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RESEARCH ARTICLE

Comparing the Risk of M. *Tuberculosis* Infection among Men and Women in an African City

Trang Ho Thu Quach[1], Sarah Zalwango[2], Robert Kakaire[1], Juliet Nabbuye Sekandi[1], Christopher C. Whalen*[1], Noah Kiwanuka[3]

1. Global Health Institute, University of Georgia
2. Kampala Capital City Authority, Kampala, Uganda
3. Department of Epidemiology and Biostatistics, School of Public Health, College of Public Health, Makerere University, Kampala, Uganda

*ccwhalen@uga.edu

ABSTRACT

Background: Despite the well-known male bias in tuberculosis disease, the underlying reasons remained elusive. We examined whether male predominance in tuberculosis disease is result of higher risk of tuberculosis infection or not. If so, whether it is due to higher likelihood of exposure or higher susceptibility to infection among men.

Methods: A household contact study and a prospective cohort study conducted in Kampala, Uganda, from 2013 to 2017 were used to estimate and compare prevalence and annual risk of tuberculosis infection among men and women. In household contact study, index tuberculosis cases and healthy index controls were asked to list their household contacts and extra-household contacts. All contacts were tested with tuberculin skin test to detect tuberculosis infection. In prospective cohort study, individuals with tuberculin skin test (TST) < 5 mm were enrolled and retested with the skin test at one year to detect new infection. Poisson regression with robust standard errors was used to estimate prevalence ratio and relative risk of tuberculous infection between men and women.

Results: In household contact study, 123 index tuberculosis cases and 124 index controls listed 382 household contacts of tuberculosis cases, 624 extra-household contacts of tuberculosis cases, and 1044 contacts of controls. Of 1681 enrolled participants in cohort study, 1213 (72%) were retested with TST at one year. There was no sex difference in prevalence of tuberculosis infection among household contacts of tuberculosis cases, but men had a higher prevalence of tuberculosis infection among extra-household contacts of tuberculosis cases (prevalence ratio 1.25, 95% CI 1.06 – 1.48) and contacts of controls (prevalence ratio 1.53, 95% CI 1.30 – 1.81). Similarly, in cohort study, there was no sex difference in annual risk of tuberculosis infection when participant reported knowing tuberculosis cases, but men had a higher annual risk of tuberculosis infection when participants no known contact with tuberculosis (relative risk 1.94, 95% CI: 1.34, 2.80).

Conclusion: Men have higher risk of acquiring tuberculous infection than women. Men and women may have the same susceptibility to tuberculosis infection given known exposure to tuberculosis cases. The observed difference in rate of infection may be partially explained by higher rates of exposure to undetected, infectious tuberculosis cases among men.

INTRODUCTION

Tuberculosis is a global disease that threatens both individual and public health with almost 10 million tuberculosis cases and nearly 1.5 million deaths per year [1]. Tuberculosis is disease known for its disparities as most of the reported tuberculosis cases (95%) are from low- or middle-income countries or regions overwhelmed by the HIV epidemic [1]. There is, however, another disparity with tuberculosis that is ubiquitous and not well understood; that is, the disparity between men and women in tuberculosis infection and disease.

Regardless of the wealth of a country or severity of human immunodeficiency virus (HIV) epidemic, the number of the reported tuberculosis cases in men outnumbers the cases in women by 2 to 3 fold [2]. The male predominance in tuberculosis disease may be the result of systematic underreporting or underdiagnosis of tuberculosis in women [3,4]. However, the male predominance remains even when active case finding surveys are performed, which mitigates reporting and diagnostic bias [5,6]. This male predominance is found not only for tuberculosis disease but also for latent tuberculosis infection. Community surveys [7-10] and community-based studies [11] have consistently found the prevalence of latent tuberculosis infection to be greater in men than women.

These epidemiologic observations raise important questions about the transmission dynamics of M. *tuberculosis*, especially in low- and middle-income countries, and the natural history of tuberculosis infection. For example, does the male predominance result from a greater susceptibility to infection among men compared to women? Or is susceptibility comparable, but men are more often exposed to infectious, undetected cases of tuberculosis in their daily lives? These questions have implications not only about host immunity [12] to tuberculosis among men and women, but also about social behaviors that may lead to greater risk of exposure among men.

Setting aside possible systematic error in measuring in the burden of tuberculosis by sex, there are other plausible explanations for male predominance of tuberculosis in a population. It is possible, for example, that men may be more susceptible than women to infection with M. *tuberculosis* or more prone to progression to active disease once infected. Indeed, females have been found to have better innate immunity to several infections [13] as shown by greater phagocytic and macrophage activity in women, as well as a more robust function of antigen presenting cells. This sexual dimorphism in innate immunity may be the result of genes found on the X chromosome, genetic modulation by sex hormones [14], or epigenetic events, such as pregnancy, that differ between males and females [15]. Based on these differences in host innate immunity between males and females, we hypothesized that men would be more susceptible to incident infection with M. *tuberculosis* than women and would, as a result, have a higher probability of infection for a given type of exposure.

