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BRIEF REPORT

Undernourished Household Contacts Are at Increased Risk of Tuberculosis (TB) Disease, but not TB Infection—a Multicenter Prospective Cohort Analysis

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Undernutrition is the leading risk factor for tuberculosis (TB) globally and in India. This multicenter prospective cohort analysis from India suggests that undernutrition is associated with increased risk of TB disease but not TB infection among household contacts of persons with TB.

Keywords. undernutrition; malnutrition; tuberculosis; infection; India.

Globally, 10.6 million people developed tuberculosis (TB) in 2022 [1, 2]. Undernutrition can suppress the innate and adaptive immune response to *Mycobacterium tuberculosis* infection and is the leading risk factor for TB worldwide [1]. India accounted for approximately a quarter of global TB cases in 2022 and also has a high prevalence of undernutrition [1, 3]. The estimated population attributable fraction (PAF) for TB related to undernutrition was 45.2% in India [4]. It is unclear whether undernutrition increases the risk of TB infection or if it simply permits progression from a latent state to active disease.

A systematic review of 6 cohort studies in high-income countries found a log-linear relationship between body mass index (BMI) and TB incidence [5]. The authors reported a 13.8% reduction (95% confidence interval [CI], 13.4%–14.2%) in tuberculosis incidence per 1 kg/m^2 increase in BMI. Five of those 6 studies were from high income countries and may not be representative of high TB burden countries. A systematic review assessed 13 cross-sectional studies and found that being underweight was not associated with an increased risk of latent TB infection [6]. However, cross-sectional studies cannot distinguish whether interferon gamma release assay (IGRA) or tuberculin skin test positivity reflects multiple exposures or a single one and cannot quantify increased risk for infection after a recent exposure.

To understand the impact of undernutrition on TB infection and TB disease, we conducted a prospective cohort study among household contacts (HHCs) of persons with TB (PWTB) in India.

METHODS

Study Design, Setting, and Participants

To conduct a prospective cohort analysis, we recruited HHCs within 2 months of the PWTB being diagnosed. All HHCs, regardless of IGRA status, were screened for tuberculosis disease at baseline. HHCs with microbiologically confirmed prevalent TB by liquid culture, GeneXpert, or microscopy at enrollment were excluded. Participants were recruited from 5 epidemiologically and geographically diverse study sites of the RePORT India consortium [7].

Variables

Our primary exposure was BMI at the beginning of follow-up. We used the World Health Organization (WHO) cutoff of BMI < 18.5 kg/m^2 to define undernutrition. Our first outcome of interest was incident TB diagnosed microbiologically or clinically during follow-up. Participants with incident TB disease were treated by India's National TB Elimination Program. We also used a more stringent definition of TB incidence in which we only included participants who were diagnosed

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more than 90 days from enrollment to avoid including co-prevalent disease.

The second outcome we considered was IGRA conversion, which was defined as having a negative Quantiferon Gold Plus test at enrollment followed by a positive test >8 weeks afterward. We defined standard IGRA conversion as having TB1Antigen (Ag)-Nil or TB2Ag-Nil >0.35 on a repeat IGRA test based on manufacturer recommendations. We also used a previously described stringent IGRA conversion criterion: TB1Ag-Nil or TB2Ag-Nil >0.70 on a repeat test [8].

Statistical Analysis

We plotted Kaplan-Meier survival curves to distinguish between undernourished (BMI < 18.5 kg/m^2) and well-nourished (BMI≥18.5 kg/m^2) participants over 55 months of follow-up. Follow-up time was calculated from enrollment to the date of incident TB diagnosis, IGRA conversion, death, loss to follow-up, or administrative censoring, whichever came first.

Subsequently, after ascertaining that conditions were met, we conducted multivariable cox proportional hazards regression to estimate the adjusted hazard ratio of incidence of TB infection and progression to TB disease among HHCs. A priori, we used age, sex, and human immunodeficiency virus (HIV) status as covariates.

