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MAJOR ARTICLE

The Impact of Diabetes and Prediabetes on Prevalence of *Mycobacterium tuberculosis* Infection Among Household Contacts of Active Tuberculosis Cases in Ethiopia

Alison G. C. Smith,[1] Russell R. Kempker,[2] Liya Wassie,[3] Kidist Bobosha,[3] Azhar Nizam,[4] Neel R. Gandhi,[2,5,6] Sara C. Auld,[5,7] Matthew J. Magee,[2,4,6] and Henry M. Blumberg,[2,5] for the Tuberculosis Research Unit: Role of Antigen Specific Responses in the Control of TB (TBRU-ASTRa) Study Group

[1]Emory University School of Medicine, Atlanta, Georgia, USA, [2]Division of Infectious Diseases, Department of Medicine, Emory University School of Medicine, Atlanta, Georgia, USA, [3]Mycobacterial Disease Research Directorate, Armauer Hansen Research Institute, Addis Ababa, Ethiopia, [4]Department of Biostatistics and Bioinformatics, Emory University Rollins School of Public Health, Atlanta, Georgia, USA, [5]Department of Global Health, Emory University Rollins School of Public Health, Atlanta, Georgia, USA, [6]Department of Epidemiology, Emory University Rollins School of Public Health, Atlanta, Georgia, USA, and [7]Division of Pulmonary and Critical Care Medicine, Department of Medicine, Emory University School of Medicine, Atlanta, Georgia, USA

Background. It is uncertain whether diabetes affects the risk of developing latent tuberculosis infection (LTBI) following exposure to *Mycobacterium tuberculosis* (*Mtb*). We assessed the relationship of diabetes or prediabetes and LTBI among close and household contacts (HHCs) of patients with active pulmonary tuberculosis (TB) disease in Addis Ababa, Ethiopia.

Methods. In this cross-sectional study, we performed interferon-γ release assays, TB symptom screening, and point-of-care glycolated hemoglobin (HbA1c) testing among HHCs of active TB cases. Diabetes status was classified into diabetes (HbA1c ≥6.5% or self-reported diagnosis), prediabetes (5.7%–6.4%), and euglycemia (≤5.6%). Multivariable logistic regression was used to determine the association of diabetes with LTBI.

Results. Among 597 study participants, 123 (21%) had dysglycemia including diabetes (n = 31) or prediabetes (n = 92); 423 (71%) participants were diagnosed with LTBI. Twelve of 31 (39%) HHCs with diabetes were previously undiagnosed with diabetes. The prevalence of LTBI among HHCs with diabetes, prediabetes, and euglycemia was 87% (27/31), 73% (67/92), and 69% (329/474), respectively. In multivariable analysis adjusted for age, sex, and HIV status, the odds of LTBI among HHCs with diabetes were 2.33 (95% confidence interval [CI], .76–7.08) times the odds of LTBI without diabetes. When assessing interaction with age, the association of diabetes and LTBI was robust among participants aged ≥40 years (adjusted odds ratio [aOR], 3.68 [95% CI, .77–17.6]) but not those <40 years (aOR, 1.15 [95% CI, .22–6.1]).

Conclusions. HHCs with diabetes may be more likely to have LTBI than those with euglycemia. Further investigations are needed to assess mechanisms by which diabetes may increase risk of LTBI after *Mtb* exposure.

Tuberculosis (TB) is an immense global public health problem and was the leading cause of infectious disease mortality worldwide prior to the coronavirus disease 2019 (COVID-19) pandemic [1]. The global prevalence of latent tuberculosis infection (LTBI) is estimated to be approximately 25% [2], and an improved understanding of the risk factors associated with LTBI is fundamental to improving global TB control [3]. An association between diabetes mellitus and active TB disease has long been recognized in epidemiologic studies [4–7], and diabetes is associated with dysfunction of both innate and adaptive immune responses involved in both the initial immune response and subsequent control of *Mycobacterium tuberculosis* (*Mtb*) [8, 9]. Diabetes increases the risk of active TB disease by 3-fold [5], and an estimated 15%–25% of active TB cases worldwide are attributable to diabetes [10, 11]. The prevalence of diabetes is increasing rapidly in Asia, sub-Saharan Africa, and other low- and middle-income countries (LMICs) [12], regions that also bear the highest burden of TB disease. The expanding epidemic of diabetes in LMICs is one of several challenges to meeting the ambitious goals of the World Health Organization (WHO) End TB Strategy [1, 10, 13, 14], making improved understanding of the relationship between LTBI and diabetes a global health research priority.

While emerging data have provided insights into the relationship between diabetes and active TB, much less is understood about the association between dysglycemia and LTBI. Importantly, it is not known whether the presence of dysglycemia (diabetes or prediabetes) increases the risk of *Mtb* infection and development of LTBI after exposure. Additionally, there are

Received 29 April 2022; editorial decision 21 June 2022; accepted 28 June 2022; published online 30 June 2022

Correspondence: Alison G. C. Smith, MD, MSc, Emory University School of Medicine, 201 Dowman Drive, Atlanta, GA 30322, USA (alison.smith@emory.edu).