Innate resistance to infection may not be the only determinant of infection with M. *tuberculosis*. It is also possible that men are more often exposed to undetected cases of tuberculosis because of their social and cultural patterns of daily life. Studies of social mixing have consistently shown assortativity according to age and sex [16-18]. Moreover, in a study of the social networks of tuberculosis cases in Kampala, Uganda, we found that male assortativity may have accounted for excess risk of transmission of M. *tuberculosis* [19] in the community. Based on the general pattern of mixing and the nature of the social networks in Kampala, we hypothesized that men would be more likely than women to acquire incident infections with M. *tuberculosis* in the community.

To parse the effect of biologic sex on tuberculosis, we adapted the current model for the natural history of tuberculosis [20,21] with special attention to the early stages of that model when infection first occurs. Most epidemiologic studies of tuberculosis in men and women rely on cross-sectional designs that measure prevalence of infection and do not condition on timing of previous, known exposure to infectious cases. In this project, we take a novel approach to measure incident infection with M. *tuberculosis* using a hybrid of two complementary study designs. One design was a contact investigation study that included household contacts and social network members from the community. In this design, we were able to condition on the duration and nature of household exposure to an index case. The other design was a prospective cohort study of adult men and women who were not infected with M. *tuberculosis*. Here we knew exposure occurred within the one year of observation. The use of these two contemporaneous designs allowed us to compare findings and arrive at an internally valid inference about the effect of biologic sex on tuberculous infection.

In the analysis of each design, we assessed whether susceptibility differed among men and women by comparing the prevalence, or incidence, of infection by sex following a defined type of exposure. We further assessed whether the social behavior of men put them at higher risk for exposure to undetected, infectious tuberculosis cases than women by comparing incidence of infection in the prospective community cohort study. We propose that the findings of our project will help frame the next set of research questions that will lead to a better understanding of the mechanisms that underlie the difference in risk for tuberculosis infection and disease between men and women in Africa.

METHODS

Study designs and populations

Household Contact Investigation: From June 2013 to January 2017, we performed a household contact study on culture-confirmed index tuberculosis cases and their household contacts in the Lubaga Division of Kampala, Uganda. We extended the household design to include social network members identified by the index cases who did not reside within the household. Detailed information regarding this study design, measurements and outcomes has been published earlier [22]. Briefly, we enrolled index tuberculosis cases 15 years or older who had pulmonary tuberculosis defined as acid-fast bacilli smear-positive sputum. We frequency-matched index tuberculosis cases with index controls based on age, sex, and parish. Index controls were selected from residents of Lubaga Division who did not have tuberculosis disease as determined by symptom screening. We asked index participants to list individuals with whom the participants had personal relationships. Contacts of index tuberculosis cases and index controls were classified as household contacts if they resided in the household of an index participant for the previous 3 months and had eaten meals in the household at least weekly; otherwise, contacts were classified as extra-household. Contacts of index participants were identified and evaluated for active tuberculosis, latent tuberculosis infection, and HIV infection using routine interviews and standard diagnostic evaluation. The tuberculin skin test (TST) was performed using the Mantoux method by injecting subcutaneously five tuberculin units of purified protein derivative on the left forearm of the participants. Two field workers independently measured the diameter of the induration within 48-72 h using the 'ball-point' technique and digital calipers to reduce digit preference bias. Latent tuberculosis infection was defined as an induration of ≥ 10 mm among HIV-seronegative contacts and 5 mm among HIV-seropositive contacts. Tuberculous infection was defined as infection with *M. tuberculosis*, either as active tuberculosis or as latent tuberculosis infection. Contacts who did not meet definitions for tuberculosis infection were classified as uninfected. HIV infection was determined using the Determine HIV-1/2 and a HIV 1/2 STAT-PAK; a Uni-gold HIV test was performed if there were discrepant results for the initial tests.

Community Cohort Study: Between June 2014 and October 2017, we performed a prospective community cohort study in Lubaga Division of Kampala, Uganda. In this study, we recruited adult residents of Lubaga in the study if they met the following inclusion criteria: (1) TST less than 5 mm at baseline; (2) age between 17 and 60 years old; and (3) no signs or symptoms of active tuberculosis. A standard clinical evaluation was performed at baseline to assess risk of acquiring new tuberculosis infection. Participants were evaluated at quarterly intervals to assess risk of getting the disease using standardized questionnaires. These questionnaires collected information about recent exposure to tuberculosis cases, hospitalizations, travel, and details of settings that participants spent time. The TST and HIV tested were performed in the same manner as the household contact study.

