Journal of Clinical Tuberculosis and Other Mycobacterial Diseases 27 (2022) 100309

Contents lists available at ScienceDirect

Journal of Clinical Tuberculosis and Other Mycobacterial Diseases

journal homepage: www.elsevier.com/locate/jctube

Attributable is preventable: Corrected and revised estimates of population attributable fraction of TB related to undernutrition in 30 high TB burden countries

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ARTICLE INFO

Keywords:
Global TB report
Undernutrition
Undernourishment
Tuberculosis
Population attributable fraction

ABSTRACT

Introduction: The Global TB Report 2020 estimated the population attributable fractions (PAF) for the major risk factors of TB. Undernourishment emerged as the leading risk factor accounting for 19% of the cases. The WHO however used the terms undernourishment and undernutrition interchangeably in its computation of PAF. Undernourishment is an indirect model derived estimate of decreased per capita energy availability, while undernutrition is defined by direct anthropometric measurements of nutritional status. An estimate of PAF for a risk factor should use the prevalence and the risk ratio of the same risk factor, which is not the case with the current methodology.

Methods: We re- estimated the PAF of undernutrition (instead of undernourishment) in 30 high TB burden countries as defined by WHO for the period 2016–2020, using the prevalence of undernutrition (age standardized estimate of BMI < 18.5 kg/m^2 in adults for both sexes), and the relative risk (RR) of 3.2. Further, we revised PAF estimates of undernutrition with an RR of 4.49 (95% CI: 2.28, 8.86), in light of recent evidence.

Findings: In 30 high TB burden countries, 24.1% (95% CI: 17.6,30.0) of incident TB is attributable to undernutrition. The PAF of undernutrition was highest in Asian countries, unlike the PAF of undernourishment that was highest in Africa. The corrected estimate led up to 65% increase in number of cases attributable to undernutrition in Asian countries. If a revised relative risk was used, 33.0% (95% CI: 10.1, 60.1) of incident TB cases in the selected countries could be attributable to undernutrition. More than one-third to nearly half of incident TB cases in India could be attributable to undernutrition.

Interpretation: Estimation of the PAF of TB related to undernutrition is methodologically valid and operationally relevant, rather than PAF related to undernourishment, and should be used for future Global TB reports by WHO. Addressing undernutrition, the leading driver of TB in high TB burden countries (especially Asia) could enable achievement of END TB milestones of TB incidence for 2025.

1. Background

Tuberculosis (TB) is a major public health problem that causes morbidity and premature mortality in the low and middle income countries (LMICs). In the year 2019, an estimated 10 million people fell ill with TB, 1.2 million HIV negative patients with TB died, and 0.21 million patient with HIV-TB co-infection died (95% in LMICs) [1]. The new END TB strategy has ambitious goals for reduction of TB incidence and mortality and end the epidemic by 2035. The strategy has milestones for 2020 and 2025 that require TB incidence to decline by 20% and 50%, and TB mortality to decline by 35% and 75% by 2020 and 2025 respectively compared to the baseline 2015 [2]. The reduction so far (9% of new cases, 14% of mortality) since 2015 is not adequate to reach these milestones [1]. The END TB strategy envisages public health

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https://doi.org/10.1016/j.jctube.2022.100309

Available online 8 March 2022

interventions that address the social determinants and risk factors of TB to complement the biomedical interventions, and achieve the 10% annual decline in TB incidence required to reach the 2025 milestone [2].

Infection with mycobacterium tuberculosis is necessary but not sufficient to result in TB disease. Latent infection of TB (LTBI) is prevalent in nearly one-quarter of the world population but only 10% progress to active TB in their life time; innate and adaptive immunity prevents the progression in the rest [3,4]. Conditions like HIV infection, undernutrition (defined for example by a low body mass index, BMI), diabetes, alcohol use disorders and tobacco use, impair immune responses, increase the risk of active TB and act as drivers of the TB epidemic at the population level [5,6]. The strong, consistent and inverse association of BMI and TB incidence has been noted in large historical cohorts [7], and in recent cohort studies that have adjusted for confounders [8–10]. A systematic review of cohort studies concluded that this association of BMI and TB was likely causal [7].

The population attributable fraction (PAF) is an epidemiologic measure that estimates the public health impact of a particular risk factor for an outcome. It is the proportion by which the incidence of an outcome in the entire population would be reduced if the risk factor was eliminated [11]. The key parameters that determine the PAF are the prevalence of a risk factor and the relative risk (RR) of disease associated with it [11].

