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Circumcision for HIV prevention in men who have sex with men: an updated meta-analysis

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Background:

Circumcision reduces men's risk of acquiring HIV through sex with women by approximately 60%.^{1,2,3} Since 2007, the World Health Organization (WHO) has recommended voluntary medical male circumcision (VMMC) for HIV prevention for men who have sex with women in countries with generalized HIV epidemics and low circumcision coverage⁴. The program's scope is large: through 2023, fifteen sub-Saharan African countries had provided over 37 million circumcisions.⁵

However, for gay, bisexual, and other men who have sex with men (MSM) – who account for 34% of all new HIV infections outside sub-Saharan Africa annually⁶ – the picture has been less clear. Observational data on potential protection via circumcision are plentiful but inconsistent. Two meta-analyses published in 2019, covering overlapping but not identical sets of studies^{7,8} (the last of several meta-analyses, including an inconclusive 2011 Cochrane review) noted that data from sub-Saharan Africa and Asia generally support protection, whereas those from the United States and Europe generally do not.

The underlying reasons for the inconsistency, especially regional differences, have not been fully understood. Confounding is one likely driver in settings where circumcision at birth is associated, positively or negatively, with socioeconomic status and other HIV risk determinants. Another is that because circumcision would protect only the insertive partner in any encounter, any effect would be visible only in primarily-insertive (PI)-MSM, so inclusion of MSM preferring receptive or versatile roles would likely dilute the measured effect. In attempting to address this through stratification, one of the 2019

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Conflicts of interest

No conflicts of interest were declared.

meta-analyses found significant protection for PI-MSM and the other did not,^{7,8} leaving the question unresolved. Finally, data on MSM has another reason for inconsistency: as a commonly “hidden” population that cannot be easily sampled in a representative way - unlike general populations - MSM have often been studied through convenience sampling in unrepresentative settings, like sexually transmitted infection clinics.

In 2024, the first and only randomized trial of VMMC for MSM⁹ reported significant protection at one year among 247 PI-MSM in China. However, because there were only five seroconversions, and a larger-than-expected effect size (over 90% risk reduction), it has not been universally regarded as definitive enough to outweigh the substantial, ambiguous prior observational data. Specifically, it has not led to updates to current WHO recommendations either on HIV prevention in MSM,¹⁰ which do not include VMMC; or on VMMC, which acknowledge 2019 meta-analysis findings but explicitly decline to recommend VMMC in MSM due to lack of definitive evidence⁴. In turn, VMMC programming, continuing to closely follow this guidance, has continued unchanged: though MSM seeking VMMC are not required to disclose their sexual practices⁴, with rare exceptions¹¹ they are also not prioritized for VMMC-focused public education campaigns and one-to-one peer outreach, which have been essential for uptake in the general population. Further, MSM seeking VMMC are counselled under current guidance that it is not known whether it will protect them from HIV.

Clarifying the existing evidence could have important effects. If circumcision protects PI-MSM from HIV, at minimum, existing VMMC programs could be recommended as an HIV risk reduction option for PI-MSM. This would be especially relevant for those facing barriers to long-term use of PrEP and other prevention interventions. Conversely, if circumcision is not protective, VMMC resources should not be used to recruit clients who will not benefit.

Yet, additional trials may be unlikely: they could require large sizes if also offering pre-exposure prophylaxis (PrEP) medications, which is becoming ethically necessary, and funding for global HIV prevention research is increasingly limited. A more feasible potential approach is determining whether all the existing data can be harmonized into a clear answer using maximally rigorous analytic techniques.

We attempted to do this by performing 1) an updated systematic review to capture any data added since the 2019 meta-analyses, 2) a standard meta-analysis of effect among PI-MSM, incorporating any new data but not necessarily addressing the data challenges discussed above, and 3) a novel meta-analysis designed to mitigate these challenges by using a ratio of odds ratios as the main metric: the comparison between circumcision effects in PI-MSM vs. in other MSM within the same set of studies.

Methods:

Search strategy:

We identified studies in five ways:

1. We assessed all articles included in the 2019 meta-analyses^{7,8} or a 2022 systematic review¹².
2. We conducted an updated literature search (details in online appendix 1) in Academic Search Complete, Pubmed, Embase, PsychInfo, Cochrane, OVID Global Health, WHO Index Medicus and Scopus for variations of the terms “circumcision”, “MSM” and “HIV” during January 1, 2018--October 16, 2024.
3. We manually searched International AIDS Society (IAS), Conference on Retroviruses and Opportunistic Infections, and HIV Research for Prevention conference abstract archives from 2018 through 2024 for abstracts with the same terms above.
4. We searched biobehavioral surveys (BBSs) among MSM in a CDC-maintained repository. These surveys typically use respondent-driven sampling to assess HIV prevalence and collect risk and behavioral data. We attempted to acquire additional BBS reports but were unsuccessful.
5. We included our own primary work shared at IAS 2025.¹³

Analysis strategy:

We planned a descriptive analysis of all observational studies reporting on the association between circumcision and HIV among MSM, followed by the two meta-analyses described above. This strategy was chosen because the former could illustrate but not address the challenges that have plagued previous analyses, including any confounding not addressed in the studies themselves; whereas the latter mitigated this by comparing findings by sex role within the same study.

Inclusion and exclusion criteria:

One author (SD) performed screening. Products (articles or abstracts) reporting primary data on any HIV outcome (prevalent or incident infection, including self-reported positive result history) with any observational study design using any metric (odds ratio, hazard ratio, etc.) were includable. Exclusion criteria are shown in table 1. Products were not excluded for being available only through a prior meta-analysis as abstracted data (e.g., dissertations not retrievable by us).