At one year, participants were retested with TST to evaluate new infection. In HIV-seronegative subjects, TST conversion was defined as having a second TST reading of ≥ 10 millimeters or greater with an increase in reaction of 6 millimeters or greater from the first to the second reading. In HIV-seropositive subjects, TST conversion was defined as having a second TST ≥ 5 millimeters with an increase in induration of 3 millimeters or greater from the first to the second reading. If the above conditions were not met, participants were classified as persistent skin test negative.

Statistical analysis

The main objective of this analysis was to compare prevalence and incidence of tuberculosis infection by sex. The cross-sectional and cohort studies were analyzed separately using the appropriate method for each design.

For the household contact study analysis, we analyzed the distribution of TST in 3 groups: household contacts of index tuberculosis cases, extra-household contacts of index tuberculosis cases, and contacts of index controls. Characteristics of the study population were stratified by types of contacts and summarized with the frequencies and proportions for categorical variables. The prevalence of tuberculosis infection and its 95% confidence interval (95% CI) were stratified by types of contacts and sex to assess sex discrepancy in tuberculosis infection across groups. Adjusted prevalence ratios (aPR) of men compared to women were obtained via Poisson regression with robust error variance [23] for each type of contact. Age and

HIV status were included in multivariate models to estimate the adjusted prevalence ratios. Distribution of TST induration was stratified by sex and types of contacts and then visualized by histogram and density plots. We stratified further by age category (< 15 years and ≥ 15 years) to evaluate for confounding and effect-modification effect of age on the prevalence of tuberculosis infection across sex and types of contacts.

For the community cohort study, we summarized the distribution of TST at 12 months by age and sex and then estimated the cumulative incidence of M. *tuberculosis* infection at one-year calculating the proportion of TST conversions per susceptible participants stratified by sex, age category, and known previous contact with a tuberculosis case. The adjusted incidence rate ratio (aRR) among men compared with women was estimated using Poisson regression with robust error variance. This model was controlled by age category and religious affiliation. We performed a test for interaction between sex and known exposure to tuberculosis during follow-up. We further performed a sensitivity analysis of the three-way interaction between age groups, known exposure status, and sex. All analyses were carried out using R v3.6.1 (R foundation for Statistical Computing, Vienna, Austria, 2019).

RESULTS

Household Contact Study

In the household contact study, we enrolled 382 household contacts of tuberculosis cases, 624 extra-household contacts of tuberculosis cases, and 1044 contacts of controls (Table 1). Children younger than 15 years old accounted for the highest proportion of household contacts of tuberculosis cases (47.1%) whereas young adults aged from 15 to 34 years old accounted for the highest proportion of extra-household contacts of tuberculosis cases (63.7%) and contacts of controls (65.4%). The proportion of male contacts was lowest among household contacts (43.5%) and highest among contacts of control index participants (55.4%). Household contacts of tuberculosis cases had highest proportion of participants who did not attend formal education or finish primary level (62.3%) and the highest proportion of participants who earned 28 USD or less per month (76.2%). The HIV sero-prevalence positive ranged 6.3% to 9.1% among the contacts of index participants (Table 1).

Table 1. Characteristics of participants from the household contact study and cohort study

Variables	Household Contact study			Cohort study
	Household contact of tuberculosis cases (N=382)	Extra household contacts of tuberculosis cases (N= 624)	Contacts of controls (N= 1044)	Cohort population (N=1213)
Age in years				
0 - 4	81 (21.2)	39 (6.2)	58 (5.6)	0 (0.0)
5 - 14	99 (25.9)	48 (7.7)	114 (10.9)	0 (0.0)
15 - 24	98 (25.7)	190 (30.4)	340 (32.6)	657 (54.2)
25 - 34	36 (9.4)	208 (33.3)	342 (32.8)	387 (31.9)
35 - 44	37 (9.7)	88 (14.1)	134 (12.8)	128 (10.6)
45 - 65	31 (8.1)	51 (8.2)	56 (5.4)	41 (3.4)
Sex				
Female	216 (56.5)	307 (49.2)	466 (44.6)	714 (58.9)
Male	166 (43.5)	317 (50.8)	578 (55.4)	499 (41.1)
Marital status				
Married	108 (28.3)	320 (51.3)	526 (50.4)	673 (55.5)
Never married	273 (71.5)	302 (48.4)	517 (49.5)	540 (44.5)
(Missing)	1 (0.3)	2 (0.3)	1 (0.1)	0 (0.0)
Religion				
Roman Catholic	115 (30.1)	251 (40.2)	451 (43.2)	495 (40.8)
Others	267 (69.9)	371 (59.5)	592 (56.7)	716 (59.0)
(Missing)	0 (0.0)	2 (0.3)	1 (0.1)	2 (0.2)
Education level				
None or Primary	238 (62.3)	291 (46.6)	529 (50.7)	380 (31.3)
Secondary/Post-secondary	144 (37.7)	331 (53.0)	514 (49.2)	830 (68.4)
(Missing)	0 (0.0)	2 (0.3)	1 (0.1)	3 (0.2)
Monthly income, USD				
28 USD or less than	291 (76.2)	313 (50.2)	513 (49.1)	434 (35.8)
29 USD – 56 USD	32 (8.4)	129 (20.7)	211 (20.2)	360 (29.7)
57 USD or more	55 (14.4)	177 (28.4)	314 (30.1)	415 (34.2)

