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Title: BMI as a predictor of progression from TB infection to active TB in PLHIV: secondary analysis of the WHIP3TB trial. R1

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Summary: This secondary analysis of a TB preventive drug trial (WHIP3TB-Trial) aimed to assess the relation between BMI measured at baseline with the risk of developing active TB in PLHIV who received 3 months of high-dose rifapentine-isoniazid given once or twice over a period of 2 years.

Keywords: BMI, TB infection, PLHIV, Fractional polynomials

Abstract

Background: Low body mass index (BMI) is a globally important risk factor for tuberculosis (TB) progression. Little is known about this association in people living with HIV (PLHIV) and the functional form of the BMI-TB incidence curve.

Methods: Secondary analysis of a randomized controlled trial of TB preventive therapy among PLHIV in South Africa, Mozambique, and Ethiopia. Participants received 3 months of weekly high-dose rifapentine-isoniazid given once or twice over a period of 2 years. Multivariable fractional polynomials (MFP) were used to investigate functional forms of BMI. Time to incident TB was modelled using Cox' proportional hazard regression.

Results: 76 TB events were documented, giving an overall TB incidence rate of 1.2 per 100 person-years (95%CI 1.0-1.6). Baseline BMI<18.5kg/m^2 was associated with a 2.6-fold increased hazard of TB compared with BMI 18.5-24.9kg/m^2 (adjusted HR 2.6, 95%CI 1.4-4.8, p<0.001). BMI ≥30kg/m^2 was associated with lower hazard of TB (adj.HR 0.5, 95%CI (0.2-1.0). Continuous and categorical BMI showed weak evidence of quadratic dose-response relationships (p=0.08 and p=0.09, respectively). MFP analysis was consistent with a decline in TB incidence for increasing BMI to around 25 kg/m^2, followed by a less steep decline in TB incidence for increasing BMI >25 kg/m^2.

Conclusions: In PLHIV, BMI showed an inverse log-linear association with TB incidence. The MFP approach showed that the relationship is more complex than a simple log-linear association.

INTRODUCTION

Tuberculosis (TB) remains a global health challenge with an estimated 10.6 million new cases in 2022, 6.3% of which were co-infected with HIV[1]. In the same year, there were an estimated 1.3 million deaths attributable to TB[1]. The Sub-Saharan region accounts for almost one-quarter of all TB cases globally of which over 60% have co-infections with HIV[1]. In this region, HIV-associated TB may be a barrier to meeting the targets to end the TB epidemic.

Around one quarter of the world's population is infected with *Mycobacterium tuberculosis (M.tb)*[2]. The risk of developing TB following infection is increased in immunosuppressed individuals, particularly among people living with HIV (PLHIV), or if other risk factors such as undernutrition, diabetes, smoking, or alcohol consumption are present[3,4]. Prevention of progression from infection to disease is possible through TB preventive therapy (TPT).

Undernutrition is common among PLHIV and is an independent predictor of death even in the era of highly active antiretroviral therapy [5,6]. Body mass index (BMI) is the most widely used indicator to measure nutritional status. Several studies have attempted to explain the relationship between low BMI and TB prevalence and/or incidence[7,8]. A systematic review observed a consistent and log-linear inverse dose-response relationship between BMI and TB incidence within the BMI range of 18.5-30kg/m^2 among HIV-negative people[9]. This finding was confirmed in a recent cohort study with 99.9% HIV-negative participants[10]. Additionally, some studies suggest that low BMI increases the risk of progressing from TB infection (TBI) to active disease due to impairment of cellular immunity[11].

Little is known about the functional form of the BMI-TB incidence relationship among PLHIV. Therefore, the present study aimed to examine the relationship between BMI measured at study enrolment (baseline) with the risk of developing active TB during 24-months of follow-up in PLHIV adults who received 3 months of weekly high-dose rifapentine-isoniazid once or twice over a period of 2 years in a large TPT drug trial. To further characterize the association between BMI and incident TB, we evaluated the functional forms of BMI as a continuous variable using multivariable fractional polynomials (MFP).

METHODS

Study Design of Parent Study

This analysis used data from the WHIP3TB trial[12]; a 3-arm, open-label study among PLHIV, receiving antiretroviral therapy (ART) in South Africa, Mozambique, and Ethiopia. Participants were randomly assigned (ratio 2:9:9) to 6 months of daily-isoniazid therapy (6H arm), 3 months of weekly rifapentine–isoniazid (3HP) therapy once (3HP arm), or annual 3HP therapy (p3HP arm)[12,13]. Participants in both 3HP arms were followed for 24 months, and 6H participants were followed for 12 months. The WHO 4-symptom screening algorithm was used to exclude TB at baseline, 12 and 24 months. At 12 months all participants submitted sputum (irrespective of symptoms) for Xpert MTB/RIF and mycobacterial culture and had chest radiography; the same procedures were repeated at 24 months in the 3HP groups. Data were collected from November 2016-November 2017, with 4027 HIV-positive individuals enrolled.

