Original article

Circumcision and STD in the United States: cross sectional and cohort analyses

Robert A Diseker, III, Thomas A Peterman, Mary L Kamb, Charlotte Kent, Jonathan M Zenilman, John M Douglas, Jr, Fen Rhodes, Michael Iatesta

Kaiser Permanente Research Department, Atlanta, Georgia, USA
R A Diseker, III

Centers for Disease Control and Prevention, National Center for HIV, STD and TB Prevention, Division of HIV/AIDS Prevention, Atlanta, Georgia, USA
T A Peterman
M L Kamb

Project RESPECT Study Group, San Francisco Health Department, San Francisco, California, USA
C Kent

Project RESPECT Study Group, Baltimore City Heath Department and Johns Hopkins University, Baltimore, Maryland, USA
J M Zenilman

Project RESPECT Study Group, Denver Department of Public Health, Denver, Colorado, USA
J M Douglas, Jr

Project RESPECT Study Group, Long Beach Health Department and California State University, Long Beach, California , USA
F Rhodes

Project RESPECT Study Group, New Jersey Health Department and Newark STD Clinic, Newark, New Jersey, USA
M Iatesta

Correspondence to:
Robert A Diseker, III, Kaiser Permanente Research Department, Nine Piedmont Center, 3495 Piedmont Road, NE, Atlanta, GA 30305-1736, USA
robert.diseker@kp.org

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Background: Male circumcision status has been shown to be associated with sexually transmitted disease (STD) acquisition in some, but not all, studies. Most studies have been cross sectional.
Objectives: We examined the association between circumcision status and the prevalence and incidence of gonorrhoea, chlamydia, and syphilis.
Methods: We analysed cross sectional and cohort study data from a multicentre controlled trial in the United States. Between July 1993 and September 1996, 2021 men visiting public inner city STD clinics in the United States were examined by a clinician at enrolment and 1456 were examined at follow up visits 6 and 12 months later. At each visit, men had laboratory tests for gonorrhoea, chlamydia, and syphilis and were examined for circumcision status. We used multiple logisitic regression to compare STD risk among circumcised and uncircumcised men adjusted for potentially confounding factors.
Results: Uncircumcised men were significantly more likely than circumcised men to have gonorrhoea in the multivariate analyses, adjusted for age, race, and site, in both the cross sectional (odds ratio (OR), 1.3; 95% confidence interval (CI), 0.9 to 1.7) and in the cohort analysis (OR, 1.6; 95% CI, 1.0 to 2.6). There was no association between lack of circumcision and chlamydia in either the cross sectional (OR, 1.0; 95% CI 0.7-1.4) or the cohort analysis (OR, 0.9; 95% CI 0.5-1.5). The magnitude of association between lack of circumcision and syphilis was similar in the cross sectional (OR, 1.4; 95% CI 0.6 to 3.3) and cohort analysis (OR, 1.5; 95% CI 0.4 to 6.1).
Conclusion: Uncircumcised men in the United States may be at increased risk for gonorrhoea and syphilis, but chlamydia risk appears similar in circumcised and uncircumcised men. Our results suggest that risk estimates from cross sectional studies would be similar to cohort findings.
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Keywords: circumcision; sexually transmitted diseases; United States

Background

Several studies have shown that compared with circumcised men, uncircumcised men are at higher risk for acquiring some sexually transmitted diseases (STDs) including chancroid, chlamydia, gonorrhoea, syphilis,[1–13] and lower risk for acquiring genital herpes and genital warts.[14 15] Other studies, however, found no association between STD acquisition and circumcision status.[16–20] Only a few studied US populations, and not all confirmed diagnosis with laboratory testing. Most studies used cross sectional designs; only four were prospective studies which provide a better measure of STD risk because they ascertain incident cases of disease.[4 7 8 13] The more troublesome concern is that these cross sectional studies are typically conducted in STD clinics where there is a strong potential for selection bias. The relation between circumcision status and STD in the STD clinic may not be the same as the relation in the community. For example, circumcised men in the community may be more likely than uncircumcised men to come to the clinic with a problem not caused by an STD. If this occurred, it would appear that circumcised men were protected from STD in a clinic based study (Berkson's bias). This bias could be overcome using a prospective study design where follow up did not depend on the development of symptoms. We analysed the role of circumcision status in the acquisition of STDs in a cross sectional and a longitudinal follow up study that included multiple examinations.

