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Possible sex difference in latent tuberculosis infection risk among close tuberculosis contacts

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ABSTRACT

Objectives: More men than women develop and die of tuberculosis (TB). Fewer data exist on sex differences in latent TB infection (LTBI). We assessed for potential sex differences in LTBI acquisition among close TB contacts.

Methods: Regional Prospective Observational Research for TB-Brazil is an observational multi-center cohort of individuals with culture-confirmed pulmonary TB and their close contacts. Participants were enrolled from five sites in Brazil from June 2015 - June 2019. Close contacts were followed for 24 months after enrollment, with LTBI defined as a positive interferon-γ release assay (IGRA; QuantiFERON 3rd or 4th generation) at baseline or 6 months. We performed univariate, bivariate, and multivariable logistic regression and propensity-score weighted models to assess odds ratios (OR) and 95% confidence intervals (CI) for LTBI acquisition by birth sex among close contacts.

Results: Of 1093, 504 (46%) female close contacts were IGRA positive compared to 295 of 745 (40%) men. The unadjusted OR for IGRA positivity among women vs men was 1.31 (95% CI: 1.08-1.58). Bivariate adjustments yielded ORs in women vs men ranging from 1.19 to 1.33 (*P*-value range: <0.01-0.07). Multivariable regression and weighted models yielded similar ORs in women vs men, of 1.14 (95% CI: 0.92-1.41) and 1.15 (95% CI: 0.94-1.40), respectively.

Conclusion: The point estimate for LTBI among close TB contacts in Brazil was higher in women, though less pronounced in multivariable models. If the sex difference in LTBI is confirmed in additional settings, studies of possible underlying differences in socio-behavioral factors or TB pathogenesis are warranted.

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Introduction

It is well known that there are sex differences in active tuberculosis (TB), with men more likely to contract and die of the disease (World Health Organization, 2021). This is particularly true in low- and middle-income countries (Horton *et al.*, 2016). While the disproportionate active TB prevalence may be due in part to underreporting in female populations (Saunders *et al.*, 2019), this alone is unlikely to explain such trends, which have been seen in multiple settings (Neyrolles and Quintana-Murci, 2009; Rhines, 2013). Instead, behavioral and physiologic differences have been posited as probable drivers (Nhamoyebonde and Leslie, 2014; Dodd *et al.*, 2016; Horton *et al.*, 2020).

There are fewer data on sex differences in latent TB infection (LTBI) testing, treatment, and outcomes. While some studies have found no significant sex differences (Ting *et al.*, 2014; Teklu *et al.*, 2018; Ncayiyana *et al.*, 2016), others appear to show higher rates of LTBI in men (Reichler *et al.*, 2020; Sabri *et al.*, 2019; He *et al.*, 2015; de Souza *et al.*, 2014; Chen *et al.*, 2015). Further analyses found that men were more likely to receive (Fiske *et al.*, 2014) and complete LTBI treatment (Hirsch-Moverman *et al.*, 2015) and have less antitubercular medication toxicity (Pettit *et al.*, 2013). Of note, several of these studies were in specific populations such as healthcare workers, and only the Tuberculosis Epidemiologic Studies Consortium Task Order-2 Team evaluated large numbers of close contacts with active TB disease (Reichler *et al.*, 2020; Fiske *et al.*, 2014).

Several known factors may interact with sex in increasing the risk for LTBI. Lower socio-economic status groups appear to have a higher prevalence of LTBI (Lule *et al.*, 2020). Heavy alcohol use is associated with LTBI risk (Puryear *et al.*, 2021) and incomplete treatment (Hirsch-Moverman *et al.*, 2010), while active and passive smoking alters host immunity (Bai *et al.*, 2018) and leads to higher infection rates (Lindsay *et al.*, 2014; Patra *et al.*, 2015). Comorbidities such as diabetes (Lee *et al.*, 2017) and renal disease on dialysis (Shu *et al.*, 2015) play a role, with diabetes, in particular, contributing to an ineffective or exaggerated immune response (Magee *et al.*, 2020). Even after accounting for these separate factors, sex differences may still impact LTBI, LTBI conversion, and LTBI treatment success.