(Missing)	4 (1.0)	5 (0.8)	6 (0.6)	4 (0.3)
HIV results				
Negative	357 (93.5)	563 (90.2)	977 (93.6)	1147 (94.6)
Positive	25 (6.5)	57 (9.1)	66 (6.3)	57 (4.7)
(Missing)	0 (0.0)	4 (0.6)	1 (0.1)	9 (0.7)

In the household study, the prevalence of tuberculosis infection was highest in household contacts of tuberculosis cases (61.5%), followed by extra-household contacts of tuberculosis cases (44.9%) and contacts of controls (37.9%). When stratifying by sex, there was no difference by sex in the prevalence of tuberculous infection among household contacts of tuberculosis cases (aRR 1.01, 95% CI 0.86, 1.19; Figure 1A). However, men had a higher prevalence of tuberculosis infection among extra-household contacts of tuberculosis cases and contacts of controls (aPR = 1.25 and aPR = 1.53, respectively; Table 2). These findings were supported by histogram and density plots of TST indurations stratified by sex and types of contacts (Figure 2).

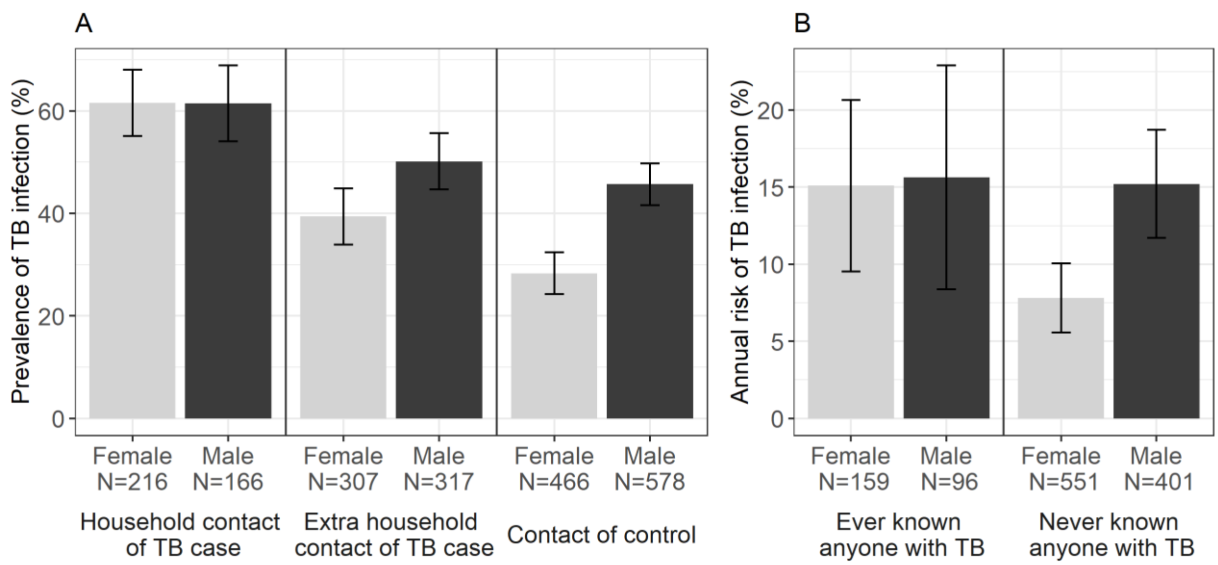

Figure 1. Sex difference in prevalence of tuberculosis infection (figure 1A) and annual risk of tuberculosis infection (figure 1B) stratified by tuberculosis exposure