An estimate of the PAFs of these risk factors in 22 high TB burden countries was first reported in 2010 [12]. These were 11.0% for HIV, 26.9% for undernutrition, 7.5% for diabetes, 9.8% for alcohol-use disorders, and 15.8% for smoking and these varied in individual countries [12]. In South Africa, the PAF for HIV was 69.1% due to high HIV prevalence (18.1%); it was 35% for alcohol in Russia and 31.6% for undernutrition in India [12]. For estimation of the PAF of undernutrition, the prevalence of *undernourishment* in the total population, according to Food and Agriculture Organization (FAO) estimates of 2008 were used, instead of prevalence of *undernutrition* [12]. The RRs of the risk factors in the above estimation were 26.7 for HIV, 3.2 for undernutrition, 3.1 for diabetes, 2.9 for alcohol-use disorders, and 2.0 for smoking [12]. The RR of 3.2 (95%CI 3.1, 3.3) for undernutrition was based on a *meta*-analysis that compared the risk of TB for BMI 16 kg/m^2 versus 25 kg/m^2 showing an average reduction in TB incidence of 13.8% (95%CI 13.4, 4.2) per unit increase in BMI [7]. This systematic review included six cohort studies, the most recent of which had not published final results at that time [7].

In 2020, the Global TB Report updated the current PAFs for these risk factors; 19% for undernourishment, 7.7% for HIV, 3.1% for diabetes, 8.1% for alcohol use disorders, and 7.1% for smoking. The number of attributable cases related to these risk factors were estimated as 2.2 million for undernourishment, 0.76 million for HIV, 0.35 million for diabetes, 0.72 million for alcohol use disorders, and 0.70 million for smoking. *Undernourishment* emerged as the leading risk factor, accounting for nearly three times the cases attributable to HIV, or that attributable to the combined diabetes, alcohol and tobacco [1].

2. Rationale for correction of population attributable fraction of "undernourishment" as reported in the Global TB report 2020

The PAF in 2010 was reported for the risk factor of *undernutrition* while in 2020 it was reported for the risk factor of *undernourishment* [1,12]. These two terms have been used interchangeably in these 2 estimates. However, *undernourishment* as defined by FAO is different from *undernutrition* for public health and clinical purposes [13].

The FAO defines undernourishment as chronic food insecurity in which food intake is insufficient to meet basic energy requirements over a continuing basis [13]. The part of the population with food consumption below energy requirement norms (expressed in terms of dietary energy in kcal) is considered undernourished [13]. Prevalence of undernourishment estimates the percentage of population with "habitual insufficient food consumption to provide, on an average, the amount of dietary energy required for maintaining a normal, active and healthy life" [14]. It is a not based on actual energy intakes but per capita energy availability [13] based on data from the food balance sheets for the country, inequality in energy intakes, and the country energy requirements by sex and age group [14]. These are used to derive the four parameters in the analytic formula of prevalence of undernourishment (Box 1). It is based on indirect national-level model-based indicator that measures chronic hunger in a population [14]. We cannot perform disaggregated analysis to identify specifically vulnerable populations nor can we compute margins of error for the prevalence of undernourishment.

Box 1

: Estimation of prevalence of undernourishment by food and Agriculture Organization (FAO)

Prevalence of Undernourishment estimates are obtained using the following analytic formula [14]:

$$\text{Prevalence of Undernourishment} = \int_{-\infty}^{MDER} f(x|DEC; CV)dx$$

$$CV = \sqrt{(CV|y)^2 + (CV|r)^2}$$

Dietary Energy Consumption (DEC): It is an estimate of the per capita level of the average habitual, daily dietary energy consumption in the population.

MDER (Minimum Dietary Energy Requirement): It is the amount of energy needed for light activity and a minimum acceptable weight for attained height, and depending upon the gender and age structure of the population, it varies by country and from year to year.

Coefficient of Variation (CV): It is an estimate of the CV of the distribution of per capita levels of habitual dietary energy consumption and is the combination of two components. The $CV|y$ is the component that is associated with differences in energy requirements in the population of a country. $CV|r$ is the part of the variation that can be associated with differences in the socio-economic characteristics of the households

Undernutrition, on the other hand, is a physiological condition resulting from prolonged low level of food intake and/or poor absorption of food consumed [13]. It is based on actual measurement of individual nutritional status [13], and "describes the status of persons whose heights and weights lie below the lower limits of the ranges established for healthy people" [15]. It is defined based on a low BMI (<18.5 kg/m^2) that reflects low body energy stores or chronic energy deficiency in adults [16], while in children it is defined in terms of wasting, stunting or underweight. It has also been accepted as a criterion for clinical diagnosis of malnutrition/undernutrition in a consensus statement [5].