We sought to fill the current knowledge gap by evaluating potential sex differences in interferon-γ release assay (IGRA) positivity among close TB contacts in Brazil. To our knowledge, no prior studies have directly assessed a sex difference in IGRA conversion after prolonged TB exposure. Brazil is a highly diverse upper-middle income country with large gaps in income equality and decreasing yet substantial TB burden. Our well-characterized multi-center cohort closely represents the TB patient population in Brazil and is well positioned to address this question (Arriaga *et al.*, 2021a). Based on preliminary data within our cohort (Souza *et al.*, 2021; Arriaga *et al.*, 2021b), we hypothesized that female close contacts would have higher rates of IGRA positivity than men, even after adjusting for potentially confounding factors.

Methods

Study population and follow-up

Regional Prospective Observational Research for TB in Brazil (RePORT-Brazil) is a prospective observational cohort study of culture-confirmed pulmonary TB cases and their close contacts (Arriaga *et al.*, 2021a). There were five sites across three high TB-burden regions in Brazil: three in the southeast (Rio de Janeiro – Rio de Janeiro), one in the northeast (Salvador – Bahia), and one in the north (Manaus – Amazonas). Study participants were enrolled from June 2015 through June 2019 and followed for 2 years, with follow-up completed in June 2021. Close contacts were defined as individuals spending at least 4 hours per week in proximity to an index case within the 6 months preceding active TB diagnosis (Loredo *et al.*, 2014). Close contacts were excluded if they had no available IGRA result at baseline or 6 months and index cases without culture-confirmed pulmonary disease. Index cases were not included if the individuals were $\leq$18 years of age, pregnant, breastfeeding, or already on antitubercular therapy for $>$7 days.

Close contacts were encouraged by phone or text to present at study enrollment sites. Baseline evaluation included questionnaires, in-person physical examination, blood work, and chest imaging. At 6 months, close contacts returned for clinical assessment and repeat blood work and chest imaging. Subsequent evaluations occurred at 6-month intervals by phone throughout the 2-years follow-up period.

Exposure, outcome, and potential confounders

Close contacts were characterized by biological sex assigned at birth (male or female) to define the exposure of interest. No information was available on participants' self-reported gender. IGRA testing was performed with QuantiFERON 3rd or 4th generation assay at baseline evaluation and again at six months in case of negative or indeterminate results at baseline to define the outcome of interest. IGRA positivity was defined as a positive result at baseline or 6 months; IGRA indeterminate results were considered IGRA negative. For this study, index case data were limited to sex, X-ray characteristics, and degree of smear positivity (scanty, 1+, 2+, and 3+). Later in the study, groups of close contacts were also asked whether they slept in the same room or bed as the index case or had at least 5 hours of indoor exposure per day. Potential confounders of the exposure-outcome relationship were as follows: close contact baseline age in years, self-identified race, region of enrollment, education level, household income, body mass index, number of household members, and index case sex, smear positivity, and X-ray cavitary disease.

Data and statistical analysis

We used Chi-square and Wilcoxon Rank Sum tests to identify unadjusted differences between male and female close contacts for categorical and continuous variables, respectively. After multiply imputing variables with $>$10% missingness over 10 iterations, we performed unadjusted, bivariate-adjusted, and multivariable logistic regression modeling to obtain the odds ratios (OR) and 95% (CI) for IGRA positivity by sex. Variance inflation factors were utilized within multivariable models to determine the possible collinearity of included covariates. We assessed the outcome association for sex by adjusting for single confounders in bivariate analyses. In contrast, we adjusted for all confounders simultaneously in the multivariable analysis. We performed propensity-score-matched models utilizing all available confounders, with exposure weights constructed and assigned according to the methods of Li and Greene (Li and Greene, 2013). We conducted sensitivity analyses accounting for possible false-positive IGRA conversion utilizing known specificities of QuantiFERON 3rd and 4th generation tests (Takasaki *et al.*, 2018). Finally, we assessed for a potential sex difference in quantitative assay measurements (nil, mitogen, TB antigen tube 1 [TB1 antigen], and TB antigen tube 2 [TB2 antigen]) using unadjusted linear regression models stratified by IGRA positivity and clustered by participant. All analyses were conducted in R version 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria. https://www.R-project.org/).

