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Diabetes and pre-diabetes among household contacts of tuberculosis patients in India: is it time to screen them all?

S. V. B. Y. Shivakumar,* P. Chandrasekaran,† A. M. V. Kumar,‡ M. Paradkar,§ K. Dhanasekaran,† N. Suryavarshini,§ B. Thomas,† R. Kohli,§ K. Thiruvengadam,† V. Kulkarni,§ L. E. Hannah,† G. N. Sivaramakrishnan,† N. Pradhan,§ C. Dolla,† A. Gupte,¶ G. Ramachandran,† A. DeLuca,¶ S. Meshram,§# R. Bhardawaj,§# R. C. Bollinger,¶** J. Golub,¶** K. Selvaraj,†† N. Gupte,§** S. Swaminathan,‡‡ V. Mave,§** A. Gupta;¶** for the CTRIUMPh-RePORT India Study Team**

*Johns Hopkins University-India Office, Pune, Maharashtra, †National Institute for Research in Tuberculosis, Chennai, Tamil Nadu, India; ‡International Union Against Tuberculosis and Lung Disease, Paris, France; §Byramjee Jeejeebhoy Government Medical College, Johns Hopkins University Clinical Research site, Pune, Maharashtra, India; ¶Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA; #Byramjee Jeejeebhoy Government Medical College, Pune, India; **Johns Hopkins School of Medicine, Baltimore, Maryland, USA; ††Pondicherry Institute of Medical Sciences (PIMS), Puducherry, ‡‡Indian Council of Medical Research, New Delhi, India

SUMMARY

SETTING: Pre-diabetes mellitus (pre-DM) and DM increase the risk of developing tuberculosis (TB). Screening contacts of TB patients for pre-DM/DM and linking them to care may mitigate the risk of developing TB and improve DM management.

OBJECTIVE: To measure the prevalence of pre-DM/DM and associated factors among the adult household contacts (HHCs) of pulmonary TB patients.

METHODS: Between August 2014 and May 2017, adult HHCs of newly diagnosed adult PTB patients in Pune and Chennai, India, had single blood samples tested for glycosylated haemoglobin (HbA1c) at enrolment. DM was defined as previously diagnosed, self-reported DM or HbA1c ⩾6.5%, and pre-DM as HbA1c between 5.7% and 6.4%. Latent tuberculous infection (LTBI) was defined as a positive tuberculin skin test (⩾5 mm induration) or QuantiFERON® Gold In-Tube (⩾0.35 international units/ml).

RESULTS: Of 652 adult HHCs, 175 (27%) had pre-DM and 64 (10%) had DM. Forty (64%) HHCs were newly diagnosed with DM and 48 (75%) had poor glycaemic control (HbA1c ⩾7.0%). Sixty-eight (22%) pre-DM cases were aged 18–34 years. Age ⩾35 years, body mass index ⩾25 kg/m^2, chronic disease and current tobacco smoking were significantly associated with DM among HHCs.

CONCLUSIONS: Adult HHCs of TB patients in India have a high prevalence of undiagnosed DM, pre-DM and LTBI, putting them at high risk for developing TB. Routine DM screening should be considered among all adult HHCs of TB.

KEY WORDS: diabetes; pre-diabetes; TB contacts; screening; latent tuberculous infection; LTBI

TUBERCULOSIS (TB) IS THE leading infectious disease killer worldwide. Of the estimated 10.4 million TB patients in 2016, 2.8 million were in India, the country with the world's largest TB burden.[1] During the same year, an estimated 425 million adults were living with diabetes mellitus (DM), 72.9 million of whom were in India. This DM burden is the second largest globally, and is expected to rise to 123 million by 2040.[2] About 50% of adults with DM in many high-burden settings, including in India, are undiagnosed.[2,3] DM increases the risk of developing TB, and patients with both TB and DM have a higher risk of adverse TB treatment outcomes.[4,5] The reason for the increased risk of TB in DM is not clear, but is linked to dysfunctional and exaggerated T-cell and cytokine responses.[6] Little is known about DM or pre-DM among the household contacts (HHCs) of TB cases. Recent publications, including a systematic review, observed a DM prevalence of 2–6% among close contacts of TB cases, but DM was not diagnosed systematically and was based on self-report.[7–9]

Pre-DM (glycosylated haemoglobin [HbA1c] 5.7–6.4%) is an independent risk factor for developing TB, and is associated with an increased risk of developing DM.[10–12] Effective glycaemic control in

PC, VM and AG contributed equally to this article.

Correspondence to: Shri Vijay Bala Yogendra Shivakumar, National Institute for Research in Tuberculosis, Room No. 209, Clinic Building, No1, Mayor Sathyamoorthy Road, Chetpet, Chennai 600 031, India. e-mail: shrivijay.md@gmail.com
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people with DM can reduce their risk of TB.[13] The intersection of TB and DM is therefore an important public health challenge that has received increasing attention by the World Health Organization (WHO) and governments, including that of India.[14,15] The WHO and the National Framework for Joint TB-Diabetes Collaborative Activities in India recommend screening for DM in adults with active TB and screening for TB among those with DM (i.e., bidirectional screening).[14] However, there is no specific guidance for DM screening among adult HHCs of TB cases. There are general guidelines that recommend screening for DM among specific groups, such as asymptomatic adults aged ⩾30 years, those with a body mass index (BMI) ⩾23 kg/m^2, individuals with a family history of DM, those with a sedentary lifestyle, and those with laboratory evidence of pre-DM, hypertension or dyslipidaemia.[16]

We hypothesised that DM and pre-DM are common among adult HHCs of TB patients. As DM is more prevalent among TB patients than in the general population, and both TB and DM are linked to households due to shared genetics and shared lifestyle/environmental risks, a high prevalence of DM and pre-DM among HHCs of TB patients might be expected.[17,18] In addition, as HHCs have a high prevalence of latent tuberculous infection (LTBI), early diagnosis and management of DM among HHCs could improve the prevention of TB.[19,20] We therefore assessed the prevalence of DM and pre-DM using systematic screening by HbA1c among adult HHCs of adult pulmonary TB (PTB) patients in India.

