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Mpox virus infection in women and outbreak sex disparities: A Systematic Review and Meta-analysis

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Abstract

Background Although the recent literature indicates that mpox (monkeypox) primarily affects men, there are also multiple reports in women. Estimates of the sex distribution of mpox patients and patterns will enable a better understanding of the ongoing mpox outbreak.

Methods In this systematic review and meta-analysis, seven databases were searched for studies published in English up to January 4th, 2023. The proportion of women with mpox was the primary outcome. A random-effects model was fitted for the primary outcome, and a sensitivity analysis was performed to check possible outliers in the studies.

Results Here we screened 470 articles and included 60 studies for qualitative synthesis. 42 studies with 3125 women out of 47,407 confirmed cases were found suitable for meta-analysis. The pooled proportion of female patients is 17.22% (95% CI: 10.49-25.11; $I^2 = 98.86\%$). Subgroup analyses reveal higher proportion before 2022 [44.09% (42.93–46.86] than 2022 onwards [2.40% (1.17–3.98)], and in endemic countries [43.13% (37.63–48.72)] than in nonendemic countries [6.15% (2.20–11.65)].

Conclusions There is considerable caseload (17.22%) amongst women, which must be seen in the context of a much higher proportion (44.09%) in studies prior to 2022 compared to 2.40% in the 2022 outbreak indicating an epidemiological shift. Data on disease characteristics among women with mpox disease are scarce. Further studies should focus on these aspects to better understand the disease in women and empower epidemiologists and clinicians to make evidence-based decisions for this vulnerable group.

Plain Language Summary

Mpox (formerly known as monkeypox) is an infection caused by the monkeypox virus. While it is known to affect men more commonly than women, there are also reports of this infection in women. We have searched the literature to find out how frequently mpox affected women. We found that 17% of mpox patients were female. However, this number was 44% before 2022, and has reduced to 2% from 2022 onwards. This indicates changes in mpox disease characteristics and in the ability to infect different sexes. Further studies are needed to better understand the disease in women and empower epidemiologists and clinicians to make evidence-based decisions for this group.

The recent resurgence of the monkeypox (or newly renamed as mpox) global outbreak with over 83000 cases in 110 countries (as on January 3, 2022), amid the looming COVID-19 pandemic, is a cause of grave concern[1]. Further, traversing mpox outbreaks to nonendemic areas like the Americas and European countries, in addition to West or Central Africa, where it is endemic, has raised the alarm for public health authorities globally[1]. This multi-country spread has led the World Health Organization (WHO) to declare this disease of viral etiology as a "Public Health Emergency of International Concern (PHEIC)"[2].

The mpox virus belongs to the orthopoxvirus genus and exists in two genetic clades[3]. The Congo basin clade has been associated with higher mortality than the West African clade[3]. Typically, the manifestations of prodromal diseases include fever, headache, myalgia, and lymphadenopathy. The appearance of a rash on the mucosa or skin, alone or in multiple sites, is a cardinal characteristic and scarring may be possible as long-term sequelae[4]. Published evidence have mainly reported mpox disease in men. However, cases in women and children have also been reported globally[5–8]. A report by the Centres for Disease Control and Prevention (CDC) describes the clinical experience with 769 women with mpox infection[9]. Recently, a report of a newborn born to an infected mother was published[10].

It has been reported that the epidemiology of mpox is changing with respect to the number of cases, age at presentation, and geographical spread of the disease[11]. Previous work has attempted to collate the evidence on multiple aspects of mpox. The characteristics of mpox are found to be

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different between the 2022-2023 multi-country outbreak compared to the previous ones between 1970 and 2021[12]. Multiple reviews have been conducted on the evolving epidemiology[13], clinical features[14–16], management[17,18], and clinical outcomes of the mpox[18–21]. However, the sex of the patients, which is a social determinant of health, has not been systematically reviewed and analyzed. Inequalities in health by gender exist in high, middle, and low-income countries[21]. This should be considered in the light of the social determinants of health and the right to health[22,23]. Understanding various dimensions of health for women in terms of disease burden, health-seeking behavior, and health profile is imperative for integrating a gender perspective in health plans. Women, including trans women, due to gender stereotypes, can experience additional stigma when accessing healthcare for mpox infection[24]. A multi-country study among women with mpox reported cases in both cis and trans-women[25]. Mpox in women in the reproductive age group has been linked with adverse perinatal outcomes[9,26,27]. It is crucial to tailor diagnostic, prevention, and treatment strategies that best suit their needs and context. This is especially important as lack of knowledge that women are also affected with mpox might reduce focus on sex-specific issues like teratogenicity when discussing treatment options. Understanding the epidemiology of mpox infection among women will enable health planners and program managers to plan mpox management for women and to formulate evidence-based policies to contain the outbreak in vulnerable populations. The epidemiology, and female predilection of the disease or the lack thereof seems to vary with time and geography.