Open Forum Infectious Diseases®

https://doi.org/10.1093/ofid/ofac323

substantial gaps in knowledge of whether diabetes and prediabetes may impair an effective immune response to *Mtb* [8, 15].

Studying close and household contacts (HHCs) of patients with TB disease provides an opportunity to assess the risk of LTBI among a high-risk group with recent TB exposure. To date, there are very limited data on the relationship between diabetes and LTBI among close contacts of active TB cases, especially in LMICs [16, 17]. We leveraged an ongoing National Institutes of Health–supported Tuberculosis Research Unit (TBRU) study, TBRU-Role of Antigen Specific T Cell Responses in the Control of TB (TBRU-ASTRa) that has enrolled a cohort of the HHCs of active pulmonary TB cases in Addis Ababa, Ethiopia, and analyzed cross-sectional data collected from HHCs at time of study enrollment. The goal of our study was to assess whether there is an increased prevalence of LTBI among HHCs with diabetes and prediabetes.

METHODS

Study Design

HHCs of newly diagnosed active pulmonary TB disease index cases were identified through ongoing public health surveillance at selected community health facilities in the 10 subcities of Addis Ababa, Ethiopia. Pulmonary TB in index active TB cases was confirmed by positive acid-fast bacilli (AFB) sputum smear or positive nucleic acid amplification test result (Xpert MTB/RIF; Cepheid, Sunnyvale, California). The HHCs identified were referred to our study staff for potential study enrollment. Demographic and medical history data were collected. Interferon-γ release assay (IGRA), human immunodeficiency virus (HIV) rapid antibody testing, and glycolated hemoglobin (HbA1c) screening were performed at the time of study enrollment.

Participants

Eligible participants included all HHCs of active TB cases who had a valid IGRA result (performed at the time of study enrollment) and an HbA1c result at time of enrollment (or within 12 months of enrollment). HHCs of active TB cases were defined as (1) persons who shared the same home residence as the index case for ≥5 nights during the 30 days prior to the date of TB diagnosis in the index case; or (2) persons who shared the same indoor living or working space as the index case ≥5 hours per day for ≥5 days during the 30 days prior to the index case's TB diagnosis. Exclusion criteria included HHCs <15 years of age; hemoglobin level <7 g/dL; positive screen for active TB disease (detailed below); a prior history of TB disease or TB treatment; pregnant; taking immunosuppressive medications (equivalent to prednisone ≥15 mg/day) within 30 days of screening; and, among HIV-seronegative patients, a history of isoniazid preventive therapy or other treatment for LTBI. HHCs were screened for active TB by history of TB-related symptoms (ie, cough, fever, night sweats, and/or weight loss). Participants with symptoms consistent with active TB received a chest radiograph and had 2 sputum samples collected for AFB smear microscopy, AFB culture, and TB polymerase chain reaction (Xpert MTB/RIF assay) to rule out active TB disease.

Measures and Definitions

The primary exposure was diabetes status, determined by a point-of-care capillary HbA1c (Siemens, Malvern, Pennsylvania) and classified according to the American Diabetes Association guidelines: euglycemia (≤5.6%), prediabetes (5.7%–6.4%), and diabetes (≥6.5%) [18]. Participants self-reporting a history of diabetes diagnosis were also defined as having diabetes regardless of HbA1c result.

The primary outcome was LTBI status at study enrollment. Prevalent LTBI was defined by a positive IGRA and a lack of symptoms suggestive of active TB. QuantiFERON-TB Gold Plus (QFT; Qiagen, Germantown, Maryland) was the IGRA utilized for this study and was performed as previously described [19, 20]. The QFT was considered positive if either TB1 minus Nil or TB2 minus Nil was. ≥0.35 IU/mL interferon-γ or ≥25% of the Nil value (based on manufacturer's recommendations). Self-reported demographic and medical history information was collected and HIV rapid antibody testing (Chembio Diagnostic Systems, Hauppauge, New York) was performed. Weight and height measurements at time of study enrollment were used to calculate body mass index (BMI), and participants were categorized as underweight (BMI <18.5 kg/m^2), normal weight (BMI 18.5–24.9 kg/m^2), overweight (BMI 25.0–29.9 kg/m^2), or obese (BMI ≥30.0 kg/m^2).

Statistical Methods

Associations between participant characteristics and prevalence of LTBI were assessed with χ^2 or Fisher exact test for categorical variables and Wilcoxon or Kruskal-Wallis test for nonnormally distributed continuous variables. Multivariable logistic models were used to estimate the adjusted association between participants' diabetes status (categorized into a 3-level variable: no diabetes, prediabetes, and diabetes) and LTBI status. Iterations of multivariable models included adjustment for age, sex, and HIV status as potential confounders. Wald 95% confidence intervals (CIs) were used for all logistic regression models. Covariates included in the multivariable models were chosen based on directed acyclic graph theory [21] (Supplementary Figure 1). We also considered interaction with age in the association between diabetes and LTBI, performing alternative logistic regression models that included product terms between age (as a dichotomous variable, <40 or ≥40 years) and diabetes status. Additional multivariable models performed as sensitivity analyses included (1) treating diabetes as a 2-category variable grouping together participants with prediabetes and euglycemia, and (2) utilizing only baseline HbA1c results to classify participants' diabetes status, such that

individuals who self-reported a diagnosis of diabetes and had HbA1c measurements <6.5% were recategorized as having either prediabetes or no diabetes. We considered an association significant if P value was < .05 or if the 95% CI excluded the null value (0 for prevalence ratios and 1 for odds ratios [ORs]). Analyses were performed using R 4.0.2 [22] and SAS version 9.4 (SAS Institute, Cary, North Carolina) software.

