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Synergism between diabetes and human immunodeficiency virus in increasing the risk of tuberculosis

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SUMMARY

SETTING: Community health screenings in KwaZulu-Natal Province, South Africa.

OBJECTIVE: To study the synergism between diabetes mellitus (DM) and human immunodeficiency virus (HIV) infection in increasing the risk of tuberculosis (TB).

DESIGN: In this cross-sectional study, we analyzed data from two community health projects, one at congregate settings, and one at household settings (n = 7708), in a rural resource-limited region where integrated communicable and non-communicable disease screening services were offered. Odds ratios (ORs) for demographic factors, socio-economic factors, DM status, and HIV positivity were calculated using multivariate analysis, and the statistical interaction between HIV and DM was tested. The primary outcome was the presence of TB symptoms.

RESULTS: Among 7708 individuals, age >65 years (OR 1.72, 95%CI 1.47–2.02), HIV infection (OR 1.66, 95%CI 1.40–1.97) and DM (OR 1.36, 95%CI 1.11–1.67) were independently associated with increased odds of TB symptoms. Receiving monthly grants (OR 0.78, 95%CI 0.66–0.91), access to a toilet (OR 0.54, 95%CI 0.35–0.83), and access to solar or electric energy (OR 0.86, 95%CI 0.77–0.97) reduced the odds. There was evidence of significant interaction between DM and HIV on the multiplicative scale.

CONCLUSION: DM and HIV synergistically increased the odds of TB symptoms according to these retrospective data. Future studies should prospectively evaluate synergism between HIV and DM in increasing the risk of active TB.

RÉSUMÉ

Dépistage sanitaire en communauté dans la province du KwaZulu-Natal, Afrique du Sud.

Etudier la synergie entre le diabète (DM) et la maladie liée au virus de l’immunodéficience humaine (VIH) dans l’augmentation du risque de tuberculose (TB).

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Cette étude transversale a analysé les données de deux projets de santé communautaire, l'un dans un milieu surpeuplé et l'autre dans le cadre de foyers (*n*=7708) dans une région rurale aux ressources limitées ; des services intégrés de dépistage des maladies transmissibles et non transmissibles y ont été offerts. Les odds ratios (OR) des facteurs démographiques, des facteurs socioéconomiques, du statut en matière de DM et de positivité du VIH ont été calculés par analyse multivariée et l'interaction statistique entre VIH etDMa été testée. Le résultat principal a été la présence de symptômes de TB.

Parmi 7708 individus, un âge >65 ans (OR 1,72 ; IC95% 1,47–2,02), l'infection à VIH (OR 1,66 ; IC95% 1,40–1,97), et le DM (OR 1,36 ; IC95% 1,11–1,67) ont été indépendamment associés avec une augmentation des risques de symptômes de TB. Recevoir une allocation mensuelle (OR 0,78 ; IC95% 0,66–0,91), avoir accès à des toilettes (OR 0,54 ; IC95% 0,35–0,83) et à une énergie solaire ou électrique (OR 0,86 ; IC95% 0,77–0,97) a diminué les risques. Il y a eu des preuves d'une interaction significative entre DM et VIH sur l'échelle multiplicative.

Le DM et le VIH ont augmenté de façon synergique les risques de symptômes de TB dans ces données rétrospectives. De futures études devraient prospectivement évaluer la synergie entre VIH et DM dans l'augmentation du risque de TB active.

RESUMEN

Los reconocimientos médicos sistemáticos de la población en la provincia de KwaZulu-Natal en Suráfrica.

Estudiar el sinergismo entre la diabetes (DM) y la infección por el virus de la inmunodeficiencia humana (VIH) frente al aumento del riesgo de contraer la tuberculosis (TB).

En el presente estudio transversal se analizaron los datos de dos proyectos de salud comunitaria, uno en un ambiente colectivo y otro en un ambiente domiciliario (*n*=7708) en una región rural con recursos limitados, donde se prestan servicios integrados de detección de las enfermedades transmisibles y las enfermedades no transmisibles. Se calcularon los cocientes de posibilidades (OR) de los factores demográficos, socioeconómicos, la situación frente a la DM y la positividad frente al VIH mediante un análisis multivariante y se midió la interacción estadística entre la infección por el VIH y la DM. El principal criterio de valoración fue la presencia de síntomas indicativos de TB.