Since there is a stark difference in the sex predilection of mpox disease with time as seen in the previous studies, we conducted a systematic review and meta-analysis to estimate the proportion of women with mpox in various settings and outbreaks, and to observe the epidemiological features of mpox in women.

Methods

Research question and selection criteria

This systematic review and meta-analysis is based on this research question: What is the proportion of women among the patients with mpox? And adopted the PRISMA-2020 checklist (Appendix 1). The question was answered by a systematic search and identification of eligible studies based on the PICO criteria mentioned in Appendix 2. This study was registered in the International Prospective Register of Systematic Reviews (PROSPERO), with the reference ID CRD42022383194.

Databases included and Search Strategy

Seven databases (PubMed, Scopus, Web of Science, EMBASE, ProQuest, EBSCOHost and Cochrane) were searched up to the cut-off date of January 4th, 2023, using a search algorithm (Appendix 3). Considering the spread of the outbreak and the constant emergence of new information each day, the pre-print servers like medRxiv, arXiv, bioRxiv, BioRN, ChiRxiv, ChiRN, and SSRN were also searched. In addition, the references of the included articles were also manually scanned. The search keywords included "mpox", "MPXV", "Monkeypox", "*women*", and "female". MeSH terms and truncated keywords were also used in the search strategy. The search strings and the results obtained are enumerated in Appendix 3. Mendeley Desktop (V1.19.5) was used to manage the articles.

Screening of studies

Title and abstract screening. Two independent authors (MAS & SM) reviewed the title and abstracts of the studies obtained from the above systematic search applying the eligibility criteria and identified articles for full text screening. If there was a disagreement regarding the inclusion of a study for full-text review, the co-authors conversed to build consensus and decided on eligibility.

Full-text screening & data extraction

Two independent authors (MAS & SM) reviewed the suitability of potentially eligible full-text articles and then extracted data. In the event of disagreement at any step, the authors conversed among themselves to build consensus. The third author (BKP) decided on the unsolved contradictions. A data sheet was prepared, including information such as the author's name, publication year, the period from which cases are reported, data collection, the location of the study site location, study design, total patients positive for mpox and the count of women with mpox. The literature search, selection, data extraction, systematic review and meta-analysis process was reported using the Preferred Reporting Standard of Systematic Reviews and Meta-Analysis (PRISMA) flow chart and checklist to ensure scientific precision (Fig. 1 & Appendix 1).

Risk of Bias assessment

Two independent authors (TKS & SM) evaluated the risk of bias in included studies using the quality assessment tools recommended by the *National Heart, Lung, and Blood Institute* (*NHLBI*)[28]. Poor-quality studies were excluded from a sensitivity analysis.

Sensitivity test

Studentized residuals and Cook distances are used to examine whether studies may be outliers and/or influential in the context of the model[29]. Studies with a studentized residual larger than the $100\times(1-0.05/(2\times k))$th percentile of a standard normal distribution are considered potential outliers (i.e., using a Bonferroni correction with two-sided $\alpha = 0.05$ for k studies included in the meta-analysis). Studies with a Cook's distance larger than the median plus six times the interquartile range of the Cook's distances are considered to be influential (Fig. 2). The sensitivity analysis of the included studies was performed using R programming language (v4.0).

Statistical analysis

After removing outliers, the analysis was carried out for the proportion of women who had mpox as the outcome measure. A random-effects model was fitted to the data with a DerSimonian & Laird estimator. Double arcsine transformation of proportions was used to resolve issues with both confidence intervals and weights[30]. The amount of heterogeneity (τ^2) was estimated using the restricted maximum likelihood estimator[31]. In addition to the estimate of τ^2, the Q-test for heterogeneity[32] and the I^2 statistic[33] are reported. If any amount of heterogeneity is detected ($\hat{\tau}^2 > 0$, regardless of the results of the Q test), a prediction interval for the true outcomes is also provided[34]. We performed a subgroup analysis to identify the source of heterogeneity: i) geography (continent-wise), ii) endemicity of the monkeypox virus (endemic vs. non-endemic countries), and iii) waves of outbreak 2022 (current) vs. pre-2022 studies. The rank correlation test[35] and the regression test[36], using the standard error of the observed outcomes as a predictor, are used to check for funnel plot asymmetry. We have also used Doi plot alongwith the LFK index to assess symmetry of study effects. The analysis was carried out using STATA (v17.0) and R[37] (version 4.0), and the metafor package[38] (version 3.8.1). A p-value of less than 0.05 was interpreted as statistically significant.