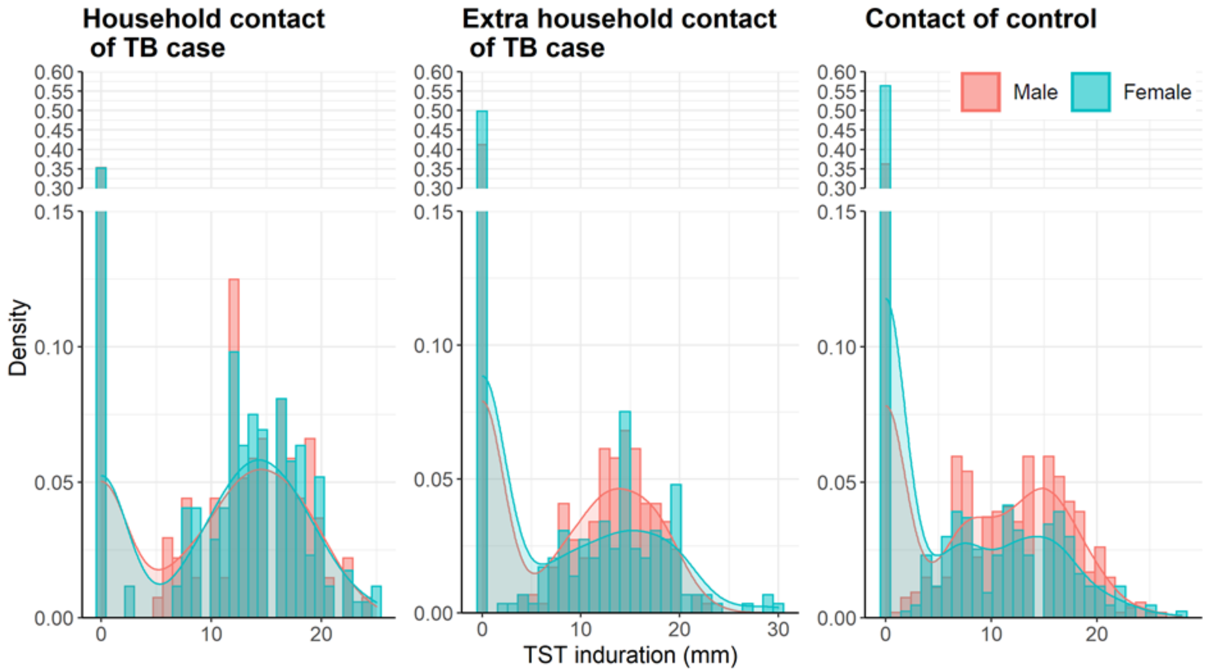

Figure 2. Distribution of TST induration by sex and type of contact from household contact study.

When stratifying the prevalence of tuberculosis infection by sex and age category (less than 15 years and 15 years or more), the prevalence of tuberculosis infection by male and female contacts was similar for household contacts less than 15 years (58.9% vs. 55.3%), and for contacts older than 15 years (64.8% vs. 65.6%; Figure 3). In both age categories, the adjusted PR was close to 1 (Table 2). Men had a higher prevalence of tuberculosis infection than women among extra-household contacts of tuberculosis cases aged 15 years or more and contacts of controls aged 15 or more (Table 2). Although the measured prevalence of tuberculosis infection was higher for boys than for girls less than 15 years, the prevalence did not differ by sex among extra-household contacts (12.8% vs 7.5%) nor contacts of controls (11.0% vs 5.6%; Table 2 and Figure 3).

Table 2. Prevalence ratios comparing men versus women according to study groups.

Study Group	aPR¥	95% CI
Household Contact Study		
Household Contacts - All	1.01	0.86, 1.19
0 – 14 years	1.07	0.83, 1.38
≥ 15 years	0.99	0.80, 1.22
Extra-Household Contacts	1.25	1.06, 1.48
0 – 14 years	1.70	0.45, 6.37
≥ 15 years	1.28	1.08, 1.52
Control Contacts	1.53	1.30, 1.81
0 – 14 years	1.98	0.69, 5.67
≥ 15 years	1.52	1.29, 1.79
¥aPR: adjusted prevalence ratio		

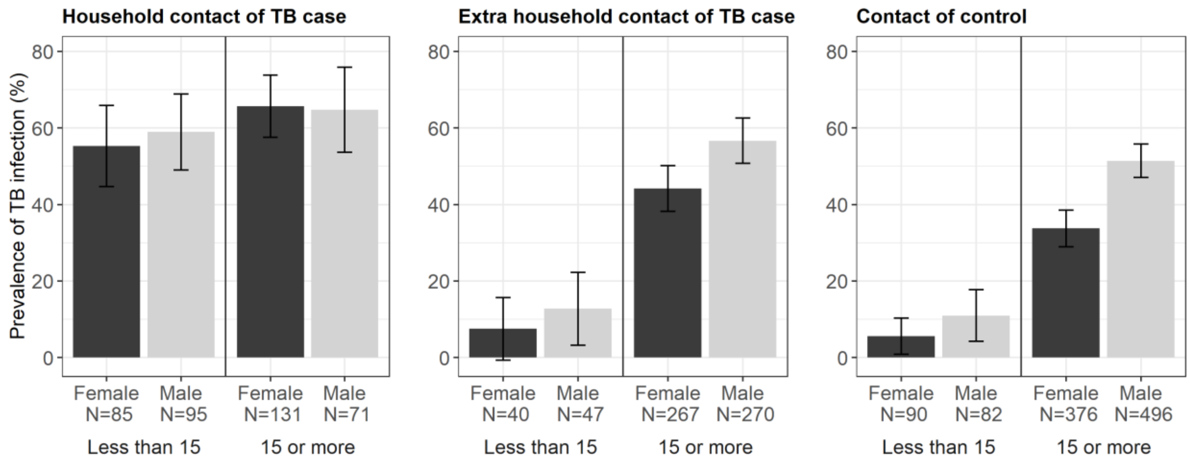

Figure 3. Sex difference in prevalence tuberculosis infection across age groups from household contact study