METHODS

Study design

We performed a cross-sectional analysis of baseline DM screening among HHCs of adult PTB patients enrolled in an ongoing study, CTRIUMPh (Cohort for TB Research with Indo-US Medical Partnership), which is described elsewhere.[21]

Setting

Since August 2014, CTRIUMPh has been prospectively recruiting and following up TB patients and their HHCs at Byramjee Jeejeebhoy Government Medical College (BJGMC), Pune (a predominantly urban metropolis of 5 million), and the National Institute for Research in TB (NIRT), Chennai, India.[21] BJGMC is affiliated with Sassoon General Hospitals, a tertiary public hospital evaluating ~4500 presumptive TB patients annually.[21] NIRT cares for TB patients from two public TB clinics in Tiruvallur District, which evaluates ~1500 presumptive TB patients annually. Tiruvallur has a predominantly rural population of ~3.4 million.[21]

Study population

The study population consisted of all consenting adult (age ⩾18 years) HHCs (defined as those who resided with an adult PTB case for at least 3 months before their TB diagnosis in their household) enrolled in CTRIUMPh between August 2014 to May 2017.

Data variables

The primary outcome variable was DM or pre-DM. All adult HHCs were tested for HbA1c using National Glycohemoglobin Standardisation Program-certified assays. DM was defined as previously diagnosed, self-reported DM or HbA1c ⩾6.5% and pre-DM as HbA1c 5.7–6.4%. The current recommendation by the American Diabetes Association and International Diabetes Federation for glycaemic control is set at HbA1c <7.0% for non-pregnant adults; we therefore defined 'poor glycaemic control' as HbA1c ⩾7.0%.[22,23]

At baseline, we assessed: 1) sociodemographic characteristics: age, sex, education, monthly total household income, residence (urban/rural/slum), study site, relationship to index case; 2) behavioural characteristics: tobacco use, alcohol use and alcohol dependency score using the AUDIT scale;[24] and 3) clinical characteristics: TB symptoms, bacteriologically confirmed TB disease (smear- or culture-positive), human immunodeficiency virus (HIV) status, LTBI status of those without TB disease based on tuberculin skin test (TST) ⩾5 mm or QuantiFERON® Gold In-Tube (QGIT) positivity according to the manufacturer's instructions (⩾0.35 international units/ml), BMI, chronic diseases and DM status of the index TB patient.[25,26] Definitions of the variables examined are provided in the Appendix*.

Data collection

Paper-based, standardised, structured and pre-tested case reporting forms were administered by trained study staff and entered into a computer cloud-based database portal developed by Persistent Systems Inc® (Santa Clara, CA, USA) using the Salesforce® (San Francisco, CA, USA) platform. Since March 2017, direct e-data capture on mobile computer tablets has been used and synchronised with the database.

Data analysis

Data were analysed using EpiData v2.2.2.183 (EpiData Association, Odense, Denmark) and Stata v12.1 (StataCorp, College Station, TX, USA). Prevalence of DM and pre-DM was calculated, and we measured associations of DM with sociodemographic, behavioural and clinical characteristics using prevalence ratios (PR) with 95% confidence intervals (CIs).

* The appendix is available in the online version of this article, at http://www.ingentaconnect.com/content/iuatld/ijtld/2018/00000022/00000006/art00019

Table 1 Characteristics of adult HHCs of adult pulmonary TB patients stratified by type of DM in Chennai and Pune (recruited in CTRIUMPh study), India, 2014–2017