Ethical statement

The ethical review does not apply to this study as it is a systematic review and meta-analysis of data available in the published literature.

Results

A total of 42 studies comprising 47,407 mpox cases were included in the analysis. The PRISMA flow chart (Fig. 1) represents the literature screening process. A systematic search resulted in 365 articles after the removal of 105 duplicates. Ninety-eight articles were found to be eligible for full text screening after the screening of titles and abstracts of these documents. Five more articles were evaluated after selection by searching citations. Then, 43 articles were excluded due to an incorrect study design (22), an incorrect patient population (17), and incorrect outcome (4). Ultimately, 60 studies were considered eligible for subsequent data extraction[4,6–8,39–94]. These were included in the qualitative synthesis, and 42 were found to be suitable for the quantitative synthesis[6–8,39–77].

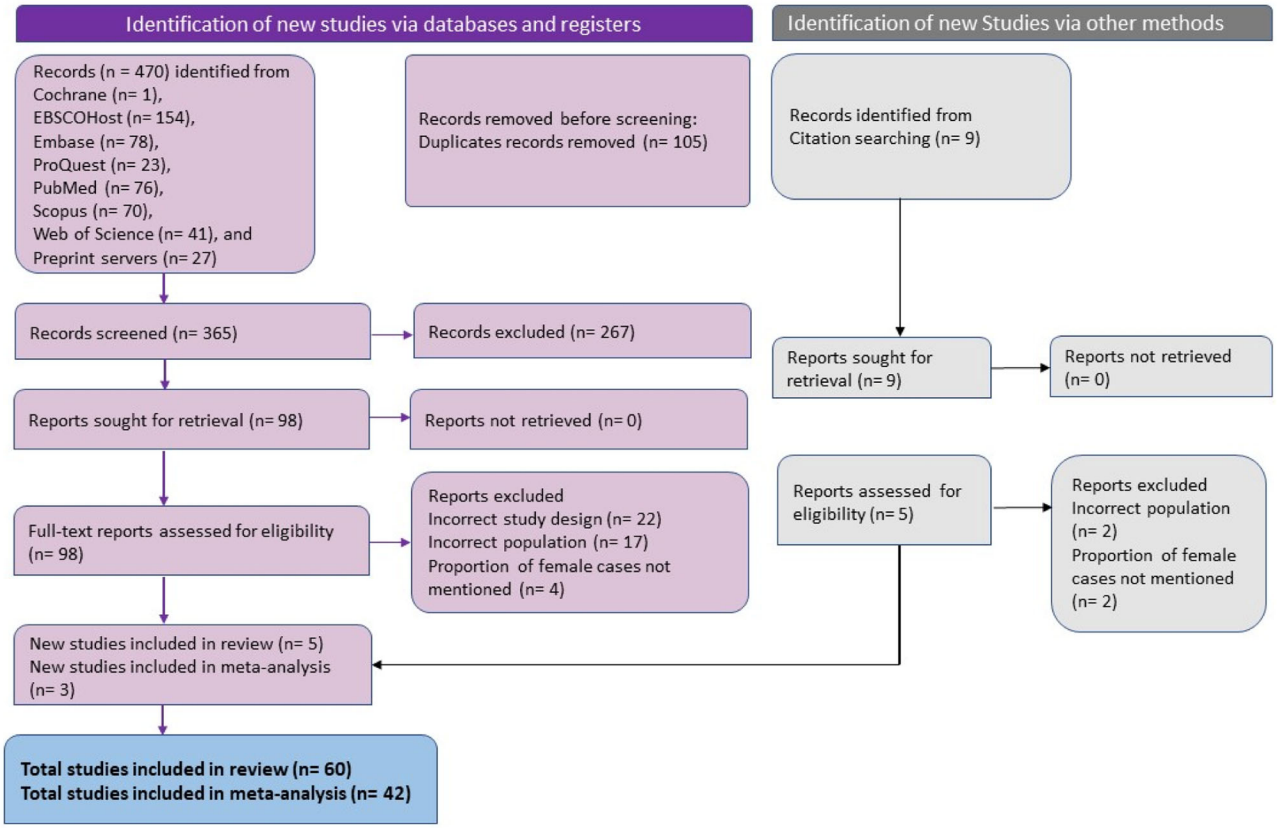


Fig. 1 | PRISMA flowchart for included studies in systematic review and meta-analysis of mpox cases in women. PRISMA flowchart for included studies in systematic review and meta-analysis of mpox cases in women.