Data abstraction:

One author (SD) abstracted measures of association for all studies in the descriptive analysis. We standardized coefficients of association so that values <1 represent lower risk of HIV infection with circumcision, whereas values >1 represent higher risk. We used adjusted coefficient of association measures where available; otherwise, we calculated an odds ratio from cell counts. Coefficients of association were also categorized as “lower-risk, significant” (coefficient < 0.94 , $p < .05$), “lower-risk, not significant” ($p \geq .05$), “neutral” (coefficient of association 0.94 – 1.06), “higher-risk, not significant” (coefficient of association > 1.1), or “higher risk, significant”.

Other fields abstracted included number of participants, country and region, years of data collection, study design, sampling and recruitment approach, variables adjusted for in calculating coefficients of association, stratifications provided, criteria for designation as “primarily insertive” when applicable, and prevalence of versatile role (neither exclusively insertive nor receptive) among participants. Study design was based on circumcision as the exposure of interest (e.g., an RCT of another intervention was termed cross-sectional if only baseline data were used.)

For studies included in the meta-analyses, initial abstraction of stratum-specific coefficients of association and cell counts for PI-MSM and other MSM was repeated by two other authors (DP, MP) and discrepancies reconciled through discussion. Cell counts were back-calculated from proportions and denominators where necessary. For studies which collected data by sex role but did not report stratum-specific coefficients of association, we contacted authors to request the additional data needed for the confounder-adjusted meta-analysis.

Risk of bias assessment:

We did not assess risk of bias on studies already included in the prior meta-analyses, but reviewed their risk-of-bias assessments. We assessed newly-identified included studies using the Newcastle-Ottawa scale for prospective cohort studies¹⁴ and a modified version for cross-sectional studies.¹⁵

Data analysis:

We performed descriptive analyses on the full set of studies in Excel, including distributions of results by number of studies, number of participants, and other variables of interest. Where relevant, some comparisons were made between what we defined as regions: US/Canada/Europe/Australia vs. Asia/Africa/Latin America.

We then completed an unadjusted random-effects meta-analysis in R using the metafor package, estimating pooled log odds ratios (logORs) and sampling variances among PI-MSM. We converted effect measures to logORs by log-transforming published ORs with their variances derived from reported 95% confidence intervals; we likewise converted risk ratios, hazard ratios, and prevalence ratios to logORs using the generic inverse-variance method. We selected adjusted effect estimates when available and used cell-count estimates otherwise. Where an adjusted estimate was unavailable, 2×2 contingency tables were used to compute logORs, replacing zero cells with 0.01 to allow estimation. Finally, we assessed the robustness of findings via two sensitivity analyses: i) a cell-count-only analysis, which excluded studies without raw counts, and ii) a prefer-cell-count analysis, which used cell-count estimates when available and adjusted estimates otherwise.

All models were fitted with restricted maximum likelihood (REML) and a random intercept for study, because several studies contributed multiple strata. The forest plot was ordered by region and variance.

Finally, to explore and mitigate confounding, we conducted the primary analysis, which we termed a “confounder-adjusted” meta-analysis, with the following rationale: Circumcision status is influenced, in childhood and adulthood, by a range of factors that may also be

associated with HIV risk. These factors are not necessarily all captured or adjusted for in the existing data, confounding the analysis and potentially driving the data inconsistencies seen, including regional variation. They may include:

1. Social or religious group: Certain groups commonly practice infant, child or adolescent circumcision (e.g., Jewish religion, some ethnic groups). Membership in these groups could be associated – positively or negatively - with adult risk behaviors, and/or with tendency to seek sexual partners from among the same group (assortive mixing), leading to differences in partner pool HIV prevalence between groups which also affect risk.
2. VMMC as risk mitigation: As described more fully in Table 1, individuals who circumcise to reduce their HIV risk are by definition HIV-negative at that time, likely leading to low HIV prevalence upon entry to the “circumcised” group as compared to the general population, introducing self-selection bias. This bias would, to our knowledge, be confined to sub-Saharan African countries implementing VMMC, in the absence of large-scale circumcision uptake done specifically for HIV prevention elsewhere.

To address these issues, the confounder-adjusted meta-analysis used the same rules described above but estimated the pooled difference of logORs between PI-MSM and other MSM, among studies providing the needed stratification. The reasoning was that while in purely non-insertive MSM, circumcision status would not directly affect HIV risk, they may have lower or higher HIV prevalence than non-circumcised MSM due to the confounding factors above. If those factors affect HIV risk in insertive and non-insertive individuals in the same way, then we could “subtract” them out by subtracting the log odds ratio among purely non-insertive MSM from the log odds ratio among insertive individuals, yielding the ratio of the odds ratios. Importantly, this approach does not depend on identifying, collecting or adjusting for individual confounding factors; it only requires that they affect both role groups equally.

If these confounding effects are not substantial, the confounder-adjusted analysis should have broadly similar findings to the unadjusted analysis, including with respect to regional heterogeneity and publication bias. Additionally, if there are confounders which do not apply equally to insertive and non-insertive individuals, they would not be subtracted out and would remain as residual confounding. The full mathematical framework is provided in online appendix 2a.

For both meta-analyses, publication bias was assessed with funnel plots with asymmetry testing (for all studies, and by region). Regional variation was assessed with estimate heterogeneity testing to determine whether our approach to confounder adjustment mitigated it. For the confounder-adjusted meta-analysis, findings were compared across study types (prospective vs. observational). Finally, we repeated the confounder-adjusted analysis dropping the de Leon¹³ et al dataset, which was our own work and the only one drawn from a VMMC country after substantial VMMC scaleup. Code to reproduce the analysis is available in online appendix 2b and the underlying data in appendix 2c.