Participant Consent

The WHIP3TB study received ethical approval from the University of the Witwatersrand-South Africa, Addis Ababa University-Ethiopia, Mozambican national ethics Committee-Mozambique and from the London School of Hygiene & Tropical Medicine ethics committee. Written informed consent was obtained from all participants prior to enrolment in the WHIP3TB study.

Data Collection Methods

Our analysis sought to quantify the association between BMI and TB incidence over 24 months, and therefore is restricted to the two 3HP arms of the parent study. The analysis is further restricted to adults aged ≥18 years. Height and weight were recorded at baseline (randomization visit). BMI was calculated by dividing the weight in kilograms (kg) by square of height in meters (m^2) and categorized using the standard WHO definitions.[14,15] Baseline covariates were socio-demographic factors (age, sex, education, country of enrolment), and clinical characteristics (CD4 count, ART regimen, time on ART, previous TB episodes that occurred more than a year before enrolment, and previous isoniazid preventive therapy (IPT) received more than a year prior to enrolment). The latest CD4 count before enrolment and ART regimen were abstracted from participant's clinical records. Clinical records were also reviewed for prior TB treatment, IPT, and TB episodes. Data collection methods and laboratory techniques are described elsewhere[12].

Statistical Analysis

The main exposure hypothesized to be associated with the outcome of incident TB was BMI. Rates of incident TB were expressed per 100 person-years. Cox regression was used in univariable and multivariable analyses to examine the association between each exposure and the time to incident TB. Two approaches were taken to examine the relationship between BMI and incident TB: i) BMI grouped as a categorical variable (4 levels defined as <18.5 "underweight", 18.5-24.9 "normal", 25.0-29.9 "overweight", ≥30kg/m^2 "obese"); and ii) BMI as continuous variable. For BMI grouped the overall effect, linear trend and departures from linear trend were assessed. For BMI as a continuous variable fractional polynomials were used. Likelihood ratio test (LRTs) was carried out for overall associations, linear trends, and departure from linearity.

Bivariate analysis with Cox regression was used to assess the presence of confounding (supplementary table 2). The final multivariable model included confounding variables if present. In our dataset, there were few events, so we used the rule of ten to avoid the sparsity bias[16]. Moreover, we examined if the effect of BMI on TB incidence was modified by pre-specified variables such as CD4 count, country of enrolment, age, sex education and time on ART by fitting interaction terms.

For the BMI grouped the linear trend and departure from linearity were examined. The simplest departure from a linear relationship between the log(hazard) and a quantitative exposure is a quadratic relationship.

For the BMI continuous, the linear trend and departure from linearity were assessed similarly to that for the BMI grouped, in addition, we analysed the BMI continuous using the MFP approach.

Multivariable second-degree fractional polynomials were used to model BMI, allowing a maximum of 2 degrees of freedom, and adjusting for the same variables as in the multivariable model with BMI grouped. The MFP modelling is a flexible method to reveal non-linear associations. MFP are more flexible than polynomial models (such as including a quadratic effect of the covariate with the linear term) and allow the selection of the best-fitting polynomial functions based on the data rather than predefined functional forms, providing a more accurate description of the BMI-TB association[17].

We assessed the proportional hazards assumption of the effect of BMI on TB incidence using the Schoenfeld test. Analyses were conducted using Stata/SE v.17 (Stata Corporation, College Station, Texas, USA).

RESULTS

Study Population

Between November 2016 and November 2017, 3610 PLHIV were enrolled into the 3HP arms, of whom 3593 where aged ≥18 years. Around sixty-nine percent were female (2496/3593), the median age of the participants was 41.0 years (interquartile range (IQR) 35.0-49.0 years), and 14.6% (526/3593), 21.9% (787/3593), 63.5% (2280/3593) where from Mozambique, Ethiopia, and South Africa, respectively (supplementary table). All participants were receiving ART (as per inclusion criteria), the median CD4 count was 483 cells/mm^3 (IQR 313-693 cells/mm^3), and median time on ART was 4.4 years (IQR 2.2-7.1 years).

At enrolment, the median BMI was 24.1kg/m^2 (IQR 21.0-28.2kg/m^2); 7.8% (272/3593) of participants had a BMI <18.5kg/m^2. Fifteen percent (538/3593) reported having taken IPT more than a year prior to enrolment into the trial. Distribution of baseline variables differed by country of enrolment (supplementary table 1). Most variables had very few missing values (<6%).

Overall, there were 76 incident TB events, among 3593 individuals (6133 person-years of follow-up), giving an overall TB incidence rate of 1.2 per 100 person-years (95% confidence interval [CI] 1.0-1.6). From these, 8 TB events were rifampin resistant with 4 events in the 3HP arm and 4 events in the p3HP arm. No cases of isoniazid-resistant TB were diagnosed. The proportional hazards assumption was met for the risk factors considered (Schoenfeld test p=0.84).