Variable	Total *n* (%)*	DM *n* (%)†	Pre-DM *n* (%)†	Euglycaemia *n* (%)	*P* value
Total, *n*	652 (100)	64 (10)	175 (27)	413 (63)	
Sociodemographic characteristics					
Sex					
Male	284 (44)	30 (11)	77 (27)	177 (62)	0.8
Female	368 (56)	34 (9)	98 (27)	236 (64)	
Age, years					
18–34	309 (48)	5 (2)	68 (22)	236 (76)	<0.01
35–44	164 (25)	20 (12)	40 (24)	104 (63)	
45–54	112 (17)	21 (19)	41 (37)	50 (44)	
⩾55	67 (10)	18 (27)	26 (39)	23 (34)	
Education					
Illiterate	104 (16)	12 (12)	34 (33)	58 (56)	0.04
Primary (0–5 years)	99 (15)	14 (14)	29 (29)	56 (57)	
High school (6–10 years)	287 (44)	30 (11)	69 (24)	188 (66)	
10+2, college and above	160 (25)	7 (4)	43 (27)	110 (69)	
Missing	2 (<1)	0	0	0	
Monthly total household income, INR (US$1 = 64.81INR)					
1 500–7 499	117 (18)	12 (10)	28 (24)	77 (66)	0.4
7 500–11 999	183 (28)	17 (9)	40 (22)	126 (69)	
12 000–17 499	161 (25)	14 (9)	47 (29)	100 (62)	
⩾17 500	158 (24)	19 (12)	47 (30)	92 (58)	
Missing	33 (5)	13 (39)	2 (6)	18 (55)	
Residence					
Urban (non-slum)	305 (47)	37 (12)	81 (27)	187 (61)	0.1
Rural (non-slum)	188 (29)	19 (10)	55 (29)	114 (61)	
Slum (both in rural and urban)	159 (24)	8 (5)	39 (25)	112 (70)	
Relationship to index case					
First degree relative‡	290 (45)	28 (10)	86 (30)	176 (61)	0.3
Other relatives§	362 (55)	36 (10)	89 (25)	237 (66)	
Study site					
Chennai	355 (54)	44 (12)	90 (25)	221 (62)	0.04
Pune	297 (46)	20 (7)	85 (29)	192 (65)	
Behavioural characteristics					
Tobacco use					
Both smoke and smokeless	17 (3)	0	6 (35)	11 (65)	0.5
Smoke tobacco only	39 (6)	9 (23)	8 (21)	22 (56)	
Smokeless tobacco only¶	108 (17)	8 (7)	34 (32)	66 (61)	
No tobacco use	488 (75)	47 (10)	127 (26)	314 (64)	
Alcohol use (AUDIT score)[24]					
Never or past user	527 (81)	53 (10)	143 (27)	331 (63)	0.7
Risky/hazardous drinking (AUDIT 8–15)	81 (12)	5 (6)	21 (26)	55 (68)	
Alcohol abuse/harmful (AUDIT16–19)	33 (5)	4 (12)	7 (21)	22 (67)	
Alcohol dependent (AUDIT ⩾20)	11 (2)	2 (18)	4 (36)	5 (46)	
Clinical characteristics					
BMI,# kg/m^2					
Undernutrition (<18.5)	102 (16)	3 (3)	25 (25)	74 (75)	<0.01
Normal (18.5–22.9)	215 (33)	13 (6)	40 (20)	162 (75)	
Overweight (23.0–24.9)	91 (14)	9 (10)	29 (36)	53 (64)	
Obesity (⩾25.0)	214 (33)	36 (17)	75 (35)	103 (48)	
Missing	30 (5)	3 (10)	6 (20)	21 (70)	
Chronic disease**					
Yes	54 (8)	16 (30)	19 (35)	19 (35)	<0.01
No	598 (92)	48 (8)	156 (26)	394 (66)	
HIV					
Positive	8 (1)	0	5 (63)	3 (38)	0.2
Negative	588 (90)	57 (10)	154 (26)	377 (64)	
Unknown	56 (9)	7 (13)	16 (29)	33 (59)	
LTBI††‡‡					
Positive	495 (77)	47 (10)	127 (26)	321 (65)	0.1
Negative	137 (21)	16 (12)	40 (29)	81 (59)	
Unknown	7 (1)	0	5 (71)	2 (29)	
TST§§					
Negative	256 (40)	23 (9)	67 (26)	166 (65)	0.4
5–9 mm	193 (30)	21 (11)	42 (22)	130 (67)	
⩾10 mm	161 (25)	16 (10)	52 (32)	93 (58)	
Unknown	29 (5)	3 (10)	11 (38)	15 (52)	

Table 1 *(continued)*

Variable	Total *n* (%)*	DM *n* (%)†	Pre-DM *n* (%)†	Euglycaemia *n* (%)	*P* value
QGIT‡‡					
Positive	354 (55)	33 (9)	89 (25)	232 (66)	0.9
Negative	231 (36)	21 (9)	61 (26)	149 (65)	
Unknown	54 (8)	9 (17)	22 (41)	23 (43)	
TB symptoms					
Yes	79 (12)	7 (9)	26 (33)	46 (58)	0.4
No	573 (88)	57 (10)	149 (26)	367 (64)	
TB disease§§					
Yes	13 (2)	1 (8)	3 (23)	9 (69)	0.9
No	639 (98)	63 (10)	172 (27)	404 (63)	
DM status of index TB patient					
DM¶¶	170 (26)	20 (12)	45 (27)	105 (62)	0.3
Pre-DM##	153 (24)	14 (9)	52 (34)	87 (57)	
Euglycaemia***	235 (36)	20 (9)	56 (24)	159 (68)	
HbA1c status of index unknown	94 (14)	10 (11)	22 (23)	62 (66)	

* Column percentages.
† Row percentages.
‡ Parents (father/mother), sibling (brother/sister), son/daughter.
§ Spouse/sexual partner, cousin/niece/nephew/uncle/aunt, grandparent, care giver and any other.
¶ Chewing tobacco and snuff.
# BMI classification (in kg/m^2) according to the Indian Consensus Group (for Asian Indians residing in India):[25] undernutrition (<18.5), normal (18.5–22.9), overweight (23–24.9), obesity (⩾25).
** Includes chronic non-communicable comorbidities such as cardiovascular diseases, hypertension, dyslipidaemia, asthma and chronic obstructive pulmonary disease.
†† TST ⩾5 mm or QGIT positivity.
‡‡ For LTBI, TST and QGIT analyses, TB disease patients have been removed from the denominator.
§§ Smear- or culture-confirmed (Mycobacterium Growth in Tube or Löwenstein-Jensen).
¶¶ Previously diagnosed self-reported DM or HbA1c ⩾6.5%.
HbA1c 5.7–6.4%.
*** HbA1c <5.7%.
DM = diabetes mellitus; HHC = household contact; TB = tuberculosis; CTRIUMPh = Cohort for TB Research with Indo-US Medical Partnership; INR = Indian rupees; AUDIT = Alcohol Use Disorders Identification Test; BMI = body mass index; HIV = human immunodeficiency virus; LTBI = latent tuberculous infection; TST = tuberculin skin test; QGIT = QuantiFERON®-TB Gold In-Tube; HbA1c = glycosylated haemoglobin.