Role of the funding source:

PEPFAR-supported staff designed and conducted all analyses.

Results:**Included data:**

For the descriptive analysis, forty-nine observational products representing unique datasets were includable^{16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63} with nine additional products excluded due to criterion 2 only (inclusion flowchart in figure 1).^{64,65,66,67,68,69,70,71,72} Of includable products, five were not included in the prior meta-analyses (two BBSs^{21,39} and three manuscripts^{27,57,61}); all products excluded by criterion 2 only were also new. Included products totaled over 150,000 participants (N's for the four unretrievable products^{33,24,25,34} were not reported); the five new includable products contributed 6,544 of these. Four of the five were cross-sectional; one was prospective.⁵⁷

There was minimal missing data for most variables, primarily occurring in studies available only as abstracted data,^{24,33,25,34} none of which met inclusion criteria for the meta-analyses. Included studies and those excluded based on location (Table 1, criterion 2) are provided in appendix 3. Additional results are in appendix 4.

The majority of products (26/49) provided only unadjusted analyses (17/27 among studies recruiting only in Asia/Africa/Latin America, vs 8/19 among those recruiting only in the US/Canada/Europe Australia group). Only two completed data collected after 2014, despite later publication dates.

For the unadjusted meta-analysis, 12/49 observational products were includable, totaling 13 with the trial. (Vs. eight and 11 in the Yuan and Zheng meta-analyses respectively). Of these, all except three^{29,46,53} prospective studies were cross-sectional. None of the five products newly identified in our search were includable for either meta-analysis.

Definitions for PI-MSM were heterogeneous. Of the 13 included studies, three used cutoffs for percent insertive or non-receptive among recent encounters, ranging from 50–90%^{9,42,62}; three used general preference^{44,49,53}; one²³ used “normally” taking only a “top” role; and the remaining six^{29,36,37,41,46} used exclusive insertivity/non-receptivity over periods ranging from two to 12 months, or a floating period based on time of infection.¹⁸ These distributions reflect a pool of participants selected to be primarily but not exclusively insertive.

For the confounder-adjusted meta-analysis, eight of the twelve observational products included in the unadjusted meta-analysis were again includable, after obtaining additional data from three products' authors. Also includable were the 2024 trial and our own work (de Leon et al¹³), for a total of 10. Of these, all except two^{29,53} prospective studies were cross-sectional.

Using the same categories for PI-MSM definitions described above, of the 10 included studies, numbers of studies were: two using percent cutoffs of 50–90%^{9,42,62}, three using general preference^{44,49,53}; zero “top”-only normal role; and five^{13,18,29,36,41} using exclusive insertivity/non-receptivity over the 2–12 past months or a floating period as above. These distributions reflect a similar primarily, not exclusively, insertive pool.

No study included in either meta-analysis adjusted for either injection drug use or PrEP use.

Descriptive analysis:

The 49 observational products were from North America, South America and the Caribbean, Europe, Asia/Pacific, and sub-Saharan Africa. Sub-Saharan Africa had only six includable products; Latin America had five. With respect to taking a versatile sex role, medians and ranges of 57% (40–64%) self-reported this role in US/Canada/Europe/Australia, vs. 27% (5–50%) in Asia/Africa/Latin America.

Of the five new includable studies, two were in Asia^{27,61}, one in the UK,⁵⁷ and two in sub-Saharan African, falling either outside the VMMC-implementing subregion (Cote d’Ivoire)²¹ or prior to VMMC scaleup (Namibia).³⁹

Of the total includable pool, eight studies were “lower risk, significant”, 23 “lower risk, not significant”, 10 neutral, 7 “higher risk, not significant”, and 1 “higher risk, significant” (figure 2a). Among the five new products included in this total, one was “lower risk, significant”; two “lower risk, not significant”; and two neutral or mixed. This distribution supports a protective association, but when measured by total participant N instead, this pattern is greatly attenuated (figure 2b). The median coefficient of association was odds ratio (OR)=0.79; among studies with significant results, it was OR=0.46, both indicating lower odds of HIV with circumcision. Protective associations were commonly seen in studies conducted in Latin America and Asia (14/17); compared to the United States, Europe and Australia (11/23); and in smaller studies (13/16 among studies with N≤500) compared to larger ones (10/26 among those with N>500). Among the 12/49 studies reporting on PI-MSM – of which all were retrievable manuscripts or abstracts - nine assessed significance: 1 “lower risk, significant”, 4 “lower risk, not significant”, 2 neutral or mixed lower and higher risk not significant (depending on stratum, when stratified by race), 2 “higher risk, significant”. The median coefficient of association was OR=0.61, indicating lower odds of HIV with circumcision.

Risk of intra-study bias:

Our review of the prior meta-analyses’ assessments of risk of bias found that Yuan et al rated 52% of their included studies (comprising 33/49 of our included studies) as low-risk for bias, and the remainder high-risk. Zhang et al did not report assessments. Our own bias assessment in the five new included studies found that 4 (cross-sectional) scored below 7/10 (high-risk); one (prospective) scored 8/9 (low-risk). Details are in Appendix 5.

Unadjusted meta-analysis:

This analysis returned an OR of 0.57 (95% CI 0.33–0.98, $p=0.043$) for HIV infection in circumcised vs. uncircumcised MSM (figure 3). The test for heterogeneity returned $p=0.02$, supporting between-study effect heterogeneity, and the test for asymmetry returned $p<0.0001$, supporting publication bias. Secondary analyses 1) using cell counts only and 2) preferring cell counts where available returned ORs of 0.56 (0.32–0.98) and 0.62 (0.37–1.03) respectively. Effect differences by region are presented in the forest plot; tests for funnel plot asymmetry returned $p<0.01$ for both regions, demonstrating publication bias. The effect of region was not significant ($p=0.15$), but the difference in point estimates was large (logOR-ratio -1.07 for Asia/Africa/Latin America vs. -0.21 for US/Canada/Europe/Australia).