En las 7708 personas, los factores que se asociaron de manera independiente con una mayor posibilidad de presentar síntomas de TB fueron la edad de >65 años (OR 1,72; IC95% 1,47–2,02), la infección por el VIH (OR 1,66; IC95% 1,40–1,97) y la DM (OR 1,36; IC95% 1,11–1,67). Esta posibilidad disminuyó con el hecho de recibir subvenciones mensuales (OR 0,78; IC95% 0,66–0,91), contar con acceso a letrinas (OR 0,54; IC95% 0,35–0,83) y con acceso a la energía solar o la energía eléctrica (OR 0,86; IC95% 0,77–0,97). Se observaron indicios de una interacción significativa entre la DM y la infección por el VIH en la escala multiplicativa.

El presente aná lisis retrospectivo puso de relieve que la DM y la infección por el VIH aumentan de manera sinérgica las posibilidades de presentar síntomas indicativos de TB. Futuros estudios deberán evaluar de manera prospectiva este efecto sinérgico sobre el riesgo de sufrir una enfermedad tuberculosa activa.

Keywords

interaction; community-based; screening; tuberculosis; diabetes

THE WORLD HEALTH ORGANIZATION (WHO) reports that tuberculosis (TB) ranks above the human immunodeficiency virus (HIV) as one of the leading infectious causes of death globally.[1] Since the 1980s, the HIV epidemic has fueled an increase in TB disease worldwide. There is increasing recognition that diabetes mellitus (DM) also contributes to the TB epidemic. Individuals with DM have an approximately three-fold increased risk of developing TB disease:[2] 15% of TB cases globally are attributed to DM, rivaling the impact of HIV.[1,3]

DM can almost double the mortality due to TB and increase the risk of recurrence.[4] In a Taiwanese study, degree of hyperglycemia correlated with the severity of symptoms such as cough and weight loss. Moreover, patients with poor glycemic control had higher bacillary loads in their sputum.[5] Although the results are heterogeneous, it appears that TB patients with DM may take longer to sputum convert, thereby prolonging the risk of transmission.[4–6] In 2011, the WHO proposed a collaborative framework for the care and control of TB and DM that stressed high-quality DM care for patients with TB.[7]

Rising DM prevalence may have important ramifications for the global TB epidemic, particularly in low- and middle-income countries. The global prevalence of DM is projected to rise from approximately 382 million in 2013 to 592 million in 2035.[8] India, China, Indonesia, Nigeria, Pakistan, and South Africa carry 60% of the global burden of TB.[1] These countries also have high DM prevalence rates and insufficient infrastructure to manage this chronic disease.[9–11]

In 2015, the WHO estimated TB incidence in South Africa at approximately 834 per 100 000 population.[1] According to the International Diabetes Federation, DM prevalence among South African adults is 2.28 million, approximately 7% of the population, and an additional 1.3 million South Africans are estimated to have undiagnosed DM.[12] While HIV remains the leading driver of the TB epidemic, DM has the potential to complicate national TB efforts. Characterizing the association between DM and TB, which is better studied in Asia, is thus also necessary in Africa.[13]

Reports from several countries have shown that screening TB patients for DM is fruitful.[9,10] Comparatively, screening for TB among DM patients yields modest case-detection rates and is dependent on the TB prevalence in a given region.[14] A systematic review estimated that between 90 and 350 patients with DM would have to be screened in India (TB prevalence, 283/100 000) to identify one additional case of TB.[15] Given that South Africa has an approximately three-fold higher incidence of TB, bidirectional screening might be cost-effective in detecting individuals with undiagnosed TB.[1]

HIV infection also predisposes patients to the metabolic syndrome, and the use of nucleoside reverse transcriptase inhibitors and protease inhibitors further increases the risk of DM.[16] Very few studies have explored interactions between DM and HIV in increasing

the risk of TB. Synergism between these two diseases would be biologically plausible. Mouse studies have indicated that DM attenuates the initial innate response to tuberculous infection, and that there are delays in activation of the adaptive immune response, leading to higher bacillary burdens.[17] HIV, in turn, dampens the adaptive response through several proposed mechanisms.[18]