RESULTS

Of the 857 HHCs enrolled, 239 (27.9%) were with BMI < 18.5 kg/m^2 and the median (IQR) BMI was 22.03 (18.25–25.77) kg/m^2. The median (IQR) age was 29 (18–40) years, 506 (59.04%) were female, 65 (7.58%) had alcohol use, 42 (4.9%) were ever smokers, and 3 (0.3%) had HIV. In total, 357 (41.7%) of participants had a household income of more than Rs. 10 000 ($125) per month. The median (IQR) follow-up period was 24 (24–34) months. There were 18 incident TB cases during follow-up; 10 cases were among HHCs with BMI < 18.5 kg/m^2. When applying the stringent criteria, 4 cases from 2 households were excluded as they occurred within one week of enrollment and within 2 weeks of the diagnosis of the index cases. All 4 participants with early TB disease were severely malnourished with BMI < 16 kg/m^2. Of the 857 HHCs enrolled, 377 had negative IGRAs at baseline. Of these, 264 participants had repeat IGRAs: 56 participants had a standard IGRA conversion, and 43 participants had an IGRA conversion with a more stringent criterion.

The Kaplan-Meier curve (Figure 1*A*) shows that undernourished individuals (BMI < 18.5 kg/m2) were at increased risk of progression to TB disease. We estimated a hazard ratio (HR) of 3.16 (95% confidence interval [CI]: 1.25, 8.02) for TB disease in undernourished individuals. When using the stringent TB incidence definition, the HR was 1.88 (95% CI: .65–5.43). Univariate cox regression analysis (Supplementary Table 1) revealed that 1 kg/m^2 increase in BMI was associated with a lower hazard of incident TB (HR 0.83, 95% CI: .74, .93). After adjusting for age, sex, and HIV status, the association between BMI and incident TB disease remained significant (adjusted hazard ratio [aHR] 0.85, 95% CI: .73, .98). When we considered the stringent definition of incident TB disease, the univariate estimate was similar, HR 0.89 (.80–1.00), but the confidence interval crossed unity on multivariable analysis: aHR 0.88 (95% CI: .76–1.02).

The survival curve did not show any clear differences in IGRA conversion between undernourished and well-nourished individuals (Figure 1*B*), and the hazard ratio based on log rank test was 1.23 (95% CI: .71, 2.13). We did not find a significant association between BMI and risk of IGRA conversion as defined by either the standard or the stringent criteria (Supplementary Table 1). Even after adjusting for age and sex, the association between BMI and IGRA conversion remained unchanged (aHR 0.98, 95% CI: .92, 1.04 for permissive IGRA conversion and aHR 0.97, 95% CI: .90, 1.04). Using the more stringent criterion for IGRA conversion did not change the association (Supplementary Table 2).

CONCLUSION

Our findings indicate that lower BMI is likely associated with increased risk of incident TB disease, but not necessarily increased risk of TB infection. These results are consistent with previous analyses that have demonstrated the significant and dose-dependent impact of undernutrition, as measured by BMI, on the risk of incident TB disease [5]. The insight that undernourished individuals are at increased risk of progression, not infection is crucial for developing and refining transmission models of TB and for targeting interventions to mitigate the impact of undernutrition on the TB pandemic.

The recently published RATIONS study has demonstrated that nutritional support can reduce incident TB among HHCs by approximately 40% over a two-year period [9]. However, the study was conducted in a population with severe multidimensional poverty where 40% of participants were below the poverty line. The impact of nutrition on TB in less deprived populations was unclear. In our cohort, at least 89% of individuals were above the poverty line, which suggests that undernutrition is also an important driver of TB in less impoverished populations in India.

This analysis has several strengths. The prospective design allows us to assess the risk of undernutrition on the incidence of TB infection and disease which is not possible in retrospective designs due to the weight loss caused by TB disease. The multicenter design makes our data more representative and diverse from a demographic, socioeconomic, and biological perspective.