Thus undernourishment and undernutrition are two temporally distinct terms derived from different analytical approaches; undernourishment precedes the potential development of undernutrition, and these are not interchangeable. The FAO considered them complementary measures (Fig. 1) [13]. Previous studies have highlighted that there

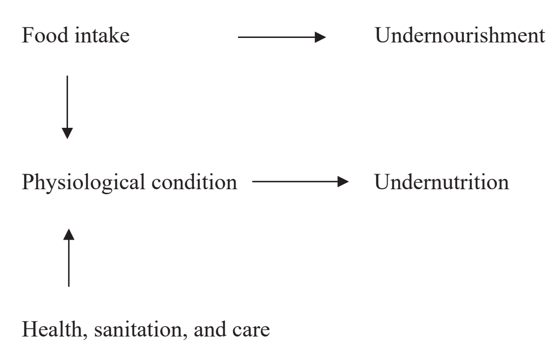

Fig. 1. Differentiating undernourishment and undernutrition. Legend: Undernourishment is defined by FAO as chronic food insecurity with food intake insufficient to meet basic energy requirements. Undernutrition is a physiological state resulting from insufficient intake or utilization of food, reflected in heights and weights below the lower limits of the ranges established for healthy people.

may be differences in their estimates as the former refers to poor food availability while the latter is its consequence identified by anthropometry, and affected by repeated infections, poor care and neglect [17].

Further, an estimate of PAF for any risk factor relies on the prevalence and the RR of the same exposure or risk factor, but this is not the case in the present methodology. For the estimation of PAF of TB due to undernourishment the prevalence used is based on chronic food insecurity (prevalence of undernourishment) while the RR is based on the risk based on a low body mass index (BMI) on an anthropometric measurement. The 2010 estimates of PAF for *undernutrition* erred in using the prevalence of undernourishment for its computation. On the other hand, the 2020 estimate of PAF for *undernourishment* errs in using the RR of undernutrition. It may be pointed out that RR for undernourishment is not available, as it is only a population level estimate.

2.1. Recent evidence in favor of revising RR of TB related to undernutrition:

Previous reviews of TB epidemiology have suggested RR of undernutrition as 4.0 (Range: 2.0–6.0) [18]. The RR of 3.2 was derived from a systematic review of cohort studies in 2009 [7]. However, studies in the past decade suggest a need for an upward revision of this RR. The final results of a US-based cohort study in a nationally representative sample of participants included in the systematic review were published in 2012 [10]. It also controlled for multiple confounders to arrive at the effects of nutritional status on TB incidence, and one of the few studies that had risk estimates for those with BMI < 18.5 kg/m^2 [10]. The hazard ratio was 12.43 (95%CI: 5.75, 26.95) and the RR was 4.49 (95%CI: 2.28, 8.86; $p < 0.0005$) for the development of TB with BMI < 18.5 kg/m^2 compared to those with normal BMI (18.5–25 kg/m^2) [10]. A modelling study estimating the impact of reducing undernutrition on TB incidence in some high TB burden states in India [19], incorporated the final published results of this study into those of the previous *meta*-analysis [7]. It estimated RRs of 4.95 and 3.00 for those with BMI quartiles of $\leq$ 17.8 kg/m^2, 17.80-$\leq$19.64 kg/m^2 compared to the reference of 22.25 kg/m^2 [19]. Recently in a cohort of household contacts of patients with active pulmonary TB in India, HIV and undernutrition were the only two independent risk factors associated with the risk of incident TB [20]. The adjusted incidence rate ratio of undernutrition was 6.16 (95%CI: 1.89, 20.03) measured as a composite index of low BMI ($<$18.5 kg/m^2) in adults, and less than two z-scores of weight or BMI for age in children [20]. Thus, the RR of 3.2 based on a comparison of BMI of 16 kg/m^2 vs. BMI of 25 kg/m^2 is a conservative estimate, since the risk and rate ratio of those with BMI$<$18.5 were exceeding 4.0 in recent studies [10,19,20].

3. Objectives

Our objective was to correct the estimates of PAF of undernutrition for TB using the prevalence and RR of undernutrition in 30 high burden countries and to revise them using an updated RR based on recent evidence.

