HIV and male circumcision—a systematic review with assessment of the quality of studies

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This Cochrane systematic review assesses the evidence for an interventional effect of male circumcision in preventing acquisition of HIV-1 and HIV-2 by men through heterosexual intercourse. The review includes a comprehensive assessment of the quality of all 37 included observational studies. Studies in high-risk populations consisted of four cohort studies, 12 cross-sectional studies, and three case-control studies; general population studies consisted of one cohort study, 16 cross-sectional studies, and one case-control study. There is evidence of methodological heterogeneity between studies, and statistical heterogeneity was highly significant for both general population cross-sectional studies (χ^2=132·34; degrees of freedom [df]=15; p<0·00001) and high-risk cross-sectional studies (χ^2=29·70; df=10; p=0·001). Study quality was very variable and no studies measured the same set of potential confounding variables. Therefore, conducting a meta-analysis was inappropriate. Detailed quality assessment of observational studies can provide a useful visual aid to interpreting findings. Although most studies show an association between male circumcision and prevention of HIV, these results may be limited by confounding, which is unlikely to be adjusted for.

According to the latest UNAIDS estimates, 42 million people were living with HIV/AIDS in 2002.[1] Half of these people were women and 3·2 million were children younger than 15 years old. Almost 30 million people living in Africa are affected by HIV/AIDS and 2·4 million Africans died of AIDS during 2002.[1] Sub-Saharan Africa is by far the worst affected region, and the national adult prevalence rates exceed 30% in the southern African countries of Botswana, Lesotho, Swaziland, and Zimbabwe. In South Africa, HIV/AIDS accounts for 38% of years of life lost and is the major contributor to disability-adjusted life years in adults.[2]

Given the enormous mortality and morbidity associated with HIV/AIDS, it seems reasonable to fully explore potential prevention measures. For over a decade many observational studies have suggested a protective effect of male circumcision (figure 1) on HIV acquisition in men. These findings are supported by the biological theory that the entry of HIV into host cells is facilitated by CD4 and other HIV coreceptors present on the Langerhans' cells of the foreskin.[3–5] Six reviews[6–11]—including two meta-analyses[9,10]—of these observational studies have reached different conclusions on the association between male circumcision and HIV infection. Search strategies were not clearly described in all the reviews, several focused only on published studies, and confounding was not always adequately assessed. None of the reviews reported on the methodological quality of included studies.

The most rigorous of these reviews is a systematic review and meta-analysis of 27 published studies on HIV-1 infection in sub-Saharan Africa by Weiss and colleagues,[10] published in 2000. Adjusted analyses produced odds ratios (ORs) indicating a benefit of circumcision: OR=0·42 (95% CI 0·34–0·54) for all studies combined (n=15); OR=0·55 (95% CI 0·42–0·72) for population-based cross-sectional studies (n=5); and OR=0·24 (95% CI 0·18–0·31) for cross-sectional studies of high-risk groups (n=4). Because ORs were less than 1, the authors concluded that there was compelling evidence of a substantial protective effect of male circumcision against HIV infection in sub-Saharan Africa, while warning that residual confounding may exist in some studies because of unknown or unmeasured behavioural or biological factors. In a review of 48 published observational studies (including studies of homosexual men), Bailey and co-workers[11] described confounding variables potentially present in these studies in general, but did not report on the quality of each included study.

We report updated results from a Cochrane systematic review in which we assessed the likelihood that male circumcision reduces acquisition of HIV-1 and HIV-2 in heterosexual men, first published in 2003.[12] We evaluate the methodological quality of each included study and quantify the level of heterogeneity between studies.

Methods

Search strategy and selection criteria

We planned to include randomised or quasirandomised controlled trials. Should data be insufficient—ie, no randomised controlled trials identified—data from

Allan Jeffries

Figure 1: **A face painted with white clay and a traditional blanket identify this Xhosa youth as an initiate**
During a period known as "ulwaluko" (male initiation), he will be ritually circumcised and instructed in the ways of manhood to be received and perceived as a man. Permission of the individual was obtained for this photograph.

observational studies (cohort, case-control, and cross-sectional studies) would be considered for inclusion in this review. Studies done in general or specific populations and in hospitals or clinics were included. Studies done in any country and published in any language were included. Studies with historic controls and ecological studies were excluded, because these studies provide less reliable data for assessing association.

We searched online for published and unpublished studies in the Cochrane controlled trials register, Medline, Embase, and Gateway/Aidsline in 2002, and again in November 2004. We also searched databases of conference abstracts, scanned reference lists of articles, and contacted authors of included studies and researchers working in the field to source unpublished studies. The full search strategy is described elsewhere.[12] Reviewers independently screened each record for eligibility by examining titles, abstracts, and keywords. Two reviewers independently applied the inclusion criteria using a standard form, and differences were resolved by discussions with a third reviewer.

