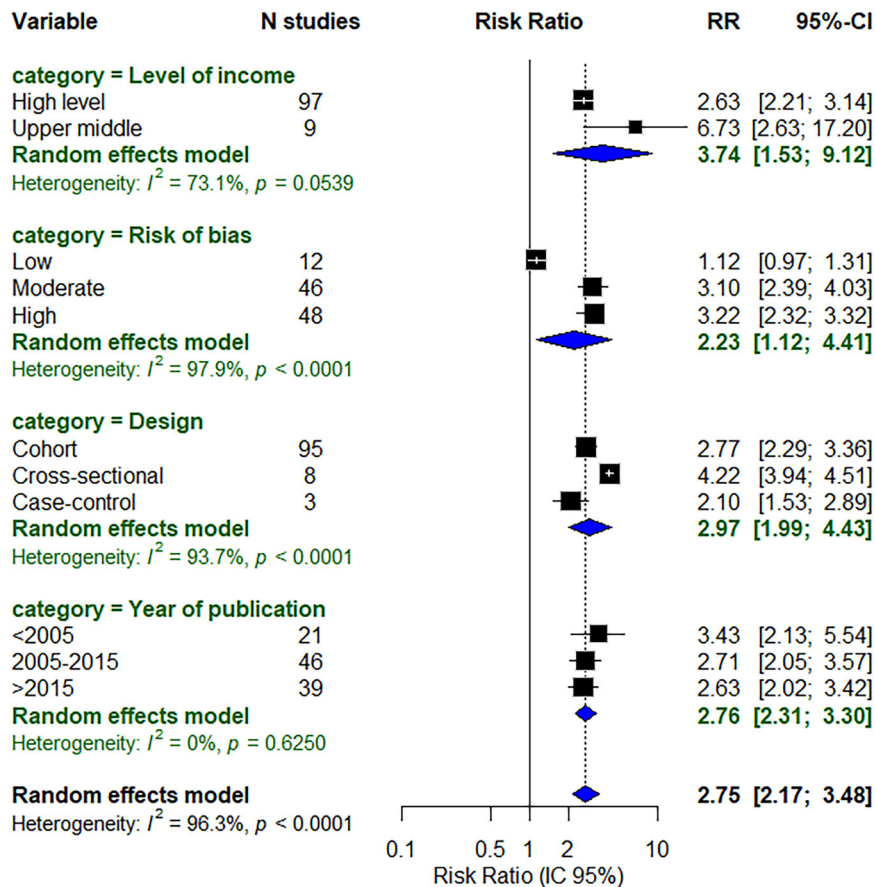


Fig. 3 | Pooled Risk of cervical cancer by level of income, risk of bias, study design and year of publication in high and upper-middle countries. WLWH: Women living with HIV, FSW: Female Sex Workers. The figure illustrates the study-level characteristics and the pooled relative risk (RR) of cervical cancer. Estimates and corresponding 95% confidence intervals were obtained using a random-effects

model (inverse-variance method). A total of 106 unique studies were included. The overall effect was statistically significant ($p < 0.0001$). All tests were two-sided, and no adjustment was made for multiple comparisons. Between-study heterogeneity was assessed using Higgins' I^2 statistic, where $I^2 > 75\%$ indicates considerable heterogeneity.

crude numbers from the study population itself, or providing a summary estimate relative to the general population, for example based on cancer registry data. These countries were selected to ensure comparability in healthcare infrastructure and screening availability, and to align with the objectives of ongoing European initiatives targeting vulnerable populations. We excluded articles that reported irrelevant outcomes (e.g., mortality or low-grade lesions), studies that focused solely on treatment, cancer recurrence, or survival after cancer treatment, populations outside our scope (e.g., paediatric, men, animals, or patients with cancer at baseline), and data that could not be analysed. We also excluded abstracts conference proceedings, case studies, protocols, systematic reviews and meta-analyses.

Our definition of vulnerability was based on the framework of the WHO and previous research²⁰, including women of low socioeconomic status: i.e., those living in deprived areas, with low levels of education or income, living with HIV (WLWH), or who are female migrants, sex workers (FSW), prisoners, or women with substance use disorders: i.e., those diagnosed with alcohol or any other drug abuse, or mental illness.

