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Oft-overlooked: controlling for undernutrition in epidemiological studies of tuberculosis

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We read with interest the large longitudinal study by Ranzani et al. which provides sobering evidence regarding the increased mortality of persons living with tuberculosis (PLWTB).[1] It is truly striking to see the high mortality rate among PLWTB, particularly in those who were disadvantaged from the socio-economic perspective. We applaud Ranzani et al. for presenting data that highlight the urgency of addressing the socioeconomic risk factors that keep tuberculosis (TB) entrenched in society. The authors controlled for numerous important risk factors, but acknowledged the potential for confounding due to the lack of nutritional status in their dataset.

Given the long-established connection between undernutrition and mortality, not accounting for malnutrition in epidemiological analyses may result in underestimations or overestimations of other risk factors. Ranzani et al. found that alcoholism and homelessness were both associated with higher mortality. Both these conditions are also associated with undernutrition. Further, as nutrition is both a cause and a consequence of TB disease, nutritional status may also serve as a marker for severity of TB disease.[2]

A large base of literature supports the importance of controlling for undernutrition. Undernutrition is the leading risk factor for TB with a population-attributable fraction of 2.3 million in 2018 which was higher than that of human-immunodeficiency virus (HIV) (1.2 million) and diabetes (0.8 million).[2,3] Undernourished individuals may also be more prone to cavitation, have greater lung involvement, and have a higher likelihood of treatment failure or relapse.[2] Furthermore, undernutrition has been associated with higher mortality. For instance, a large Indian study found that, after controlling for other risk factors, every unit increase in BMI decreased risk of death during TB treatment (aOR, 0.78 per kg/m^2 [95% CI, .68–.90].[4] In an Ethiopian cohort with a high rate of HIV (18.3%), PLWTB who weighed <35 kg at the time of treatment initiation had a four-fold higher risk of mortality despite treatment (aHR 3.9 [95% CI, 1.6–9.3]).[5]

We encourage future epidemiological studies to *a priori* include markers of nutrition such as BMI, mid-upper-arm circumference, or WHO-recommended Z scores (in children) as predictor variables. Large TB programs should incorporate screening for undernutrition just

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as they would for other important risk factors such as HIV infection. Analyses that don't account for undernutrition may have to be taken with a pinch of salt.

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