

Male circumcision and risk of HIV infection in sub-Saharan Africa: a systematic review and meta-analysis

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Objective: To systematically review studies of male circumcision and the risk of HIV-1 infection in men in sub-Saharan Africa, and to summarize the findings in a meta-analysis.

Design: A meta-analysis of observational studies.

Methods: A systematic literature review was carried out of studies published up to April 1999 that included circumcision as a risk factor for HIV-1 infection among men in sub-Saharan Africa. A random effects meta-analysis was used to calculate a pooled relative risk (RR) and 95% confidence interval (CI) for all studies combined, and stratified by type of study population. Further analyses were conducted among those studies that adjusted for potential confounding factors.

Results: Twenty-seven studies were included. Of these, 21 showed a reduced risk of HIV among circumcised men, being approximately half that in uncircumcised men (crude RR = 0.52, CI 0.40–0.68). In 15 studies that adjusted for potential confounding factors, the association was even stronger (adjusted RR = 0.42, CI 0.34–0.54). The association was stronger among men at high risk of HIV (crude RR = 0.27; adjusted RR = 0.29, CI 0.20–0.41) than among men in general populations (crude RR = 0.93; adjusted RR = 0.56, CI 0.44–0.70).

Conclusion: Male circumcision is associated with a significantly reduced risk of HIV infection among men in sub-Saharan Africa, particularly those at high risk of HIV. These results suggest that consideration should be given to the acceptability and feasibility of providing safe services for male circumcision as an additional HIV prevention strategy in areas of Africa where men are not traditionally circumcised.

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Introduction

HIV prevalence in the general population in Africa varies widely both within and between countries. The magnitude of the variation seems to be only partly explained by different sexual behaviour patterns or factors known to influence HIV transmission, such as the presence of sexually transmitted diseases (STD) or condom use [1]. The hypothesis that male circumcision may reduce the risk of acquiring HIV infection was first suggested early in the HIV epidemic [2], and many epidemiological studies have since included circumci-

sion as a potential risk factor in studies of HIV infection.

There is substantial evidence that circumcision is associated with a reduced risk of ulcerative STD such as chancroid and syphilis [3]. As STD, both ulcerative and non-ulcerative, are known to enhance the risk of acquiring and transmitting HIV [4], it is likely that circumcision has an indirect effect on HIV infection. Circumcision may also protect against HIV directly, as viral entry may occur through micro-traumatic lesions or mini-ulcerations of the foreskin [5] or through

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trauma to the non-keratinized inner mucosal surface of the foreskin [6]. Furthermore, the foreskin contains a higher density of Langerhans cells than the urethra or rectum [7], and these cells may be primary target cells for HIV transmission [8]. Genital ulcers may also be less easily recognized in uncircumcised men, thus delaying treatment and increasing susceptibility to HIV [6].

Male circumcision is practised in many parts of Africa, but there is wide regional variation [5,9]. In particular, there are many ethnic groups in eastern and southern Africa in which male circumcision is not traditionally practised. This area of non-circumcision covers most of Uganda, parts of western Kenya, western Tanzania, the north-eastern Democratic Republic of the Congo, virtually all of Rwanda, Burundi, Zambia, Malawi and Zimbabwe, and parts of Botswana, Namibia, Mozambique and South Africa. Circumcision is almost universally practised in most parts of West Africa, including Nigeria. There is, however, a large area of traditional non-circumcision covering central/eastern Ivory Coast and western/central Ghana.

Within Africa, there is a broad correlation between areas where there is little circumcision, and those with high HIV rates [5,9]. This ecological association means little, however, without looking at individuals within populations, and taking into account other factors associated with circumcision status. There may be other factors associated with HIV risk (such as sexual mixing patterns, or the presence of other STD) that are less prevalent among circumcising than non-circumcising populations.

Four previous reviews of the literature have been carried out on HIV and male circumcision [3,10–12]. The present review differs in being restricted to female–male transmission in sub-Saharan Africa, where heterosexual transmission is the predominant mode of transmission. It thus addresses the specific role of male circumcision in the heterosexual acquisition of HIV in Africa. Only one previous meta-analysis of the role of circumcision in HIV transmission has been performed [12], and this had several statistical and epidemiological limitations [13]. A re-analysis of the studies included in that report found that uncircumcised men were at a significantly increased risk of HIV infection, but concluded that a systematic review of the literature was urgently needed to minimize bias, and to clarify the issue [14].