Community Cohort Study

The cohort study enrolled 1681 participants of whom 1213 completed 12 months of follow-up and had an outcome evaluation. The characteristics of the participants who had TST results at 12 months did not differ from the 468 participants who either refused the test or were lost to follow-up as regards age, sex, marital status, religion, education level, monthly income, HIV status at baseline, and ever known anyone with tuberculosis status. The mean age of the cohort was 25.91 years (SD 7.28); 41.1% were men. Most participants were married and had some secondary or post-secondary education. The HIV seroprevalence was 4.7%, which is comparable to the prevalence in Kampala (Table 1).

The cumulative incidence of tuberculosis infection was 15.2% (95% CI 12.3, 18.7) among men and 9.0% (95% CI 7.2, 11.3) among women, but there was effect modification by known exposure to a tuberculosis cases (interaction chi-square=3.717, d.f=1, p-value=0.054). When stratifying by known exposure status, the cumulative incidence of infection at one year did not differ among men and women who reported previous known exposure to a tuberculosis case (aRR 0.92, 95% CI: 0.51, 1.68) but did differ among participants who had not reported knowing anyone with tuberculosis (aRR 1.94, 95% CI 1.34, 2.80) (Figure 1B).

We examined the effect of age groups (cutoff at median, < 25 years and ≥ 25 years) on sex discrepancy in cumulative incidence infection and found no interaction between age group and sex (Chi-square=0.004, d.f=1, p-value=0.947). Men consistently showed a higher annual risk of infection across age groups: aRR 1.60 (95% CI 1.01, 2.54 for less than 25 years old); aRR 1.57 (95% CI 1.04, 2.36) for 25 years old or older. Because there was a two-way interaction between sex and known exposure status, we further examined three-way interactions among age group, sex, and known exposure status; no interactions reached statistical significance.

DISCUSSION

The world health organization consistently reports a predominance of tuberculosis among men from most countries in the world. One possible explanation for this male predominance of tuberculosis disease is that men are more frequently infected with *M. tuberculosis* than women, and as a result, more often progress to active disease. The main aim of this project was to compare the cumulative risk of tuberculous infection among men and women living in an African city with endemic tuberculosis. We found that men and women had comparable susceptibility to tuberculous infection given known exposure, but that men were more likely to acquire new infection than women as they carried out their daily lives among social network members who did not have pulmonary TB disease.

For respiratory infectious diseases, the incidence of infection depends on the prevalence of infectious cases in the population and the way people mix in that population. The incidence of infection is therefore non-linear and depends on three fundamental parameters: the frequency of contact between an infectious case and a susceptible contact, the probability of transmission given adequate contact, and the likelihood of encountering an infectious case (i.e., prevalence of disease) in the population at a given time [24]. These parameters combine to define the dependent nature of exposure to an infectious disease in a population setting and determine the epidemic behavior of that disease. Given these complexities of respiratory epidemics, we used two different study designs to tease apart this unified model and estimated its parameters for tuberculosis. Once we obtained these parameter estimates, we compared them between men and women.

In the household contact study, we used the prevalence of infection at the time of household evaluation as a measure of the transmission probability given household contact and found that male and female contacts had a similar prevalence, even when stratifying by age category and household. We inferred from these findings that the susceptibility of infection with *M. tuberculosis* was similar among men and women given household exposure to an infectious index case. This inference, however, depends on several assumptions that are inherent in the study design. First, for the transmission probability to reflect susceptibility, we must assume that mixing within a home is similar among all contacts and did not vary by sex. We believe that there is parity in mixing by sex within the households because the houses in an African urban setting are often small one or two room domiciles, which are primarily used for sleeping or sharing meals. This built environment creates opportunity for entire families to share airspace for extended periods of time. Thus, it is reasonable that all family members share a similar level of exposure to the index case in this type of setting. It is possible, however, that women stayed at home more often than men and that they provided care to the index case, thereby creating opportunities for closer and more sustained contact.

Second, we assumed that the infectiousness of an index case does not vary within a house, so that all household contacts are exposed to a similar level of infectiousness. Although infectiousness may vary among cases in the study, leading to different levels of infectiousness from one house to the next, this type of heterogeneity would not result in differential exposure by sex within a given household. To account for the heterogeneity in infectiousness among households, we use generalized estimating equations to adjust for clustering within and between households.