In 2011, however, a cross-sectional study in Tanzania found that the association between DM and TB was decreased in HIV patients compared with patients without HIV.[19] In 2014, a study from Botswana did not find increased rates of TB symptoms in patients with DM and HIV compared with patients with DM but no HIV.[20]

Here we present a cross-sectional study using two discrete data sets from community health screenings in South Africa to investigate the interplay between DM and HIV in modifying an individual's risk for TB.

METHODS

The present study had a cross-sectional design. Individuals included in the study were screened in rural regions of Msinga subdistrict in the KwaZulu-Natal Province of South Africa.

Data were extracted from community-based TB-HIV intensive case finding (ICF) projects integrated with non-communicable disease (NCD) screening targeting different types of community venues to reach different demographic groups. Briefly, the first data set (n = 4985) pertains to individuals screened at community congregate settings (2010–2015), as previously described.[21] Data were extracted using the same survey instrument from a community-based household-level communicable and NCD screening project (2015–2016) conducted in the same region (n = 2723). All participating individuals were included in this study, totaling 7708 rural South African community members.

Data collected included demographics, socio-economic data such as receipt of a monthly grant, source of drinking water, toilet access, and source of energy used for heating, as well as a history of DM, random blood glucose (RBG) testing, HIV testing history and results, and presence of TB symptoms. Individuals with a history of DM or an RBG of >11 mmol/l were designated as having DM type 2.[22] Individuals with missing RBG test results and missing history of DM were considered to be non-diabetic (n = 6). Individuals with a self-reported history of HIV or a positive screening result were considered to be infected with HIV. Those with missing HIV testing results and missing history of HIV testing were considered to be HIV-negative (n = 21).

The χ^2 test and Wilcoxon rank-sum test were used to assess differences between the two populations and to conduct univariate analyses. The dependent outcome was the presence of at least one of the four effective TB screening symptoms endorsed by the WHO (cough of any duration, fever of any duration, weight loss, and night sweats).[23] We also defined the outcome using a sequentially increasing number of TB symptoms. Multivariate logistic regression analyses were conducted using demographic and socioeconomic variables and HIV and DM status to calculate adjusted odds ratios (aORs) for TB symptoms. We defined

synergism as a positive statistical interaction, assessed using multiplicative and additive scales. Interaction between DM and HIV was entered into the logistic regression model to evaluate for statistical interaction on a multiplicative scale. Relative excess risk due to interaction (RERI) was calculated on the additive scale.[24] Two-sided P values ⩽0.05 were considered statistically significant. Data were analyzed using SAS v9.4 (Statistical Analysis System, Cary, NC, USA).

Ethical approval of the study protocol was obtained from the University of KwaZulu-Natal Biomedical Research Ethics Committee, Durban; the South African Medical Association Research Ethics Committee, Pretoria, South Africa; and the Yale School of Medicine, New Haven, CT, USA.

RESULTS

A total of 7708 rural South African community members, 4985 from community congregate settings and 2723 from households, were screened for TB. Table 1 shows the demographic and socio-economic features of the population studied as well as the prevalence of DM and HIV in the two groups.

Women formed the majority in both data sets. A significantly larger proportion of individuals from household settings were aged >65 years ($P < 0.001$). The majority of individuals in both groups received monthly government welfare grants, and relied on wells, streams, dams, water trucks, and rainwater, although a similar proportion in both groups had access to tap water. The majority of the individuals screened had toilet access, significantly more so in congregate settings ($P < 0.001$).

Individuals screened in household settings had a higher burden of DM than those screened in congregate screenings (9.4% vs. 6.9%, $P < 0.001$). HIV was also significantly more prevalent in the household group than in congregate settings (12.1% vs. 10.2%, $P = 0.01$). The prevalence of dual HIV and DM diagnoses in congregate settings (0.6%) and households (0.7%) did not differ. The presence of at least one TB symptom was higher in the household group (29.2% vs. 17.1%, $P < 0.001$).