Data extraction and outcome measures

Two reviewers independently extracted data on the type of study and the participants in the study. Only studies that included participants defined as heterosexual males 12 years of age or older were included. Studies of discordant couples were excluded. We also recorded whether the intervention—circumcision—was a medical intervention or done for cultural or religious practices, and whether circumcision status was determined by self-report, partner-report, or direct observation. The primary outcome was HIV-1 or HIV-2 infection (incidence or prevalence) in men, based on laboratory results. The specific tests used to ascertain and confirm HIV status were recorded, as well as the reporting of ten possible confounding factors (panel). We reported any medical adverse events associated with circumcision if recorded in the studies. Reviewers were not blinded to the names of the authors, institutions, journal of publication, or results of the studies.

A number of the included studies are described in more than one publication. In some cases, additional analyses conducted after completion of a study were reported. Where methods of study design were described in additional publications, we used all reports to inform our data extraction. Where additional analyses were conducted, we chose to include the analysis that provided the most information and avoided duplication of results. The full description is available in the Cochrane review.[12]

Data analysis and statistical methods

We used REVMAN software to analyse our data. For each study, we expressed findings as crude and adjusted ORs with their 95% CIs. An OR below 1 indicated a protective effect of circumcision. Statistical significance was indicated by p values less than 0·05. The χ^2 test for heterogeneity was used to provide an indication of between-study heterogeneity (statistical significance was taken as $p<0·1$). In addition, the degree of heterogeneity observed in the results was quantified using the I^2 statistic,[13] which can be interpreted as the percentage of variation observed between the studies caused by between-study differences rather than chance. Studies are presented stratified by study design, further stratified by general population or high-risk groups. High-risk groups included participants who are considered at greater risk of contracting HIV due to the nature of their lifestyle and activities—eg, truck drivers, men who have sex with sex workers, patients attending sexually transmitted infection (STI) clinics.

Methodological quality of included studies

We developed a standardised quality assessment form for observational studies specifically for the review. The form included three separate sections for cohort studies, cross-sectional studies, and case-control studies. We appraised the quality of each study using a "star system".[14] This system included appraisal of external and internal validity and biases relevant to observational studies in general, and specific to circumcision and HIV. Two reviewers independently evaluated study quality and differences were resolved by discussions with a third reviewer.

Results

We identified three randomised controlled trials currently underway in Africa. We included 37 observational studies: 18 conducted in the general population and 19 in high-risk populations. Two new studies not included in the original review and one updated study were identified. Meta-analysis was not done because many of the studies had a high likelihood of bias and there was substantial heterogeneity, suggesting that any overall summary statistic could be misleading. Synthesis focused on describing the direction and consistency of effect, assessing the likelihood of bias, and investigating factors that may explain differences between the results of studies. No

***Panel*: Potential confounding factors**

Age
Location of study (eg, rural, urban)
Religion
Education, occupation, and socioeconomic status
Sexual behaviour (eg, measured by age at first intercourse, number of sexual partners, contact with sex workers)
Any STIs
Condom use
Migration status
Travel to different countries
Other possible exposures (eg, injections, blood transfusions, homosexual intercourse)