Incident TB differed by BMI level with BMI<18.5kg/m^2 being associated with a shorter time to developing TB (Figure 1; p=0.002). The hazard of TB decreased with increasing BMI. Low BMI (<18.5 kg/m^2) was associated with a 2.5-fold increased hazard of TB (HR 2.5 95%CI 1.4-4.6) compared with BMI of 18.5-24.9kg/m^2 (Table 1). There was strong evidence for linear trend for the effect of BMI on the log(hazard) of TB (p<0.001) and no evidence for departure from linearity (p=0.23). Although the confidence intervals include one, BMI ≥30kg/m^2 may be associated with a 40% lower risk of developing TB than the normal range (Table1).

Univariable analyses of other baseline sociodemographic measures showed that age, sex, and country of enrolment were associated with TB incidence rates. Data were consistent with no association between incident TB and ART regimen, time on ART, CD4 count, prior TB treatment, or IPT prior enrolment (Table 1).

In multivariable analyses adjusted for age (categorical variable) and country of enrolment, BMI (categorical variable) remained strongly associated with TB incidence. Being underweight (BMI <18.5kg/m^2) was associated with 2.6-fold increased hazard of TB compared to those with normal BMI (18.5-24.9kg/m^2). Individuals with BMI ≥30kg/m^2 had 50% lower hazard of incident TB than individuals with normal BMI (18.5-24.9kg/m^2). Assuming a linear effect for BMI as a continuous variable, a BMI increase of 10kg/m^2 resulted in a HR of 0.4 (95% CI 0.3-0.7) (Table 2).

There was weak evidence for a quadratic dose-response relationship between BMI and hazard of TB for BMI grouped (p=0.09) and BMI continuous (p=0.08). (Table 2).

The main MFP model, adjusting for country of enrolment and age group, found the FP power of -1. A steep decline in log hazard of TB was observed with increasing BMI, becoming less steep for BMI>25 kg/m^2 (Figure 2).

DISCUSSION

In this trial population of 3593 HIV-positive adults, BMI showed an inverse log-linear association with TB incidence with no evidence for departure from linearity. The risk of incident TB was lower in individuals with a BMI ≥30kg/m^2 than in individuals with a normal BMI. The MFP approach showed non-linear relationship between BMI and TB incidence.

Low baseline BMI was associated with a slightly stronger effect on TB risk than the unadjusted estimate, as shown by the increased HR from 2.5 to 2.6 after adjustment. Consequently, the confounders slightly masked the true effect of low baseline BMI on TB risk. This small increase suggests that the relationship between BMI and TB is robust and is not heavily influenced by the confounders in our model.

Our results are consistent with previous findings supporting that a low BMI is associated with an increased risk of TB[6]. The association between BMI and TB that had been described for HIV-negative individuals also exists for PLHIV suggesting a mechanism that is independent of HIV infection. Overall, the finding that the association between BMI and TB exists in both HIV-negative and HIV-positive individuals hint on the importance of addressing common risk factors (socioeconomic status, undernutrition, inadequate healthcare access, or environmental factors) and underlying mechanisms contributing to TB risk in diverse populations. Therefore, there is a need for comprehensive public health strategies and interventions to reduce TB burdens and improve overall health.

Like our study, recent studies have shown that individuals with BMI ≥30kg/m^2 might have a lower risk of TB than individuals with a normal and underweight BMI. However, the effect of high BMI on incident TB, especially BMI ≥ 30kg/m^2 is uncertain. A linear inverse relationship between log(TB incidence) and BMI was reportedly uncertain for BMI ≥30 kg/m^2 [9]. Furthermore, very high BMI (≥30 kg/m^2) did not reduce the risk of TB in certain subgroups, including young females and participants with diabetes mellitus in a Korean population[18]. Additionally, Zhang et al[7]. found that a BMI exceeding 28 kg/m^2 was independently associated with increased risk of TB in rural China. Although we observed the same effect of high BMI on TB risk, our study settings differed from these studies, that were conducted in a low TB endemic area with low HIV prevalence.

Uncertainty persists about the biological mechanisms behind the increased risk of TB among individuals with a low BMI. Undernutrition alters immune homeostasis, increasing an individual's susceptibility to infections or progression of infection to disease. In addition, undernutrition impairs cell-mediated and humoral immune responses[19]. Both innate and adaptive immune cytokines are important mediators of immune responses against M.tb[19]. Recent studies have shown associations between low BMI and inflammatory cytokines of TB[20,21]. Anuradha et al.[22] found that low BMI is associated with decreased levels of pro-inflammatory cytokines (IFNγ/TNFα/IL-4/IL-22/IL-1α/IL-1β/IL-6), but higher levels of regulatory cytokines (IL-5/IL-13/IL-10/TGFβ) in patients with latent TB (TBI). In another study, they also reported that high BMI was positively correlated with circulating levels of pro-inflammatory cytokines (IFNγ/TNFα/IL-22/IL-1α/IL-12/GM-CSF), while low BMI was negatively correlated with circulating levels of anti-inflammatory cytokines (IL-4/IL-5/TGFβ)[23] in patients with TBI. High BMI may protect against disease progression from TB infection by altering an individual's cytokine environment. Kumar et al.[21] showed that low BMI was associated with diminished plasma cytokines (IFNγ/TNFα/IL-2/IL-17A/IL-22/IL-1β/IL-6/IL-12/GM-CSF/IL-4/IL-5/IL-13/IL-10/TGFβ) and chemokines (CCL1/CCL2/CCL3/CCL4/CCL-11/CXC/CXCL1/CXCL2/CXCL9/CXCL10/CXCL11) in both active and latent TB patients. Although BMI is often used as a measure of adiposity, it is not solely responsible for modulating the immune system[24]. Rather, it is the physiological processes associated with excess adiposity, particularly fat accumulation, that are believed to influence immune function[25]. Excess adipose tissue, especially visceral fat, is associated with the activation of pro-inflammatory adipokines and chronic low-grade inflammation. This can lead to immune dysregulation as well as an increased susceptibility to inflammatory diseases. In turn, obesity suppresses the secretion of anti-inflammatory adipokines[26]. In this study, the biological mechanisms underlying the harmful effect of underweight BMI on TB are not explored. Further research is needed to clarify these mechanisms.