In the prospective community cohort study, we used the incidence of *M. tuberculosis* infection as an indirect measure of the rate of contact between undetected, infectious tuberculosis cases and susceptible contacts in the community. We found that the overall incidence of infection was greater in men than women, suggesting that the annual cumulative incidence of infection among men and women may be an indicator of differential mixing by sex. This effect, however, was modified by known contact with a tuberculosis case during the follow-up period. Among the minority of participants who reported contact with an index case, the incidence did not differ between men and women, a finding that corresponds to the results of the household contact analysis. Among most of participants, who did not report any known contact with a tuberculosis case, the incidence of infection was higher in men. From this analysis, we conclude that the social movements of men and women differ, such that men more often encounter undetected infectious cases of tuberculosis and acquire new infection through those contacts. This type of assortativity by sex has been shown to occur in social networks of index tuberculosis cases in Kampala [19] and in general networks of adults [17,18].

As before, this inference requires some assumptions about other parameters in the unified model. One assumption is that the transmission probability is similar between men and women; indeed, the household contact analysis provides coherent evidence for this assumption. Another assumption is that the prevalence of infectious tuberculosis in the community did not change appreciably during the three-year period of the study. This assumption is supported the findings of two community prevalence studies performed in Kampala divisions 10 years apart which found nearly the same prevalence of active tuberculosis in the community (0.8%, or 800 per 100,000) [20,25].

Apart from the assumptions we made in interpreting the parameters of the model, several issues arise that may bias our conclusions. First, we used the TST to measure tuberculous infection. Although the TST is the traditional test for assessing tuberculosis infection and has well-understood performance characteristics in Uganda [26,27], we may have overestimated the prevalence of tuberculous infection because of false-positive tests associated with BCG vaccination and environmental mycobacterial infection. This effect may be mitigated by our use of ratios as measures of effect (e.g., cumulative incidence ratio) which would cancel the effect of misclassification if it occurred in a similar proportion among men and women. Second, in the household contact study, we used prevalence as a measure of infection which may include both remote and recent infections and may therefore be confounded by the higher incidence of infection in men. Third, although we made efforts to limit the losses to follow-up in the cohort study, it is possible that a selection bias may have occurred if the participants lost to follow-up had a different risk of tuberculous infection than those who remained in the cohort.

Although our findings suggest that susceptibility to infection is comparable between men and women and that new infections relate to differences in social and behavioral factors, the study did not examine the underlying hormonal, immunologic, or genetic mechanisms that may lead to differential risks of infection [13]. Others have explained how biologically plausible mechanisms that may account for difference by sex in host immune response to *M. tuberculosis* [12,28,29]. This study may help to frame new questions about the interaction between the endocrine and immune systems, but it does not provide answers. Along these same lines, our study does not specifically evaluate whether men are more likely than women to progress to active tuberculosis disease once they have acquired infection. To answer this question, one would need to perform a large cohort study of men and women with tuberculous infection and compare the incidence of tuberculosis disease.

CONCLUSION

In conclusion, in an urban setting in Africa with endemic tuberculosis, adult men had a higher risk of acquiring new infection with *M. tuberculosis* than women. This additional risk may relate to social and behavioral factors that lead to preferential attachment to contact networks that include undetected, infectious tuberculosis cases. Understanding the social or cultural determinants of this type of engagement in the community may have implications for designing targeted intervention strategies to interrupt *M. tuberculosis* transmission.

Conflict of Interest Statement: All authors declare that they have no conflict of interest.