Patient Consent Statement

All participants provided written informed consent. The study was approved by the institutional review boards at Emory University, the Armauer Hansen Research Institute, and the National Research Ethics Review Committee of Ethiopia.

RESULTS

Among the HHCs of active pulmonary TB cases identified at selected collaborating health centers in Addis Ababa, 857 provisionally eligible contacts were contacted and agreed to participate in screening. Following screening, 693 HHCs of active pulmonary TB cases consented and enrolled in the study, and 597 HHCs met study inclusion criteria for this analysis (Figure 1). Of these, 528 (88.4%) participants had their first HbA1c measurement completed on the same day as the IGRA. Among the 597 HHCs, 357 (60%) were female, the median age was 28.5 years (interquartile range [IQR], 22.6–37.6 years), median BMI was 21.0 kg/m^2 (IQR, 19.0–24.2 kg/m^2), and 20 (3.4%) were HIV seropositive. Based on IGRA testing and lack of symptoms suggestive of TB, 423 (71%) HHC participants had LTBI (Table 1). HHCs were highly exposed to active TB cases, with 168 (28%) sleeping in the same bed as their index case and an additional 217 (36%) sleeping in the same room (Table 2). Additional demographic data are shown in Tables 1 and 2.

Distribution of Diabetes Mellitus and Prediabetes Among Participants

Among 597 HHC participants, 31 (5.2%) had diabetes, 92 (15%) had prediabetes, and 474 (79%) were euglycemic at time of study enrollment. Median HbA1c measurements among those with prediabetes and diabetes was 5.8% (IQR, 5.7%–6.0%; Table 1), and 10 (32.2%) participants with diabetes had uncontrolled diabetes (defined as HbA1c measurement >8.0%). Median BMI was higher among those with prediabetes (23.3 kg/m^2) and diabetes (26.1 kg/m^2) compared to those with euglycemia (20.5 kg/m^2) (P < .01; Table 1). Participants with prediabetes or diabetes were older than those without diabetes (median ages 44.6, 37.7, and 28.5 years, P < .01; Table 2). Among the 31 HHC participants with diabetes, 19 (61%) had previously been diagnosed with diabetes, while the remaining 12 (39%) were unaware of their diabetes status at the time of study enrollment. Twenty-eight of 31 (90%) participants with diabetes had a HbA1c measurement of ≥6.5% and 3 participants with self-reported diabetes diagnoses had HbA1c <6.5% at study enrollment. Among all HHCs with diabetes, 11 (33%) were receiving metformin, 4 (13%) were receiving sulfonylurea, and 2 (11%) reported insulin use (Supplementary Table 1).

Latent Tuberculosis Infection

Four hundred twenty-three of 598 (71%) HHC study participants had LTBI. The median age of participants with LTBI (30.2 years [IQR, 23.6–38.8 years]) was older than the median age of those without LTBI (24.7 years [IQR, 19.8–34.5 years]) (P < .01). Median BMI was also higher among participants with LTBI (21.4 kg/m^2 [IQR, 19.0–24.5 kg/m^2]) compared to those without LTBI (20.5 kg/m^2 [IQR, 18.8–22.9 kg/m^2]) (P < .01). The prevalence of LTBI did not substantially differ by sex, ethnic group, or HIV status (Table 2).

Association of Diabetes and LTBI

The prevalence of LTBI was significantly higher among persons with diabetes (86.7%) compared to those with euglycemia (69.4%), with a prevalence difference of 17.7% (95% CI, 5.2%–30.2%, P < .01; OR, 2.97 [95% CI, 1.14–10.2], P = .04; Table 2). Prevalence of LTBI did not significantly differ between those with prediabetes (69.6%) and euglycemia (69.4%, P = .50).

In multivariable analysis adjusted for age, sex, and HIV status (model 1, Table 3), those with diabetes had an increased but not statistically significant odds of LTBI as compared to those without diabetes (adjusted OR [aOR], 2.33 [95% CI, .76–7.08]). In a multivariable analysis of LTBI prevalence by per-unit change in HbA1c, the adjusted odds of LTBI increased by 1.13 times (95% CI, .88–1.58, P = .05) per 1% increase in HbA1c. Additional multivariable models and prevalence difference information are shown in Supplementary Tables 2 and 3, respectively.

Interaction of Age and Diabetes Status With Prevalence of LTBI

The association of diabetes and LTBI was pronounced among participants aged ≥40. years (diabetes vs no diabetes prevalence difference, 16.7% [95% CI, 1.1%–32.2%], P = .04) compared to those aged <40 years (prevalence difference 2.8% [95% CI, −84.6% to 54.4%], P = .87). In the multivariable logistic model assessing statistical interaction with age, the association between diabetes and adjusted odds of LTBI was robust among participants ≥40 years of age (aOR, 3.68 [95%, CI, .77–17.6]) but not among those <40 years of age (aOR, 1.15 [95% CI, .22–6.1]). The assessment of statistical interaction in the adjusted logistic model was not significant (likelihood ratio test of models with vs without interaction terms, P = .55).