Information sources and search strategy

We searched MEDLINE, EMBASE, CENTRAL and ISI Web of Science from database inception until February 2024. For the WLWH group, we considered only articles published since 2004, after highly active antiretroviral therapy (HAART) had been approved^{70,71}. This restriction was applied to ensure relevance to the HAART era, during which

antiretroviral therapies became the standard of care in high- and upper-middle-income countries, leading to improved immune function and reduced persistence of HPV infections^{72,73}. This enhances comparability across studies by reflecting the current risk of cervical cancer among women living with HIV. We searched a combination of MeSH terms and controlled vocabulary, which we adapted to each database, for 1) cervical neoplasia and/or cancer, 2) vulnerability group, and 3) risk-related terms including relative risk, incidence, prevalence and epidemiology (Supplementary Table 1).

We also used the 'similar articles' feature and manually screened the reference lists of included studies to identify any additional relevant publications not captured through the database search. For articles not available online, we sent a reprint request to the authors.

Selection process and data collection process

After a systematic search, we imported the articles into EndNote® (X9, Clarivate Analytics) and both automatically and manually eliminated duplicates. All citations and full-text articles were independently screened twice by three qualified reviewers (AH, AT, MM) using pre-defined inclusion and exclusion criteria. Discrepancies were resolved by a fourth reviewer (MB).

Data were extracted into an Excel® (Office 365, Microsoft, Redmond, WA, USA) sheet. If several publications reported the same study, we extracted the data from the main publication, which described the authors' methods in the greatest detail and contained the most complete data on our criteria of interest.

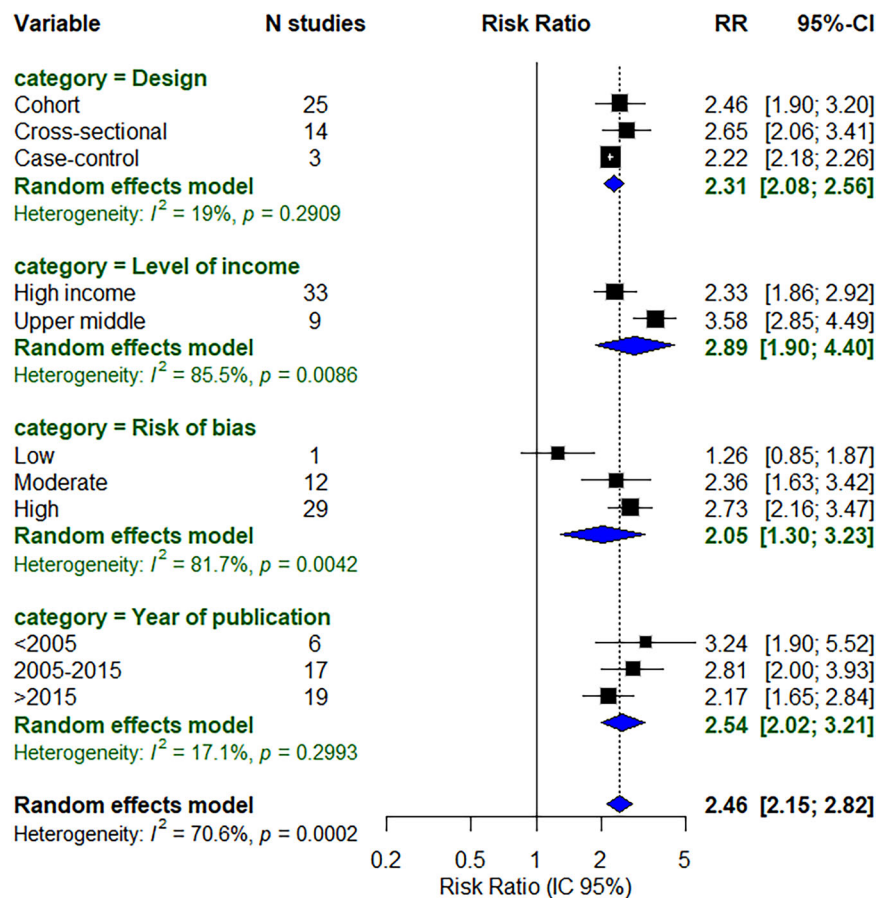


Fig. 4 | Pooled risk of high-grade lesions by level of income, risk of bias, study design and year of publication in high and upper-middle countries. The figure illustrates the study-level characteristics and the pooled relative risk (RR) of high-grade lesions. Estimates and corresponding 95% confidence intervals were obtained using a random-effects model (inverse-variance method). A total of 42

unique studies were included. The overall effect was statistically significant ($p < 0.0001$). All tests were two-sided, and no adjustment was made for multiple comparisons. Between-study heterogeneity was assessed using Higgins' I^2 statistic, where $I^2 > 75\%$ indicates considerable heterogeneity.