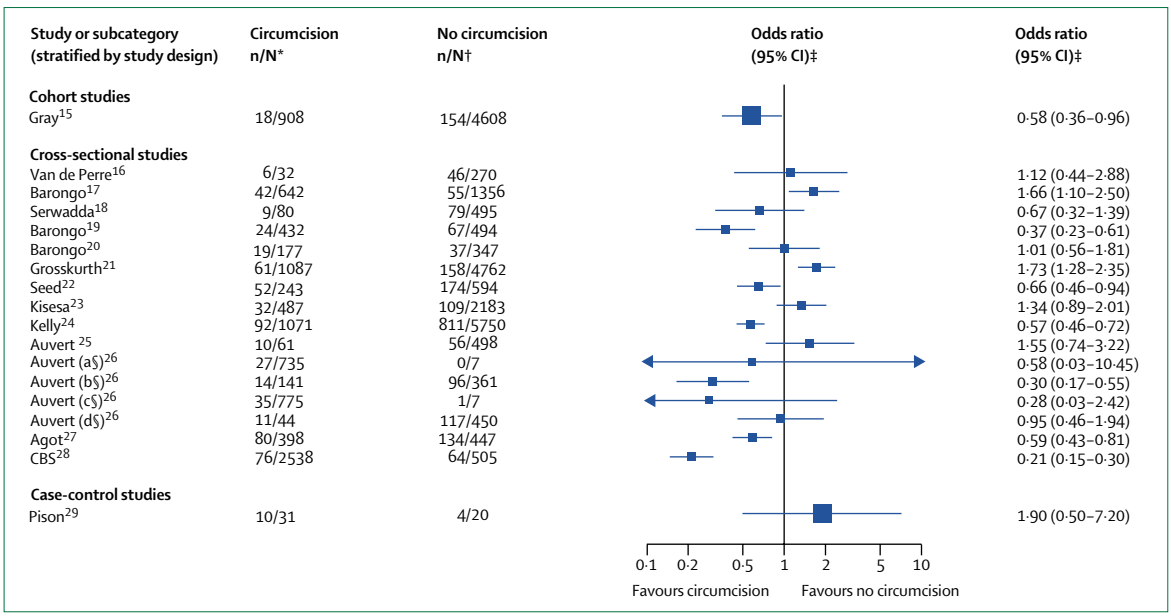

Figure 2: **Crude results of general population studies assessing HIV and circumcision status**
The point estimate (odds ratio, OR) for each study is represented by a square. The 95% CI for each study is represented by a horizontal line intersecting the square. The size of the square represents the relative precision of the study estimates within each study design strata. The data are displayed on a logarithmic scale. *n/N represents the number of HIV-positive participants (n) in the circumcised group over the total number of participants (N) in the circumcised group. †n/N represents the number of HIV-positive participants (n) in the uncircumcised group over the total number of participants (N) in the uncircumcised group. ‡Odds ratio and 95% CI. ORs greater than 1 indicate increased risk of HIV infection with circumcision and ORs less than 1 indicate decreased risk of HIV infection with circumcision. §a, b, c, and d represent different studies discussed by Auvert et al.[26]

studies reported on the medical complications of circumcision. In most studies, exposure to circumcision had reportedly taken place during childhood or adolescence, before the studies commenced.

General population study results

We identified one cohort study, 16 cross-sectional studies, and one case-control study conducted in general populations. The crude results are shown in figure 2.

The single cohort study[15] (n=5516) showed a significant difference in HIV transmission rates between circumcised and uncircumcised men (OR=0·58; 95% CI 0·36–0·96). Adjustment for potential confounders did not alter this result.

The 16 cross-sectional studies had inconsistent findings.[16–28] Ten studies indicated circumcision was beneficial whereas six indicated it was harmful, with odds ratios varying between 0·21 and 1·73. Eight studies had statistically significant results, six indicating a benefit and two indicative of harm. The test for heterogeneity was highly significant (χ^2=132·34; df=15; p<0·00001). 89% of the variability observed between the studies was attributable to between-study differences and not random variation (I^2=88·71%). Ten studies reported adjusted ORs, with nine of these studies showing a benefit for circumcision, ranging from OR=0·26 to 0·80. Five of these studies had significant results and three insignificant results. The study that indicated a harmful effect of circumcision reported an adjusted OR of 1·25, but did not report CIs. The studies all adjusted for different sets of potential confounders. Use of adjusted results accounted for only 3% of the unexplained variability in results, 86% of the variability remaining inexplicable. The quality of each study is shown in table 1.

Only one case-control study in a general population setting was identified.[29] This study (n=51) found no significant difference in HIV transmission rates between circumcised and uncircumcised men (OR=1·90; 95% CI 0·50–7·20).

High-risk group study results

We identified four cohort studies, 12 cross-sectional studies, and three case-control studies conducted in high-risk groups (figure 3). One cross-sectional study presented only an adjusted estimate.[35]

Results from the four cohort studies[42–45] all indicated benefit from circumcision and three of them had statistically significant results. Point estimates from crude ORs varied from 0·10 to 0·39. The χ^2 test for between-study heterogeneity was marginal (χ^2=6·17; df=3; p=0·10) and 51% of the variability in results was not explicable by chance (I^2=51·4%).

Crude results from 11 cross-sectional studies were indicative of a benefit from the intervention, eight being statistically significant.[30–34,36–41] Estimates of effect varied from ORs of 0·10 to 0·66. Between-study heterogeneity was significant (χ^2=29·70; df=10; p=0·001). 66% of the