Study characteristics

The studies included in this systematic review reported data from 1970 to 2022. These 60 studies include nine case series, eight cross-sectional studies, 18 prospective cohort studies, and 25 retrospective studies. The sample sizes ranged from six[39,78], to 25,816[65]. Twenty-six (43%) of the 60 included studies reported data from Europe alone. Africa, North America, South Africa, and Asia had 16, 15, 1, and 1 studies, respectively (Supplementary Data 1). A study in the Central African Republic[57] reported the highest proportion of women with mpox (71.43%), while 18 reported no cases among women. There was a high heterogeneity between the studies ($I^2 = 98.86\%$; $p < 0.001$) (Fig. 2).

Risk of bias

The quality assessment of the findings of the included studies is illustrated in the supplement file (Appendix 4a & 4b). Fifty-nine studies were rated as fair or good quality. Only one study was rated as poor quality. However, it was only included in the systematic review for qualitative synthesis. Given that we are just collecting baseline data in all the studies, this was an expected finding.

Sensitivity analysis

Figure 2a-d shows the sensitivity analysis. All these plots (Baujat plot) show the contribution of each study to the overall Q-test statistic for heterogeneity on the horizontal axis versus the influence of each study on the vertical axis (Fig. 2a–d). The influence of each study is defined as the standardized squared difference between the overall estimate based on a fixed-effects model, with and without the i-th study included in the model. The numbers refer to the study, in order of appearance alphabetically. Examination of studentized residuals revealed that one of the studies had a value greater than ±2.8905. Hence, there was an indication of outliers in the context of this model. According to Cook's distances, the same study could be considered as overly influential.

Pooled estimate

The meta-analysis included 47,407 cases of mpox, of which 3125 were women. The pooled proportion of women among all patients with mpox was 17.22% (95% confidence interval [CI], 10.49-25.11) (Fig. 3).

Publication bias

Doi plot demonstrates the lack of symmetry in the studies (Fig. 4a). In the right limb, there are more studies and the area under the points is higher. This can also be seen by an LFK index of 5.69 which shows asymmetry towards a higher proportion. A funnel plot of the estimates is shown in Fig. 4b. Studies were distributed asymmetrically. The linear regression test of the funnel plot asymmetry (Egger's test) indicates some evidence of small study effects ($z = 3.02$; P-value = 0.0026). A Trim-and -fill test applied through imputed studies reveals that three of the eight imputed studies fall within the white region corresponding to a p-value of less than 1%.

Meta-Regression

A bubble plot of the estimate is shown in Fig. 5. The size of the bubbles represents the precision of the studies. The flat regression line indicates that there is no relationship between sample size and proportion of women with mpox.

Subgroup analysis

As decided apriori, we performed subgroup analysis according to the waves (year of origin) of the outbreak [pre-2022 vs. current outbreak (2022)]; endemicity (endemic vs. nonendemic countries); geographic location (continent); and study design (prospective, retrospective, and cross-ectional/case-series). The subgroup analysis based on the year of origin of mpox cases showed contrasting results. In studies reporting cases originating before the current outbreak (before 2022), the pooled proportion of women was 44.09% (95% CI 39.58–48.64). On the contrary, studies