Data items

We extracted the following information: author; title; year; journal; country; study design; data sources; age; inclusion and exclusion criteria; study period; duration of follow-up (if applicable); definition of cervical high-grade lesions and cancer; definition of vulnerable group, exposure, and control group (if any); sizes; point estimates and 95% confidence intervals (CI).

Study risk of bias assessment

Two reviewers (AH and AT) used Newcastle-Ottawa Scale (NOS) tool⁷⁴ to independently rate the quality of studies, NOS uses a grid, which is adapted to each study design, and a star system with maximum of nine stars to rate a study in three domains: selection of participants; comparability of study groups; and ascertainment of outcomes of interest. Studies with nine stars were considered to be at low risk of bias, studies with seven or eight stars were at moderate risk, and studies with six or fewer stars were at high risk⁷⁵.

Effect measures

Our primary outcome was overall risk of CC (regardless of the stage) or high-grade lesions (HGL) compared to controls (general female population). HGL was defined as Cervical Intraepithelial Neoplasia (CIN) 2+, CIN 3+, and carcinoma in situ⁷⁶, and high-grade squamous intraepithelial lesion (HSIL), as per the Bethesda system⁷⁷.

Secondary outcome included pooled risk estimate of CC and HGL by vulnerability type.

Statistics and reproducibility

The risk estimates in our studies included incidence rate ratio (IRR), risk ratio (RR), and standardised incidence ratio (SIR) or odds ratio (OR). We considered these outcomes equivalent to pool our analyses for both CC and HGL. When point estimates and confidence intervals were reported, we derived the corresponding log-transformed effect sizes and their sampling variances using formulas based on the Wald-type approximation, as implemented in the meta package. If crude numbers were available, we created 2 x 2 tables and calculated log-transformed relative risk (RR) and variability for each treatment group based on sample size. Data are available in Supplementary Data 3.

To combine these data, we applied random-effects models that gave more weight to studies with more precise estimates while accounting for differences between studies. We reported results as percentages with 95% confidence intervals (CIs)^{78,79}. An inverse variance weighting method combined the summary measures, with random-effects models minimising the impact of between-study heterogeneity⁸⁰. We used the I^2 statistic to assess heterogeneity⁸¹. below 25% (low); 25%-50% (moderate); above 75% (High). Additionally, a Chi-square test of homogeneity at a 0.10 significance level helped determine whether differences between studies were incidental or indicated real variability in the effects.

When at least 10 studies were available, we used funnel plots to assess publication bias.

Subgroup analysis was provided for each type of vulnerability. The results were also stratified by country income level (high-income

vs. upper-middle-income countries), study design (cohort, case-control or cross-sectional), risk of bias (Low, Moderate or High) and year of publication. For the latter, studies were grouped into three time periods: before 2005, between 2005 and 2015, and after 2015. These intervals were selected to reflect key phases in cervical cancer prevention strategies—namely, the cytology and colposcopy era, the introduction of the HPV vaccine, and the implementation of HPV testing in screening programmes, respectively⁸². All statistical analyses were performed with the Meta package in R version 4.3.3, (R Foundation for Statistical Computing, Vienna, Austria, 2008).

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

The dataset generated and analysed in this study is available in the Figshare repository (<https://doi.org/10.6084/m9.figshare.30518828>)⁸³. Detailed data supporting the findings of this study are available in supplementary Data 3.

Code availability

The R code used for the analyses is publicly available at: <https://github.com/Amir-Hassine/Cervical-Cancer-Meta-analysis.git>.

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- Agreement No 964049; Principal investigator: MB). The funder had no role in the conduct of the review. We also acknowledge the contribution of Kali Tal for her valuable assistance with medical writing.

Author contributions

M.B. is the originator of the idea. A.H., A.T., M.M. and M.B. designed the study. A.H., A.T. and M.M. extracted, analysed and interpreted the data. A.H. and A.T. did the risk bias assessment and drafted the initial report. M.M. and M.B. made critical revisions of the manuscript bringing important content. All authors approved the final version of the article.

Competing interests

The authors declare no competing interest.

Additional information

Supplementary information The online version contains supplementary material available at <https://doi.org/10.1038/s41467-026-70050-w>.

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Peer review information *Nature Communications* thanks Emilia Prospero who co-reviewed with Katuscia Di Biagio and the other anonymous, reviewer(s) for their contribution to the peer review of this work. A peer review file is available.

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Acknowledgements

We acknowledge the EU Horizon 2020 research and innovation programme for providing sufficient funding to perform this work (Grant