Confounder-adjusted meta-analysis:

The geographic distribution of studies included in both meta-analyses is shown in supplemental figure 1 (appendix 6). Nine of the ten included studies had ratio of ratio point estimates indicating a protective effect. The meta-analysis returned a pooled ratio of ratios estimate of 0.53 ($p = 0.006$; 95% CI 0.34–0.83), indicating a significant protective association (forest plot, figure 4). There was no evidence for between-study heterogeneity of effect ($p=0.32$) indicating that the studies were relatively uniform in their estimation of the circumcision effect. Additionally, the test for funnel plot asymmetry returned $p = 0.34$ (funnel plot, figure 5) showing a lack of evidence for any publication bias.

Differences by region were also not significant ($p=0.65$), with a small difference in point estimates (logOR-ratio -0.77 (-1.52 – -0.03) for Asia/Africa/Latin America vs -0.54 (-1.44 – 0.36) for US/Canada/Europe/Australia). These findings indicate protective point estimates for circumcision in both regions, with no regional heterogeneity. Dropping de Leon et al did not impact the estimate (log ratio of ratios = -0.54) or test for heterogeneity; it did impact significance ($p = 0.055$). Both prospective studies (Templeton and Jameson) had point estimates in the direction of a protective effect (ratio of ratios of .1 and .78 respectively), with magnitudes consistent with the cross-sectional studies.

Discussion:

The results of these meta-analyses, along with the 2024 trial, provide new evidence that circumcision protects PI-MSM from HIV acquisition.

The contributions of the updated literature search and the unadjusted meta-analysis were moderate. The updated search partially filled the gap in data from sub-Saharan Africa, and, through the addition of two BBSs - which are reliably released regardless of circumcision findings - slightly mitigated publication bias. In other respects, though - study types and effect estimates - the five new products were similar to the prior literature. The unadjusted meta-analysis found a significant, protective association based on substantially more data (13 studies) than the prior meta-analyses (eight and 11 studies), but remained limited by regional heterogeneity and publication bias.

However, the adjusted meta-analysis, by comparing the associations of circumcision with HIV between PI-MSM and other MSM in the same participant pool to correct for any confounding affecting both groups equally, confirmed the protective association and eliminated the evidence for study heterogeneity and publication bias. This “escape” from publication bias is possible because this bias can exist in the same body of data on one outcome but not another, particularly one (like the ratio of two odds ratios) that was not previously visible to affect publication decisions. It was also notable that there was no pattern of difference in findings in this analysis between the prospective and cross-sectional studies.

Our confounder adjustment approach is conceptually simple and the underlying mathematics have been detailed here. The approach is not usually feasible with observational data, because participants at risk for an outcome cannot usually be stratified into a subgroup potentially more responsive (PI-MSM) to the exposure of interest (circumcision) and one which would be less responsive (other MSM). Here, though, this stratification is possible using self-report of sexual positioning, allowing us to use the “other MSM” group to subtract out any confounding that affects both groups equally. The analysis thus provides a clearer view of the true association than a simple pooled meta-analysis of odds ratios.

However, important limitations and opportunities to improve the data remain. This is a new finding from a novel approach. If correct, it should be reproducible using newer data from the US/Canada/Europe/Australia region, where the adjusted findings differed from the unadjusted findings. Fortunately, these countries already have large datasets which could be used to support or challenge our results: MSM cohort registries and past and ongoing HIV prevention trials, in which MSM were randomized on other interventions but also self-reported circumcision status.¹ The combination of low incidence and small sample sizes for the PI-MSM subgroup may still require data pooling, however.

Similarly, while the overall quantity of data is high (>150,000 participants), it is limited in some regions, particularly Latin America and sub-Saharan Africa. Although the lack of regional heterogeneity mitigates this issue, these regions - including, in sub-Saharan Africa, non-VMC-implementing countries – have existing BBS datasets which often capture circumcision status and sexual positioning. Similar secondary analyses of these could add evidence. All these approaches would be more feasible and rapid than a second trial.

As another limitation, while findings from our statistical approach support confounding as the cause of the lack of effect seen in prior analyses in US/Canada/Europe/Australia, they cannot clarify which specific factors caused it. Any risk factor or protective factor with higher prevalence in these regions, making it an important driver of HIV risk, could be such a confounder. There is evidence for several. This region had far more PrEP availability when studies in the descriptive analysis were collecting data: only two extended enrollment beyond 2014, while even by early 2017⁷³, fewer than 3,000 PrEP initiations had been

¹Based on N, capturing circumcision status, and numbers of seroconversions, excellent candidates could include: MOSAICO (HVTN 706), iPrEX, STEP and its extension (HVTN 502), and HPTN 075. (Some include data from VMC-implementing countries but would be protected from the self-selection bias problem by virtue of being prospective designs.) Other candidates, especially for pooled analysis, could include the Amsterdam Cohort Studies, PROUD, ANRS Prevenir, and IPERGAY.

tracked in the entire world outside US/Canada/Europe/Australia vs. over 100,000 within it. Similarly, with respect to injection drug use, while we did not find MSM-specific multicountry data, a recent global review found prevalences of 0.55–1.92% among all men in the US/Canada/Europe Australia vs. 0.18–0.86 outside those regions⁷⁴. The studies included in our meta-analyses did not adjust for these variables (PrEP or injection drug use.) Finally, the higher prevalences of versatile sex role reported in our descriptive dataset in these regions could also attenuate measured effect. However, risk behavior surveys and questions are highly heterogeneous across and within regions: not all countries conduct surveys BBS of MSM, and their questions vary by country⁷⁵. Thus a comprehensive assessment would require a systematic search.