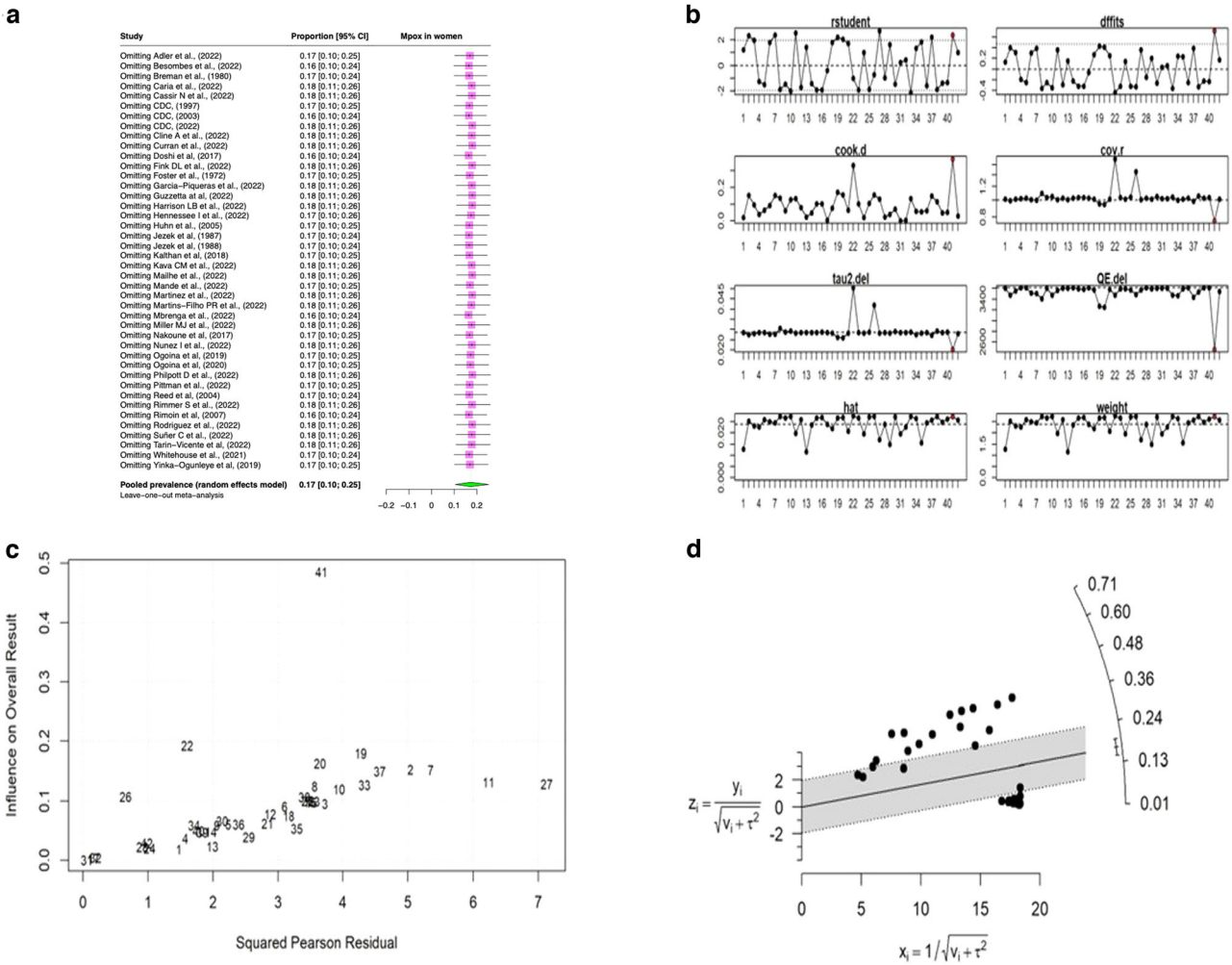


Fig. 2 | Sensitivity analysis of the included studies. a Describes the leave-one-out analysis; **b** describes the outlier/influence diagnostics; **c** describes the Baujat plot; **d** describes the radial plot

reporting data for the 2022 outbreak showed a much lower pooled proportion of 2.40% (95% CI: 1.17–3.98) (Appendix 5a). This contrasting difference was also observed when comparing the geographical location of the studies (endemic vs. non-endemic countries). Endemic countries reported a much higher proportion of women than non-endemic countries, that is, 43.13% (95% CI 37.63–48.72) *vs* 6.15% (95% CI: 2.20–11.65) (Appendix 5b). Among the non-endemic study sites, the proportion of women in Africa was 43.13% (95% CI 37.63–48.72), while it was only 0.68% (0.29–1.17) in Europe (Appendix 5c).

This subgrouping reduced the initial heterogeneity ($I^2 = 98.86\%$; $p < 0.01$) to a lower value among the studies in cases before this outbreak ($I^2 = 58.90\%$; p-<0.01). The subgroup based on geography also reduced heterogeneity between the reports of endemic countries ($I^2 = 66.55\%$; $p < 0.01$).