Methods

STUDY POPULATION

We used data collected from a randomised controlled trial of HIV prevention counselling efficacy.[21] The study population included men who visited public inner city STD clinics between July 1993 and September 1996 and enrolled in Project RESPECT. The STD clinics were in Baltimore, Maryland; Denver, Colorado; Long Beach, California; Newark, New Jersey; and San Francisco, California. Participants were heterosexual patients 15 years or older who came to the clinics for an STD examination, spoke English, and who reported having had vaginal sex in the past 30 days. All participants gave written, informed consent, and members of institutional review boards at each site reviewed and approved the trial protocol. Participants were examined by a clinician (registered nurse, nurse practitioner, physician's assistant, or physician) at enrolment and at follow up visits 6 and 12 months later. They were also examined if they revisited the clinic at other times for a

Table 1 Cross sectional analysis: associations between participant characteristics and sexually transmitted diseases (N=2021)

			Baseline STD‡					
			Gonorrhoea (n=404)		Chlamydia (n=312)		Syphilis (n=28)	
	Total	Without STD* (n=834)	OR	p Value	OR	p Value	OR	p Value
Circumcised								
Yes	1518	622	1.0	—	1.0	—	1.0	—
No	503	212	1.1	0.50	0.9	0.41	1.6	0.22
Site								
Baltimore	377	101	8.7	<0.001	2.5	<0.001	1.2	0.80
Denver	393	155	4.3	<0.001	1.0	0.90	0.8	0.76
Long Beach	332	132	3.3	<0.001	0.9	0.62	0.3	0.16
Newark	476	195	1.5	0.01	1.0	0.87	0.4	0.23
San Francisco	443	251	1.0	—	1.0	—	1.0	—
Race/ethnicity								
White	364	204	1.0	—	1.0	—	1.0	—
African-American	1259	424	15.5	<0.001	3.4	<0.001	12.0	0.02
Hispanic	300	152	3.3	0.001	2.0	0.005	2.7	0.42
Other	98	54	3.8	0.003	2.1	0.03	—	—
Age								
<20	276	87	2.3	<0.001	6.8	<0.001	—	—
20–24	584	210	1.8	<0.001	4.7	<0.001	0.4	0.09
25–29	413	171	1.1	0.72	2.6	<0.001	0.7	0.45
30–34	326	154	1.1	0.76	2.0	0.02	0.9	0.79
⩾35	422	212	1.0	—	1.0	—	1.0	—
No of sex partners past 3 months†								
1	898	419	1.0	—	1.0	—	1.0	—
2	584	226	1.9	<0.001	1.2	0.19	0.7	0.54
⩾3	535	186	2.2	<0.001	1.7	0.001	1.1	0.91
New partner at baseline†								
Yes	1040	408	1.4	0.001	1.1	0.47	0.8	0.51
No	970	421	1.0	—	1.0	—	1.0	—

*People with each STD were compared with the group with no STD.
†Numbers in partners column do not total 2021 because of missing values.

checkup, evaluation of symptoms, or because of partner referral for STDs.

We performed a cross sectional analysis of prevalent STDs at baseline and a cohort analysis of incident STDs during the follow up period. This two part analysis allowed us to compare our cross sectional results with (1) those of other studies to determine if our results were similar and (2) those of our cohort to determine if the associations were similar between prevalent and incident data.

Circumcision status was assessed by study clinicians as part of the physical examinations. We excluded men with no circumcision status recorded at baseline and men whose circumcision status was recorded differently at baseline and follow up. The cross sectional study included men who were examined for STDs at baseline. Men diagnosed with gonorrhoea, chlamydia, or syphilis at the baseline visit were compared with a referent group without any STD at baseline—that is, did not have these or other STDs such as herpes, warts, and balanitis. The cohort study included men who returned for at least one follow up visit. Men diagnosed with gonorrhoea, chlamydia, or syphilis at any follow up visit were compared with a referent group without any STD during the follow up period. At baseline and follow up visits, the following STD tests were done; Gram stain of a smear prepared from a urethral swab specimen, culture for *Neisseria gonorrhoeae*, nucleic acid amplification assay for *Chlamydia trachomatis* using a first catch urine specimen, and syphilis serology on serum obtained by venepuncture.

Sexually transmitted diseases were defined by laboratory test results: gonorrhoea was a positive culture for *N gonorrhoeae* or Gram negative intracellular diplococci on a Gram stain of a specimen obtained using a urethral swab; chlamydia was a positive *C trachomatis* polymerase chain reaction from a urine specimen; syphilis was a suggestive history and physical examination with supportive treponemal and non-treponemal antibody test results.

Our multivariate models adjusted for the following factors as they potentially distort the true association between circumcision and disease status: study site, age group, race/ethnicity, number of sex partners, and sex with a new partner.