Ethical conduct of research and role of funders

The study was approved by the Institutional Review Boards at all enrollment sites and Vanderbilt (CAAE: 25102412.3.1001.5262); all participants provided written informed consent before inclusion. Funding was obtained through the Brazilian Ministry of Health, Department of Science and Technology (DECIT), as well as the United States National Institutes of Health (NIH). Funders played no role in cleaning data, conducting analyses, or interpreting results.

Results

The source population included 1917 close contacts and 1181 index cases, of which there were 1840 close contacts of 601 culture-confirmed pulmonary TB index cases. Two close contacts were excluded because IGRA results were unavailable at baseline or 6 months. Of the 1838 remaining close contacts, 1093 (59%) were female and 745 (41%) were male. Female close contacts had a median age of 36 years (interquartile range [IQR]: 20, 50), compared with 26 years for males (IQR: 13, 42). Both female and male contacts had similar percentages in self-reported race categories: 19% vs 20% White, 21% vs 20% Black, and 59% vs 59% Pardo/Mixed, respectively. Very few close contacts identified as Asian, Indigenous, or unknown (1%). Female close contacts were more often living in Rio de Janeiro (38% vs 34%) or Salvador (19% vs 13%) and residing within a poor community (*favela*, 25% vs 20%) than males. Female close contacts had similar exposure to index case cavitary disease (53% vs 50%; P=0.40) and high smear positivity (3+: 29% vs 28%; P=0.24) than males. Furthermore, female close contacts described similar household exposure – sleeping in the same room (35% vs 31%; P=0.22) and sleeping in the same bed (19% vs 17%; P=0.58) – but more daily five-hour indoor exposure (87% vs 78%; P <0.001) than males. 46 participants were living with HIV, including 22 females (2%) and 24 males (3%); 13 participants living with HIV were IGRA positive (28%). Two participants had end-stage renal disease, eight were on chemotherapy, and 20 received immunosuppressive medications.

A total of 799 close contacts had a positive IGRA result, including 504 (46%) females and 295 (40%) males (Table 1). 433 (40%) female and 246 (33%) male close contacts were IGRA positive at baseline, with 71 (6%) female and 49 (7%) male close contacts IGRA positive at 6 months. IGRA-positive close contacts were older (median age 36 years [IQR: 18, 50]) in comparison to IGRA-negative close contacts (median age 29 years [IQR: 15, 44]). Black race (53%), Rio de Janeiro region (55%), Salvador region (52%), community settings (*favela*, 63%), and exposure to cavitary disease (54%) or high smear positivity (2+: 54%; 3+: 53%) resulted in high IGRA positivity. There were two pregnant female participants at the time of enrollment, one of whom had a positive IGRA result at baseline. See Supplemental Tables 1 and 2 for detailed close contact demographics and exposure characteristics.

The unadjusted odds of IGRA positivity were significantly higher for females compared with males (OR = 1.31; CI: 1.08-1.58). Sensitivity analyses accounting for possible false-positive IGRA results yielded the same unadjusted OR of 1.31 (CI: 1.09-1.59). Bivariate ORs for IGRA positivity, adjusted for single potential confounding factors, resulted in sex-specific effect estimates ranging from 1.19-1.33. Of these, only the bivariate OR adjusting for age had a CI including the null (OR=1.19; CI: 0.98-1.45) (Table 1).