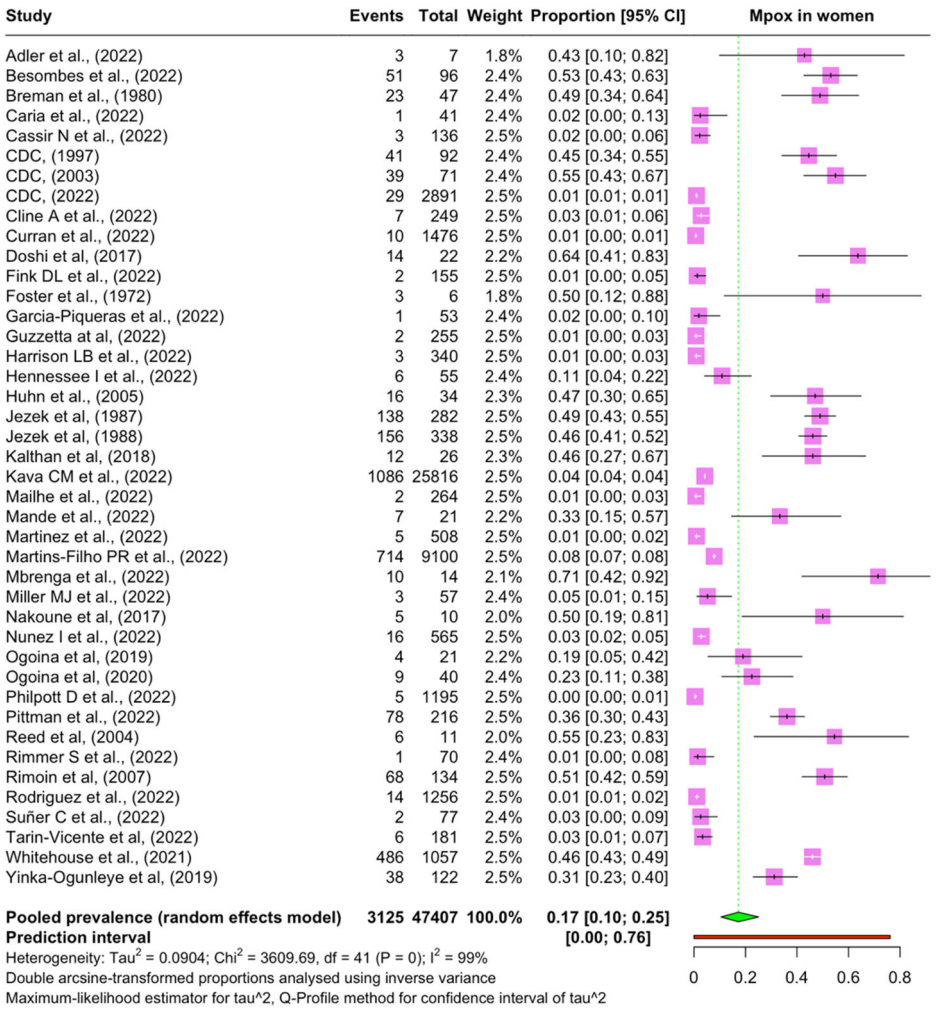
Testing for between-group differences for each of the four subgroup analyses yielded significant results ($p < 0.001$) (Appendix 5a-5d).

Discussion

This meta-analysis is the first to estimate the pooled prevalence of mpox among women. The pooled analysis included 42 reports that included 47,407 mpox cases; of these, 3,125 were women. The pooled proportion of women was 17.22% (95% CI: 10.49–25.11). The proportion was almost 20 times lower in this outbreak than that reported in studies before 2022 (2.40% vs. 44.09%). As expected, the pooled proportion of women with mpox in endemic regions (central and western African countries) was almost ten times higher than that in non-endemic areas, since most of the studies in the pre-2022 era were from endemic countries.

Over the past half century, mpox has been reported primarily in Central and western African countries, with sporadic cases in high-income countries[4,95,96]. Up to recently, there has been minimal research on mpox origin, sex distribution, prevention and treatment options. In countries where it is endemic, mpox incidence in men and women was reported to be similar[42,95,97]. However, in the Nigerian outbreak, there was a preponderance of adult males (nearly 70%), suggesting a sex and age shift[51,76,95]. The recent outbreak paints an entirely different picture. Based on initial reports, cases of the majority of the mpox were reported in men (>95%), specifically men who had sex with men (MSM), particularly those who have multiple and often anonymous partners[4,95]. In fact, some epidemiologists suggest that in this outbreak, the disease pattern has changed. MSMs are the predominantly affected population now[98]. The predominant clinical features are painful anal, genital and oral mucosal lesions, even without systemic manifestations. Recent reports suggest that women are also affected by mpox, and that the condition is more common among transwomen who are sexually active with multiple partners[95], which in turn points highlights the risk factors. In the index review, though the overall pooled proportion of women was one-sixth of men (nearly 16%); however, if we limit ourselves to the current outbreak, it was only 2.3%. A large proportion of women with mpox have multiple sex partners, and a significant proportion has concomitant HIV infection[95]. This emphasises that women susceptable to mpox infection, and similar to other sexually tract diseases, they are also at high-risk if safe sexual