Study	External validity		Internal validity																OR (95% CI)	
			Performance		Detection			Attrition	Selection bias/control of confounding											
	Representative*	Participation rate†	Direct observation	Blinded assessors	1st HIV test	2nd HIV test	Blinded assessors	Completeness‡	Age	Location	Religion	SES/education	Marital status	Sexual behaviour	Any STI	Condom use	Travel/ migration	Other exposure	Crude	Adjusted
General population groups																				
Agot[27]	✓	..	✓	✓	✓	✓	✓	..	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	0·59 (0·34–0·81)	0·48 (0·33–0·67)
Auvert[25]	✓	✓	..	..	✓	..	✓	..	..	✓	..	..	..	..	..	..	..	..	1·55 (0·74–3·22)	
Auvert (a§)[26]	✓	✓	✓	✓	✓	✓	✓	..	..	✓	..	..	..	..		..	..	..	0·58 (0·03–10·46)	
Auvert (b§)[26]	✓	..	✓	✓	✓	✓	✓	..	✓	✓	..	..	✓	✓	✓	✓	✓	..	0·30 (0·17–0·55)	0·26 (0·12–0·56)
Auvert (c§)[26]	✓	..	✓	✓	✓	✓	✓	..	..	✓	..	..	..	..	..	..	..	..	0·28 (0·03–2·42)	
Auvert (d§)[26]	✓	..	✓	✓	✓	✓	✓	..	..	✓	..	..	..	..	..	..	..	..	0·95 (0·46–1·94)	
Barongo[17]	✓	✓	..	..	✓	✓	✓	..	✓	✓	..	..	✓	✓	✓	..	✓	✓	1·6 (1·10–2·50)	0·8 (0·5–1·3)
Barongo[19]	✓	..	..	..	✓	✓	✓	✓	✓	✓	..	✓	✓	..	✓	..	✓	✓	0·37 (0·23–0·61)	0·40 (0·23–0·71)
Barongo[20]	✓	..	..	..	✓	✓	✓	✓	..	✓	✓	✓	..	✓	✓	✓	..	..	0·21 (0·15–0·30)	
Grosskurth[21]	✓	✓	..	✓	✓	✓	✓	✓	✓	✓	..	✓	✓	..	✓	..	✓	✓	1·73 (1·28–2·35)	1·25 (Not reported)
Kelly[24]	✓	..	..	..	✓	✓	✓	✓	✓	✓	..	✓	✓	✓	✓	✓	..	..	0·57 (0·46–0·72)	0·44 (0·35–0·56)
Kisesa[23]	✓	..	..	..	✓	✓	..	✓	..	✓	✓	✓	..	✓	✓	✓	..	..	1·34 (0·89–2·01)	0·66 (0·41–1·08)
Seed[22]	..	..	✓	✓	✓	✓	✓	✓	✓	✓	..	..	..	..	✓	..	..	..	0·66 (0·46–0·94)	0·59 (0·40–0·86)
Serwadda[18]	✓	..	..	..	✓	✓	✓	✓	✓	✓	..	..	..	✓	✓	..	..	..	0·67 (0·32–1·39)	0·4 (0·2–0·9)
Van de Perre[16]	✓	✓	..	..	✓	✓	✓	✓	..	✓	..	..	..	..	..	..	..	..	1·12 (0·44–2·28)	
High-risk groups																				
Bwayo[30]	✓	..	..	..	✓	✓	✓	✓	✓	..	..	✓	✓	✓	✓	✓	..	..	0·24 (0·17–0·34)	0·20 (0·12–0·36)
Diallo[31]	✓	..	✓	✓	✓	✓	✓	✓	..	..	..	✓	..	✓	✓	..	✓	..	0·30 (0·19–0·48)	
Gilks[32]	✓	✓	..	..	✓	✓	✓	✓	..	..	..	..	..	..	..	..	..	..	0·17 (0·09–0·35)	
Greenblatt[33]	✓	..	✓	✓	✓	✓	✓	✓	✓	✓	..	..	..	✓	✓	..	..	✓	0·30 (0·11–0·82)	
Lankoande[34]	✓	✓	✓	✓	✓	✓	✓	✓	..	..	..	..	..	..	..	..	..	..	0·66 (0·23–1·93)	
Mbugua[35]	✓	..	..	..	✓	✓	✓	✓	✓	..	..	✓	..	✓	..	..	✓	..	–	0·27 (0·11–0·65)
Mehendale[36]	✓	..	✓	✓	✓	✓	✓	✓	✓	✓	..	✓	✓	✓	✓	✓	..	✓	0·61 (0·43–0·87)	0·59 (0·41–0·84)
Nasio[37]	..	✓	✓	✓	..	..	✓	✓	..	..	..	..	..	..	✓	..	..	..	0·21 (0·15–0·31)	0·22 (Not reported)
Pepin[38]	..	..	✓	✓	✓	✓	✓	✓	..	..	..	..	..	..	..	..	..	..	0·45 (0·15–1·33)	
Simonson[39]	✓	..	✓	✓	✓	✓	✓	..	..	..	..	..	..	✓	✓	..	✓	..	0·36 (0·18–0·72)	
Tyndal[40]	✓	✓	✓	✓	✓	✓	✓	✓	✓	..	..	..	✓	✓	✓	✓	..	✓	0·22 (0·15–0·31)	0·21 (0·14–0·30)
Vaz[41]	✓	..	..	..	✓	✓	✓	✓	..	..	..	..	..	..	..	..	..	..	0·10 (0·01–1·81)	

SES=socioeconomic status; STI=sexually transmitted infection; ✓indicates the measure was adequately addressed in the study; *studies received a ✓ if the sample included all eligible HIV-negative men over a defined period of time, or in a defined catchment area, or a random or systematic sample of those men; †studies received a ✓ if the percentage participation was 80% or more; ‡studies received a ✓ if the percentage participants in the final analysis was 80% or more, or if a full description of those lost-to-follow-up was not suggestive of bias. For selection bias/control of confounding a ✓ indicates that the group variable was either balanced between groups (10% or less difference) or adjusted for in analysis. §a, b, c, and d represent different studies discussed by Auvert et al.[26]

Table 1: **Quality assessment of cross-sectional studies**

variability in results was not explicable by chance (I^2=66·4%). Five of the cross-sectional studies report adjusted ORs ranging from 0·20 to 0·59, four of these studies were significant and one did not provide data to calculate CIs, although it was reported as a significant OR.[37] None of these studies adjusted for the same set of potential confounders. The quality of each study is shown in table 1.