Materials and methods

The aim of our literature search was to identify all published studies of risk factors for HIV-1 infection among men in sub-Saharan Africa that included cir-

cumcision as a potential risk factor. The Medline, Pre-Medline, HealthStar and Popline databases were searched for papers published up to April 1999 that included 'circumcision' and 'HIV' as keywords or text in the abstract. Twenty-two original research papers were identified in this way, 20 of which appeared in Medline. A further Medline search was carried out using keywords to search for all published studies of HIV risk factors in men in sub-Saharan Africa using the search condition ['HIV-infections (epidemiology, aetiology, transmission)' OR 'HIV-seroprevalence' OR 'HIV-seropositivity (epidemiology, transmission)'] AND 'sub-Saharan Africa' AND ('risk factors' or 'odds ratios' or 'risk'). A total of 397 articles were identified in this way, including all 20 papers identified in the initial search. Of these, the abstracts of 59 papers referred to risk factors for female–male transmission of HIV, and these papers were manually scanned for references to circumcision, yielding a further seven eligible papers. Finally, the reference lists of all 29 papers were checked, and nine further potential papers were identified. However, none of these included circumcision as a risk factor. We did not include papers that used a proxy for circumcision, such as Muslim religion. Conference abstracts were also excluded.

Of the 29 eligible papers, two were studies of risk factors for HIV-2 only, and were excluded from the analysis [15,16]. A further three studies contained insufficient details to calculate a crude relative risk (RR) and were excluded from the meta-analysis [17–19]. These studies were relatively small (study sizes of 125, 81 and 63 men, respectively) and were thus unlikely to have influenced the meta-analysis substantially. One study [20] did not report a crude RR, but did report an adjusted RR, and was included in the adjusted meta-analysis.

Several studies from Mwanza, Tanzania, appeared in more than one publication. To avoid duplication of data in the meta-analysis, study 1 and study 5 from the Urassa paper [21] were excluded because they were included elsewhere [22,23]. A study by Barongo *et al.* [24] was a subset of Urassa study 4, and was excluded. Another eligible paper [25] was not included as the study population formed the basis for a case–control study that allowed adjustment for confounding variables [22].

Three papers [23,26,27] included stratified analyses of different population groups, and these strata were included as separate studies in the meta-analysis to reduce confounding.

It is plausible that the effect of circumcision varies according to the background prevalence of HIV and co-factors such as ulcerative STD. Three broad groups of studies were identified: population-based studies

[21–23,26,28–31]; studies of men at high risk of HIV [20,27,32–41]; and other studies (of factory workers and volunteers) [21,42,43]. Sub-group analyses were carried out on the population-based and high-risk studies.

All types of study design (cohort, case–control and cross-sectional studies) were included in the main analysis, and analyses were also carried out for cross-sectional studies alone. In case–control and cross-sectional studies, the odds ratio (OR) was used as an estimate of the risk ratio. The OR was used in cross-sectional studies because it is not possible to obtain an adjusted risk ratio from published data as these were calculated using logistic regression.

However, when the prevalence of HIV in the population is greater than approximately 20–25%, the OR will be more extreme than the risk ratio. The sensitivity of the meta-analysis to the measure of effect was assessed by re-analysing the data for cross-sectional studies using the risk ratio. Statistical and graphical analyses were performed using Stata 6 [44]. A random effects meta-analysis was used to calculate a pooled RR [45,46]. This model assumes a different underlying effect for each study, and heterogeneity between studies was also assessed [46]. Publication bias was assessed with a funnel plot and Begg's test for correlation between the effect estimates and their variances [47,48].

Results

The studies included in the review are shown in Table 1, grouped by type of population. The review incorporated 28 studies (19 cross-sectional, five case–control, three cohort and one partner study) reported in 22 published papers. The studies covered a range of population types, including general populations (11 studies), STD clinic attenders (eight studies), truck drivers (three studies), factory workers (two studies), and tuberculosis patients, hospital patients, volunteers and married couples (one study of each).

Meta-analysis

Crude RRs were reported in 27 studies (see Table 1; Fig. 1a). One study [20] reported an adjusted RR but not a crude RR. In 21 of the studies, circumcised men were at lower risk of HIV than uncircumcised men, and the association was statistically significant ($P < 0.05$) in 14 of these. Of the six studies with a positive association between circumcision and the risk of HIV, four were from Mwanza [21–23], and none found a statistically significant association. Overall, circumcision was associated with a highly significant reduction in HIV risk [pooled RR = 0.52, 95% confidence interval (CI) 0.40–0.68; Fig. 1a; Table 2].

There was significant between-study heterogeneity ($P < 0.001$).

Some adjustment for confounders was reported for 15 studies. Most studies adjusted for age and one or more factors from the following: sociodemographic factors (marital status, area of residence, ethnic group), sexual behaviour (number of sexual partners in lifetime, last year or last 4 months, contact with sex workers), and factors associated with the risk of transmission (condom use, presence of ulcerative STD). Details are given in the footnote to Table 1. The study by Barongo *et al.* [23] was stratified by area of residence for the crude analysis, but residence was included as a confounder in the multivariate analysis, and hence the study contributed only once to the meta-analysis of adjusted effects. In addition, one study reported no significant association after adjustment for confounders but no details were given [39] and the study was not included in the adjusted meta-analysis.