Our analysis of the association between nutrition and incident TB disease does have limitations. The sample size

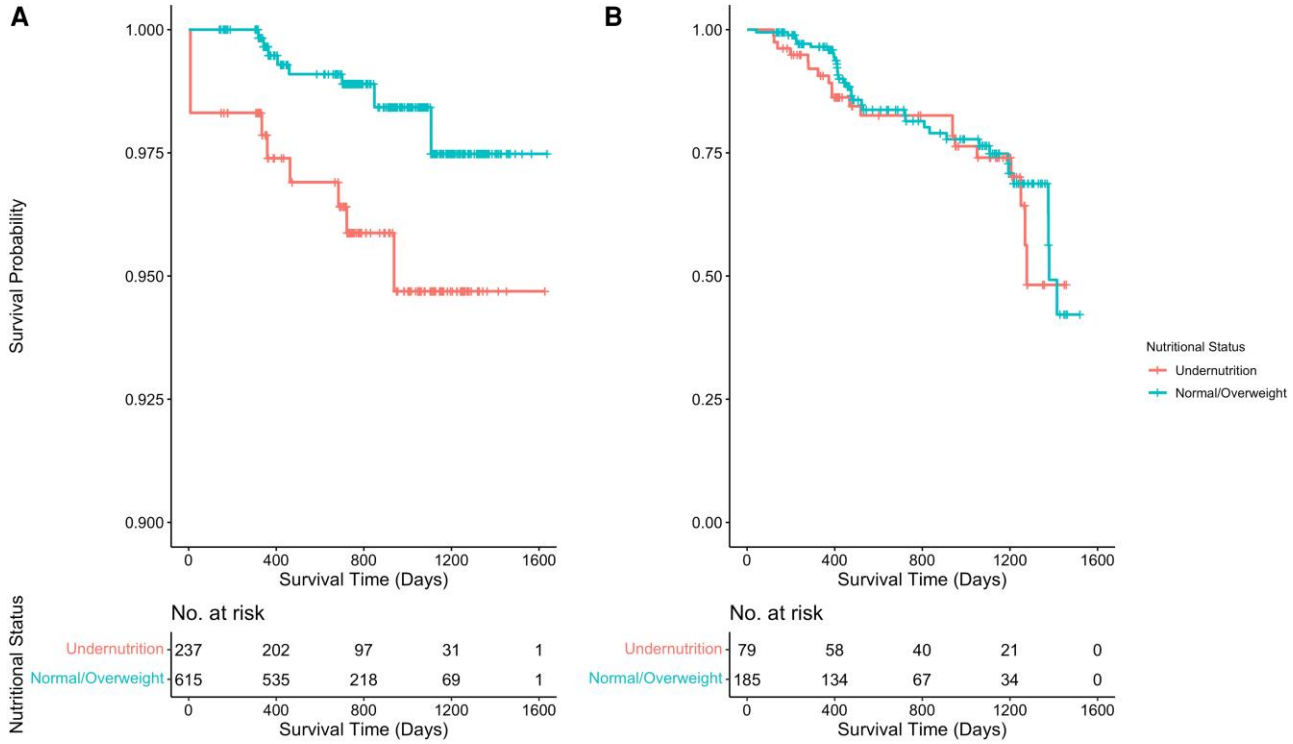

Figure 1. Survival curve of household contacts of persons living with TB showing (*A*) time to incident TB disease (*B*) time to IGRA conversion for household contacts who had a negative IGRA test at baseline. Abbreviations: IGRA, interferon gamma release assay; TB, tuberculosis.

was too small to permit subgroup analyses and limited number of covariates in multivariable analyses. Additionally, the 4 HHCs who developed TB disease within a week of enrolment may have had co-prevalent TB that precipitated weight loss. In these cases, the causal relationship may have been reversed. That said, it is also possible that they progressed to primary tuberculosis disease promptly after exposure due to their nutritionally acquired immunodeficiency. Further, we lacked data on some risk factors that can increase risk of TB disease: diabetes status, quantitative data regarding alcohol and tobacco use, and micronutrient deficiencies [1, 2]. Larger prospective studies are needed to validate these findings and understand the interplay between undernutrition and other TB risk factors. Given that TB risk is not constant and individual risk factors —particularly nutritional status—are dynamic, future studies should collect longitudinal data and consider an extended cox model with time-dependent variables.