DISCUSSION

In this study of HHCs of active TB cases in Addis Ababa, Ethiopia, we found a high prevalence of LTBI (>70%) and

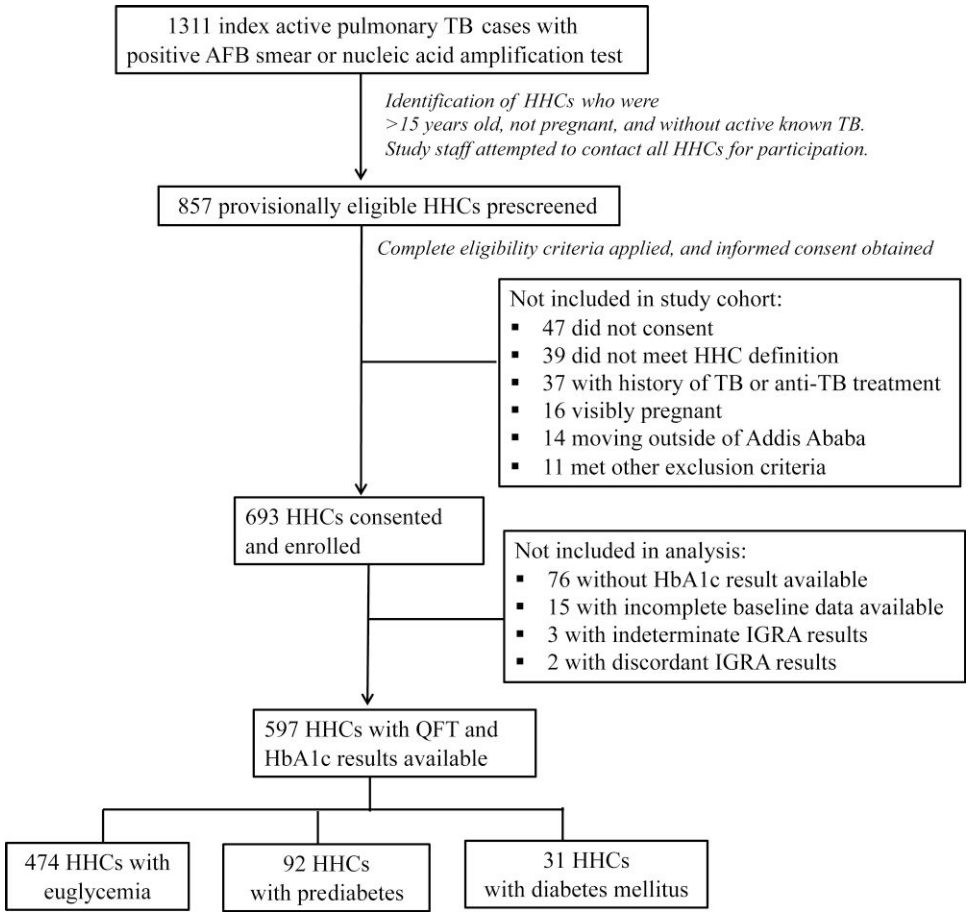

Figure 1. Study flow diagram illustrating selection of participants among the close and household contacts of active pulmonary tuberculosis cases in Addis Ababa, Ethiopia, 2018–2021. Abbreviations: AFB, acid-fast bacilli; HbA1c, glycated hemoglobin; HHC, close and household contact; IGRA, interferon-γ release assay; QFT, QuantiFERON-TB Gold Plus; TB, tuberculosis.

determined that HHCs with diabetes had a significantly higher prevalence of LTBI compared to those with euglycemia. The increased prevalence of LTBI among HHCs with diabetes was not significant after adjustment for age, sex, and HIV status, suggesting that these key demographic factors may confound the observed association of diabetes and LTBI infection. Our data also suggest that the association between diabetes and LTBI may differ by age group. When assessing interaction with age, we found a strong association between diabetes and LTBI prevalence among those ≥40 years old and almost no association among those <40 years old. Our results indicate that the effect of diabetes on LTBI prevalence may only become apparent in older age groups who are at elevated risk of diabetes. These results also underscore the need to prioritize testing for LTBI among high-risk groups including those with diabetes and known exposure to active TB disease.

This study is the first to our knowledge to examine an association of prediabetes and diabetes with LTBI in sub-Saharan Africa, and our results suggest that an association of diabetes and LTBI may be present in this highly exposed population. We also found that a substantial proportion of study participants with diabetes (38%) were previously unaware of their diabetes diagnosis, highlighting the importance of increasing availability of HbA1c screening globally [23]. Recently updated WHO LTBI guidelines emphasize the importance of diagnosing and treating LTBI in high-risk populations worldwide including LMIC settings [3]. Our findings highlight how the use of surveillance data has the potential to focus future efforts on the treatment of LTBI among high-risk groups, in this case the HHCs of active TB cases.