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REFERENCES

1. WHO. *Global tuberculosis report 2021*. World Health Organization; 2021.
2. Horton KC, MacPherson P, Houben RM, White RG, Corbett EL. Sex differences in tuberculosis burden and notifications in low-and middle-income countries: a systematic review and meta-analysis. *PLoS medicine*. 2016;13(9):e1002119.
3. Thorson A, Hoa N, Long N, Allebeck P, Diwan V. Do women with tuberculosis have a lower likelihood of getting diagnosed?: Prevalence and case detection of sputum smear positive pulmonary TB, a population-based study from Vietnam. *Journal of clinical epidemiology*. 2004;57(4):398-402.
4. Holmes CB, Hausler H, Nunn P. A review of sex differences in the epidemiology of tuberculosis. *The International Journal of Tuberculosis and Lung Disease*. 1998;2(2):96-104.
5. Weiss M, Sommerfeld J, Uplekar M. Social and cultural dimensions of gender and tuberculosis [editorial][special section on gender and TB]. *The International Journal of Tuberculosis and Lung Disease*. 2008;12(7):829-830.
6. Mbonye AK, and Aceng, Jane. The Uganda National Tuberculosis Prevalence Survey, 2014 - 2015. *Survey report Uganda: Ministry of Health*. 2017;
7. Ncayiyana JR, Bassett J, West N, et al. Prevalence of latent tuberculosis infection and predictive factors in an urban informal settlement in Johannesburg, South Africa: a cross-sectional study. *BMC infectious diseases*. 2016;16(1):661.
8. Kizza FN, List J, Nkwata AK, et al. Prevalence of latent tuberculosis infection and associated risk factors in an urban African setting. *BMC infectious diseases*. 2015;15(1):165.
9. Legesse M, Ameni G, Mamo G, Medhin G, Bjune G, Abebe F. Community-based cross-sectional survey of latent tuberculosis infection in Afar pastoralists, Ethiopia, using QuantiFERON-TB Gold In-Tube and tuberculin skin test. *BMC infectious diseases*. 2011;11(1):89.
10. Martinez L, Arman A, Haveman N, et al. Changes in tuberculin skin test positivity over 20 years in periurban shantytowns in Lima, Peru. *The American journal of tropical medicine and hygiene*. 2013;89(3):507.
11. Kakaire R, Kiwanuka N, Zalwango S, et al. Excess risk of tuberculosis infection among extra-household contacts of tuberculosis cases in an African City. *Clinical Infectious Diseases*. 2021;73(9):e3438-e3445.
12. Neyrolles O, Quintana-Murci L. Sexual inequality in tuberculosis. *PLoS medicine*. 2009;6(12):e1000199.
13. Klein SL, Flanagan KL. Sex differences in immune responses. *Nature Reviews Immunology*. 2016;16(10):626-638.
14. Jaillon S, Berthenet K, Garlanda C. Sexual dimorphism in innate immunity. *Clinical reviews in allergy & immunology*. 2019;56(3):308-321.
15. Shepherd R, Cheung AS, Pang K, Saffery R, Novakovic B. Sexual dimorphism in innate immunity: the role of sex hormones and epigenetics. *Frontiers in immunology*. 2021;11:604000.
16. Edmunds W, Kafatos G, Wallinga J, Mossong J. Mixing patterns and the spread of close-contact infectious diseases. *Emerging themes in epidemiology*. 2006;3(1):1-8.
17. Mossong J, Hens N, Jit M, et al. Social contacts and mixing patterns relevant to the spread of infectious diseases. *PLoS medicine*. 2008;5(3):e74.
18. Mousa A, Winskill P, Watson OJ, et al. Social contact patterns and implications for infectious disease transmission–a systematic review and meta-analysis of contact surveys. *ELife*. 2021;10:e70294.
19. Miller PB, Zalwango S, Galiwango R, et al. Association between tuberculosis in men and social network structure in Kampala, Uganda. *BMC Infectious Diseases*. 2021/09/30 2021;21(1):1023. doi:10.1186/s12879-021-06475-z
20. Kendall EA, Kitonsa PJ, Nalutaaya A, et al. The spectrum of tuberculosis disease in an urban Ugandan community and its health facilities. *Clinical Infectious Diseases*. 2021;72(12):e1035-e1043.
21. Drain PK, Bajema KL, Dowdy D, et al. Incipient and subclinical tuberculosis: a clinical review of early stages and progression of infection. *Clinical microbiology reviews*. 2018;31(4):e00021-18.
22. Kakaire R, Kiwanuka N, Zalwango S, et al. Excess Risk of Tuberculosis Infection Among Extra-household Contacts of Tuberculosis Cases in an African City. *Clinical Infectious Diseases*. 2020;
23. Zou G. A modified poisson regression approach to prospective studies with binary data. *American journal of epidemiology*. 2004;159(7):702-706.
24. Halloran ME, Struchiner CJ, Longini Jr IM. Study designs for evaluating different efficacy and effectiveness aspects of vaccines. *American journal of epidemiology*. 1997;146(10):789-803.
25. Sekandi J, List J, Luzze H, et al. Yield of undetected tuberculosis and human immunodeficiency virus coinfection from active case finding in urban Uganda. *The International journal of tuberculosis and lung disease*. 2014;18(1):13-19.

26. Musoke Mudido P, Guwatudde D, Nakakeeto M, et al. The effect of bacille Calmette-Guerin vaccination at birth on tuberculin skin test reactivity in Ugandan children. *The International Journal of Tuberculosis and Lung Disease*. 1999;3(10):891-895.
27. Castellanos M, Kirimunda S, Martinez L, et al. Performance of the QuantiFERON®-TB Gold In-Tube assay in tuberculin skin test converters: a prospective cohort study. *The International Journal of Tuberculosis and Lung Disease*. 2018;22(9):1000-1006.
28. Grossman CJ. Interactions between the gonadal steroids and the immune system. *Science*. 1985;227(4684):257-261.
29. Nhamoyebonde S, Leslie A. Biological differences between the sexes and susceptibility to tuberculosis. *The Journal of infectious diseases*. 2014;209(suppl_3):S100-S106.