In congregate settings, in addition to female sex and age >65 years, DM (OR 1.29, 95% confidence interval [CI] 0.98–1.69) and HIV (OR 1.58, 95%CI 1.27–1.97) were independently associated with increased odds of having TB symptoms (Table 2). Access to tap water and solar or electric energy were associated with decreased odds. DM (OR 1.61, 95%CI 1.24–2.11) and HIV (OR 1.34, 95%CI 1.05–1.70) both had independently increased odds for TB symptoms among those screened in household settings. Age >65 years also had increased odds, although female sex, receipt of grant, and access to solar or electric energy had a reduced risk (Table 2). Access to a toilet was associated with decreased odds in both data sets but was not statistically significant.

Multivariate logistic regression among those screened in congregate settings found female sex (aOR 1.24, 95%CI 1.04–1.48), age >65 years (aOR 1.86, 95%CI 1.50–2.30), and HIV (aOR 1.69, 95%CI 1.35–2.11) to be independently associated with increased odds of having at least one TB symptom, whereas receipt of monthly grants, and access to solar or electric

energy lowered these odds (Table 3). DM (aOR 1.19, 95%CI 0.90–1.57) did not significantly increase the odds of TB symptoms in the adjusted analysis. Multivariate logistic regression among those screened in household settings found that age (aOR 1.35, 95%CI 1.06–1.72), DM (aOR 1.57, 95%CI 1.15–2.14) and HIV (aOR 1.46, 95%CI 1.11–1.91) had increased odds for TB symptoms, whereas female sex, receipt of grant, and access to solar or electric energy were associated with decreased odds. The aORs for HIV and DM increased when the analysis was restricted to individuals with ⩾2 and ⩾3 TB symptoms (Table 3). In the combined analysis of the congregate and household settings, age >65 years (aOR 1.72, 95%CI 1.47–2.02), DM (aOR 1.36, 95%CI 1.11–1.67), and HIV (aOR 1.66, 95%CI 1.40–1.97) continued to exhibit increased odds for TB symptoms, whereas receipt of grant, access to a toilet, and access to solar or electric energy were protective (Table 4).

Interactions on the multiplicative scale were not seen in patients with ⩾1 symptoms of TB (Table 5). However, in the subgroup of patients with ⩾3 symptoms, the aOR for TB symptoms in individuals with HIV increased in the presence of DM. These increases were significant in the combined analysis (aOR 2.86, 95%CI 2.03–4.03 to aOR 3.36, 95%CI 1.28–8.85) and the household screening group (aOR 2.09, 95%CI 1.30–3.36 to aOR 3.79, 95%CI 1.05–13.70). There was a trend towards significance in the congregate screening group. Additive interaction analysis did not find evidence of interaction in any group (Table 6).

DISCUSSION

This study is one of the first and the largest to investigate possible synergism between HIV and DM in increasing odds for TB. In our review of 7708 community members screened in congregate and household settings, HIV and DM both independently increased the odds for TB symptoms. The aOR for HIV and DM corresponding to TB symptoms increased when the analysis was restricted to patients with increasing numbers of TB symptoms. One could hypothesize that patients with more TB symptoms were more likely to have TB disease than individuals with just one symptom.

Community members with both DM and HIV at screening had higher odds of having TB symptoms than patients who had HIV but not DM. Our analysis found evidence of statistical interaction on a multiplicative scale. Risk factors that impact on different stages in a multistage biological process tend to interact multiplicatively.[25] Given the attenuation of innate immunity in DM and the depleted adaptive immunity in HIV, a multiplicative model would seem appropriate and consistent with our findings. The household screening population contributed substantially to the demonstrated synergy between DM and HIV, likely because it had a greater proportion of older individuals and a higher prevalence of DM and HIV. However, interaction between HIV and DM was also seen in the younger group screened in congregate community settings. This finding suggested that there is value to integrating communicable and NCD screening in different demographic groups and community venues.