When assessing whether an interaction with age modified the association between diabetes and LTBI prevalence, we found that the odds of LTBI among those with diabetes were >3 times those without diabetes in the HHCs who were ≥40 years old. However, among those <40 years old, the odds of LTBI were nearly the same among those with and without diabetes. Because our results come from a study population with a relatively narrow age group (IQR, 22.6–37.6 years), it is more

Table 1. Prevalence of Diabetes and Prediabetes Among Household Contacts in Addis Ababa, Ethiopia, 2018–2021

Characteristic	Overall (N = 597)	Euglycemic (n = 474 [79.4%])	Prediabetes (n = 92 [15.4%])	Diabetes (n = 31 [5.2%])	Prediabetes vs Euglycemic: *P* Value[a]	Diabetes vs Euglycemic: *P* Value[a]
Age, y						
Median (IQR)	28.5 (22.6–37.6)	26.0 (22.2–34.2)	37.7 (27.0–48.1)	44.6 (40.3–50.4)	**<.01**	**<.01**
<40	474 (79)	414 (87)	53 (11)	7 (1.5)	**<.01**	**<.01**
≥40	123 (21)	60 (49)	39 (32)	24 (20)	**<.01**	**<.01**
Sex (male)	240 (40)	201 (84)	28 (12)	11 (4.6)	**.04**	.66
Ethnic group[b]						
Oromo	115 (19)	93 (81)	18 (16)	4 (3.5)	.67	.39
Amhara	193 (32)	154 (80)	28 (15)	11 (6)		
Tigraway	22 (3.7)	15 (68)	5 (23)	2 (9)		
Sidama	10 (1.8)	10 (100)	0 (0.0)	0 (0.0)		
HIV positive	20 (3.4)	16 (80)	1 (5.0)	3 (15)	.33	.10
BMI, kg/m^2, median (IQR)	21.0 (19.0–24.2)	20.5 (18.8–23.0)	23.3 (19.9–26.9)	26.1 (23.7–30.4)	**<.01**	**<.01**
BMI category						
Underweight (<18.5 kg/m^2)	119 (20)	103 (87)	15 (13)	1 (0.8)	**<.01**	**<.01**
Normal weight (18.5–24.9 kg/m^2)	367 (62)	315 (85)	41 (1)	11 (3.0)		
Overweight (25.0–30.0 kg/m^2)	85 (14)	47 (55)	27 (32)	11 (13)		
Obese (>30.0 kg/m^2)	26 (4.4)	9 (35)	9 (35)	8 (31)		
Tobacco smoker	41 (6.9)	30 (73)	8 (20)	3 (7.3)	.55	.45
Ever been in prison	29 (4.9)	25 (86)	4 (14)	0 (0.0)	>.99	.39
Alcohol consumption in past 6 mo	234 (39)	191 (80)	33 (14)	10 (4.3)	.50	.49
Received the BCG vaccine	279 (47)	224 (80)	39 (14)	16 (4.2)	.43	.66
Ever a healthcare worker	22 (3.7)	13 (59)	7 (32)	2 (9.1)	**.03**	.23
LTBI[c]	423 (71)	329 (78)	67 (16)	27 (6.4)	.60	.06

Data are presented as No. (%) unless otherwise indicated. Bold indicates statistical significance ($P < .05$).

Abbreviations: BMI, body mass index; HIV, human immunodeficiency virus; IQR, interquartile range; LTBI, latent tuberculosis infection.

[a]Statistical tests performed: Wilcoxon rank-sum test of medians, and χ^2 or Fisher exact test for categorical comparisons.

[b]Ethnicity information not available for 257 (43.0%) participants; 209 (35.0%) reported their ethnicity as "Other" and 48 (8.0%) declined to answer the question.

[c]LTBI defined as positive interferon-γ release assay (QuantiFERON Gold+) and negative symptom screen for active tuberculosis infection.

likely that age is modifying the association between diabetes and LTBI rather than confounding it. However, definitive conclusions about how age impacts the association of diabetes and LTBI cannot be determined from this study given it was underpowered to assess interaction with age. Additional work is needed to understand how diabetes impacts LTBI risk across the lifespan and whether repeated or prolonged exposure to LTBI also influences this relationship.

Our finding of higher prevalence of LTBI among participants with diabetes is consistent with emerging literature on the association of diabetes and LTBI in the general population. In a meta-analysis that pooled the aORs from 13 observational studies, a modest increase in the odds of LTBI (OR, 1.18 [95% CI, 1.06–1.30]) was found among patients with diabetes despite the fact that only 2 included studies yielded a significant increase in the adjusted odds of LTBI among patients with diabetes [24]. A number of these prior studies may have not been adequately powered to detect a modest increased risk of LTBI in patients with diabetes, particularly when accounting for variation in LTBI prevalence by age, sex, and other key demographic characteristics. Most early studies of the association of LTBI and diabetes were limited by a reliance on self-reported diabetes diagnosis, which is known to lead to substantial underreporting [23, 24]. Recent evidence from 2 studies in the United States utilizing National Health and Nutrition Examination Survey (NHANES) data also indicates that patients with diabetes may have increased susceptibility to TB infection (aOR, 1.90 [95% CI, 1.15–3.14]) and suggests a dose-response relationship between glycemic control and risk of TB infection [25, 26].