The MFP approach showed a sharp decrease in log (TB incidence) at BMI <25 kg/m^2 and a plateau in log (TB incidence) at BMI >25 kg/m^2. This pattern indicates a non-linear relationship between BMI and TB incidence and is consistent with weak evidence of a quadratic effect for BMI, whether grouped or continuous. The MFP approach provides a robust and precise method for determining the functional form of BMI covariate and its relationship with incident TB. This approach has many advantages over other ways of modelling BMI and has been used to study various

associations in the past. Although the use of fractional polynomial to establish relationship between BMI and TB incidence has not been documented previously, its use in this current dataset strengthens the robustness of these analysis.

This study had some limitations. The data set for this analysis was small in terms of the number of TB events (76), which limited multivariable adjustment. Observed associations between low BMI and incident TB could be biased by uncontrolled confounding, which is one limitation of this study. Due to data limitations, we could not fully account for factors like nutritional intake and socioeconomic status. We therefore believe that our findings may be limited in their internal validity by residual confounding.

BMI is a simple, rapid, and accurate way to determine a person's metabolic status. However, it has some limitations. BMI does not distinguish between adipose fat, muscle, bone, and water, which are important factors in assessing health risks and nutritional status, particularly in TB. Hence, BMI should be supplemented with other nutritional measures in TB studies to provide an accurate assessment of nutritional status[18,27].

Conclusions

Lower BMI was independently associated with a higher risk of TB development among PLHIV on ART living in TB endemic areas. Individuals with BMI <18.5 kg/m^2 are at increased risk of developing TB, versus those with BMI≥18.5 kg/m^2. Across multiple methods for modelling the association between BMI and TB incidence (linear, nonlinear, and categorical) BMI showed a log-linear association with TB incidence. However, the MFP approach revealed that the relationship is more complex than a simple log-linear association.

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Author contributions

AGB, FC, KF and GC designed the study. BS, EM, performed laboratory analysis. DN, FN, SA and GY collected data at the enrolment sites. KF, FK, DN, SA, VC, VC, AG, and GY made substantial contributions on the data analysis and interpretation of results. DN wrote the first draft of the manuscript. All authors edited the manuscript and/or revised it critically for important intellectual content.

All authors have contributed to the study according to the international consensus on authorship and have approved the final draft and agree with the interpretation and the conclusions of the manuscript.

References

1 World Health Organization (WHO). Global tuberculosis report 2023. Geneva, 2023.

2 Houben RMGJ, Dodd PJ. The Global Burden of Latent Tuberculosis Infection: A Re-estimation Using Mathematical Modelling. PLoS Med. 2016; **13**. DOI:10.1371/journal.pmed.1002152.

3 Duarte R, Lönnroth K, Carvalho C, *et al.* Tuberculosis, social determinants and co-morbidities (including HIV). *Pulmonology* 2018; **24**: 115–9.

4 Silva DR, Muñoz-Torrico M, Duarte R, *et al.* Risk factors for tuberculosis: Diabetes, smoking, alcohol use, and the use of other drugs. *J Bras Pneumol* 2018; **44**: 145–52.

5 Paton NI, Sangeetha S, Earnest A, Bellamy R. The impact of malnutrition on survival and the CD4 count response in HIV-infected patients starting antiretroviral therapy. HIV Med. 2006; **7**: 323–30.

6 Maro I, Lahey T, MacKenzie T, *et al.* Low BMI and falling BMI predict HIV-associated tuberculosis: A prospective study in Tanzania. *Int J Tuberc Lung Dis* 2010; **14**: 1447–53.

7 Zhang H, Li X, Xin H, *et al.* Association of Body Mass Index with the Tuberculosis Infection: a Population-based Study among 17796 Adults in Rural China. *Sci Rep* 2017; **7**. DOI:10.1038/SREP41933.

8 Cegielski JP, McMurray DN. The relationship between malnutrition and tuberculosis: Evidence from studies in humans and experimental animals. *Int J Tuberc Lung Dis* 2004; **8**: 286–98.