All the 15 studies reporting an adjusted RR found a protective effect of circumcision on HIV risk (RRs ranging from 0.12 to 0.8), and in 10 studies the effect was statistically significant (Table 1; Fig. 1b). In general, the effect of adjustment was to strengthen the association between circumcision and a reduced risk of HIV, with the adjusted RR being smaller than or equal to the crude RR in 10 of the 14 studies that reported both measures. For two studies from Mwanza [21,22], the adjusted RR showed a decreased risk of HIV among circumcised men, although the crude RR had shown a non-significant increased risk of HIV associated with circumcision. The four studies in which the adjusted RR was closer to one than the crude RR were the studies from the Ivory Coast [32,36] and of STD clinic attenders in Nairobi [38,40]. In each of those studies, the difference between the crude and adjusted RR was small (Table 1).

The adjusted analysis showed a slightly stronger effect than the crude analysis (pooled adjusted RR = 0.42; CI 0.34–0.54; Table 2). For the 14 studies reporting both crude and adjusted RR, the crude RR was 0.54 (CI 0.39–0.74) and the adjusted RR was 0.45 (CI 0.34–0.58).

Analyses were then stratified by type of population. The crude analysis showed little evidence of an association between circumcision and HIV in population-based studies (crude RR = 0.93, CI 0.71–1.21). Of these 12 studies, six adjusted for confounders. The crude RR was reported in five of the six studies and was similar to that for all population-based studies (RR = 0.90, CI 0.59–1.36). The adjusted RR showed a significantly decreased risk of HIV among circumcised men (adjusted RR = 0.56, CI 0.44–0.70, based on six studies; Table 2, Fig. 2a). There was no significant

Table 1. Summary of studies included in the meta-analysis of the association between circumcision and risk of HIV-1 infection among men in sub-Saharan Africa.

First author	Design	Location	Study population	Size	% Circumcised ^a	Crude RR (95% CI)	Adjusted RR (95% CI)
Population-based							
Barongo 1 [23]	Cross-sectional	Tanzania–Mwanza	Village	972	16%	1.08 (0.38–3.07)	–
Barongo 2 [23]	Cross-sectional	Tanzania–Mwanza	Roadside	431	31%	0.79 (0.31–1.99)	–
Barongo 3 [23]	Cross-sectional	Tanzania–Mwanza	Urban	595	59%	1.19 (0.66–2.13)	–
Barongo [23]	Cross-sectional	Tanzania–Mwanza	All	1998	32%	–	0.8 (0.5–1.3) ^c
Carael [31]	Partner study	Rwanda–Kigali	Married couples	274	79%	0.88 (0.52–1.49)	–
Kelly [28]	Cross-sectional	Uganda–Rakai	Rural	6821	16%	0.57 (0.46–0.72)	0.44 (0.35–0.56) ^d
Pison [29]	Case–control	Senegal (SW)	Rural	51	57%	4.00 (0.54–29.6)	–
Quigley [22]	Case–control	Tanzania–Mwanza	Rural	543	31%	1.07 (0.71–1.60)	0.65 (0.38–1.12) ^e
Serwadda [30]	Cross-sectional	Uganda–Rakai	Rural	575	17%	0.67 (0.33–1.37)	0.40 (0.20–0.90) ^f
Urassa 2 [21] ^b	Cross-sectional	Tanzania–Mwanza	Village	2603	18%	1.46 (0.97–2.20)	0.66 (0.41–1.08) ^g
Urassa 3 [21]	Cross-sectional	Tanzania–Mwanza	Village	524	34%	0.98 (0.55–1.75)	0.55 (0.27–1.14) ^h
Wawer 1 [26]	Cohort	Uganda–Rakai	Rural–control	2044	20%	0.97 (0.36–2.25)	–
Wawer 2 [26]	Cohort	Uganda–Rakai	Rural–intervention	2307	15%	0.45 (0.09–1.40)	–
High-risk groups							
Bwayo [34]	Cross-sectional	Kenya–Mombasa Hwy	Truck drivers	970	82%	0.24 (0.17–0.34)	0.20 (0.12–0.36) ⁱ
Cameron [38]	Cohort	Kenya–Nairobi	STD clinic attenders	293	73%	0.10 (0.04–0.22)	0.12 (0.04–0.33) ^j
Diallo [36]	Cross-sectional	Cote d'Ivoire–Abidjan	STD clinic attenders	1083	93%	0.30 (0.18–0.50)	0.34 (0.20–0.62) ^k
Gilks [35]	Cross-sectional	Kenya–Nairobi	Hospital patients	207	72%	0.17 (0.08–0.37)	–
Greenblatt [39]	Cross-sectional	Kenya–Nairobi	GUD patients	115	66%	0.30 (0.11–0.81)	–
Hira [37]	Case–control	Zambia–Lusaka	STD patients	610	5%	0.41 (0.17–0.98)	–
Lankoande [41]	Cross-sectional	Burkina Faso	Truck drivers	236	91%	0.66 (0.23–1.85)	–
Mbugua [20]	Cross-sectional	Kenya–Mombasa Hwy	Truck drivers	283	–	–	0.27 (0.11–0.65) ^l
Nasio 1 [27]	Cross-sectional	Kenya–Nairobi	GUD patients	607	78%	0.21 (0.14–0.31)	–
Nasio 2 [27]	Cross-sectional	Kenya–Nairobi	Urethritis patients	276	89%	0.33 (0.15–0.74)	–
Sassan–Morokro [32]	Case–control	Cote d'Ivoire–Abidjan	TB patients	729	92%	0.45 (0.25–0.77)	0.50 (0.30–0.77) ^m
Simonsen [40]	Case–control	Kenya–Nairobi	STD clinic attenders	340	77%	0.37 (0.19–0.74)	0.50 (0.21–1.03) ⁿ
Tyndall [33]	Cross-sectional	Kenya–Nairobi	GUD patients	810	78%	0.22 (0.15–0.31)	0.21 (0.14–0.30) ^o
Other							
Seed [42]	Cross-sectional	Rwanda–Kigali	Volunteers	837	29%	0.65 (0.45–0.94)	0.59 (0.40–0.86) ^p
Urassa 4 [21]	Cross-sectional	Tanzania–Mwanza	Factory workers	1574	47%	0.50 (0.35–0.70)	0.50 (0.33–0.73) ^q
Van de Perre [43]	Cross-sectional	Rwanda–Kigali	Factory workers	302	11%	1.12 (0.45–2.82)	–