As an additional limitation, while our adjusted meta-analysis would correct for confounders like these to the extent that they affect PI-MSM and other MSM equally, if they also vary in prevalence between these groups, they may still be acting as residual confounders, and could be contributing to the smaller point estimate for protection in the US/Canada/Europe/Australia region (–.54, vs. –.77 in Asia/Africa/Latin America). However, the further analyses suggested above could adjust for these confounders, where they were captured. Finally, even without residual confounding, circumcision would confer less absolute population-level benefit in US/Canada/Europe/Australia to the extent that HIV risk is driven more by factors like PrEP and injection drug use, and because of their lower HIV incidence.

There are additional limitations. As noted above, most included datasets were collected in 2014 or earlier; with the later global scaleup of PrEP, MSM using it would derive less absolute, though not relative, protection from circumcision. We chose not to include available raw datasets, as they did not meet key quality standards: analysis by authors familiar with the datasets, and some degree of peer review. Conversely, we chose for completeness to include in the descriptive analysis the few datasets we could only access in the prior meta-analyses, though none qualified for our meta-analyses. Our search also did not capture regional conferences and was an update search from 2018 onwards, relying on the prior meta-analyses for the earlier literature. Finally, a single author screened search results, potentially increasing risk for missed relevant publications.

However, this work introduces important strengths to the existing literature. In addition to the more rigorous analytic approach, and the capture of more data points in all analyses than previous work, it provides a conservative estimate for the per-act protection for insertive sex or for exclusively insertive MSM overall, while reflecting the real-world effect for PI-MSM with less consistent sex roles. This is because in reality most MSM do not neatly fall into exclusively insertive or non-insertive categories, so that the “least-insertive” category can still contain individuals engaging in some insertive sex, diluting the true effect of circumcision through crossover bias.² The common reliance on self-report for circumcision status and sexual role would also be expected to create crossover bias, further underestimating the effect.

²Another possible source of bias toward the null is retaining studies that adjusted for STI outcomes. Where these included penile STIs, if circumcision is protective for these in MSM as it is in men who have sex with women, these adjustments introduced collider bias toward the null for HIV outcomes.

Finally, a major remaining question is what proportion of unprotected penetrative sex acts must be insertive for an MSM to qualify as “primarily insertive”. An ideal definition might both reflect a true cutpoint for substantial benefit, and make it easy for individual MSM to determine if they meet it. One approach could be to consider rarity of unprotected receptive anal sex the most important factor; since its per-unprotected-act infection risk is over 12 times higher⁷⁶ than insertive sex, its attributable risk would be expected to confer most of the total sexual risk for a given MSM if it exceeded 8–10% of all his unprotected sex acts. This ratio (“approximately 90% or more of all unprotected penetrative sex acts are insertive”) might be one cutoff worth testing, though lower magnitudes of partial protection would still be expected below this threshold.

Conclusions:

The existing evidence indicates that circumcision partially protects PI-MSM from acquiring HIV. Our analytic approach resolves prior issues with regional heterogeneity and publication bias. The development of the original evidence base for VMMC in men who have sex with women used three clinical trials to address the ambiguity and publication bias in the prior observational data.⁷⁷ In the current context, where further trials in MSM are unlikely to be funded or feasible, but plausibility of the mechanism is already established and one trial has shown effect, we believe this more rigorous approach to the existing data is the most feasible way forward. Similar approaches to existing datasets in specific regions could further strengthen or challenge our conclusions. Particularly for PI-MSM who have high HIV risk from sex, lack access to injectable PrEP, and cannot or do not wish to take oral PrEP effectively, circumcision could be a valuable option for lasting HIV risk reduction.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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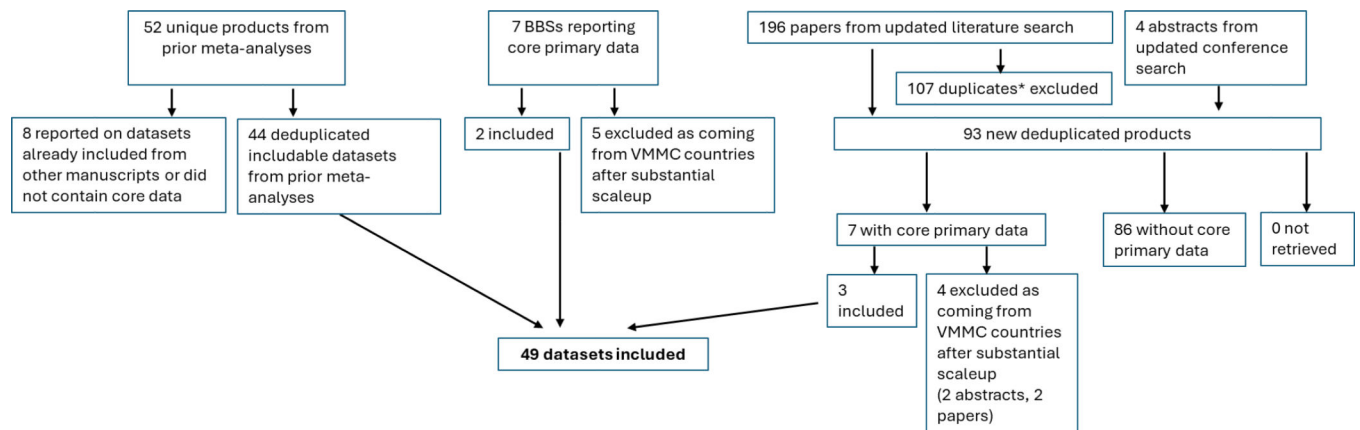
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**Figure 1:**