Factors with $P < 0.1$ in unadjusted analysis were included in the multivariable analysis (log-binomial regression), and adjusted PRs with 95%CIs were calculated.

Ethical approval

The CTRIUMPh study has ethical approval from the Institutional Review Boards of NIRT, BJGMC and Johns Hopkins University, Baltimore, MD, USA. In addition, approval was obtained from the Ethics Advisory Group of the International Union Against TB and Lung Disease, Paris, France.

RESULTS

Sociodemographic and clinical characteristics of household contacts

A total of 413 adults with drug-susceptible PTB were enrolled in the ongoing CTRIUMPh study between August 2014 and May 2017. Of 1385 HHCs living with them at the time of TB diagnosis, 859 were adults aged ⩾18 years, 677 (79%) of whom consented to enrolment. Of these, 25 who did not have information on HbA1c were excluded. A final total of 652 adult HHCs were included in the analysis. The sociodemographic, behavioural and clinical characteristics are shown in Table 1. The median age of the HHCs was 35 years (interquartile range [IQR] 26–45); 56% were female. A quarter of the HHCs were living in slums and reported using some form of tobacco (predominantly smokeless). Nearly 20% of HHCs were currently consuming alcohol, and one fifth had a household income of <US$100 per month. According to the Asian Indian BMI classification, 47% were either overweight (BMI 23–24 kg/m^2) or obese (BMI ⩾25 kg/m^2). Twelve per cent had at least one TB symptom. A total of 13 (2%) HHCs had bacteriologically confirmed PTB. Of 639 HHCs who did not have TB disease, 495 (77%) had LTBI based on TST or QGIT.

Prevalence of diabetes and pre-diabetes

Of the 652 HHCs, 239 (37%, 95%CI 33–40) had DM or pre-DM; 64 (10%, 95%CI 8–12) had DM and 175 (27%, 95%CI 24–30) had pre-DM. Of 64 HHCs with DM, 40 (64%) were newly diagnosed using HbA1c screening. The median HbA1c among HHCs with pre-DM, known DM and newly diagnosed DM was respectively 5.9% (IQR 5.8–6.1), 7.4 (IQR 7.0–9.2) and 7.4 (IQR 6.4–10.4). The majority (75%) of those with known (17/24, 71%) and newly diagnosed (31/40, 78%) DM had poor glycaemic control (HbA1c ⩾7.0%) (Figure). Of 175 newly diagnosed HHCs with pre-DM, 68 (22%) were aged 18–34 years.

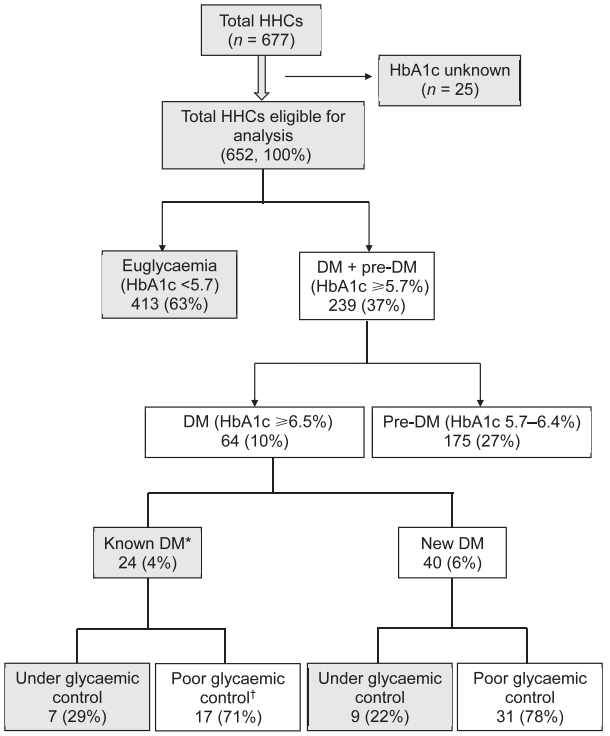

Figure Prevalence of DM and pre-DM among adult HHCs of pulmonary tuberculosis patients in Chennai and Pune (recruited in the CTRIUMPh study), India, 2014–2017.* Previously diagnosed self-reported DM.† HbA1c ⩾7.0%. HHC = household contact; HbA1c = glycosylated haemoglobin; DM = diabetes mellitus; CTRIUMPh = Cohort for TB Research with Indo-US Medical Partnership.

Factors associated with diabetes and pre-diabetes

HHCs with age ⩾35 years, BMI ⩾25 kg/m^2, co-existing chronic diseases, currently smoking tobacco and those from Tamil Nadu had a significantly higher prevalence of DM (Table 2). In adjusted multivariable analysis, age ⩾35 years, BMI ⩾25 kg/m^2, presence of chronic disease and tobacco smoking remained significant for DM. In adjusted multivariable analysis, considering 'either DM or pre-DM' as an outcome, age ⩾45 years, BMI 23–24 kg/m^2 and BMI ⩾25 kg/m^2 were significantly associated (results not shown). Considering 'pre-DM' alone as an outcome, none of the factors were significantly associated (results not shown). Finally, we did not find a significant association between DM in the index TB patient and DM (PR 1.4, 95%CI 0.8–2.5) or pre-DM (PR 1.1, 95%CI 0.6–2.0) among HHCs.