CI, 95% Confidence interval; GUD, genital ulcer disease; RR, relative risk; STD, sexually transmitted diseases; TB, tuberculosis.

^aFor case–control studies, the proportion of controls circumcised is presented.

^bStudies 1 and 5 from the paper by Urassa are excluded because of overlap with other studies [27,28].

^cAdjusted for age, marital status, residence, travel to Mwanza town, number of sexual partners in past 5 years, genital discharge or syphilis (ever), injection in past year.

^dAdjusted for age, marital status, number of wives, number of sexual partners in past 5 years, reported presence of genital ulcer, current/active syphilis.

^eAdjusted for age, marital status, community, job, number of lifetime sexual partners, genital ulcer/discharge in the past year, perceived risk of STD.

^fAdjusted for age, residence, number of sexual partners in past 5 years, history of STD.

^gAdjusted for age, education, religion, ethnic group, occupation, STD in past year, number of sexual partners in past year.

^hAdjusted for age, education, ethnic group, occupation, STD in past year, number of sexual partners in past year.

ⁱAdjusted for age, sexual contact with a sex worker, history of GUD or urethritis in past 5 years, current/active syphilis.

^jAdjusted for current GUD, regular contact with sex worker.

^kAdjusted for education, occupation, migration status, regular partner, previous or current GUD or other STD.

^lAdjusted for education, income, duration as truck driver.

^mAdjusted for duration in Abidjan, lifetime contacts with sex workers, genital ulcers and urethritis in past 5 years (controls matched by age).

ⁿAdjusted for travel to neighbouring countries, regular contact with sex workers, history of genital ulcers.

^oAdjusted for age, marital status, contact with sex workers, lifetime number of sexual partners, cigarette smoking, alcohol use, history of GUD or urethral discharge.

^pAdjusted for age, religion, education, residence, lifetime number of sexual partners, lifetime number of contacts with sex workers, history of GUD or non-ulcerative STD.

^qAdjusted for age, religion, education, place of birth, number of partner in past year, STD in past 4 months.