After performing multiple imputations for household income, education level, and index case smear positivity, multivariable logistic regression yielded a sex-specific OR of 1.14 (CI: 0.92-1.41). Propensity-score-matched weighted regression within and across multiple imputed datasets found similar ORs of 1.15 (CI: 0.94-1.40) and 1.15 (CI: 0.94-1.40), respectively. The multivariable-adjusted OR and propensity-score-matched ORs had CIs that included the null. However, they all yielded effect estimates that remained in the same direction as the unadjusted and bivariate-adjusted models.

For IGRA-negative participants, Wilcoxon Rank Sums revealed slight differences in IGRA quantitative assay measurements between male and female sex (Table 2). This was not seen, however, for IGRA-positive participants. Univariate linear regression modeling demonstrated no differences in quantitative assay measurements by birth sex when stratified by IGRA positivity.

Discussion

For all analyses, the odds of LTBI acquisition (i.e., IGRA positivity) among female close contacts were higher than among males (Figure 1). Bivariate adjustments had a limited effect on the sex-specific effect size. Of these, only the adjustment for age resulted in a CI containing the null. Unweighted and weighted multivariable regression modeling resulted in more attenuated ORs, again with CIs containing the null. These findings suggest a small possible difference in sex-specific IGRA positivity within our close contact population.

If replicated in other settings, a sex difference in LTBI would be informative from a health equity standpoint. TB disease stigma persists in Brazil, with higher stigmatization paradoxically among those with knowledge of LTBI (Rebeiro *et al.*, 2020). Identifying and dismantling structural barriers that reinforce stigma can decrease the active TB disease burden – this can be achieved partly through early recognition, education, and treatment of LTBI. While there have been advances in sex and gender health equity in Brazil, there remains a divide in wages and labor force participation, resulting in downstream healthcare access disparities (Chant, 2006). Knowledge of LTBI risk in female close contacts can provide clinicians with the impetus for broader outreach and education within vulnerable populations.

Excess unadjusted LTBI acquisition was at least partially attributable to age, region, and income. Age is known to correlate with IGRA positivity and may indirectly represent the duration of exposure (Zelner *et al.*, 2014). The median age of our female cohort was 10 years older than that of the male cohort, with proportionately more female close contacts aged 25 years and older (Figure 2). Accordingly, female close contacts in all age groups were found to have slightly higher IGRA positivity rates compared to males. Region and household income are likely to be correlated with other factors such as unstable housing, lower health awareness, overcrowding, and air pollution in contributing to LTBI and active TB disease. We measured residence in rural, suburban, and community settings. However, given collinearity with other confounders, we did not include this in the multivariable model. Instead, we utilized the number of household members as this was thought to be a better proxy for overcrowding.

Behavioral factors that affect sex differences in active TB disease may play a role in LTBI. Women may be at increased risk for LTBI as they represent a growing percentage of the total workforce in Brazil (Bruschini, 2007). Furthermore, women spend more time performing indoor household tasks on a weekly basis (Bruschini, 2007), which could affect exposure dynamics for domestic close contacts. Female-headed households have increased over time within Brazil, with female single-parent families often remaining within the lowest income quintile (Gukovas *et al.*, 2016). The intersection between female sex and poverty has shown to be exceedingly complex (Chant, 2006), yet this may provide some explanation for LTBI risk, at least among female population subsets.

Physiologic mechanisms may be important in driving sex differences in LTBI among close contact populations. Macrophages are the primary targets of *Mycobacterium tuberculosis* upon inhalation into the lung, with multiple surface receptors to facilitate en-