Association of diabetes and pre-diabetes with LTBI

Overall, 77% (495/639) of the HHCs had LTBI on either TST or QGIT: 55% (354/639) on TST, 55% (354/639) on QGIT and 33% (213/639) on both. We did not find an association between LTBI and DM or pre-DM among HHCs ($P > 0.1$); 75% (47/63) of DM, 74% (127/172) of pre-DM and 79% (321/404) of euglycaemic cases had LTBI on either TST or QGIT. This trend remained consistent whether we defined LTBI based on TST alone, QGIT alone or on both TST and QGIT combined (Table 2).

DISCUSSION

Our study, which is among the first to assess the prevalence of DM and pre-DM among HHCs of TB cases using systematic HbA1c screening in a high TB and DM burden setting, had five key findings. First, we found that nearly four in 10 HHCs had DM or pre-DM. Second, most of these HHCs were previously undiagnosed. Third, we observed many of the expected risk factors associated with DM, such as increased age and BMI. Fourth, we observed a high prevalence of pre-DM among those aged 18–34 years, a population not typically captured in DM screening guidelines. Finally, we did not find any independent association between LTBI and DM or pre-DM.

It is now well established that persons recently exposed to TB,[27] as well as those with DM and pre-DM, are at higher risk for developing TB. However, current guidelines for high TB burden settings do not yet recommend screening for DM or pre-DM or preventive therapy for adult HHCs unless they are HIV-infected. Finding such high rates of undiagnosed, poorly controlled DM and pre-DM among HHCs recently exposed to PTB patients in a high TB burden setting is alarming, and likely represents a critical missed opportunity for both TB prevention and early detection of DM.

The finding that nearly 40% of adult HHCs had DM or pre-DM was higher than expected, compared with observations in the general adult population of India and in many high-income settings. The INDIAB study, which used the oral glucose tolerance test, a more sensitive tool for DM diagnosis, found a DM prevalence of respectively 8.4% and 10.4% and a pre-DM prevalence of 8.3% and 12.8% among adults (⩾20 years) in Maharashtra and Tamil Nadu, India (the location of our study sites).[28,29] We identified a high prevalence of pre-DM (>20%), irrespective of age, sex, BMI, place of residence, smoking status or alcohol consumption. The three-fold higher pre-DM prevalence among adult HHCs compared with the general adult (⩾20 years) population of India is intriguing; 22% of HHCs with pre-DM were aged 18–34 years, a population not typically screened for DM. Pre-DM itself is associated with an increased risk of developing both TB disease[10,19] and DM.[30,31]

Most individuals were unaware of their DM and pre-DM diagnosis. This is not entirely surprising, as at least 50% of adults with DM in many settings are not aware of their status.[2] We found that approximately two thirds of DM cases were newly detected as a result of screening by HbA1c. Furthermore, among both known and newly detected DM, 75% had poor

Table 2 Factors associated with DM among adult HHCs of adult pulmonary TB patients in Chennai and Pune (recruited in CTRIUMPh study), India, 2014–2017

Variable	PR (95%CI)	aPR (95%CI) diabetes
Sociobehavioural characteristics		
Age, years		
18–34	Reference	Reference
35–44	7.5 (2.9–19.7)*	4.7 (1.8–12.2)*
45–54	11.6 (4.5–30.0)*	8.4 (3.2–22.1)*
⩾55	16.6 (6.7–43.0)*	10.3 (3.7–28.4)*
Sex		
Male	Reference	
Female	0.9 (0.6–1.4)	
Education		
Illiterate	Reference	
Primary (0–5 years)	1.2 (0.6–2.5)	1.3 (0.7–2.7)
High school (6–10 years)	0.9 (0.5–1.7)	1.4 (0.7–2.7)
10+2, college and above	0.4 (0.2–0.9)	1.0 (0.4–2.4)
Monthly total household income, INR (US$1 = 64.81INR)		
1 500–7 499	Reference	
7 500–11 999	0.9 (0.5–1.8)	
12 000–17 499	0.9 (0.4–1.8)	
⩾17 500	1.2 (0.6–2.3)	
Residence		
Rural	0.8 (0.5–1.4)	0.9 (0.6–1.6)
Slum	0.4 (0.2–0.9)	0.6 (0.2–1.1)
Urban	Reference	
Relationship to index case		
First degree relative†	1.0 (0.6–1.6)	
Others‡	Reference	
Study site		
Chennai	1.8 (1.1–3.1)*	1.4 (0.7–2.6)
Pune	Reference	
Tobacco use		
Both smoke+ smokeless§	—	—
Smoke tobacco only	2.4 (1.3–4.5)*	2.3 (1.2–4.5)*
Smokeless tobacco only¶	0.8 (0.4–1.6)	0.6 (0.3–1.2)
No tobacco use	Reference	
Alcohol use		
Risky/hazardous drinking	0.6 (0.3–1.5)	
Alcohol abuse/harmful	1.2 (0.5–3.1)	
Alcohol dependent	1.8 (0.5–6.5)	
Never or past user	Reference	
Clinical characteristics		
BMI,# kg/m^2		
Under nutrition(<18.5)	0.5 (0.1–1.7)	0.5 (0.2–1.8)
Normal (18.5–22.9)	Reference	
Overweight (23.0–24.9)	1.6 (0.7–3.7)	1.4 (0.7–3.0)
Obesity (⩾25.0)	2.8 (1.5–5.1)*	2.1 (1.2–3.6)*
Chronic disease**		
Yes	3.4 (2.3–6)*	1.7 (1.0–3.0)*
No	Reference	
HIV		
Positive§	—	
Negative	Reference	
LTBI†††‡‡		
Positive (TST or QGIT)	0.9 (0.5–1.7)	
Positive (TST and QGIT)	1.1 (0.5–2.1)	
Negative (TST and QGIT)	Reference	
TST		
Positive (⩾5 mm)	1.2 (0.7–2.0)	
Negative (0–4 mm)	Reference	
QGIT		
Positive	1.1 (0.6–1.8)	
Negative	Reference	
TB symptoms		
Symptoms	0.9 (0.4–1.9)	
No symptoms	Reference	
TB disease§§		
Yes	0.8 (0.1–5.2)	
No	Reference	