STATISTICAL ANALYSIS

We used SAS software version 6.12 (SAS Institute, Cary, NC, USA) to perform logistic regression, which estimated odds ratios (OR) and 95% confidence intervals (CI) for both analyses. The OR were computed by comparing each group of patients with a particular STD during the analysis period against a referent group with no STD during the analysis period. A multivariate model was built using backwards elimination at alpha = 0.05 to identify final predictors of each disease. Beginning with a full model including all predictors, covariates were eliminated one at a time based on the highest p value for the relation between the predictor and disease. Log likelihood ratio tests were used to confirm the results.

Results

Of 3269 men enrolled in Project RESPECT, we omitted 812 (25%) whose study group (by design) did not have standard laboratory tests performed, 403 (12%) whose circumcision status was recorded differently on a subsequent visit, and 33 (1%) whose circumcision status

Table 2 Cross sectional analysis: associations between sexually transmitted diseases and uncircumcised status at baseline (N=2021)

	Crude distribution (No)		Crude OR	Adjusted* OR	95% CI
	Uncircumcised	Circumcised			
Without STD†	212	622	1.0	1.0	
Gonorrhoea	110	294	1.1	1.3	0.9, 1.7
Chlamydia	72	240	0.9	1.0	0.7, 1.4
Syphilis	10	18	1.6	1.4	0.6, 3.3

*Each model adjusted for age group, race/ethnicity, and site.
†People with each STD were compared with the group with no STD.

was not recorded at any visit. A total of 2021 men remained in the cross sectional analysis. For the cohort analysis we also omitted 564 (28% of baseline) men who did not return for a follow up visit, and one who had no recorded STD examination results. A total of 1456 men remained in the cohort analysis.

At the enrolment visit, 69% of the men were categorised by the clinician as circumcised. Circumcision was more common among men aged <35 (72%) than those >35 (60%). Circumcision was more common among white men (86%) than African-American (68%) or Hispanic men (52%). Circumcision status was not associated with having a new partner or with the number of partners at baseline or follow up. Follow up rates were similar between circumcised and uncircumcised men.

CROSS SECTIONAL ANALYSIS

Univariate analysis showed no statistically significant association between circumcision status and any of the STDs. However, STD diagnosis was associated to some extent with study site, race/ethnicity, age, and partners (table 1). African-American men were more likely than white men to be diagnosed with gonorrhoea, chlamydia, and syphilis, and men under the age of 25 were more likely than older men to be diagnosed with gonorrhoea and chlamydia. Men who had three or more partners in the past 3 months were more likely to be diagnosed with gonorrhoea or chlamydia than were men with fewer partners. Men with a new partner at baseline were more likely than men with no new partner to have gonorrhoea.

After we eliminated variables that were not statistically significantly associated with circumcision status such as number of sex partners and sex with a new partner, each multivariate model of disease adjusted for the potential effects of age group, patient race/ethnicity, and study site (table 2). In the adjusted analysis, uncircumcised men were slightly more likely than circumcised men to have gonorrhoea (OR 1.3) or syphilis (OR 1.4), but these associations were not statistically significant at $p < 0.05$.

COHORT ANALYSIS

In the cohort study, characteristics associated with acquiring a new STD (table 3) closely resembled those found in the cross sectional analysis (table 1). Uncircumcised men had higher ORs for syphilis (1.9) and gonorrhoea (1.2), but the strengths of these associations were not statistically significant. The cohort study also found associations between disease and the different potential confounders. The incidence of most STDs was higher in Baltimore, Long Beach, and Newark. Compared with others, men younger than 25 years of age and men with an average of two or more partners during the follow up period were more likely to have had gonorrhoea or chlamydia. African-Americans were more likely than white people to have gonorrhoea or chlamydia. Having a new partner during follow up did not increase the risk for STD.

Table 3 Cohort analysis: associations between participant characteristics and sexually transmitted diseases (N=1456)