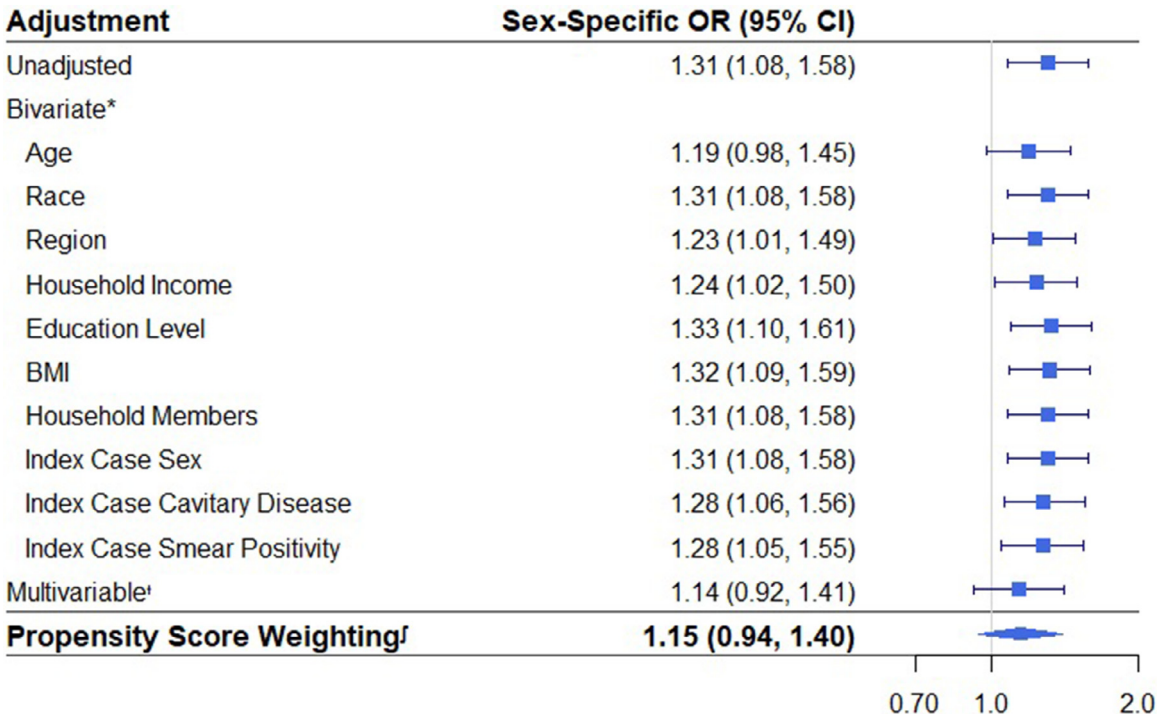

Figure 1. Forest plot for unadjusted, adjusted, and propensity-score weighted sex-specific IGRA positivity odds ratios among close contacts of an index pulmonary TB source case.
IGRA positivity was defined as a single positive QuantiFERON 3rd or 4th generation result at baseline or 6 months from enrollment. IGRA indeterminate results were considered IGRA-negative.
Abbreviations: BMI = body mass index; CI = confidence interval: IGRA = interferon-γ release assay; OR = odds ratio; TB = tuberculosis
*For bivariate-adjusted OR, IGRA positivity was adjusted for sex and the following factor. Multiple imputations were performed for household income, education level, and index case smear positivity before bivariate regression modeling.
†For multivariable-adjusted OR, IGRA positivity was adjusted for sex, age, region, race, household income, education level, BMI, household members, index case sex, index case cavitary disease, and index case smear positivity. Multiple imputations were performed for household income, education level, and index case smear positivity before multivariate regression modeling.
‡Multiple imputations were performed for all missing variables before propensity-score weighting with univariate regression modeling.