Table 2 *(continued)*

Variable	PR (95%CI)	aPR (95%CI) diabetes
DM of index TB patient		
DM[¶¶]	1.1 (0.6–2.0)	
Pre-DM[##]	1.4 (0.8–2.5)	
Euglycaemia***	Reference	

* Statistically significant
† Parents (father/mother), sibling (brother/sister), son/daughter.
‡ Spouse/sexual partner, cousin/niece/nephew/uncle/aunt, grandparent, care giver and any other.
§ None of these HHCs had this (HIV and use of both smokeless and smoke tobacco) comorbidity.
¶ Chewing tobacco and snuff.
# BMI classification (in kg/m^2) according to the Indian Consensus Group (for Asian Indians residing in India):[25] undernutrition (<18.5), normal (18.5–22.9), overweight (23–24.9), obesity (⩾25).
** Includes chronic non-communicable comorbidities such as cardiovascular diseases, hypertension, dyslipidaemia, asthma and chronic obstructive pulmonary disease.
†† TST ⩾5 mm or QGIT positivity.
‡‡ For LTBI analysis, patients with TB disease have been removed from the denominator.
§§ Smear- or culture-confirmed (Mycobacterium Growth in Tube or Löwenstein-Jensen).
¶¶ Previously diagnosed self-reported DM or HbA1c ⩾6.5%.
HbA1c 5.7–6.4%.
*** HbA1c <5.7%.
DM = diabetes mellitus; HHC = household contact; TB = tuberculosis; CTRIUMPh = Cohort for TB Research with Indo-US Medical Partnership; PR = prevalence ratio; CI = confidence interval; aPR = adjusted PR; INR = Indian rupees; BMI = body mass index; HIV = human immunodeficiency virus; LTBI = latent tuberculous infection; QGIT = QuantiFERON®-TB Gold In-Tube; TST = tuberculin skin test; HbA1c = glycosylated haemoglobin.

glycaemic control (HbA1c ⩾7.0%), which is associated with a 2–4-fold higher risk of developing TB and an increased risk of DM-related microvascular and macrovascular complications.[4,23,32] Universal screening for DM and pre-DM among HHCs thus not only has the advantage of identifying a particularly high-risk group for developing TB disease, it also has the added advantage of early detection for pre-DM, undiagnosed DM at an earlier stage and DM with poor glycaemic control.

Although DM screening guidelines do not recommend screening asymptomatic adults aged <30 years, our finding of high DM and pre-DM, including in persons aged 18–34 years, suggests that these guidelines should be revisited to specifically include adult HHCs of TB cases.

As with HIV disease, HHCs with DM and pre-DM may be the very group for whom targeted TB preventive therapy may be of particular benefit. Current recommendations on preventive therapy published by the WHO, India and many other high TB burden settings do not include TB preventive therapy for adult HHCs of index TB patients.[15,33]

The reasons for high DM and pre-DM among HHCs are not entirely clear. Could recently infected LTBI cases be associated with increased pre-DM or DM? Although we found a high prevalence of LTBI among our adult HHCs, this was not associated with pre-DM/DM as defined by HbA1c screening criteria. Interestingly, we also did not find a significant association between DM among HHCs and DM in index TB patients. However, there is some biological plausibility that LTBI may be associated with DM and pre-DM. A study conducted in guinea pigs experimentally infected with *Mycobacterium tuberculosis* found increased development of insulin resistance and chronic hyperglycaemia.[34] A recent meta-analysis assessing DM and LTBI among HHCs and refugees reported a DM prevalence of 2–6%, and DM had a small but statistically significant increased association with LTBI.[7] However, the authors noted several limitations, such as the small sample size and the fact that DM was self-reported.[7] Further studies are needed to better define the relationship of LTBI with pre-DM/DM among HHCs.[7]

A major strength of our study is that we used HbA1c, a highly sensitive and specific screening tool to measure DM and pre-DM, which can be measured using point-of-care devices as opposed to more cumbersome capillary/venous random glucose or fasting blood glucose methods.