Three case-control studies met inclusion criteria and all indicated a protective effect of circumcision on HIV status, two being statistically significant.[46–48] ORs varied from 0·37 to 0·88. The test for between-study heterogeneity was marginal (χ^2=4·36; df=2; p=0·11). 54% of the variation in results could not be explained by chance (I^2=54·1%). One study reported an adjusted OR of 0·50 (95% CI 0·30–0·77), adjusting for location, socioeconomic status, marital status, sexual behaviour, any STI, and condom use.[47]

Subgroup analysis

Our decision to stratify results by risk group and study design was supported by the results of the studies. Studies in high-risk groups were significantly more in favour of circumcision than those done in general population studies (p=0·00006 by meta-regression of adjusted results), and differences were observed between study designs for the high-risk studies (p=0·044 for cross-sectional studies compared with case-control studies; p=0·029 for cohort studies compared with case-control studies). Insufficient numbers of cohort and case-control studies were included to make the same comparison among general population studies.

We were able to do a subgroup analysis on mode of establishing circumcision status: self-report versus direct observation. Because of the small number of studies in some strata, it was only possible to assess cross-sectional studies within the general population group (figure 4). All six cross-sectional studies using direct observation indicated a benefit of circumcision (OR 0·28–0·95), with three of the studies indicating a significant benefit. The ten studies based on self-report described a mixture of benefit (four studies) and harm (six studies) with OR ranging from 0·21 to 1·88. Between-study heterogeneity was substantial in the subgroup of self-reported studies

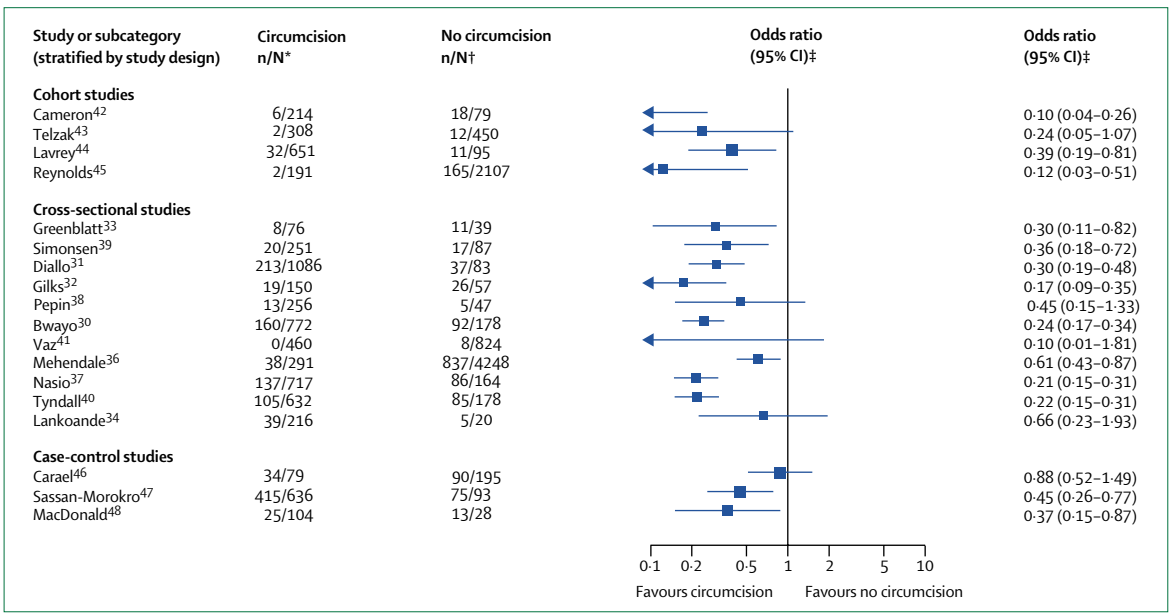

Figure 3: **Crude results of high-risk group studies assessing HIV and circumcision status**
The point estimate (odds ratio, OR) for each study is represented by a square. The 95% CI for each study is represented by a horizontal line intersecting the square. The size of the square represents the relative precision of the study estimates within each study design strata. The data are displayed on a logarithmic scale. *n/N represents the number of HIV-positive participants (n) in the circumcised group over the total number of participants (N) in the circumcised group. †n/N represents the number of HIV-positive participants (n) in the uncircumcised group over the total number of participants (N) in the uncircumcised group. ‡Odds ratio and 95% CI. ORs greater than 1 indicate increased risk of HIV infection with circumcision and ORs less than 1 indicate decreased risk of HIV infection with circumcision.

(χ^2=135·23; df=9; p<0·00001; I^2=93%), but marginal in the direct observation subgroup (χ^2=7·20; df=5; p=0·21; I^2=31%). The difference between the groups did not reach statistical significance (p=0·27). Results from studies using direct observation were still heterogeneous, 31% of the observed variability not being explicable by chance.