Dataset exclusion flowchart for association of circumcision with HIV among men who have sex with men

* Includes duplicates of products in prior meta-analyses

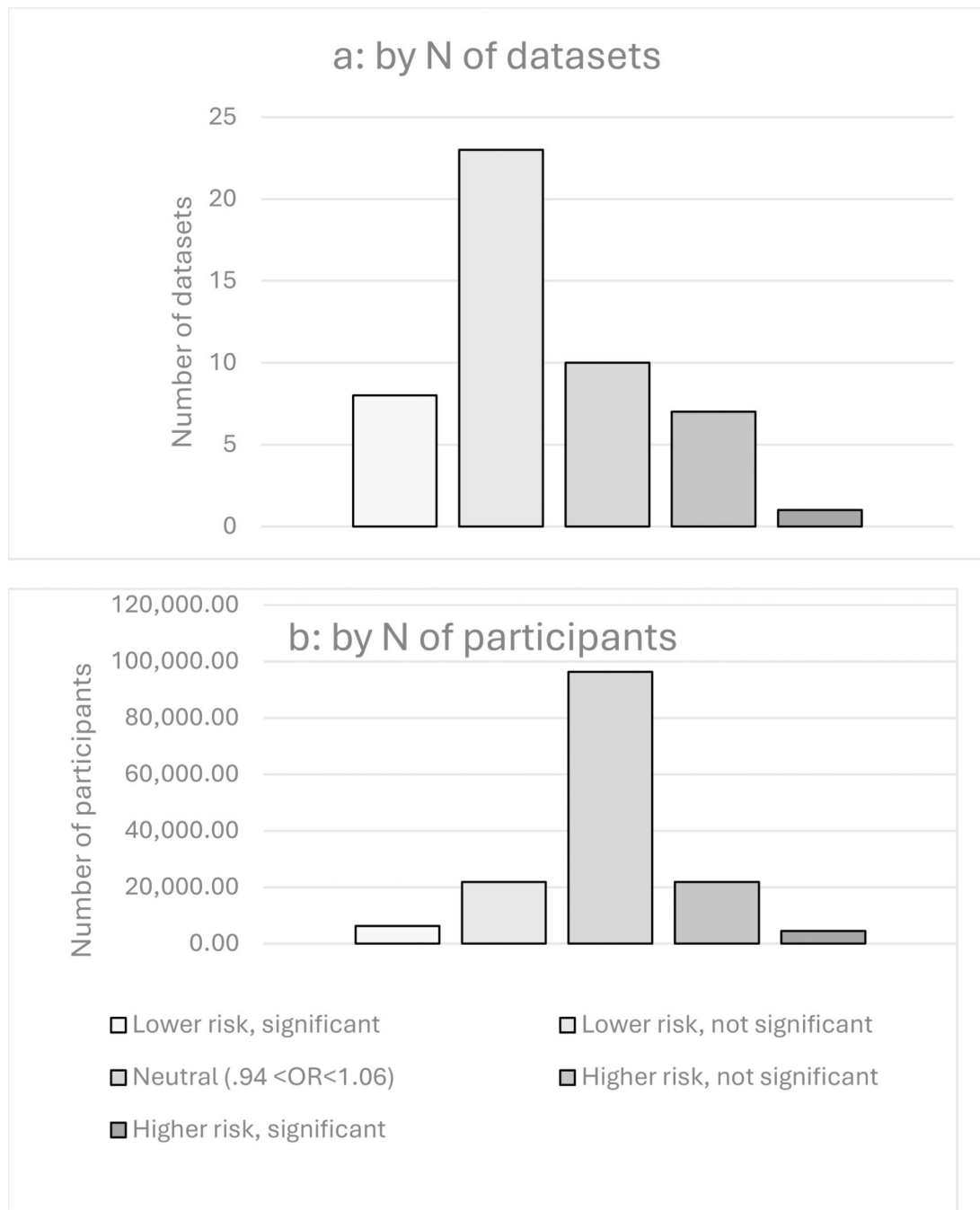


Figure 2:

Histogram: datasets on association of circumcision with HIV among men who have sex with men, by category of direction and significance