9 Lönnroth K, Williams BG, Cegielski P, Dye C. A consistent log-linear relationship between tuberculosis incidence and body mass index. *Int J Epidemiol* 2010; **39**: 149–55.

10 Chen J, Zha S, Hou J, *et al.* Dose-response relationship between body mass index and tuberculosis in China: a population-based cohort study. *BMJ Open* 2022; **12**: e050928.

11 Sinha P, Davis J, Saag L, *et al.* Undernutrition and Tuberculosis: Public Health Implications. *J Infect Dis* 2019; **219**: 1356–63.

12 Churchyard G, Cárdenas V, Chihota V, *et al.* Annual Tuberculosis Preventive Therapy for

Persons with HIV Infection. *Ann Intern Med* 2021; **174**: 1367–76.

13 Berhanu RH, Jacobson KR. Tuberculosis Preventive Therapy for People with HIV Infection in High Tuberculosis Burden Settings: How Much Is Enough? *Ann Intern Med* 2021; **174**: 1462–3.

14 Novosad S, Khan S, Wolfe B, Khan A. Role of Obesity in Asthma Control, the Obesity-Asthma Phenotype. *J Allergy* 2013; **2013**: 1–9.

15 Losing Weight, Body Mass Iindex. https://www.nhlbi.nih.gov/health/educational/lose_wt/BMI/bmi_dis (accessed Aug 1, 2022).

16 Vittinghoff E, McCulloch CE. Relaxing the rule of ten events per variable in logistic and cox regression. *Am J Epidemiol* 2007; **165**: 710–8.

17 Royston P, Ambler G, Sauerbrei W. The use of fractional polynomials to model continuous risk variables in epidemiology. *Int J Epidemiol* 1999; **28**: 964–74.

18 Kim SJ, Ye S, Ha E, Chun EM. Association of body mass index with incident tuberculosis in Korea. *PLoS One* 2018; **13**. DOI:10.1371/JOURNAL.PONE.0195104.

19 Chandrasekaran P, Saravanan N, Bethunaickan R, Tripathy S. Malnutrition: Modulator of immune responses in tuberculosis. *Front Immunol* 2017; **8**: 1–8.

20 Rambaran S, Naidoo K, Lewis L, *et al.* Effect of Inflammatory Cytokines/Chemokines on Pulmonary Tuberculosis Culture Conversion and Disease Severity in HIV-Infected and -Uninfected Individuals From South Africa. *Front Immunol* 2021; **12**: 1–10.

21 Kumar NP, Nancy AP, Moideen K, *et al.* Low body mass index is associated with diminished plasma cytokines and chemokines in both active and latent tuberculosis. *Front Nutr* 2023; **10**: 1–10.

22 Anuradha R, Munisankar S, Bhootra Y, *et al.* Coexistent malnutrition is associated with perturbations in systemic and antigen-specific cytokine responses in latent tuberculosis infection. *Clin Vaccine Immunol* 2016; **23**: 339–45.

23 Anuradha R, Munisankar S, Bhootra Y, Dolla C, Kumaran P, Babu S. High body mass

index is associated with heightened systemic and mycobacterial antigen – Specific pro-inflammatory cytokines in latent tuberculosis. *Tuberculosis (Edinb)* 2016; **101**: 56.

24 She Y, Mangat R, Tsai S, Proctor SD, Richard C. The Interplay of Obesity, Dyslipidemia and Immune Dysfunction: A Brief Overview on Pathophysiology, Animal Models, and Nutritional Modulation. *Front Nutr* 2022; **9**: 1–10.

25 Ghigliotti G, Barisione C, Garibaldi S, *et al.* Adipose tissue immune response: Novel triggers and consequences for chronic inflammatory conditions. *Inflammation* 2014; **37**: 1337–53.

26 Kirichenko T V., Markina Y V., Bogatyreva AI, Tolstik T V., Varaeva YR, Starodubova A V. The Role of Adipokines in Inflammatory Mechanisms of Obesity. *Int J Mol Sci* 2022; **23**. DOI:10.3390/ijms232314982.

27 Wu Y, Li D, Vermund SH. Advantages and Limitations of the Body Mass Index (BMI) to Assess Adult Obesity. *Int J Environ Res Public Health* 2024; **21**: 757.