			Follow up STD					
			Gonorrhoea (n=119)		Chlamydia (n=111)		Syphilis (n=10)	
	Total	Without STD* (n=855)	OR	p Value	OR	p Value	OR*	p Value
Circumcised								
Yes	1109	634	1.0	—	1.0	—	1.0	—
No	347	221	1.2	0.31	0.8	0.24	1.9	0.32
Site								
Baltimore	229	106	6.3	<0.001	2.4	0.04	2.4	0.30
Denver	290	185	3.1	<0.001	1.6	0.23	5.2	0.15
Long Beach	252	161	6.1	<0.001	0.8	0.52	4.6	0.19
Newark	332	152	0.9	0.80	0.4	0.008	2.2	0.41
San Francisco	353	251	1.0	—	1.0	—	1.0	—
Race/ethnicity								
White	287	208	1.0	—	1.0	—	1.0	—
African-American	869	430	17.1	<0.001	2.8	<0.001	—	—
Hispanic	227	166	2.9	0.12	1.2	0.70	—	—
Other	73	51	4.1	0.09	0.6	0.48	—	—
Age								
<20	177	85	3.0	<0.001	6.8	<0.001	—	—
20–24	397	210	1.8	0.05	4.6	<0.001	0.4	0.20
25–29	294	192	1.1	0.86	2.1	0.07	—	—
30–34	252	147	1.2	0.66	2.0	0.12	0.5	0.40
⩾35	336	221	1.0	—	1.0	—	1.0	—
No of sex partners past 3 months†								
1	907	566	1.0	—	1.0	—	1.0	—
2	250	136	1.3	0.26	1.0	0.94	0.7	0.75
⩾3	238	119	1.9	0.01	1.7	0.30	2.4	0.21
New partner at follow up†								
Yes	785	439	1.8	0.003	1.2	0.42	2.2	0.26
No	644	408	1.0	—	1.0	—	1.0	—

*People with each STD were compared with the group with no STD.
†Numbers in partners column do not total 2021 because of missing values.

Table 4 Cohort analysis: associations between sexually transmitted diseases and uncircumcised status (N=1456)

	Crude distribution (No)				
	Uncircumcised	*Circumcised*	*Crude OR*	*Adjusted* OR*	*95% CI*
Without STD†	221	634	1.0	1.0	
Gonorrhea	36	83	1.2	1.6	1.0, 2.6
Chlamydia	23	88	0.8	0.9	0.5, 1.5
Syphilis	4	6	1.9	1.5	0.4, 6.1

*Each model adjusted for age group, race/ethnicity, and site.
†People with each STD were compared with the group with no STD.

After we eliminated variables that were not significantly associated with circumcision such as number of sex partners and sex with a new partner, each multivariate model of disease was adjusted for age group, patient race/ethnicity, and study site (table 4). In the adjusted analysis, compared with circumcised men uncircumcised men had a higher risk for gonorrhoea (OR, 1.6; 95% CI, 1.0 to 2.6), a slightly higher risk of syphilis (OR, 1.5; 95% CI, 0.4 to 6.1), and a similar risk for chlamydia (OR, 0.9; 95% CI, 0.5 to 1.5).

Discussion

The cross sectional and cohort studies found associations between circumcision and gonorrhoea, syphilis, and chlamydia that were similar in magnitude, although most risk estimates were not significant at $p < 0.05$. In this analysis, circumcised men had a slightly lower risk than uncircumcised men for gonorrhoea or syphilis, but their risks for acquiring chlamydia were similar. Finding the same results with both study designs increases the likelihood that these findings are valid. The similar results also suggest that there was no strong selection bias operating in our cross sectional study; however, this does not exclude the potential for selection bias in other cross sectional studies of circumcision

GONORRHOEA

We found that lack of circumcision may increase risk for gonorrhoea by 30% (cross sectional estimate) to 60% (cohort estimate). Some previous cross sectional studies found no association between circumcision and gonorrhoea,[15 16 20] while other cross sectional studies found similar results with risk estimates ranging from 1.6 to 2.3.[1 2 10] The only previous prospective cohort study of gonorrhoea and circumcision[13] found an increased infection rate for uncircumcised men ($p < 0.1$). Given the additional strength of cohort studies, the bulk of evidence suggests that circumcision could prevent some gonorrhoea.

SYPHILIS

Both analyses showed a slight increased risk for syphilis among uncircumcised men; however, the small number of syphilis cases in this population limited our statistical power to adequately examine this relation. One previous cross sectional studies mirrored the relation we found[20] while two others indicated a stronger association.[1 10] All of these studies, including ours, lacked an adequate number of cases, and thus precision, to be conclusive. It is difficult to study the risk factors for syphilis in the United States because the incidence is quite low. A future cohort study would need to follow 38 415 circumcised men and as many uncircumcised men long enough to see a cumulative incidence of 0.7% (the annual incidence in our study population) in order to have a power of 80% to detect a 25% increase in risk (with $p = 0.05$).