Poverty is an established risk factor for TB.[26] Higher socio-economic status is associated with a reduced risk of several diseases, including TB.[27–29] We therefore included receipt of

monthly grants, access to clean water, access to toilets, and access to electricity or solar energy in our multivariate model to account for the impact of the socio-economic determinants of health. Receiving monthly grants, access to toilets, and access to electricity or solar energy were indeed protective in this analysis. Efforts to end TB need to be based on a deeper understanding of the impact of the social and structural determinants of health.[30,31]

Integrating TB and HIV care is a core component of the End TB Strategy, and harnessing networks of community health workers for TB and HIV case finding can improve outcomes cost-effectively.[1,32,33] Given that DM is a common comorbidity in both HIV and TB patients, integrating DM care into existing integrated TB-HIV care frameworks is necessary. The significant association of DM with TB symptoms in a community setting suggests the feasibility, if not the necessity, of combined communicable and NCD screening for these two diseases.

The main limitation of our study was that we used symptoms as surrogate markers of TB disease. The majority of the patients were referred to clinics where further clinical evaluation for TB took place. Confirmation of laboratory or radiographic results was not possible. The rate of TB diagnoses among symptomatic patients is likely a combined function of prevalence and diagnostic capacity. Extrapolation is difficult, but we expect rates of TB disease among symptomatic patients in this South African study to resemble those in similar sub-Saharan countries such as Tanzania (7.4%) or Botswana (13.9%).[20,34]

Despite the large study population, the small number of patients with dual diagnoses may have limited our ability to study this interaction, as evidenced by the wide CIs seen in the interaction analyses. Significant statistical interaction is not evidence of a clinical interaction. Due to the nature of the community-based screening process, RBG was used instead of more robust DM screening tools such as fasting blood glucose, oral glucose tolerance test, or glycated hemoglobin. The data used in this study were collected programmatically and evaluated retrospectively, and were subject to missing data. Systematic underestimation of patients with DM and HIV is therefore possible, and could have reduced the power of this study. Furthermore, given the cross-sectional nature of data, etiologic conclusions could not be drawn.

Undernutrition, a known risk factor for TB, was unaccounted for in our regression model due to the lack of anthropometry during screenings. Other unmeasured confounders are also possible. Length-biased sampling is important to consider, although less likely, as these data sets were drawn from relatively healthy individuals in congregate screenings or in their own homes who were not seeking clinical services at health care facilities in the traditional manner. Another potential limitation was that the majority of screened individuals were female. However, the preponderance of females in our study population reflects the demographics of this rural impoverished population, where most men leave to find work in urban areas and return home only annually. As the study population was predominantly a rural impoverished population, the results may be generalizable to most of sub-Saharan Africa, but perhaps not to other global regions.

In conclusion, in this large retrospective cohort, HIV and DM acted synergistically to increase the odds of TB symptoms among rural South African community members. Further prospective analyses are necessary to validate synergism between HIV and DM in increasing the risk for TB.

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Table 1

Demographic and socio-economic characteristics and disease prevalence among community members undergoing screening in congregate and household settings in rural South Africa [*]

	Congregate (*n* = 4985) *n* (%)	Household (*n* = 2723) *n* (%)	*P* value
Female	3651 (73.2)	2169 (79.7)	<0.001 [†]
Age, years, mean + SD	40.8 ± 20.4	44.3 ± 20.5	<0.001 [†]
Age >65 years	580 (11.6)	508 (18.7)	<0.001 [†]
Grant recipients	4164 (83.5)	2324 (85.3)	<0.001 [†]
Access to tap water	2152 (43.2)	1007 (36.9)	0.09
Access to a toilet	4929 (98.9)	2635 (86.8)	<0.001 [†]
Access to electricity or solar power	1523 (30.6)	1459 (53.6)	<0.001 [†]
RBG, mmol/l, median [IQR]	6.0 [1.0]	6.0 [1.9]	0.99
DM	343 (6.9)	257 (9.4)	<0.001 [†]
HIV	508 (10.2)	329 (12.1)	0.01 [†]
Any TB symptoms	867 (17.4)	794 (29.2)	<0.001 [†]
DM + HIV dual diagnosis	30 (0.6)	19 (0.7)	0.60
Total individuals	4985 (100)	2723 (100)	

[*] Differences between groups were analyzed using χ^2 and Wilcoxon rank-sum test.