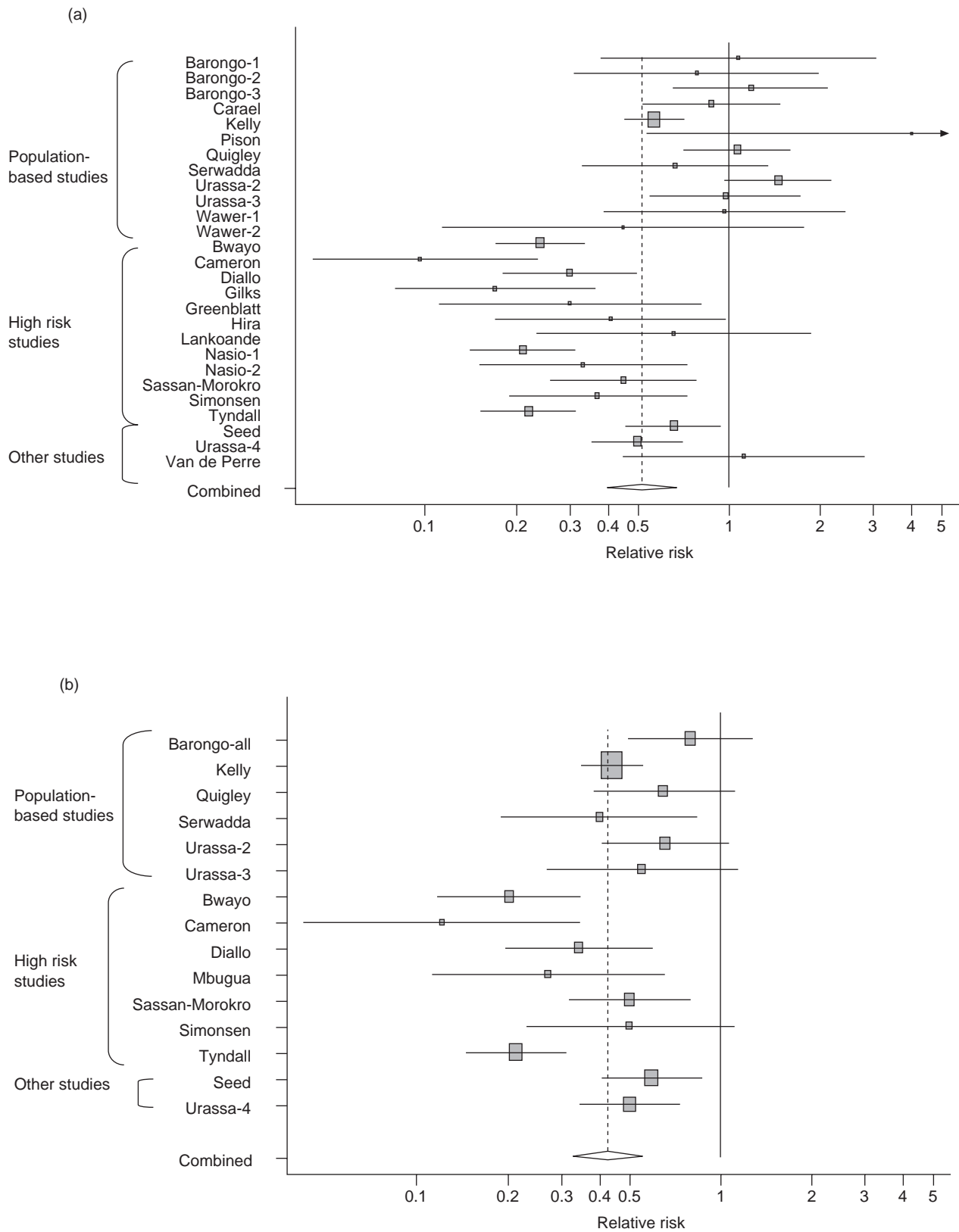


Fig. 1. Relative risk of HIV-1 infection associated with male circumcision in 27 studies of men in sub-Saharan Africa. (a) Crude analysis; (b) Adjusted analysis. The black square and horizontal line correspond to the relative risk and 95% confidence interval for each study. The area of the black square reflects the weight of each trial. The diamonds represent the combined relative risk and 95% confidence interval using the random effects model.

Table 2. Meta-analysis of the association between circumcision and risk of HIV-1 infection among men in sub-Saharan Africa.

Study population	Crude analysis			Adjusted analysis		
	N	RR (CI)	<i>P</i> for heterogeneity	N	RR (CI)	<i>P</i> for heterogeneity
All study designs						
All ^a	27	0.52 (0.40–0.68)	< 0.001	15	0.42 (0.34–0.54)	< 0.001
Population-based	12	0.93 (0.71–1.21)	0.008	6	0.56 (0.44–0.70)	0.21
High-risk	12	0.27 (0.22–0.33)	0.09	7	0.29 (0.20–0.41)	0.03
Cross-sectional studies only						
All	18	0.51 (0.37–0.69)	< 0.001	11	0.42 (0.32–0.55)	< 0.001
Population-based	7	0.91 (0.63–1.32)	0.003	5	0.55 (0.42–0.72)	0.17
High-risk	8	0.24 (0.20–0.29)	0.48	4	0.24 (0.18–0.31)	0.49

CI, Confidence interval; RR, relative risk.

^aIncludes crude relative risks for three studies [21,42,43], which were not included in the sub-group analyses. Two of these [21,42] also reported adjusted relative risks.