CHLAMYDIA

Neither the cross sectional nor the cohort study showed an association between the lack of circumcision and chlamydia infection. Two previous cross sectional studies showed no association[1 10] and one showed a slight increase in risk for chlamydia among uncircumcised males.[2] Considering the majority of the evidence, there does not appear to be a relation between circumcision status and chlamydia. A future cohort study, which could provide additional evidence towards a conclusion, would need to follow 2802 circumcised men and as many uncircumcised men long enough to see a cumulative incidence of 7.6% (the annual incidence in our study population) in order to have a power of 80% to detect a 25% increase in risk (with $p = 0.05$).

OTHER INFECTIONS

Although we collected data regarding genital warts and genital herpes, we did not report them because the results are difficult to interpret. For genital warts and genital herpes, a new diagnosis does not necessarily represent an incident infection.[22–26] The true prevalence and incidence of genital warts and genital herpes are very difficult to determine; the tests we used were not sensitive and specific diagnostic tests to determine infection in a symptomatic individual, and most human papillomavirus and herpes infections are asymptomatic.[23–26]

Why might circumcision lower the risk of certain STDs (gonorrhoea, syphilis) but not others? Theories about how circumcision decreases the risk include: (1) trauma of the intact foreskin during sexual intercourse might produce microscopic lesions that increase the susceptibility to sexually transmitted organisms; (2) the environment under the foreskin might enhance the survival of certain infectious agents and thus prolong exposure to them; (3) the epithelium of the glans of uncircumcised men may be thinner and less cornified than in circumcised men, and might provide less of a physical barrier to sexually transmitted microbes; and (4) non-specific balanitis, more common in uncircumcised men, may predispose to certain STDs, possibly because of an inflammatory response.[1 9] These theories do not explain why circumcision might influence transmission of gonorrhoea and syphilis, but not chlamydia. However, *T pallidum* and *N gonorrhoeae* are known to be highly infectious microbes,[27 28] and may not require as much inoculum for transmission as chlamydia. Each of these infections affects different populations, so there may be non-biological reasons to explain these different effects.

The greatest strength of this study was the ability to measure both prevalence and incidence of most STDs of interest. While many studies have been cross sectional or case-control in design, only one cohort study has examined the association between circumcision status and the development of any of the STDs that we studied (gonorrhoea).[13] A second strength was that follow up was high for circumcised and uncircumcised men and all were screened for asymptomatic infection, resulting in less bias from treatment seeking behaviour. Lastly, circumcision status was determined by clinicians which is more likely to be valid than asking the participant or his partner.[9–12]

Although our cohort study design reduced the likelihood of selection bias, other potential biases remain. Misclassification bias could have occurred because the original intervention study was not designed specifically to address circumcision status.[29] Clinicians may not have spent enough time clearly determining or recording circumcision status. This could lead to non-differential measurement error which would bias results toward finding no difference. A more troubling measurement error would be differential misclassification which could occur if clinicians were more likely to classify men with STDs at baseline as uncircumcised. Misclassification of STD at follow up is less likely because our definition of STD was based on laboratory tests which all men had at follow up. Secondly, although this was a large study, the small number of men with disease, especially with syphilis, limited our ability to detect true differences. Finally, we were not able to examine the relation between circumcision and chancroid owing to the lack of cases in our population. Previous studies have shown that circumcision decreases the risk of chancroid by over half.[4–8] Chancroid is a particularly important infection in some sub-Saharan African areas because it appears to facilitate HIV-1 transmission,[4–8] and the decreased risk of HIV-1 associated with a decreased risk of chancroid may justify circumcision as an intervention strategy in those areas.

We found suggestive but inconclusive evidence of an association between circumcision and both gonorrhoea and syphilis in our study population. Our findings indicate that circumcision may decrease the risk of incident gonorrhoea by 38% and incident syphilis by 33%. There have been very few primary studies of circumcision status and STD acquisition. A primary cohort study would be able to address hygiene and other non-biological differences between circumcised and uncircumcised men, reduce study bias, and detect incident infection. Well designed prospective studies are needed if we are to fully understand the relation between circumcision status and STDs and the potential use of circumcision as a prevention intervention.

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Contributors: RAD, data analyst, manuscript writer, and editor; TAP, principal investigator of primary study, consultant for data analysis, manuscript writer, and editor; MLK, principal investigator of primary study, consultant for data analysis, manuscript writer, and editor; CK, principal investigator, San Francisco, CA, study site for data collection, manuscript editor; JZ, principal investigator, Baltimore, MD, study site for data collection, manuscript editor; JD, principal investigator, Denver, CO, study site for data collection, manuscript editor; FR, principal investigator, Long Beach, CA, study site for data collection, manuscript editor; MI, investigator, Newark, NJ, study site for data collection; manuscript editor.

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