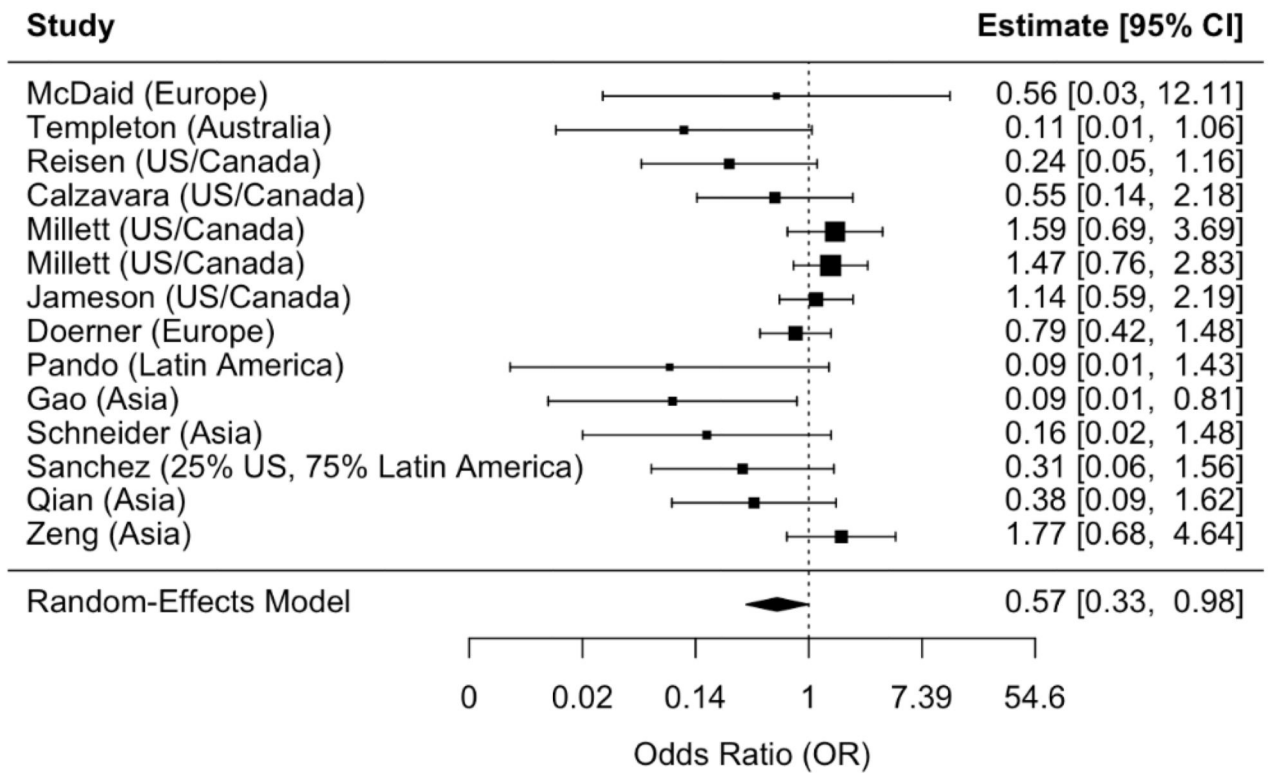
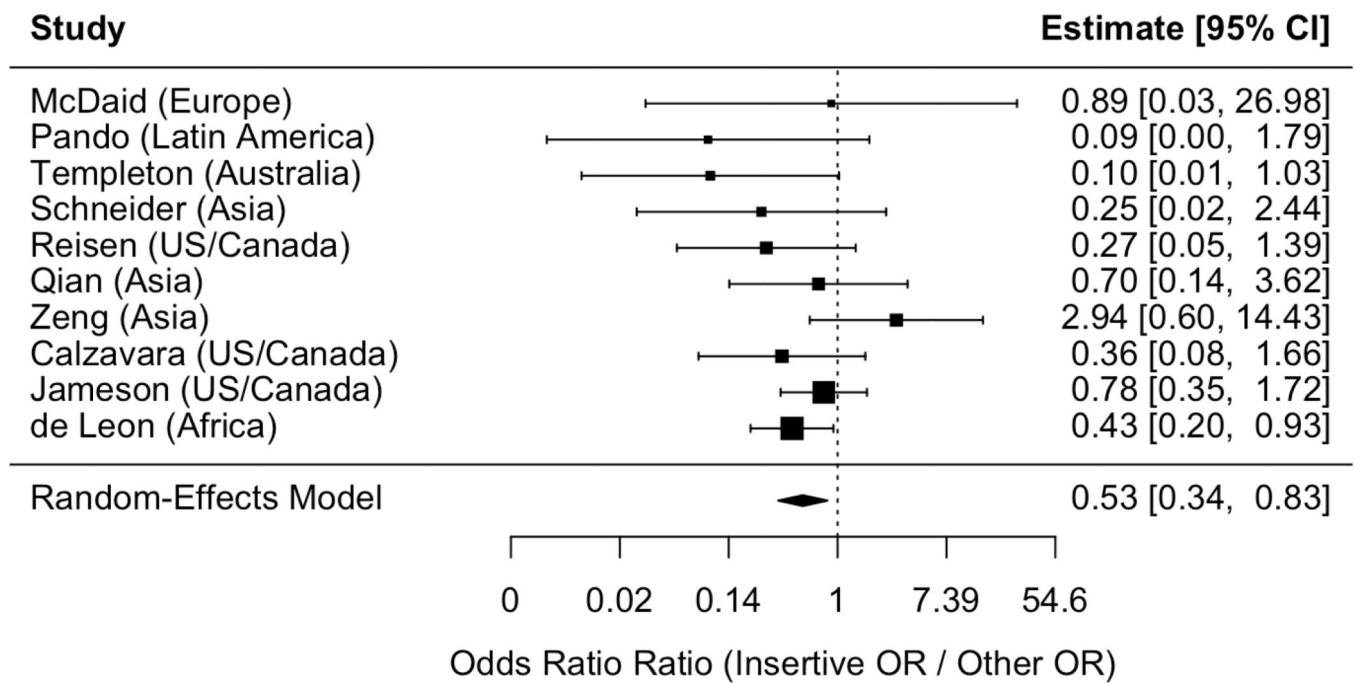


Figure 3:

Forest plot, unadjusted meta-analysis of association of circumcision with HIV among primarily-insertive men who have sex with men

**Figure 4:**

Forest plot, confounder-adjusted meta-analysis (ratio of associations of circumcision with HIV, comparing primarily-insertive MSM to other MSM)