We were not able to conduct subgroup analysis on HIV-1 versus HIV-2 status, because many studies did not clearly report on the type of HIV, and those studies that measured both often did not differentiate between the two types in analysis. 21 of the studies assessed HIV-1 status only, one study only included HIV-2, six studies included both HIV-1 and HIV-2, and six studies were unclear whether HIV-1 or HIV-2 was measured.

We were not able to conduct subgroup analysis on background prevalence of HIV in the sampled populations because this information was unavailable for almost all studies.

Quality of included studies

The overall study quality was highly variable (tables 1–3). Performance bias (misclassification of exposure) may be present in all studies where circumcision status was obtained by self-report rather than direct observation.

Study	External validity	Internal validity																			OR (95% CI)	
		Performance			Detection			Attrition	Selection bias/control of confounding													
	Representative	Participation rate*	Direct observation	Blinded assessors	1st HIV test	2nd HIV test	Cases=control†	Completeness‡	Case selection	Control selection	Age	Location	Religion	SES/education	Marital status	Sexual behaviour	Any STI	Condom use	Travel/migration	Other exposure	Crude	Adjusted
General population groups																						
Pison[29]	✓	..	..	✓	✓	✓	✓	✓	✓	✓	✓	✓	..	..	✓	✓	✓	✓	✓	✓	1·90 (0·50–7·20)	
High-risk groups																						
Carael[46]	..	..	..	✓	✓	✓	✓	✓	..	..	✓	..	..	..	..	✓	..	..	✓	..	0·88 (0·52–1·49)	
MacDonald[48]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	..	..	✓	..	✓	✓	..	..	..	0·37 (0·15–0·87)	
Sassan-Morokro[47]	..	..	..	✓	..	..	..	✓	✓	✓	..	✓	..	✓	✓	✓	✓	✓	..	✓	0·45 (0·26–0·77)	0·50 (0·30–0·77)

SES=socioeconomic status; STI=sexually transmitted infection; ✓indicates the measure was adequately addressed in the study; *studies received a ✓ if the percentage participation was 80% or more; †studies received a ✓ if the same method of ascertainment was used for cases and controls; ‡studies received a ✓ if the percentage participants in the final analysis was 80% or more, or if a full description of those lost-to-follow-up was not suggestive of bias. For selection bias/control of confounding a ✓ indicates that the group variable was either balanced between groups (10% or less difference) or adjusted for in analysis.

Table 2: **Quality assessment of case-control studies**

17 studies assessed circumcision status by self-report and 20 by direct observation. Detection bias (misclassification of outcome) was unlikely, because nearly all studies (n=35) used blinded methods for assessing and confirming HIV status. All five cohort studies included in the review were classified as susceptible to attrition bias as loss-to-follow-up was either greater than 20%,[44] unequal between circumcised and uncircumcised groups,[42] not reported, or unclear.[15,43,45]

Selection bias was problematic in all studies. Circumcised and uncircumcised groups (in cohort and cross-sectional studies) and HIV-positive and HIV-negative groups (in case-control studies) were seldom balanced (less than 10% difference between circumcised and uncircumcised groups) for all or most of the ten risk factors that we identified as potential confounders before the quality assessment. Statistical adjustments for measured confounding factors were made in only 20 of the 37 included studies. The adjusted confounders differed across studies in number and type.

Discussion

There are currently no completed randomised controlled trials assessing the effectiveness of male circumcision in preventing HIV acquisition in heterosexual men. However, three large trials have commenced in Kenya (n=2776), Uganda (n=5000), and South Africa (n=3500), and are scheduled for completion in 2006–2007. 37 observational studies met the review inclusion criteria: 18 conducted in the general population and 19 in high-risk groups.

Methodological issues

The strengths of this review are its comprehensive coverage, our assessment of the biases often found in traditional narrative reviews,[49] and our extensive assessment of the quality of existing studies. Firstly, to reduce publication and language bias, we conducted an extensive search to source all studies, regardless of publication status or language. Secondly, we did not limit the review to studies conducted in a particular geographic region and included both HIV-1 and HIV-2 infection. We therefore included 37 studies, making this the largest systematic review of male circumcision and heterosexual transmission of HIV to date. Thirdly, we undertook an appraisal of the quality of all included studies using a quality assessment tool specifically developed for this review. This tool allowed for an intense interrogation of the quality of each study and let us make a more informed judgment regarding the appropriateness of pooling the results in a meta-analysis.