[†] $P < 0.05$.

SD = standard deviation; IQR = interquartile range; RBG = random blood glucose; DM = diabetes mellitus; HIV=human immunodeficiency virus; TB = tuberculosis.

Table 2

Correlates of the presence of one or more TB symptoms for demographic and socioeconomic factors as well as DM and HIV in congregate and household settings in rural South Africa calculated using the χ^2 test*

Variable	Congregate OR (95%CI)	Household OR (95%CI)
Female sex	1.29 (1.09–1.53)	0.64 (0.53–0.78)
Age >65 years	1.77 (1.44–2.16)	1.26 (1.03–1.55)
Grant recipients	0.88 (0.73–1.07)	0.76 (0.60–0.96)
Access to tap water	0.92 (0.70–0.95)	1.01 (0.85–1.21)
Access to a toilet	0.59 (0.32–1.08)	0.71 (0.42–1.23)
Access to electricity or solar power	0.76 (0.64–0.90)	0.62 (0.52–0.75)
DM	1.29 (0.98–1.69)	1.61 (1.24–2.11)
HIV	1.58 (1.27–1.97)	1.34 (1.05–1.70)

*Variables assessed: female sex, age >65 years, receipt of monthly grant, access to tap water, access to a toilet, access to solar or electric energy, DM, and HIV.

TB = tuberculosis; DM = diabetes mellitus; HIV = human immunodeficiency virus; OR = odds ratio; CI = confidence interval.

Table 3

Multivariable logistic regression evaluating factors associated with at least one TB symptom, ⩾2 symptoms, and ⩾3 symptoms in congregate and household settings*

	Congregate			Household		
Variables	**⩾1 TB symptom OR (95%CI)**	**⩾2 TB symptoms OR (95%CI)**	**⩾3 TB symptoms OR (95%CI)**	**⩾1 TB symptom OR (95%CI)**	**⩾2 TB symptoms OR (95%CI)**	**⩾3 TB symptoms OR (95%CI)**
n	867	296	96	794	493	152
Female sex	1.24 (1.04–1.48)	0.88 (0.68–1.16)	1.02 (0.63–1.65)	0.71 (0.56–0.90)	0.66 (0.51–0.86)	0.86 (0.55–1.33)
Age >65 years	1.86 (1.50–2.30)	2.03 (1.47–2.81)	1.55 (0.86–2.82)	1.35 (1.06–1.72)	1.35 (1.01–1.80)	1.29 (0.81–2.05)
Grant recipients	0.79 (0.64–0.96)	0.73 (0.53–0.99)	1.04 (0.58–1.87)	0.71 (0.54–0.93)	0.66 (0.49–0.90)	1.09 (0.63–1.90)
Access to tap water	0.90 (0.77–1.05)	1.02 (0.80–1.31)	1.11 (0.73–1.70)	1.04 (0.86–1.26)	0.97 (0.77–1.22)	1.07 (0.73–1.56)
Access to a toilet	0.64 (0.34–1.20)	0.65 (0.25–1.67)	0.51 (0.12–2.15)	0.63 (0.34–1.17)	0.86 (0.42–1.78)	0.74 (0.25–2.17)
Access to electricity or solar power	0.75 (0.65–0.90)	0.65 (0.49–0.87)	0.58 (0.35–0.96)	0.6 (0.49–0.73)	0.28 (0.23–0.35)	0.27 (0.18–0.40)
DM	1.19 (0.90–1.57)	1.24 (0.81–1.91)	1.23 (0.58–2.58)	1.57 (1.15–2.14)	1.59 (1.11–2.27)	1.95 (1.15–3.31)
HIV	1.69 (1.35–2.11)	2.06 (1.48–2.85)	3.17 (1.94–5.16)	1.46 (1.11–1.91)	1.53 (1.12–2.09)	2.23 (1.43–3.49)

*Covariates used: female sex, age >65 years, receipt of monthly grant, access to tap water, access to a toilet, access to solar or electric energy, diabetes, and HIV.