Table 1: *Distribution of socio-demographic & clinical factors at baseline, and rates and univariable hazard ratios for time to incident TB (n=3593, 76 TB cases)*

	N (column %)	Events/PY	Rate/100PY	HR	95%CI	p-values*
Overall	3593 (100)	76/6133	1.2			
BMI, kg/m^2						
<18.5	272 (7.8)	15/456.5	3.3	2.5	(1.4-4.6)	
18.5-24.9	1756 (48.9)	39/3000	1.3	1		0.002
25.0-29.9	897 (25.0)	13/1500	0.8	0.6	(0.4-1.2)	<0.001$^{\Phi}$
≥30.0	668 (18.6)	9/1100	0.8	0.6	(0.3-1.2)	
Country of enrolment						
South Africa	2280 (63.5)	59/3900	1.5	1		
Ethiopia	787 (22.0)	6/1400	0.4	0.3	(0.1-0.7)	0.004
Mozambique	526 (14.6)	11/895.2	1.2	0.8	(0.4-1.5)	
Age, years						
18-29	401 (11.2)	10/653.5	1.5	2.1	(1.0-4.8)	
30-39	1086 (30.2)	29/1900	1.6	2.2	(1.2-4.1)	0.039
40-49	1243 (34.6)	15/2100	0.7	1		0.517$^{\Omega}$
50+	863 (24.0)	22/1500	1.5	2.2	(1.1-4.1)	
Sex						
Male	1097 (30.5)	33/1900	1.8	1.8	(1.1-2.8)	0.017
Female	2496 (69.5)	43/4300	1.0	1		
Education						
Non/primary	1264 (35.2)	22/2200	1.0	1		0.261
Secondary/tertiary	2329 (64.8)	54/4000	1.4	1.3	(0.8-2.1)	
ART						
TDF+FTC/3TC+EFV	3406 (94.8)	74/5800	1.3	1		0.278
Other	1817(5.2)	2/320.1	0.6	0.5	(0.1-2.0)	
Time on ART, years						
>2	763 (21.2)	21/1300	1.6	1.4	(0.8-2.4)	0.401
2-4	880 (24.5)	17/1500	1.1	1.0	(0.6-1.8)	0.234$^{\Omega}$
≥4	1950 (54.3)	38/3400	1.1	1		
CD4 count, cells/mm^3						
≤200	419 (11.7)	13/701.2	1.9	2.0	(1.0-3.9)	0.137
201-500	1480 (41.2)	33/2500	1.3	1.4	(0.8-2.3)	0.046$^{\Omega}$
≥501	1488 (41.4)	24/2600	0.9	1	(0.3-1.0)	
Missing	206 (5.7)	6/349	1.7	-	-	-
Previous TB treatment						
No	2734 (76.1)	56/4700	1.2	1		0.630
Yes	859 (23.9)	20/1500	1.4	1.1	(0.7-1.9)	
Previous IPT						
No	3055 (85.0)	67/5200	1.3	1		0.390
Yes	538 (15.0)	9/925.3	1.0	0.7	(0.4-1.5)	

Abbreviations: N=number individuals; PY=person-years at risk; HR=hazard ratio; CI=confidence interval; p-values*=from the likelihood ratio test. $^{\Omega}$ LRT for trend; ART=antiretroviral therapy; BMI=body mass index; IPT=isoniazid preventive therapy; $^{\Phi}$p<0.001 from LRT for linear association (no evidence for departure from linearity p=0.23)

Table 2: *Adjusted hazard ratios for TB incidence from multivariate analysis for a linear and quadratic dose-response relationships (n=3593, 76 TB events)*

Baseline BMI	HR*	95%CI	p-value
Categorical			
<18.4	2.6	(1.4-4.8)	
18.5-24.9	1		<0.001[Ω]
25.0-29.9	0.6	(0.3-1.1)	
≥30	0.5	(0.2-1.0)	
Categorical-linear			
linear	0.6	(0.5-0.8)	<0.001[Ω]
Categorical-linear & quadratic			
Linear	0.3	(0.2-0.7)	<0.001
Quadratic	1.2	(0.9-1.5)	
			0.09[§]
Continuous -linear			
Linear[¥]	0.9	(0.9-1.0)	<0.001[Ω]
Continuous -linear & quadratic			
Linear	0.8	(0.7-0.9)	<0.001
Quadratic	1.0	(1.0-1.0)	
			0.08[§]

Abbreviations: HR=hazard ratio; CI=confidence interval; *adjusted for age and country of enrolment; [Ω]from likelihood ratio test; [§]LRT for departure from linearity; [¥] for an increase in BMI of 10kg/m^2 this represents a HR of 0.4 (95% CI 0.3-0.7).

Categorical linear: linear effect assumed for BMI grouped into 4 levels; Categorical linear & quadratic: linear & quadratic effects assumed for BMI grouped into 4 levels; Continuous linear: linear effect assumed for BMI ungrouped (continuous); Continuous linear & quadratic: linear & quadratic effects assumed for BMI ungrouped (continuous)