Observational studies, unlike randomised controlled trials, can only adjust for known confounders and only those that are measured without error.[50] In assessing the quality of the observational studies we identified ten potentially important confounders (panel). Many studies either did not measure or report these variables. Where confounders were reported, they were often not balanced between groups or not adjusted for. Religion commonly fell into this category. Among studies that did report confounders, choice of potential confounders was highly variable across studies. The effect of unknown

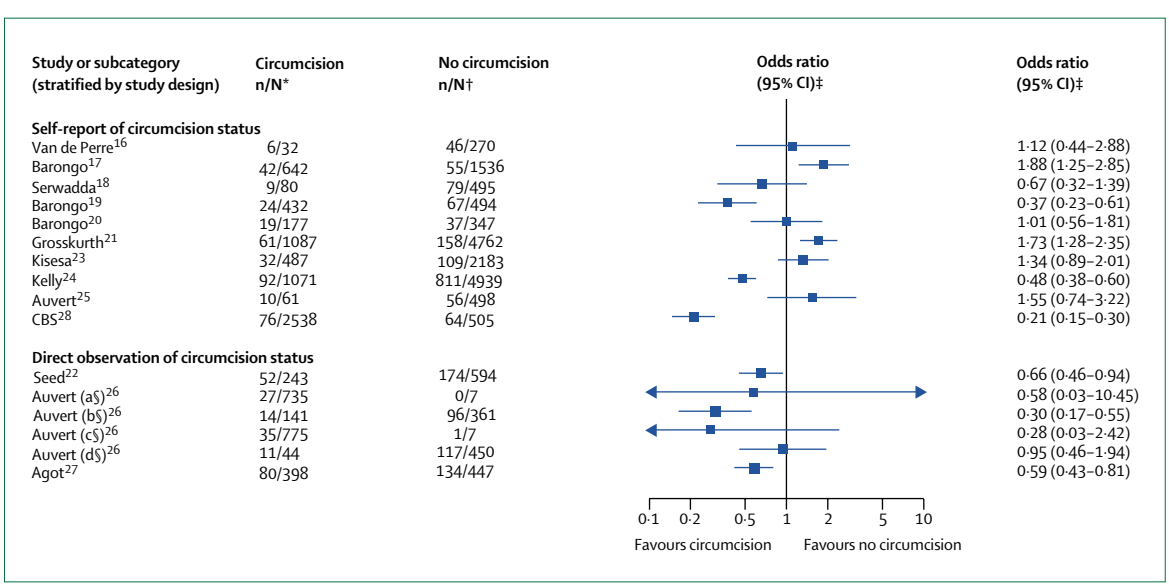

Figure 4: **Crude results of cross-sectional general population studies assessing HIV and circumcision status: self-report of circumcision *vs* direct observation**
The point estimate (odds ratio, OR) for each study is represented by a square. The 95% CI for each study is represented by a horizontal line intersecting the square. The size of the square represents the relative precision of the study estimates within each study design strata. The data are displayed on a logarithmic scale. *n/N represents the number of HIV-positive participants (n) in the circumcised group over the total number of participants (N) in the circumcised group. †n/N represents the number of HIV-positive participants (n) in the uncircumcised group over the total number of participants (N) in the uncircumcised group. ‡Odds ratio and 95% CI. ORs greater than 1 indicate increased risk of HIV infection with circumcision and ORs less than 1 indicate decreased risk of HIV infection with circumcision. §a, b, c, and d represent different studies discussed by Auvert et al.[26]

Study	External validity		Internal validity																OR (95% CI)	
			Performance	Detection			Attrition	Selection bias/control of confounding												
	Representative*	Participation rate†	Direct observation	1st HIV test	2nd HIV test	Blinded assessors	Equal follow-up‡	Completeness§	HIV-negative at commencement	Age	Location	Religion	SES/ Education	Marital status	Sexual behaviour	Any STI	Condom use	Travel/ migration	Other exposure	Crude	Adjusted
General population groups																				
Gray[15]	✓	✓	..	✓	✓	✓	..	..	✓	✓	✓	..	✓	✓	✓	✓	✓	..	..	0·58 (0·36–0·96)	0·53 (0·33–0·87)
High-risk groups																				
Cameron[42]	✓	✓	✓	✓	✓	✓	✓	..	✓	..	..	..	..	..	✓	✓	..	..	..	0·10 (0·04–0·26)	0·12 (0·04–0·33)
Lavrey[44]	✓	✓	✓	✓	✓	✓	✓	..	✓	..	..	..	✓	✓	✓	✓	..	..	..	0·39 (0·19–0·81)	
Reynolds[45]	✓	..	✓	✓	✓	✓	..	..	✓	✓	✓	..	✓	✓	✓	✓	✓	..	✓	0·12 (0·03–0·51)	0·15 (0·04–0·62)
Telzak[43]	..	..	✓	✓	✓	✓	..	..	✓	..	✓	..	..	..	✓	✓	..	..	..	0·24 (0·05–1·07)	0·29 (0·06–1·25)

SES=socioeconomic status; STI=sexually transmitted infection; ✓indicates the measure was adequately addressed in the study; *studies received a ✓ if the sample included all eligible HIV-negative men over a defined period of time, or in a defined catchment area, or a random or systematic sample of those men; †studies received a ✓ if the percentage participation was 80% or more; ‡studies received a ✓ if both groups were followed-up for the same amount of time or within 10% of each other; §studies received a ✓ if the percentage participants in the final analysis was 80% or more or if a full description of those lost-to-follow-up was not suggestive of bias. For selection bias/control of confounding a ✓ indicates that the group variable was either balanced between groups (10% or less difference) or adjusted for in analysis.