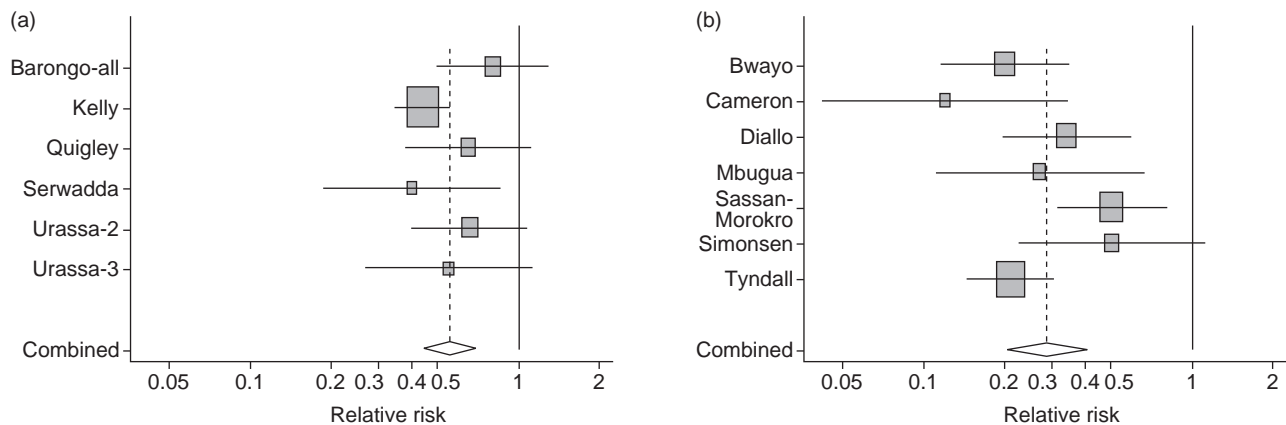


Fig. 2. Adjusted relative risk of HIV-1 infection associated with male circumcision among men in sub-Saharan Africa, by type of population (see Fig. 1 text for explanation). (a) Population-based populations; (b) High-risk groups.

heterogeneity between these studies ($P = 0.21$). When analyses were restricted to cross-sectional studies alone, results were very similar (crude RR = 0.91, CI 0.63–1.32; adjusted RR = 0.55, CI 0.42–0.72; Table 2).

Among the 12 studies of men at higher risk of HIV (STD clinic attenders, truck drivers, tuberculosis patients and hospital patients), the crude RR was 0.27 (CI 0.22–0.33). Seven of those studies included adjustment for confounders, which had little effect on the effect estimate (adjusted RR = 0.29, CI 0.20–0.41; Table 2, Fig. 2b). All adjusted RR were 0.5 or less, but there was significant between-study heterogeneity ($P = 0.03$). Results for cross-sectional studies alone were similar (crude RR = 0.24, CI 0.20–0.29; adjusted RR = 0.24, CI 0.18–0.31; P value for heterogeneity 0.49; Table 2).

Sensitivity analysis

There was wide variation in study size, with the largest study [28] consisting of 6821 men (25% of the total subjects included in the meta-analysis), whereas the second largest study consisted of 2603 men [21]. To

examine the influence of the largest study on the meta-analysis, we re-analysed the data excluding this study. The resulting RRs were similar (crude RR = 0.52, CI 0.40–0.68; adjusted RRs = 0.42, CI 0.32–0.55), indicating that the study did not influence the meta-analysis unduly.

Funnel graphs of the data are presented in Fig. 3a and Fig. 3b. There is no evidence to suggest that smaller studies (i.e. those with a larger standard error) were more likely to report a positive association, indicating no evidence of publication bias (Begg's rank correlation test: $P = 0.56$ for the crude analysis; $P = 0.24$ for the adjusted analysis).

The effect of using the OR instead of the risk ratio was assessed by re-analysing the cross-sectional studies using the risk ratio. For these 18 studies, the crude OR was 0.51 (CI 0.37–0.69) and the crude risk ratio was 0.59 (CI 0.47–0.73). In the high-risk studies, in which the prevalence of HIV was higher, the crude OR was 0.24 (CI 0.20–0.29), and the crude risk ratio was 0.37 (CI 0.33–0.41).

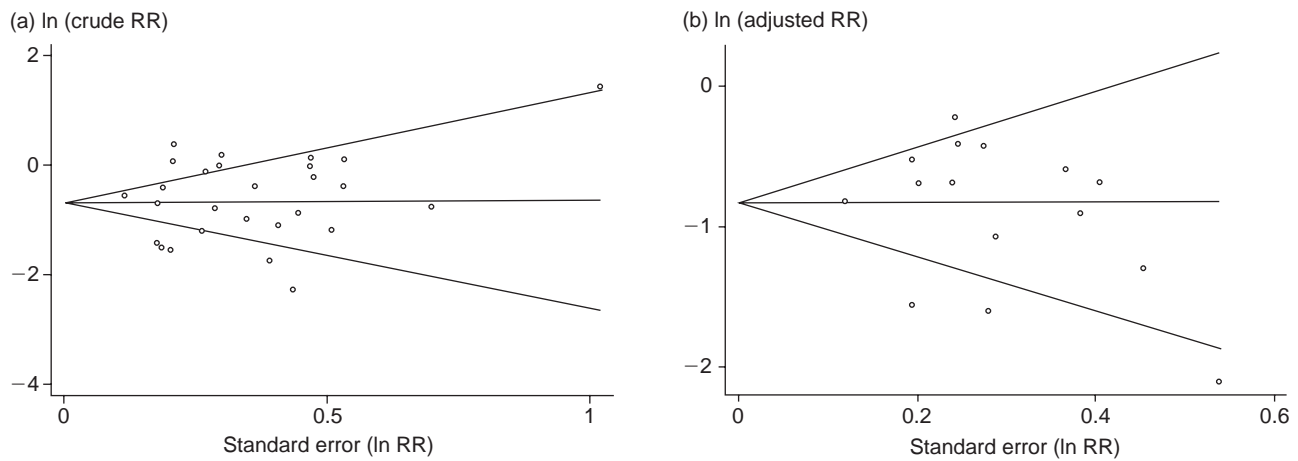


Fig. 3. Funnel plots to detect publication bias in the meta-analysis of HIV-1 infection and male circumcision. The horizontal line indicates the pooled log relative risk (RR), and guidelines to assist in visualizing the funnel are plotted at the 95% pseudo confidence interval limits for this estimate. (a) Crude analysis; (b) Adjusted analysis.