Similarly, our analysis of TB infection was limited by some factors. We did not have the inputs necessary to calculate the Mandalakas score which predicts risk of TB infection in HHCs [10]. Additionally, there may have been some selection bias as we only had follow-up IGRAs on 70% of participants with negative initial IGRAs. Some IGRA conversions may have reflected exposure to *M. tuberculosis* outside the household. Furthermore, although IGRA conversion reflects infection with *M. tuberculosis*, it is unable to determine if the infection has been cleared through an adaptive immune response. In future studies, transcriptomic tests may be able to distinguish between current and past TB infections [11].

Our findings highlight that undernourished individuals are a key and vulnerable population. Correcting nutritional deficits is likely to have an outsize impact on eliminating TB while being cost-effective [9, 12]. We must prioritize operational and policy research to identify cost-effective nutritional interventions to reduce the incidence of TB disease.

Supplementary Data

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

Notes

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References

1. WHO. Global tuberculosis report 2023. Geneva, Switzerland: World Health Organization, **2023**.
2. Dauphinais MR, Koura KG, Narasimhan PB, et al. Nutritionally acquired immunodeficiency must be addressed with the same urgency as HIV to end tuberculosis. BMC Glob Public Health **2024**; 2:1–9.
3. FAO India, UNICEF, WFP, WHO. The state of food security and nutrition in the world 2023. Urbanization, agrifood systems transformation and healthy diets across the rural–urban continuum 2023. **2023**:1–316. Available at: https://fao.org. Accessed 25 February 2024.
4. Bhargava A, Bhargava M, Beneditti A, Kurpad A. Attributable is preventable: corrected and revised estimates of population attributable fraction of TB related to undernutrition in 30 high TB burden countries. J Clin Tuberc Mycobact Dis **2022**; 27:100309.
5. Lönnroth K, Williams BG, Cegielski P, Dye C. A consistent log-linear relationship between tuberculosis incidence and body mass index. Int J Epidemiol **2009**; 39: 149–55.
6. Saag L, LaValley M, Hochberg N, et al. Low body mass index and latent tuberculous infection: a systematic review and meta-analysis. Int J Tuberc Lung Dis **2018**; 22:358–65.
7. Sinha P, Ponnuraja C, Gupte N, et al. Impact of undernutrition on tuberculosis treatment outcomes in India: a multicenter prospective cohort analysis. Clin Infect Dis **2023**; 76:1483–91.
8. Sloot R, Shanaube K, Claassens M, et al. Interpretation of serial interferon-gamma test results to measure new tuberculosis infection among household contacts in Zambia and South Africa. BMC Infect Dis **2020**; 20:1–19.
9. Bhargava A, Bhargava M, Meher A, et al. Nutritional supplementation to prevent tuberculosis incidence in household contacts of patients with pulmonary tuberculosis in India (RATIONS): a field-based, open-label, cluster-randomised, controlled trial. Lancet **2023**; 402:627–40.
10. Mandalakas A, Kirchner H, Lombard C, et al. Well-quantified tuberculosis exposure is a reliable surrogate measure of tuberculosis infection. Int J Tuberc Lung Dis **2012**; 16:1033–9.
11. VanValkenburg A, Kaipilyawar V, Sarkar S, et al. Malnutrition leads to increased inflammation and expression of tuberculosis risk signatures in recently exposed household contacts of pulmonary tuberculosis. Front Immunol **2022**; 13:1011166.
12. Sinha P, Lakshminarayanan SL, Cintron C, et al. Nutritional supplementation would be cost-effective for reducing tuberculosis incidence and mortality in India: the ration optimization to impede tuberculosis (ROTI-TB) model. Clin Infect Dis **2022**; 75:577–85.