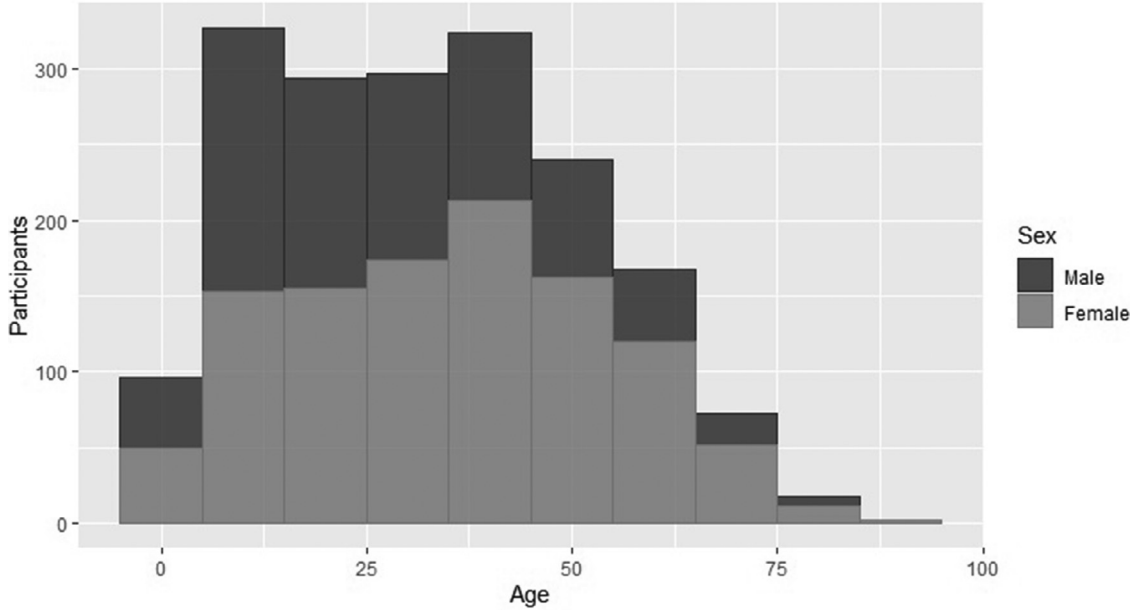

Figure 2. Histogram with number of close contacts by age and sex.
There were proportionately more female close contacts from age 25 and on, as compared with males.

Table 1
The association of female sex with IGRA positivity, accounting for various demographic, contextual, and clinical characteristics, among close contacts of an index pulmonary TB source case.

Factor	IGRA negative N(%) or median(IQR)[a]	IGRA positive N(%) or median(IQR)[a]	Unadjusted OR (95% CI)[b]	Sex-specific, bivariate adjusted OR (95% CI)[c]	Sex-specific, multivariable-adjusted OR (95% CI)[d]
Sex					
Male	450 (60)	295 (40)	Referent		
Female	589 (54)	504 (46)	1.31 (1.08-1.58)		1.14 (0.92-1.41)
Age	29 (15, 44)	36 (18, 50)	1.02 (1.01-1.02)	1.19 (0.98-1.45)	
Race				1.31 (1.08-1.58)	
White	227 (64)	130 (36)	Referent		
Black	173 (47)	199 (53)	2.01 (1.49-2.70)		
Asian	1 (20)	4 (80)	6.98 (0.77-63.25)		
Pardo/Mixed	629 (58)	460 (42)	1.28 (1.00-1.63)		
Indigenous	9 (64)	5 (36)	0.97 (0.32-2.96)		
Region				1.23 (1.01-1.49)	
Rio de Janeiro	301 (45)	371 (55)	Referent		
Manaus	590 (69)	270 (31)	0.37 (0.30-0.46)		
Salvador	145 (48)	156 (52)	0.87 (0.66-1.15)		
Household Income				1.24 (1.02-1.50)	
>Minimum	405 (60)	269 (40)	Referent		
<= Minimum	375 (52)	353 (48)	1.38 (1.13-1.69)		
Education Level				1.33 (1.10-1.61)	
Primary	425 (53)	380 (47)	Referent		
Secondary	299 (55)	240 (45)	0.90 (0.73-1.12)		
Higher	195 (64)	108 (36)	0.63 (0.48-0.83)		
BMI				1.32 (1.09-1.59)	
Normal Weight	473 (57)	355 (43)	Referent		
Underweight	48 (59)	34 (41)	0.94 (0.59-1.49)		
Overweight	277 (54)	232 (46)	1.12 (0.89-1.39)		
Obese	217 (56)	172 (44)	1.05 (0.82-1.34)		
Household Members[e]	3 (2, 5)	3 (2, 5)	0.98 (0.95-1.02)	1.31 (1.08-1.58)	
Index Case Sex				1.31 (1.08-1.58)	
Female	393 (56)	310 (44)	Referent		
Male	646 (57)	489 (43)	0.96 (0.79-1.16)		
Index Case				1.28 (1.06-1.56)	
Cavitary Disease					
No	424 (67)	211 (33)	Referent		
Yes	442 (46)	511 (54)	2.32 (1.89-2.86)		
Indeterminate	173 (69)	77 (31)	0.89 (0.65-1.22)		
Index Case Smear				1.28 (1.06-1.56)	
Positivity					
Scanty	124 (72)	49 (28)	Referent		
1+	322 (59)	222 (40)	1.63 (1.13-2.33)		
2+	163 (46)	192 (54)	2.79 (1.91-4.07)		
3+	203 (47)	230 (53)	2.81 (1.96-4.03)		