Fig. 3 | Forest plot showing the pooled proportion of women mpox cases. Forest plot showing the pooled proportion of women mpox cases. Forest plots showing heterogeneity in the prevalence data of women having mpox. Only the first author's name is given for each reference.



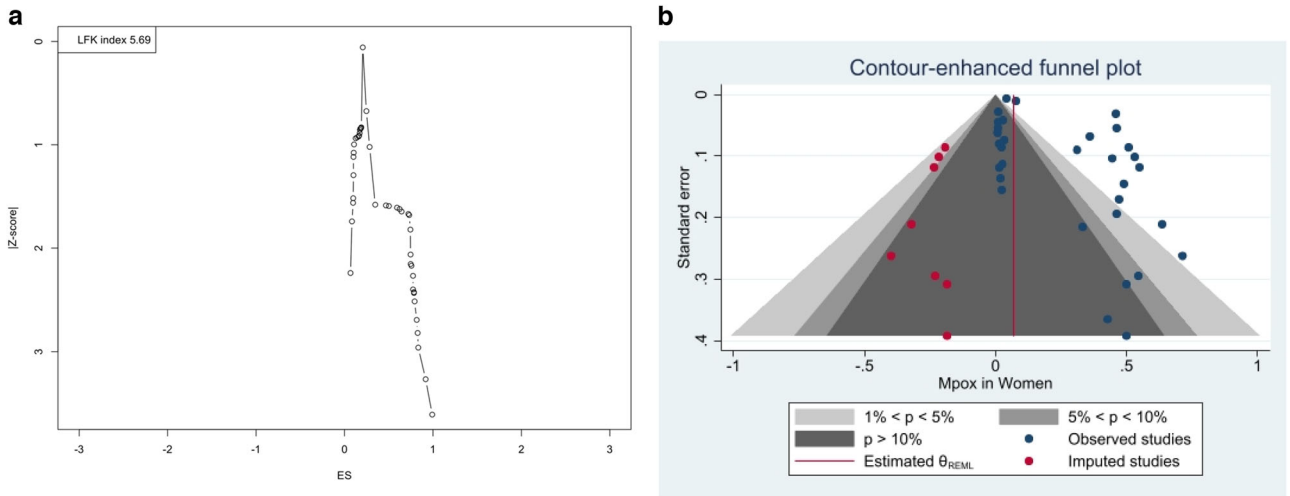


Fig. 4 | Publication bias. a The asymmetric Doi plot with a high LFK index indicates potential publication bias in favour of studies reporting a higher prevalence. **b** Each point (blue) represents a separate study on the indicated association. The vertical line represents the mean effect size. The points are distributed asymmetrically. Linear regression test of funnel plot asymmetry (Egger's test) indicates some evidence of small-study effects ($z = 3.02$; P value = 0.0026). A Trim-and -fill test applied through imputed (red points) studies reveals that three of the eight imputed studies fall within the white region corresponding to a p value of less than 1%.