TB = tuberculosis; OR = odds ratio; CI = confidence interval; DM = diabetes mellitus; HIV = human immunodeficiency virus.

Table 4

Multivariable logistic regression evaluating factors associated with having at least one TB symptom, ⩾2 symptoms, and ⩾3 symptoms in combined analysis*

Variables	⩾1 TB symptom OR (95%CI)	⩾2 TB symptoms OR (95%CI)	⩾3 TB symptoms OR (95%CI)
n	1661	789	248
Female sex	1.05 (0.92–1.21)	0.84 (0.70–1.00)	0.98 (0.71–1.35)
Age >65 years	1.72 (1.47–2.02)	1.84 (1.50–2.27)	1.64 (1.15–2.35)
Grant recipients	0.78 (0.66–0.91)	0.72 (0.58–0.88)	1.05 (0.71–1.56)
Access to tap water	0.92 (0.82–1.03)	0.93 (0.79–1.09)	1.018 (0.77–1.34)
Access to a toilet	0.54 (0.35–0.83)	0.59 (0.34–1.02)	0.51 (0.22–1.18)
Access to electricity or solar power	0.86 (0.77–0.97)	0.66 (0.56–0.78)	0.55 (0.41–0.74)
DM	1.36 (1.11–1.67)	1.47 (1.13–1.91)	1.69 (1.11–2.57)
HIV	1.66 (1.40–1.97)	1.93 (1.55–2.39)	2.9 (2.10–4.02)

*Covariates used: female sex, age >65 years, receipt of monthly grant, access to tap water, access to a toilet, access to solar or electric energy, diabetes, and HIV.

TB = tuberculosis; OR = odds ratio; CI = confidence interval; DM = diabetes mellitus; HIV = human immunodeficiency virus.

Table 5

Multiplicative interaction analysis displaying the association between HIV and TB symptoms across the strata of DM status

	Exposure levels*	⩾1 TB symptom OR (95%CI)	⩾2 TB symptoms OR (95%CI)	⩾3 TB symptoms OR (95%CI)
Congregate	HIV yes; DM no	1.74 (1.39–2.19)	2.11 (1.51–2.96)	3.19 (1.91–5.31)
	HIV yes; DM yes	1.02 (0.40–2.61)	1.57 (0.44–5.62)	3.79 (0.72–19.95)
Household	HIV yes; DM no	1.45 (1.09–1.92)	1.45 (1.05–2.01)	2.09 (1.30–3.36)
	HIV yes; DM yes	1.57 (0.58–4.24)	2.71 (0.94–7.85)	3.79 (1.05–13.70)
Combined	HIV yes; DM no	1.70 (1.43–2.03)	1.93 (1.54–2.42)	2.86 (2.03–4.03)
	HIV yes; DM yes	1.20 (0.62–2.32)	1.87 (0.88–3.96)	3.36 (1.28–8.85)

*HIV yes; DM no = OR of TB symptoms for patients with HIV, but no DM. HIV yes; DM yes = OR of TB symptoms for patients with HIV who also have DM.

HIV = human immunodeficiency virus; TB = tuberculosis; DM = diabetes mellitus; OR = odds ratio; CI = confidence interval.

Table 6

RERI calculated from additive interaction analysis evaluating the possible synergism between DM and HIV in congregate screenings, household screenings, and combined analysis

	⩾1 TB symptom RERI (95%CI)	⩾2 TB symptoms RERI (95%CI)	⩾3 TB symptoms RERI (95%CI)
Congregate	−0.63 (−1.54 to 0.28)	−0.75 (−1.88 to 0.38)	−0.77 (−2.02 to 0.49)
Household	−0.45 (−0.88 to −0.03)	−0.25 (−0.84 to 0.34)	−0.33 (−1.24 to 0.57)
Combined	−0.42 (−1.55 to 0.72)	0.35 (−1.67 to 2.36)	2.01 (−2.87 to 6.88)

RERI = relative excess risk due to interaction; DM = diabetes mellitus; HIV = human immunodeficiency virus; TB = tuberculosis; CI = confidence interval.