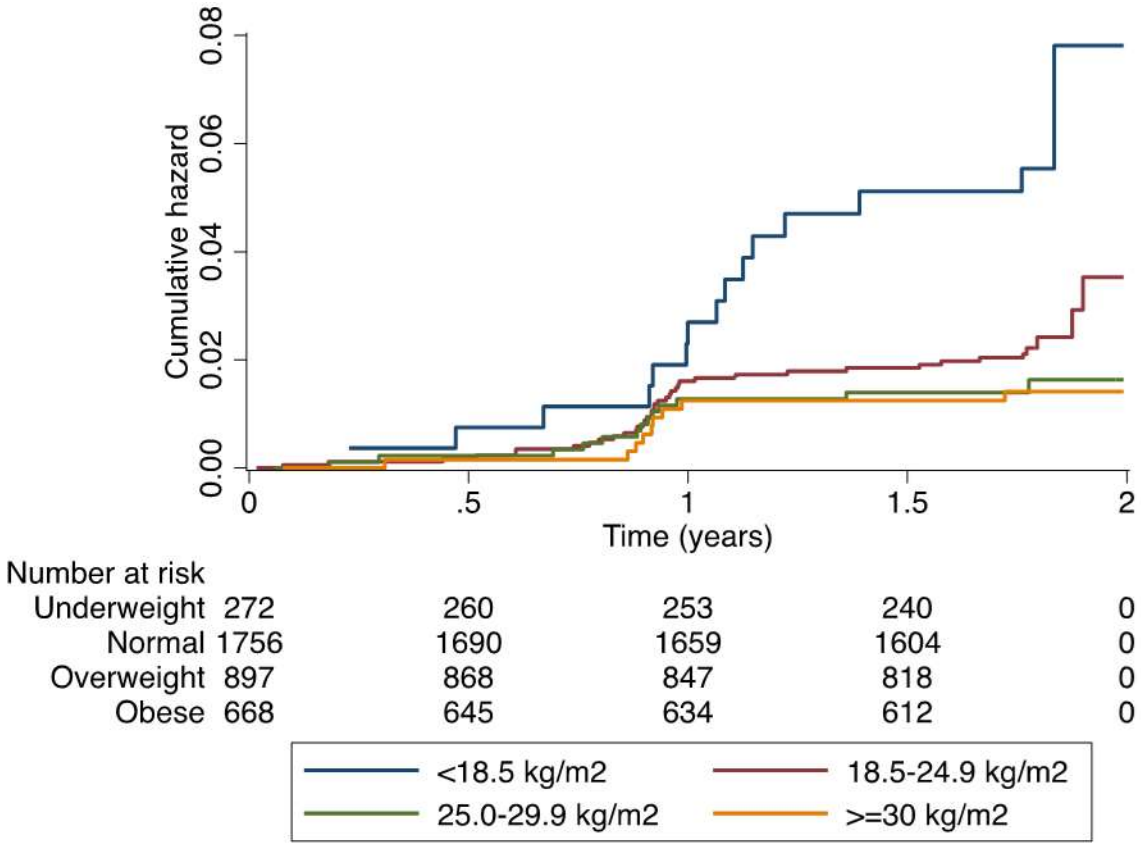
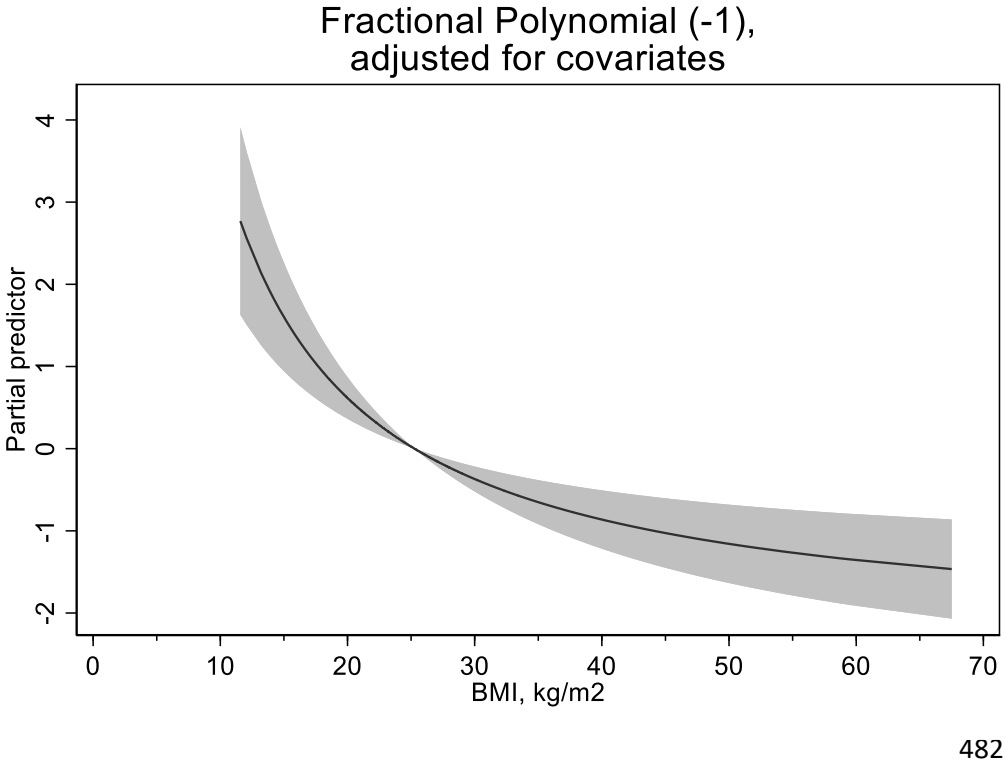


Figure 1: Kaplan-Meier plot of cumulative hazard of TB by BMI. The blue line (underweight) represents lower BMI (<18.4 kg/m^2), the red line (normal) represents the BMI between 18.5-24.9 kg/m^2, green line (overweight) represents the BMI between 25.0-29.9 kg/m^2, orange line (obese) represents BMI over 24 kg/m^2. Log rank test p<0.001.