Our study also had limitations. In the absence of symptoms, DM diagnosis generally requires a second test to confirm the presence or absence of DM. We also did not specifically assess the signs or symptoms of DM, as we were focusing on symptoms associated with TB disease. We may therefore have misclassified some individuals with DM or pre-DM by relying on a single HbA1c result. Another consideration is that anaemia may affect HbA1c levels.[35] As respectively only 3% and 7% of those diagnosed with DM and pre-DM had anaemia, it is unlikely that anaemia impacted our ascertainment of DM or pre-DM by HbA1c screening. Another limitation is that we missed enrolling about 20% of the eligible HHCs in our study for various reasons, and were not able to assess if these HHCs were similar to those enrolled. Our data are from two regions of India only, and might not be generalisable to the whole of India.

Nevertheless, despite the above limitations, we performed a large, community-based cohort study of HHCs in two regions in India, a country with the

highest burden of TB and the second highest DM burden in the world, making our findings of great public health relevance.

In summary, nearly four in 10 HHCs of TB cases had DM or pre-DM, and nearly 80% had LTBI. Given the potential for TB prevention and future DM prevention, routine DM screening may be of great benefit to adult HHCs. National Non-Communicable Disease Programmes and National TB programmes should consider expanding DM screening to all adult HHCs of newly diagnosed TB cases as part of an integrated TB screening and HIV testing package to identify undiagnosed but at-risk populations who would benefit from targeted prevention programmes.

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APPENDIX

DEFINITIONS

Smoking

Current smoker: An adult who has smoked at least 100 manufactured cigarettes/hand-rolled cigarette/*bidi*/hookah/cigars in his or her lifetime and who currently smokes.

Smokeless tobacco

Chewing tobacco: A type of shredded or twisted smokeless tobacco that the user keeps in his/her mouth between the cheek and gum.

Snuff: A type of finely ground smokeless tobacco contained in a small teabag-like pouch that is kept in the mouth. Snuff can also be sniffed.

Alcohol definitions

Alcohol use: Anyone who is currently consuming and had consumed a standard drink of beer, wine, liquor/spirit or aperitif/cocktail in the past year, according to World Health Organization definitions.

AUDIT (Alcohol Use Disorders Identification Test) scale: AUDIT is a 10-item alcohol screen that can help identify persons who are hazardous drinkers or have active alcohol use disorders (including alcohol abuse or dependence).[24]

AUDIT score interpretation

Hazardous or risky drinking: Scores between 8 and 15 are most appropriate for simple advice focused on the reduction of hazardous drinking.

Harmful use/alcohol abuse: Scores of between 16 and 19 suggest brief counselling and continued monitoring.

Alcohol dependence: AUDIT scores of $\geqslant$20 clearly warrant further diagnostic evaluation for alcohol dependence.

Education

Illiterate: Aged $\geqslant$7 years and cannot read and write with understanding.

Primary school: A person who had undergone 0–5 years of schooling.

High school: A person who had undergone 6–10 years of schooling.

10+2, college and above: Studied 10+2 years of schooling or diploma courses after high school or college and above.

Residence

Rural: Rural areas are also known as the 'countryside' or a 'village' in India, typically located outside towns and cities. A rural area has very low population density and small settlements.

Urban: All places with a municipality, corporation, cantonment board or notified town area committee.

Slum: Residential areas unfit for human habitation by reasons of dilapidation (in a state that needs repair), overcrowding, faulty arrangements and design of such buildings, narrowness or faulty arrangement of street, lack of ventilation, light or sanitation facilities.

Relationship to index case

First degree relative: Parent, a person's father or mother; sibling, each of two or more children or offspring having one or both parents in common; a brother or sister; daughter, a girl or woman in relation to either or both of her parents; son, a boy or man in relation to either or both of his parents.

Other: Spouse, a husband or wife, sexual partner, considered in relation to their partner; Grandparent, a parent of one's father or mother; a grandmother or grandfather, any other distant relatives such as cousin, nephew, niece, nephew, uncle, aunt, roommate, care giver, any other.

Diabetes

Known diabetes mellitus (DM): Previously diagnosed self-reported DM diagnosed by a physician at any time, either on enrolment in the study or before, irrespective of their current anti-DM treatment status or glycosylated haemoglobin (HbA1c) levels.

Newly diagnosed: HbA1c $\geqslant$6.5% with or without the classic symptoms of hyperglycaemia or hyperglycaemic crisis at the time of the first visit in the study.

Poor glycaemic control: HbA1c $\geqslant$7.0% of a known or newly diagnosed DM case irrespective of treatment status.

Pre-DM: HbA1c $\geqslant$5.7–6.4% and not known to have been diagnosed with DM was considered to be pre-DM.

Euglycaemia: HbA1c $<$5.7% and not known to have been diagnosed with DM.

Body mass index

Body mass index (BMI) classification was according to the Indian Consensus Group (for Asian Indians residing in India):[25] undernutrition was defined as BMI $<$18.5 kg/m^2, normal as 18.5–22.9 kg/m^2, overweight as BMI $\geqslant$23 kg/m^2 and obesity as BMI $\geqslant$25 kg/m^2.

Human immunodeficiency virus

Anyone on antiretroviral therapy (ART) or diagnosed by human immunodeficiency virus (HIV) testing at the time of enrolment or in the past 90 days with a verifiable source document.

Any tuberculosis symptoms

Household contact of adult pulmonary tuberculosis (TB) case with cough, fever, night sweats, unexpected weight loss, wheezing, pleuritic chest pain, fatigue/lethargy, loss of appetite, excessive thirst, nausea/

vomiting, diarrhoea, worms in stool, headaches, irritability, convulsions/seizures, neck swelling, or pain in bones/joints.