IGRA positivity was defined as a single positive QuantiFERON 3rd or 4th generation result at baseline or 6 months from enrollment. IGRA indeterminate results were considered IGRA-negative.
Abbreviations: BMI = body mass index; CI = confidence interval; IGRA = interferon-γ release assay; IQR = interquartile range; N = number; OR = odds ratio.
[a] Percentages are row percentages. Interquartile ranges denote the 25th and 75th percentiles.
[b] Unadjusted odds ratios were obtained for IGRA positivity and the following specified factor.
[c] For bivariate-adjusted odds ratios, IGRA positivity was adjusted for sex and the following specified factor.
[d] For multivariable-adjusted odds ratios, IGRA positivity was adjusted for sex, age, race, region, household income, education level, BMI, number of household members, index case sex, index case cavitary disease, and index case smear positivity.
[e] Number of members living in the same household, excluding the participating close contact.

try via phagocytosis (Glickman and Jacobs, 2001). At the same time, macrophages within females have enhanced phagocytic activity (Nhamoyebonde and Leslie, 2014). Once within phagosome vacuoles, *M. tuberculosis* alters compartmental characteristics for intracellular survival. This may not result in higher rates of active TB disease in females, as hormonal exertion of various proapoptotic effects counteracts mycobacterial proliferation. However, sex differences in macrophage activation could contribute to higher initial mycobacterial uptake among female close contacts.

There were limitations to our study. We could not provide detailed commentary on *M. tuberculosis* transmission dynamics. We did not assess the impact of multiple index cases or whether there were social or occupational exposures, nor did we have information on the total duration of exposure, of which 250 hours may predict risk for LTBI (Reichler *et al.*, 2020). Nevertheless, we obtained information on exposure via chest X-ray findings and smear positivity results that could only be ascertained with a parallel enrollment of index cases and close contacts, a strength of this cohort. Furthermore, 5 -hour daily indoor exposure was likely a strong proxy for the total duration of exposure, as this represented high average exposure in the 6 months preceding index case diagnosis.

Our second limitation was that IGRA testing remains a surrogate marker for LTBI, measuring disease via immune reactivity. Individuals with immunodeficiency are more likely to test falsely negative or indeterminate. Only small subsets of our population had end-stage renal disease, HIV, or the use of chemotherapy or immunosuppressive medications; due to their effects on model fit,

Table 2
Close contact IGRA quantitative assay measurements by sex and participant IGRA positivity.

	Male median (IQR)[a]	Female median (IQR) [a]	Wilcoxon *P*-value	Beta Coefficient (SE)	Beta *P*-value
IGRA Negative (N)	818	1,076			
QFT Nil	0.05 (0.02, 0.08)	0.05 (0.03, 0.1)	0.003	0.006 (0.029)	0.842
QFT Mitogen	10 (7.07, 10)	10 (7.11, 10)	0.783	-0.029 (0.139)	0.833
QFT TB1	0.05 (0.03, 0.12)	0.07 (0.04, 0.14)	<0.001	0.02 (0.022)	0.382
QFT TB2	0.05 (0.02, 0.11)	0.07 (0.03, 0.13)	<0.001	0.028 (0.027)	0.308
IGRA Positive (N)	347	578			
QFT Nil	0.06 (0.03, 0.14)	0.07 (0.04, 0.15)	0.073	0.033 (0.038)	0.383
QFT Mitogen	10 (7.71, 10)	10 (8.22, 10)	0.457	-0.02 (0.157)	0.897
QFT TB1	1.28 (0.5, 4.38)	1.51 (0.6, 4.45)	0.398	0.215 (0.213)	0.313
QFT TB2	1.09 (0.46, 3.31)	1.32 (0.56, 3.64)	0.268	0.329 (0.23)	0.153