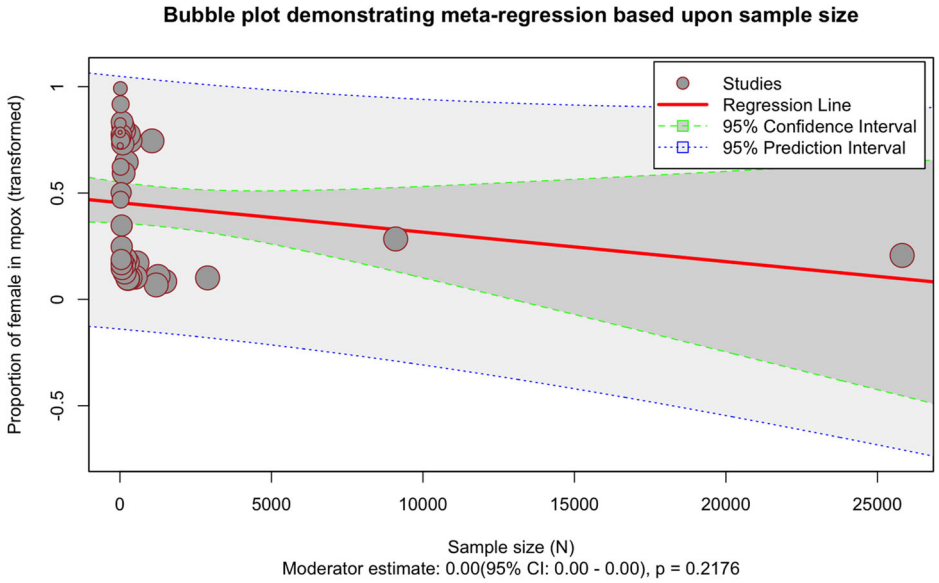


Fig. 5 | Bubble plot. The size of the bubbles represents the precision of the studies; the flat regression line indicating no relationship between sample size and proportion of mpox in women.

practises are not used. In the initial part of the outbreak, when cases were limited exclusively to men, much emphasis was placed on the risk factors seen in MSM. However, with the current data, there is a need to follow preventive practices for women, especially transwomen and female sex workers too. The mpox infections in women may also impact fetuses. Fetal death, and preterm delivery secondary to mpox infection have been reported in pregnant women[4,26,95,99]. As pregnant women are considered vulnerable, there is a need for more active surveillance and the formulation of guidelines for preventive strategies.

The mpox infection is again one of the many examples of the social and geographical divide where African countries have never received global attention. Before the pandemic, almost all cases were limited to some African countries. In fact, in countries like the Democratic Republic of the Congo (DRC), mortality related to mpox is as high as 7–10%[4,100]. In African countries, there is a large mpox sex disparity, which is evident in the index review. In endemic countries, the proportion of women is almost 10 times that in nonendemic countries (most of which are high-income countries). Reports suggest that even among high-income countries, the incidence is higher among the black ethinc groups than among the white ethnic groups[73]. This again emphasises the need for a comphrehensive approach to achieve sustainable development goals at a global level[101].

A higher incidence of mpox infection has been reported among people living with HIV. Whether this association is due to similar risk factors or whether HIV predisposes to mpox is yet to be explored[102]. However, recent data suggest that women with HIV are likely to be more symptomatic and more likely to require hospitalization than those without HIV. Therefore, there is a increased attention for increased protection and mpox prevention for women living with HIV[102,103].

Limitations

This meta-analysis was performed using a standard methodology and included published and unpublished reports from multiple databases. The risk of bias in the included studies was evaluated using standard tools. All except one study were of fair to good quality, after which a sensitivity analysis was done. However, this study has several limitations. There are limited studies on mpox in women, most of which are small case series. Most of the studies (95%) were from Europe, Africa and North America; hence, they may not be true representatives of global prevalence. Significant heterogeneity among the included studies remained largely unexplained despite sensitivity, subgroup analyses, and meta-regression. This heterogeneity may be due to biological reasons and behavioral differences between continents. The high heterogeneity is a limitation, which can pose a challenge in interpreting the findings of the index meta-analysis. There is a substantial difference in data between pre-outbreak (before 2022) and ongoing outbreak. The low prevalence and proportion in the current outbreak may be due to under-representation in initial reports, and future data from larger studies might change this proportion. Overlapping reports have also been reported from the same institution and region. Although efforts have been made to identify duplicate reports, the small number of patients may be overrepresented.

Conclusion

Overall, the proportion of women among mpox cases is 17.22% reducing from 44.09% in studies prior to 2022 compared to 2.40% from 2022 onwards. There is a significant variation in the proportion based on geography, the endemic nature of the country, and the period of the mpox cases reported. The ongoing outbreak has a relatively lower proportion of cases in women. Data on concurrent HIV infection and symptomatology among women with mpox disease are scarce. More studies should focus on these aspects to better understand the disease in women and empower epidemiologists and clinicians to make evidence-based preventive strategies for this vulnerable group.

Data availability

Documents containing all extracted data have been made available in the plots in the manuscript and the accompanying supplementary material. Numerical data in the source underlying the graphs and charts have been made available. Further data can be obtained from the corresponding authors upon requests deemed to be reasonable.

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Compting interests

The authors declare no competing interests.

Additional information

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