Discussion

This systematic review and meta-analysis provide compelling evidence that male circumcision is associated with a reduced risk of HIV infection in sub-Saharan Africa. The strongest association is seen among men at high risk of HIV, but circumcised men in the general population are also at significantly reduced risk after adjusting for potential confounding factors. This supports results from the previous meta-analysis [14], which included 33 studies from around the world, and found an overall crude OR of 0.60 (CI 0.45–0.80), with a stronger effect in high-risk groups (crude OR = 0.33, CI 0.26–0.43) than in general population groups (crude OR = 1.04, CI 0.77–1.41). This was a re-analysis of previously collected data and had several major limitations (no systematic literature review, lack of adjustment for confounding factors, and lack of exploration of heterogeneity), which have been addressed in the present analysis.

Overall, there was significant heterogeneity between studies, indicating that the magnitude of the protective effect varies between populations. We would, however, expect any protective effect of circumcision to be heterogeneous across different populations because of differences in a number of factors, including variations in sexual exposure to HIV, timing of circumcision, but particularly differences in the prevalence of STD. There is evidence that male circumcision protects against some ulcerative STD (particularly chancroid and syphilis) [3], which in turn enhance HIV transmission, and this could explain the greater protection afforded by circumcision in populations in which genital ulcer disease (GUD) is more prevalent. Indeed, several studies adjusted specifically for previous or current GUD, and as GUD is likely to act on the

causal pathway, the effect of circumcision on HIV may be stronger than that estimated by an adjusted RR.

When the analysis was stratified by the type of population, heterogeneity was reduced substantially and was not significant in the population-based studies. There was still significant heterogeneity among the seven high-risk populations, and the lack of reliable and consistent data from those studies on other potential effect modifiers (such as penile hygiene) prevented further exploration of this heterogeneity. However, the studies all found a strong protective effect (RRs from 0.12 to 0.50), and although this is a wide range, it suggests that a substantial protective effect was a consistent finding in all high-risk populations.

The main limitation of observational studies is that the effect of circumcision on HIV infection may be confounded by factors that are associated with HIV risk, and that may differ between circumcised and uncircumcised men. It is therefore important to note that adjustment for confounding strengthened the association in all the population-based studies, and generally made little difference in the high-risk studies. This is not surprising, because most studies that reported behavioural patterns [21,27,28,30,33,34,42,49] found that circumcised men tended to report higher risk behaviours than uncircumcised men in the same population. This would tend to result in higher HIV prevalence among circumcised men if there were no protective effect of circumcision. It remains a possibility, however, that there is residual confounding as a result of behavioural or biological factors that are unknown or poorly measured in some studies.

Religion and ethnicity are potentially important confounding factors in those observational studies, because

they are likely to be associated with both circumcision and HIV risk. Three studies explored this by stratifying analyses by religion. Among Muslims in Kigali, Rwanda [42], circumcision was associated with a protective effect (crude RR = 0.18, CI 0.02–1.20). Little association was seen among Christians (crude RR = 0.79, CI 0.50–1.23), although this could be because, unlike Muslims, most Christians were circumcised post-puberty. A study in Rakai, Uganda [28], where 98.5% of Muslim men were circumcised, found that among non-Muslim men, those circumcised before the age of 12 years had a lower risk of HIV compared with uncircumcised men (crude RR = 0.62, CI 0.29–1.28). Furthermore, in Mwanza, Tanzania [22], the association between circumcision and HIV was similar when results were re-analysed excluding Muslims. Therefore the evidence suggests that circumcision has an effect on HIV infection independently of the confounding effect of religion.

It has been suggested that prepubertal circumcision (performed for religious or traditional reasons) is more likely to protect against STD and HIV, whereas postpubertal circumcision is likely to be performed as a consequence of infections, such as balanitis [28]. Only two studies included in the meta-analysis asked about age at circumcision [22,28]. In Rakai [28], the strongest effect of circumcision on HIV risk was seen among those circumcised below 12 years (adjusted RR = 0.39, CI 0.29–0.53). There was also a significantly reduced risk of HIV associated with circumcision between 13 and 20 years (adjusted RR = 0.46, CI 0.28–0.77), and a non-significant effect above 20 years (adjusted RR = 0.78, CI 0.43–1.43). In contrast, among men in rural Mwanza [22], circumcision before 15 years was associated with an increased risk of HIV (adjusted RR = 1.50, CI 0.57–3.90), whereas circumcision at age 15 years or older was associated with a lower HIV risk (adjusted RR = 0.37, CI 0.18–0.74). The reasons for these discrepant findings are unclear, and further work on the effect of age at circumcision on HIV susceptibility is needed.