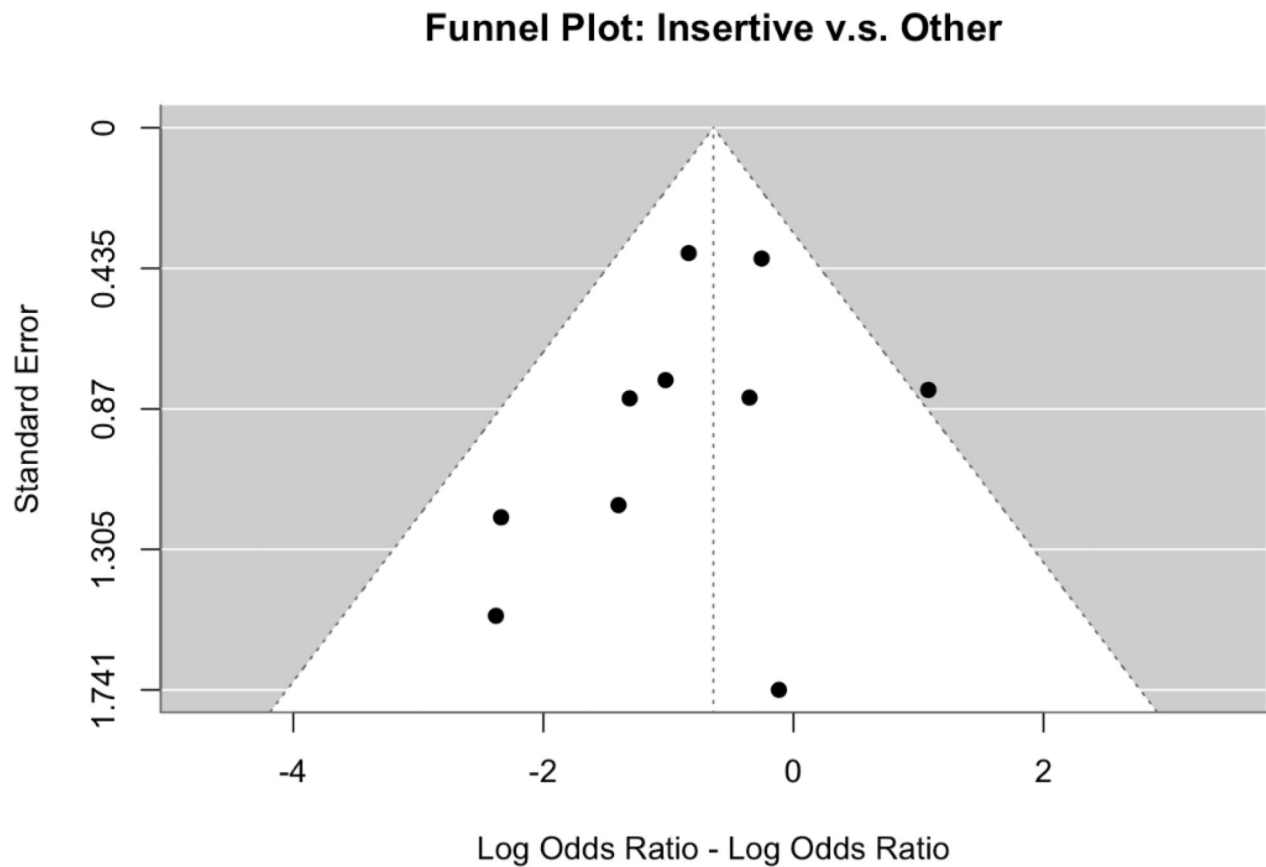


Figure 5:

Funnel plot, confounder-adjusted meta-analysis (difference in log odds ratios for associations of circumcision with HIV among men who have sex with men, comparing primarily-insertive MSM to other MSM)

Table 1:

Exclusion criteria for descriptive analysis of the association of circumcision with HIV among all MSM and two meta-analyses of this association among PI-MSM

Exclusion criterion	Rationale	Descriptive analysis	Unadjusted meta-analysis	Confounder-adjusted meta-analysis
Duplication, including reporting on the same dataset as another included product. *	Avoids over-weighting datasets with more publications	x	x	x
Reporting data from a VMMC-implementing country after substantial scaleup of the VMMC program (>20,000 VMMCs).	VMMC is popularly known in these settings as being primarily an HIV prevention tool; offer of HIV testing and immediate return of results is part of the VMMC standard service package; and men living with HIV who seek VMMC are counseled it will not affect their HIV-related health (though they can proceed if they choose). This contrasts with regions without VMMC programs, where HIV status is commonly not a direct consideration in circumcision decisions. In VMMC regions, it is thus plausible that men living with HIV are less likely to obtain circumcision than men without HIV. (This may be a contributing factor to the observed low HIV positivity among VMMC clients, as compared to men in the general population.) [‡] If this effect is substantial, the disproportionate flow of HIV-negative men into VMMC will create self-selection bias, inflating circumcision's apparent protective effect in VMMC regions.	x	x	(Counters dataset-wide bias by comparing results between PI-MSM and other MSM within the same study.)
Reporting only non-observational data (the RCT)	Allows descriptive analysis to represent the observational data for easy comparison with the trial results, while the other analyses synthesize all available evidence.	x		(However, RCT excluded anyway by final criterion below)
Not reporting results for a PI-MSM subgroup	Method requires these data		x	x
Not reporting results for other MSM (non-PI) MSM	Method requires these data			x

* In these situations, we prioritized manuscripts over abstracts, more inclusive and more highly-stratified results, and those representing longer follow-up.

[‡] Davis SM, Hines JZ, Habel M, et al. Progress in voluntary medical male circumcision for HIV prevention supported by the US President's Emergency Plan for AIDS Relief through 2017: longitudinal and recent cross-sectional programme data. *BMJ Open*. 2018 Sep 1;8(8):e021835. doi: [10.1136/bmjopen-2018-021835](https://doi.org/10.1136/bmjopen-2018-021835). PMID: 30173159; PMCID: PMC6120649.