Importantly, our study's focus on the HHCs of active TB cases enabled us to examine the effect of hyperglycemia on LTBI risk following known recent exposure to *Mtb*. There is very limited evidence to date on the association of dysglycemia and LTBI among HHCs. One recent study conducted in Brazil found that the HHCs of persons with pulmonary TB and dysglycemia were more likely to have LTBI at baseline and 6-month follow-up than the contacts of pulmonary TB patients who were euglycemic [17]. However, this study measured HbA1c in the index pulmonary TB patients but did not investigate the association of dysglycemia in the close contacts with LTBI incidence in this cohort [17]. The only other study to examine the association of diabetes and LTBI in a highly exposed

Table 2. Summary of Household Contact Characteristics Stratified by Interferon-γ Release Assay Result

Characteristic	Overall (N = 597)	Without LTBI (n = 174 [29.1%])	With LTBI (n = 423 [70.9%])	Prevalence Difference, % (95% CI)
Diabetes status				
Euglycemic	474 (79.4)	145 (30.6)	329 (69.4)	Ref
Prediabetes	92 (19.4)	25 (26.1)	67 (72.8)	3.4 (–6.6 to 13.4)
Diabetes[a]	31 (5.2)	4 (13.3)	27 (87.1)	17.7 (5.2–30.2)*
HbA1c, median (IQR)	5.4 (5.1–5.6)	5.3 (5.1–5.5)	5.4 (5.1–5.6)	*P* = .37
Age, y				
Median (IQR)	28.5 (22.6–37.6)	24.7 (19.8–34.5)	30.2 (23.6–38.8)	*P* < .01*
<40	474 (79.4)	147 (31.0)	327 (69.0)	Ref
≥40	123 (20.6)	27 (22.0)	96 (78.0)	9.6 (.1–17.5)*
Sex				
Female	357 (59.8)	113 (31.7)	244 (68.3)	Ref
Male	240 (40.2)	61 (25.4)	179 (74.6)	6.2 (–1.1 to 13.6)
Ethnic group[b]				
Amhara	193 (32.3)	59 (30.6)	134 (68.3)	Ref
Oromo	115 (19.3)	33 (28.7)	82 (71.3)	1.9 (–8.6 to 12.4)
Tigraway	22 (3.7)	4 (18.2)	18 (81.8)	12.4 (–5.0 to 29.8)
Sidama	10 (1.7)	2 (20.0)	8 (80.0)	10.6 (–15.1 to 36.2)
HIV test result				
Negative	577 (96.6)	169 (29.3)	408 (70.7)	Ref
Positive	20 (3.3)	5 (25.0)	15 (75.0)	4.3 (–15.0 to 23.6)
BMI, kg/m^2, median (IQR)	21.0 (19.0–24.2)	20.5 (18.6–22.9)	21.4 (19.0–24.5)	*P* < .01*
BMI category				
Underweight (<18.5 kg/m^2)	119 (19.9)	43 (36.1)	76 (63.9)	–6.4 (–16.3 to 3.4)
Normal weight (18.5–24.9 kg/m^2)	367 (61.5)	109 (29.7)	258 (70.3)	Ref
Overweight (25.0–30.0 kg/m^2)	85 (14.2)	17 (20.0)	68 (80.0)	9.7 (.0–19.4)
Obese (>30.0 kg/m^2)	26 (4.4)	5 (19.2)	21 (80.8)	10.5 (–5.4 to 26.3)
Tobacco smoker				
No	556 (93.3)	164 (28.9)	392 (70.5)	Ref
Yes	41 (6.9)	10 (24.4)	31 (75.6)	5.1 (–8.6 to 18.8)
Ever been in prison				
No	568 (95.1)	164 (31.0)	404 (71.1)	Ref
Yes	29 (4.9)	10 (34.5)	19 (65.5)	–5.6 (–23.3 to 12.1)
Alcohol consumption (past 6 mo)				
No	363 (60.8)	111 (30.6)	252 (69.4)	Ref
Yes	234 (39.2)	63 (26.9)	171 (73.1)	3.7 (–3.7 to 11.1)
Received the BCG vaccine				
No or unsure	318 (53.3)	99 (31.1)	219 (68.9)	Ref
Yes	279 (46.7)	75 (26.9)	204 (73.1)	4.3 (–3.0 to 11.6)
Ever a healthcare worker				
No	575 (96.3)	170 (29.6)	405 (70.4)	Ref
Yes	22 (3.7)	4 (18.2)	18 (81.8)	11.4 (–5.2 to 27.9)
Extent of HHC participant's exposure to active TB index cases				
Household members with active TB within past 3 mo				
1 with active TB	588 (98.5)	172 (29.3)	416 (70.7)	Ref
2 with active TB	2 (0.3)	0 (0.0)	2 (100.0)	29.3 (25.6–32.9)*
None (exposure at workplace)	7 (1.2)	2 (28.6)	5 (71.4)	0.6 (–33.0 to 34.3)
Sleeping arrangement with the index case[c]				
Same bed	168 (28.1)	45 (26.8)	123 (73.2)	Ref
Other bed in same room	217 (36.3)	58 (26.7)	159 (73.3)	–0.0 (–8.9 to 9.0)
Other room in same building	156 (26.1)	57 (36.5)	99 (63.5)	–10.2 (–20.2 to .0)*
Other building in household	40 (6.7)	12 (30.0)	28 (70.0)	–3.2 (–18.9 to 12.5)
Ever workplace exposure to active TB				
No	586 (98.0)	170 (29.4)	416 (70.6)	Ref
Yes	11 (1.8)	4 (36.4)	7 (63.6)	–7.4 (–36.0 to 21.3)

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: BMI, body mass index; CI, confidence interval; HbA1c, glycated hemoglobin; HHC, close and household contact; HIV, human immunodeficiency virus; IQR, interquartile range; LTBI, latent tuberculosis infection; Ref, reference group; TB, tuberculosis.