The observational studies included in this meta-analysis cannot definitively establish a causal role for circumcision in protecting against HIV infection. It is biologically plausible that the foreskin may enhance HIV transmission both directly and indirectly [50], although there is little direct evidence for this. Causality also implies that circumcision occurs before infection with HIV, and we cannot be certain of this with retrospective data, although the studies that reported age at circumcision [21,22,28,42] indicated that it usually occurs by 20 years, and hence is likely to precede HIV infection.

The present analysis was restricted to studies of HIV infection in men. Therefore we were able to assess only

the effect of circumcision on male susceptibility, and not on male infectiousness. However, the advantages of this restriction are considerable. First, an effect of male circumcision on susceptibility is arguably more plausible on biological grounds than an effect on infectiousness. Second, only the circumcision status of the study subject is needed, and not the status of partners, thus reducing the potential misclassification of exposure. Third, a study on the effect of male circumcision on male–female transmission is complex, because a woman may have had more than one male sexual partner, with differing circumcision status. However, recent data from Rakai have shown that among discordant couples in which the male partner was HIV positive, there was a non-significant reduction in the transmission rate if the man was circumcised (rate ratio = 0.44, CI 0.15–1.32), and this reduction in risk was statistically significant among couples with male HIV viral loads of less than 50 000 copies per ml [51].

Circumcision was determined by self-report in 16 studies, and by clinical examination in eight studies. For four further studies [35–38] the method of ascertainment was not clear. Validity of self-reported circumcision was assessed among factory workers in Mwanza [21]. Of the 111 men who had reported they were circumcised, only 69% were found to be so on examination. Among the 91 men who reported themselves as uncircumcised, 94% were found to be uncircumcised on examination. This suggests that self-reported circumcision may overestimate the proportion of men circumcised in this population, and suggests that genital examination should be carried out whenever possible in future studies. Assuming this misclassification is non-differential with respect to HIV status, the effect would be to underestimate the association between the lack of circumcision and HIV. All but one study performed HIV tests by one or two enzyme-linked immunosorbent assay (ELISA) tests, with confirmatory Western blot for discrepant or indeterminate ELISA results. The remaining study [37] performed only one ELISA with no confirmatory testing. Overall, therefore, there is likely to be little misclassification of HIV results.

Meta-analyses are vulnerable to bias, as a result of their failure to identify all eligible articles and also because research yielding statistically significant results is more likely to be submitted and published. Therefore, even if all published studies have been identified, these may be only a subset of the studies actually carried out. However, this seems unlikely to cause substantial bias in the present review because studies of risk factors for HIV almost always examined a range of behavioural and biological risk factors, and it is unlikely that the published studies were biased in terms of finding circumcision as a risk factor. However, it is possible that if no association with circumcision was found, this

was sometimes not mentioned in the paper. The results of the funnel plot suggest that publication bias was not a problem in this meta-analysis, although the existence of such bias cannot be excluded. It was decided to exclude conference abstracts from the review because it is probable that these are more likely to report significant than non-significant findings, and therefore the inclusion of abstracts might increase bias.

The 28 studies reviewed were from just eight countries, including nine studies from Kenya (seven of these from Nairobi) and seven from Mwanza Region, Tanzania. As expected, there were few studies from West Africa, where circumcision in most areas is almost universal, although 39% of men in the study in Ziguinchor region, south-west Senegal were uncircumcised [29].

To our knowledge, two further studies on the effect of circumcision on HIV infection have been published since our literature review. A cohort study of trucking company employees in Kenya [52] found a very similar effect to our summary measure for high-risk populations (adjusted RR = 0.25, CI 0.1–0.5). A recently published study of HIV-discordant couples from Rakai, Uganda [53] found that the rate of female–male transmission was significantly higher among couples with uncircumcised male partners compared with couples with a circumcised male partner (rates of 16.7 per 100 person-years compared with 0 per 100 person-years; $P < 0.001$).

Conclusion

The data from observational studies provide compelling evidence of a substantial protective effect of male circumcision against HIV infection in sub-Saharan Africa, especially in populations at high risk of HIV/STD. The continuing rapid spread of HIV infection, especially in eastern and southern Africa, suggests that the potential public health benefit of introducing safe services for male circumcision on a wider scale should be explored. However, there are many concerns around such an introduction, including the possibility that men may increase their risky sexual behaviour if they think circumcision confers a high degree of protection, as well as the risk of bleeding or infection, cost, and issues of cultural identity. Studies are therefore needed to examine the acceptability, feasibility and safety of introducing male circumcision as an HIV/STD prevention strategy in high prevalence areas where men are not traditionally circumcised. Results from one such study among the Luo people in Nyanza Province, western Kenya, who are traditionally non-circumcising, showed that 60% of men would prefer to be circumcised, and 62% of women would prefer a

circumcised partner [54]. In areas where male circumcision is acceptable to the local community, randomized controlled trials of male circumcision performed by trained health workers as part of a package intervention incorporating safe sex education are needed. Such trials would overcome the inherent limitations of observational studies, and provide reliable empirical evidence on the overall impact of the introduction of male circumcision on HIV incidence.

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