Tuberculosis disease

Any adult (age $\geqslant$18 years) newly diagnosed as having pulmonary TB disease using sputum smear acid-fast bacilli (AFB) staining or culture using MGIT™ (Mycobacteria Growth Indicator Tube) testing or Löwenstein-Jensen medium as *Mycobacterium tuberculosis*.

Latent tuberculous infection

Household contacts of the index TB patient who tested positive on QuantiFERON®-TB Gold In-Tube (QGIT) according to manufacturers' standard criteria ($\geqslant$0.35 international units/ml) or on tuberculin skin test (TST $\geqslant$5 mm) are considered to be have latent tuberculous infection (LTBI) or to be LTBI-positive. QGIT results are interpreted as positive, negative or indeterminate. TST (2 or 5 tuberculin units) is administered to detect *M. tuberculosis*. Any reading with $\geqslant$5 mm is considered TST-positive.

Chronic diseases

Heart disease, high blood pressure (hypertension), high cholesterol (dyslipidaemia), stroke, chronic obstructive pulmonary disease, asthma, cancer, seizure/epilepsy, chronic kidney disease/failure.

RÉSUMÉ

CONTEXTE : Le pré-diabete (pre-DM) et le DM augmentent le risque de développer une tuberculose (TB). Dépister les contacts de patients TB à la recherche d'un pré-DM/DM et les mettre en contact avec une prise en charge pourrait atténuer le risque de développer une TB et améliorer le traitement du DM.

OBJECTIF : Mesurer la prévalence du pré-DM/DM et des facteurs associés parmi les contacts familiaux adultes (HHC) de TB pulmonaire.

MÉTHODE : Entre août 2014 et mai 2017, les HHC adultes de patients TB adultes nouvellement diagnostiqués à Pune et à Chennai, Inde, ont eu, lors de leur enrôlement, un prélèvement unique de sang dosant l'hémoglobine glycosylée (HbA1c). Le DM a été défini comme déjà diagnostiqué et déclaré par le patient ou par une HbA1c ⩾6,5% et un pré-DM comme une HbA1c entre 5,7% et 6,4%. L'infection tuberculeuse latente (LTBI) a été définie comme un test cutané à la tuberculine positif (⩾5 mm d'induration) ou un QuantiFERON® Gold In-Tube positif (⩾0,35 IU/ml).

RÉSULTATS : Sur 652 (76%) HHC, 175 (27%) avaient un pré-DM et 64 (10%) avaient un DM. Quarante (64%) HHC ont eu un diagnostic nouveau de DM et 48 (75%) avaient un contrôle médiocre de leur glycémie (HbA1c ⩾7,0%). Soixante-huit (22%) des pré-diabétiques étaient âgés de 18 à 34 ans. Un âge ⩾35 ans, un indice de masse corporelle ⩾25 kg/m^2, une maladie chronique et la consommation de tabac en cours ont été significativement associés au DM parmi les HHC.

CONCLUSION : Les HCC adultes des patients TB en Inde ont une prévalence élevée de DM, de pré-DM et de LTBI non diagnostiqués, ce qui les met à risque élevé de développer une TB. Le dépistage de routine du DM devrait être envisagé parmi tous les HCC adultes de TB.

RESUMEN

MARCO DE REFERENCIA: La pre-diabetes (pre-DM) y la DM aumentan el riesgo de contraer la tuberculosis (TB). La detección sistemática de estas afecciones en los contactos de pacientes con TB y su vinculación con los servicios de atención puede aminorar el riesgo de padecer TB y mejorar el tratamiento de la DM.

OBJETIVO: Medir la prevalencia de pre-DM y DM y los factores asociados en los contactos domiciliarios adultos de los pacientes con TB pulmonar.

MÉTODOS: De agosto del 2014 a mayo del 2017 se incorporaron al estudio los contactos domiciliarios adultos de los casos nuevos de TB pulmonar de Pune y Chennai, en la India y se obtuvieron muestras únicas de sangre en el momento de su inclusión, con el fin de determinar la glucohemoglobina (HbA1c). La DM se definió por un diagnóstico anterior y autonotificado o mediante una determinación de HbA1c ⩾6,5% y la pre-DM como una HbA1c entre 5,7% y 6,4%. Se definió la infección tuberculosa latente (LTBI) como un resultado positivo de la prueba cutánea de la tuberculina (induración ⩾5 mm) o la prueba QuantiFERON® Gold en tubo (⩾0,35 UI/ml).

RESULTADOS: De 652 contactos domiciliarios (76%), en 175 se encontró pre-DM (27%) y DM en 64 (10%). En 40 de los contactos, se trataba de un diagnóstico nuevo de diabetes (64%) y 48 presentaban una regulación deficiente de la glucemia (75%; HbA1c ⩾7,0%). Sesenta y ocho de los pacientes prediabéticos (22%) tenían de 18 a 34 años de edad. Los factores que se asociaron de manera significativa con el diagnóstico de DM en los contactos domiciliarios fueron una edad de ⩾35 años, un índice de masa corporal ⩾25 kg/m^2, una enfermedad crónica y el tabaquismo actual.

CONCLUSIONES: En los contactos domiciliarios adultos de los pacientes con TB en la India se observa una alta prevalencia de DM, pre-DM e LTBI no diagnosticadas, que los hacen muy vulnerables a la enfermedad tuberculosa. Es preciso considerar la práctica de la detección sistemática de la DM en todos los adultos en contacto estrecho con los casos de TB.