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483 **Figure 2**: Plot of the fractional polynomial (-1) Cox regression model adjusted for age and country of enrolment. Shaded regions
484 denote 95% confidence interval for the fractional polynomial model.

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***Supplementary table 1**: Baseline data by country of randomization (n=3593)*

	N (%)	Mozambique	Ethiopia	South Africa
Overall*	3593 (100)	526 (14.6)	787 (21.9)	2280 (63.5)
Age, years				
18-29	401 (11.2)	93 (17.7)	35 (4.5)	273 (12.0)
30-39	1086 (30.2)	193 (36.7)	155 (19.7)	738 (32.4)
40-49	1243 (34.6)	141 (26.8)	325 (41.3)	777 (34.1)
≥50	863 (24.0)	99 (18.8)	272 (34.6)	492 (21.6)
Sex				
Male	1097 (30.5)	142 (27.0)	323 (41.0)	632 (27.7)
Female	2496 (69.5)	384 (73.0)	464 (59.0)	1648 (72.3)
BMI, kg/m^2				
<18.5	272 (7.6)	18 (3.4)	92 (11.7)	162 (7.1)
18.5-24.9	1756 (48.9)	327 (62.2)	482 (61.3)	947 (41.5)
25.0-29.9	897 (25.0)	137 (26.1)	167 (21.2)	593 (26.0)
≥30	668 (18.6)	44 (8.4)	46 (5.8)	578 (25.4)
CD4, cells/mm^3				
≤ 200	419 (11.7)	37 (7.1)	75 (9.5)	307 (13.5)
201-500	1480 (41.2)	207 (39.4)	347 (44.1)	926 (40.6)
≥501	1488 (41.4)	281 (53.5)	362 (46.0)	845 (37.1)
missing	206 (5.7)	1 (0.2)	3 (0.4)	202 (8.9)
ART regimen				
TDF+FTC/3TC+EFV	3406 (94.8)	525 (99.8)	644 (81.8)	2237 (98.1)
Other	187 (5.2)	1(0.2)	143 (18.2)	43 (1.9)
Time on ART, years				
< 2	763 (21.2)	110 (20.9)	88 (11.2)	565 (24.7)
2-4	880 (24.5)	224 (42.6)	87 (11.1)	569 (25.0)
≥4	1950 (54.3)	192 (36.5)	612 (77.8)	1146 (50.3)
Previous IPT				
Yes	538 (15.0)	142 (27.0)	66 (8.4)	330 (14.5)
Previous TB				
Yes	859 (23.9)	34 (6.5)	257 (32.7)	568 (24.9)

* Row percentages. All other percentages refer to column percentages. BMI: Body Mass Index; ART: Antiretroviral Therapy; TDF: Tenofovir Disoproxil Fumarate; FTC: Emtricitabine; 3TC: Lamivudine; EFV: Efavirenz; IPT: Isoniazid Preventive Therapy

***Supplementary table 2**: Bivariate analysis for selection of confounding variables for BMI, grouped*

	HRs for BMI, grouped			
Variable	**<18.4**	**18.5-24.9**	**25.0-29.9**	**≥30**
Unadjusted:	2.5 (1.4-4.6)	1	0.6 (0.4-1.2)	0.6 (0.3-1.2)
Adjusted for				
Age (4 levels)	2.6 (1.4-4.7)	1	0.6 (0.3-1.2)	0.6 (0.3-1.2)
Sex (2 levels)	2.5 (1.4-4.5)	1	0.7 (0.4-1.3)	0.7 (0.3-1.4)
Country (3 levels)	2.6 (1.4-4.7)	1	0.6 (0.3-1.1)	0.5 (0.2-1.0)
Randomization arm	2.5 (1.4-4.6)	1	0.6 (0.3-1.2)	0.6 (0.3-1.2)
Education (2 levels)	2.5 (1.4-4.6)	1	0.6 (0.3-1.2)	0.6 (0.3-1.2)
ART regimen (2 levels)	2.6 (1.4-4.6)	1	0.6 (0.3-1.2)	0.6 (0.3-1.2)
CD4 (3 levels)	2.5 (1.4-4.6)	1	0.6 (0.3-1.3)	0.5 (0.2-1.2)
Previous TB (2 levels)	2.5 (1.4-4.6)	1	0.6 (1.4-4.6)	0.6 (0.3-1.2)
Previous IPT (2 levels)	2.5 (1.4-4.6)	1	0.7 (0.3-1.2)	0.6 (0.3-1.6)

Abbreviations: BMI=body mass index; HR=hazard ratio; CI=confidence interval; ART=antiretroviral therapy; IPT=isoniazid preventive therapy;