IGRA positivity was defined as a single positive QuantiFERON 3rd or 4th generation result at baseline or 6 months from enrollment. IGRA indeterminate results were considered IGRA-negative. Among 1039 IGRA-negative participants, there were 1894 IGRA results: 1853 negative and 41 indeterminate. Among 799 IGRA-positive participants, there were 925 IGRA results: 114 negative, seven indeterminate, and 804 positives. Quantitative assay measurements were clustered by participants to account for repeat testing. Wilcoxon Rank Sums and univariate linear regression models were performed to assess for a possible sex difference in quantitative assay measurements for IGRA-negative and positive groups.
Abbreviations: IGRA = interferon-γ release assay; IQR = interquartile range; QFT = QuantiFERON; N = number; SE = standard error; TB1 = TB antigen tube 1 (CD4 response); TB2 = TB antigen tube 2 (CD4 and CD8 response).
[a] Interquartile ranges denote the 25th and 75th percentiles.

none of these variables were included in our regression analyses. False-positive results were likely uncommon because all close contacts had culture-confirmed pulmonary TB exposure. This was reflected in our sensitivity analysis to account for false-positive testing, which did not alter our results. Although not described in the literature, IGRA reactivity could theoretically differ between male and female individuals – mouse models have shown a more robust T_h1 response with increased interferon-γ production in the presence of estradiol (Klein and Flanagan, 2016). An inverse relationship may occur following testosterone exposure, with lower levels of interferon-γ secretion in natural killer cells of female-treated mice. In our cohort, there were slightly higher quantitative assay measurements among female populations compared with males, with significant Wilcoxon Rank Sums for nil, TB1 antigen, and TB2 antigen by sex among IGRA-negative participants. Even though no linear relationships were found between IGRA quantification and sex, future studies would help to tease out subtle differences.

Our last limitation involved losses across the cascade of care, which have been reported previously (Souza *et al.*, 2021). This included attrition from initial outreach to informed consent, baseline and follow-up evaluations, and treatment start and completion. We could not assess whether the individuals who did not participate in our study differed significantly from those who enrolled. This could have led to sampling or selection biases, although less likely as we identified all new TB diagnoses for each site for enrollment over the study period.

Our findings suggest a possible sex difference in LTBI among close contacts in Brazil. Effect estimates were consistent across multiple analyses, although adjusted and weighted regression models resulted in attenuated sex-specific associations with IGRA positivity. If these findings are confirmed in other study populations, an investigation of underlying socio-behavioral and biological mechanisms to explain apparent sex disparities would be warranted.

Ethical approval statement

The study was approved by the Institutional Review Boards at all enrollment sites and at Vanderbilt (CAAE: 25102412.3.1001.5262); all participants provided written informed consent before inclusion. Funding was obtained through the Brazilian Ministry of Health, Department of Science and Technology (DECIT), as well as the United States National Institutes of Health (NIH). Funders played no role in cleaning data, conducting analyses, or interpreting results.

Author Contributions

PYW, PFR, and TRS conceptualized the research question. PYW, PFR, and TRS made substantial contributions to data analysis and interpretation. AGC, MAP, BBD, ABS, MSR, MCF, MMT, VCR, ALK, MCS, and BBA were responsible for data acquisition. All authors contributed important intellectual content to subsequent revisions of the manuscript and approved the final version to be published.

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Declaration of Competing Interest

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Supplementary materials

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