[a]Three participants were determined to have diabetes based solely on self-reported diagnosis (with HbA1c <6.5), while the remainder had HbA1c ≥6.5 at time of study enrollment.

[b]Ethnicity information not available for 257 (43.0%) participants; 209 (35.0%) reported their ethnicity as "Other" and 48 (8.0%) declined to answer the question.

[c]"During the 30 days before the index case started treatment for TB, how close did you sleep with the index case?"

*Indicates that the prevalence difference or statistical test comparing median values was statistically significant (*P* < .05). Prevalence difference is defined as the difference between the prevalence of LTBI among participants in the comparison group for a characteristic and the prevalence of LTBI among participants in the reference group for that characteristic. Statistical tests performed for comparison of medians: Kruskal-Wallis test, Wilcoxon rank-sum test.

Table 3. Multivariable Models for Risk of Latent Tuberculosis Infection Stratified by Diabetes Group Among the Close and Household Contacts of Active Pulmonary Tuberculosis Cases in Addis Ababa, Ethiopia

Characteristic	LTBI Prevalence, no./No. (%)	Unadjusted OR (95% CI)	Adjusted OR[a] (95% CI)
HbA1c as continuous exposure			
Per 1% increase in HbA1c	…	1.34 (.99–1.82)	1.13 (.88–1.58)
Diabetes status as 3-level exposure[d]			
Euglycemic (n = 474)	329/474 (69)	Ref	Ref
Prediabetes (n = 92)	67/92 (73)	1.18 (.72–1.95)	1.08 (.64–1.82)
Diabetes (n = 31)[b]	27/31 (87)	**2.97 (1.02–8.67)**	**2.33 (.76–7.08)**
Assessing interaction between age and diabetes status[c]			
Age <40 y			
Euglycemic (n = 414)	284/414 (69)	Ref	Ref
Prediabetes (n = 53)	38/53 (72)	1.16 (.62–2.18)	1.22 (.65–2.32)
Diabetes (n = 7)[b]	5/7 (71)	1.14 (.22–5.98)	1.15 (.22–6.05)
Age ≥40 y			
Euglycemic (n = 60)	45/60 (75)	Ref	Ref
Prediabetes (n = 39)	29/39 (74)	0.97 (.38–2.44)	0.98 (.39–2.49)
Diabetes (n = 24)[c]	22/24 (92)	3.67 (.77–17.47)	3.68 (.77–17.56)

Bold indicates statistical significance ($P < .05$).

Abbreviations: CI, confidence interval; HbA1c, glycated hemoglobin; LTBI, latent tuberculosis infection; OR, odds ratio; Ref, reference group.

[a]Adjusted for age, sex, and human immunodeficiency virus test result. Age was considered as a categorical variable with 4 groupings for each age quartile, as follows: first quartile: <22.6 years; second quartile; 22.6–28.5 years; third quartile: 28.5–37.6 years; fourth quartile: >37.6 years of age).

[b]Diabetes status determined by self-report (answered "yes" to having been told by a doctor or health professional that he/she had diabetes) and according to American Diabetes Association guidelines [18]; participants who self-reported diabetes were classified as having diabetes regardless of HbA1c.

[c]In models assessing the interaction between age and diabetes, age was considered as a dichotomous variable, grouping participants who were <40 years and ≥40. years of age, and was included as an effect modifier and not a covariate in the model.

[d]HbA1c categories determined according to American Diabetes Association guidelines [18].

HHC population was conducted in India in 2014–2017 and found that the increased prevalence of LTBI among HHCs with diabetes was not significantly different to those without diabetes (prevalence ratio, 1.4 [95% CI, .8–2.5]) [16]. Our results provided needed data to further investigate the association of diabetes and LTBI among a highly exposed HHC cohort.

One secondary finding of our study was the high prevalence of LTBI in this highly exposed participant group. LTBI prevalence in this cohort was >2-fold higher than previously published estimates of LTBI prevalence in Africa [27]. Prevalence of LTBI in our cohort was also higher than documented in prior investigation of LTBI among HHCs in Kenya (55.7%) [28]. The high prevalence of LTBI in this HHC cohort is likely related to HHCs' intensive exposure to index cases, as nearly two-thirds (64.5%) of HHCs slept in the same bed or room as the index case. Taken together with recent evidence that HHCs are at high risk for progression to active TB disease [29], this finding highlights the urgent need for public health action to increase case detection and implement LTBI treatment among HHCs, which is consistent with current WHO guidelines on the treatment of LTBI in LMICs [3].