Table 3: **Quality assessment of cohort studies**

confounders may well be operating in either direction within and across all of the included studies. Furthermore, misclassification of confounders can greatly hinder the effectiveness of any statistical adjustment procedure.[51]

We observed differences in results according to study design, confirming that study design is an important consideration in the interpretation of results. Also, we noted that the method of ascertaining circumcision status had an influence on study results, with studies using direct observation consistently reporting a protective effect of circumcision. How much the results are influenced by other aspects of study quality is unclear.

Although use of adjusted results tended to show stronger evidence of an association than the crude results in general population studies, adjustment explained very little of the substantial between-study heterogeneity. Population studies done with direct observation were more in favour of circumcision. Since self-report of circumcision status may be a poor means of assessing exposure,[52] it would seem reasonable to favour the results generated from those studies that used direct observation only. Self-report could affect the results in either direction depending on what the reason for over-reporting or under-reporting in a particular setting is.

When assessing the effects of interventions, it is important to note that observational studies differ in two key ways from randomised controlled trials. Firstly, the intervention (circumcision) did not occur as part of the study, nor was it likely that it occurred directly for reason of possible HIV prevention. Most study participants were likely to be circumcised for cultural or religious reasons. Secondly, the studies were not designed to have comparable circumcised and non-circumcised groups. Since HIV is related to sexual behaviour, which may in turn be partly determined by culture and religion, strong confounding in these studies seems likely. Circumcision itself may be a proxy measure of the knowledge and behaviour learnt during the process of initiation, in which time young men are taught about traditional sexual practices, including monogamy, and penile hygiene (figure 1). Worth noting is that the possible adverse effects of circumcision, such as haemorrhage, infection (including the transmission of HIV), and fistula, were not reported in any of the included studies.[53] No studies measured the acceptance, or otherwise, of circumcision by the sampled communities.

Comparison with other studies

Our review aimed to assess the interventional benefit of male circumcision in reducing HIV acquisition in heterosexual men. The observational studies of high-risk groups included in our review show a strong association between circumcision and reduced rates of HIV acquisition, measured by both crude and adjusted ORs. These results are in accordance with the findings of Weiss and colleagues,[10] who included eight cross-sectional studies in their meta-analysis of the crude results in high-risk groups (OR=0·24; 95% CI 0·20–0·29) and those of a review by Bailey and co-workers.[11] Like Weiss and colleagues, we found a high degree of statistical heterogeneity in population-based cross-sectional studies when only crude results were considered. However, we chose not to conduct a meta-analysis within any of the study categories, based on our findings of the inherent methodological and statistical heterogeneity between studies and the variable quality of all the included studies.

Limitations of the review

Despite our rigorous methods, the review is still subject to a number of limitations. The review may be prone to indexing bias, publication bias, and reporting bias.[49] Our initial search strategy was limited to the term

Search strategy and selection criteria

The search strategy and criteria for selection are described in detail in the Methods section.

"circumcision", which yielded between 143 and 360 abstracts, depending on the database searched. However, when the search included the broader term "risk factors", the yield was over 12 000 abstracts. Appraisal of this many abstracts was not considered feasible. Therefore, it is possible that studies appraising circumcision, but not indexed as such, may have been missed. Although every effort was made to trace unpublished studies, we were not always able to track down authors of abstracts presented at conferences organised during the 1980s and early 1990s.

Reporting bias may have affected our study, as well as other published reviews. Unless we were able to contact researchers to obtain missing data, we relied on the information reported in the article. In many cases reporting was unclear regarding factors relating to study quality, provision of actual numbers, percentages, and details of statistical analyses. Some studies may have included circumcision as a risk factor and, on finding it to be not significant, failed to report on it. In general, we chose to report unclear issues as such, rather than making assumptions. Where necessary, we have been explicit about assumptions that we have had to make. The strength of the review could be greatly improved if it were possible to contact all researchers and obtain summary, or even individual person, data on outcome, exposure, and potential confounders.

Conclusion

The possibility exists that the observed results included in this review could be explained by confounding. Although the positive results of these observational studies suggest that circumcision is an intervention worth evaluating in randomised controlled trials, the current quality of evidence is insufficient to consider implementation of circumcision as a public-health intervention. Therefore, the results of the three randomised controlled trials underway will provide essential evidence about the effects of male circumcision as an intervention to prevent HIV infection. Doing detailed quality assessment of observational studies can aid decision-making about doing a meta-analysis and assist interpretation of results in systematic reviews.

Conflicts of interest

ME has researched circumcision previously in publications in the public domain. No reviewers are part of any of the trial groups investigating the link between circumcision and HIV.

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