Our study is subject to several limitations. First, as this was a cross-sectional observational study leveraging data from a larger ongoing clinical research project, we were not able to control for several potential sources of confounding. Among the unmeasured potential sources of confounding are serum vitamin D (25[OH]D) level and the prevalence of hemoglobinopathies. Vitamin D deficiency is associated with both active TB disease and dysglycemia [30, 31], while hemoglobinopathies accelerated red blood cell turnover that decreases HbA1c, reducing the sensitivity of HbA1c as a screening tool for diabetes and prediabetes. The cross-sectional design also did not enable us to distinguish between prevalent and incident LTBI cases among HHCs, or to determine which HHCs had been previously exposed to *Mtb*. Both the higher-than-expected rate of LTBI (>70%) and the lower-than-expected rate of diabetes (5.2%) limited the power of our study to detect the true association of diabetes and LTBI in the study population and as a consequence the analysis may have been underpowered. Additionally, we were not able to capture all HHCs of active TB cases as some could not be contacted or did not consent to participate.

CONCLUSIONS

Among the HHCs of active pulmonary TB cases in Addis Ababa, Ethiopia, those with diabetes were significantly more likely to have LTBI compared to HHCs with euglycemia (crude prevalence difference of 17.7%). In multivariable analysis, the increased risk of LTBI among HHCs with diabetes was not significant when adjusting for sex, age, and HIV status (aOR, 2.33 [95% CI, .76–7.08]). When assessing interaction with age, the association of diabetes and LTBI was most pronounced among HHCs ≥40 years old (aOR, 3.68 [95% CI, .77–17.6]). A very high prevalence (>70%) of LTBI was found among the HHC cohort, which had intensive exposure to index cases with active TB disease. Our results highlight opportunities for scaling up detection and treatment of LTBI according to the latest WHO guidelines for LTBI treatment [3] and support the inclusion of both HHCs and individuals with diabetes among high-risk groups prioritized for LTBI treatment in LMICs.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. A. G. C. S., R. R. K., H. M. B., and M. J. M. participated in the design of the study. A. G. C. S. led data analysis and interpretation of the data and drafting of the manuscript. A. N., L. W., N. R. G., S. C. A., and K. B. provided key leadership of the data collection, which was completed in association with other members of the Tuberculosis Research Unit: Role of Antigen Specific Responses in the Control of TB

(TBRU-ASTRa) Study Group. All authors assisted with data analysis and interpretation, provided critical revision of the article, and reviewed and approved the final manuscript.

Acknowledgments. The authors thank the members of the TBRU-ASTRa Study Group, who designed, led, and implemented the TBRU study and without whom data for this analysis would not be available: Joel Ernst, Rafi Ahmed, Lisa Sharling, Devin Columbus, Lance Waller, Lisa Elon, Andrea Knezevic, Shirin Jabbarzadeh, Hao Wu, Seegar Swanson, Yunyun Chen, Jyothi Rengarajan, Cheryl Day, Wendy Whatney, Melanie Quezada, Loren Sasser, Ranjna Madan Lala, Tawania Fergus, Paul Ogongo, Anthony Tran, Toidi Adekambi, Deepak Kaushal, Toidi Adekambi, Nadia Golden, Taylor Foreman, Allison Bucsan, Chris Ibegbu, John Altman, Susanna Contraras Alcantra, Alessandro Sette, Cecilia Lindestam Arlehamn, Salim Allana, Angela Campbell, Sarita Shah, Susan Ray, James Brust, Jeffrey Collins, Meghan Franczek, Jenna Daniel, Anirudh Rao, Rebecca Goldstein, Madeleine Kabongo, Alawode Oladele, Abraham Aseffa, Medina Hamza, Yonas Abebe, Fisseha Mulate, Mekdelawit Wondiyfraw, Firaol Degaga, Daniel Getachew, Dawit Tayachew Bere, Meaza Zewdu, Daniel Mussa, Bezalam Tesfaye, Selam Jemberu, Azeb Tarekegn, Gebeyehu Assefa, Gutema Jebessa, Zewdu Solomon, Sebsibe Neway, Jemal Hussein, Tsegaye Hailu, Alemayehu Geletu, Edom Girma, Million Legesse, Mitin Wendaferew, Hirut Solomon, Zenebech Assefa, Mahlet Mekuria, Misker Kedir, Eleni Zeleke, Rediet Zerihun, Selam Dechasa, Emebet Haile, Nahom Getachew, Firaol Wagari, Ruth Mekonnen, Samuel Bayu, Melat Gebre-Medhin, and Alemayehu Kifle. We are also grateful for all study participants and participating health facilities in Addis Ababa for their time, dedication, and willingness to participate in the study.

Financial support. This study was supported in part by the National Institutes of Health (U19 AI111211 and to H. M. B.; UL1 TR002378; TL1 TR002382 to H. M. B., which provided support to A. G. C. S.; K24 AI11444 to N. R. G.; and K23AI134182 to S. C. A.). The study was also supported in part by a Grants for Emerging Researchers/Clinicians Mentorship Program (G.E.R.M.) grant from the Infectious Diseases Society of America (to A. G. C. S.).

Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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