4. Methods

The list of 30 high TB burden countries is as defined by the WHO for the period 2016–2020. These include 20 countries with the highest estimated number of incident TB cases, and in addition the top 10 countries which have the highest estimated TB incidence rate but do not feature in the list top 20 based on the absolute numbers of incident TB cases [1].The current estimated PAFs and prevalence of undernourishment were taken from the Global TB Report 2020 [1]. Undernutrition was defined as a low BMI ($<$18.5 kg/m^2) in adults [16]. For the prevalence of undernutrition, we used the age-standardized estimate of prevalence of underweight (BMI < 18.5 kg/m^2) in both sexes in 30 high TB burden countries from the BMI database of the WHO Global Health Observatory [21]. PAFs were derived using the Levin formula [22]:

$$\text{PAF} = \frac{\text{Prevalence}(\text{relativerisk} - 1)}{\text{Prevalence}(\text{relativerisk} - 1) + 1}$$

First, we derived a corrected estimate of PAF by substituting the prevalence of undernourishment with prevalence of undernutrition. We further revised the PAF using RR for undernutrition as 4.49. Confidence intervals (CI) for the PAFs were estimated using the method suggested by Natarajan et al. [23]. We also derived the number of cases attributable to undernutrition by multiplying the annual number of incident TB cases from the Global TB Report 2020 by the estimated PAFs (Fig. 2). The overall PAF related to undernutrition for the 30 high TB burden countries in turn was estimated by dividing the total number of cases attributable to undernutrition by the total number of incident cases of TB in the selected countries. We estimated the 95% confidence intervals for the overall PAF by summing up the lower limit and the upper limit of the attributable cases and dividing them by the total number of incident cases in the 30 high TB burden countries.

5. Results

Table 1 shows the TB incidence and prevalence of undernourishment in 30 high TB burden countries, the estimated PAF using a RR of 3.2 and the number of cases attributable to undernourishment The median (IQR) of the prevalence of undernourishment was 18% (10.6, 29.5), that for PAF related to undernourishment was 28.3% (18.9, 39.3). An estimated 23.6% (1.96 million) of the estimated 8.30 million incident cases in 28 high burden countries (excluding Democratic Republic of Congo, DRC and Papua New Guinea as they do not have data on prevalence of undernourishment) were attributable to undernourishment In Asian countries, the prevalence of undernourishment ranged from 7.8% in Thailand to 20% in Pakistan, while in African countries it ranged from 6.2% in South Africa to 60% in Central African Republic. The PAFs of undernourishment in African countries ranged from 12% in South Africa to 56% in Central African Republic, and in Asian countries from 14% in Thailand to 30% in Pakistan. The three countries with the highest PAFs of undernourishment globally were Central African Republic, Zimbabwe, and Democratic Republic of Korea; and overall the PAFs

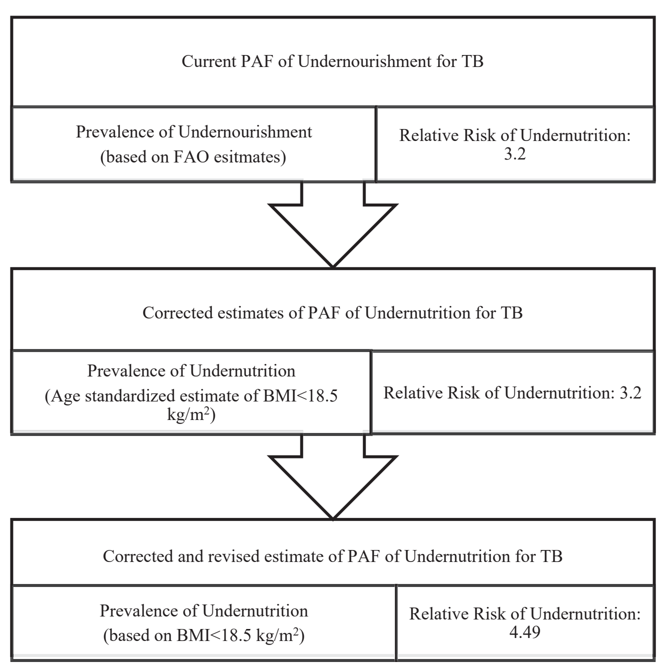

Fig. 2. Steps in arriving corrected and revised estimates of Population Attributable Fraction of undernutrition for TB.

Table 1
Population Attributable Fraction for Tuberculosis and attributable TB cases in high burden countries using prevalence of undernourishment (FAO estimates) and RR = 3.2.

High TB burden Countries	Incident TB cases per year#	Prevalence of undernourishment (%)*	Population attributable fraction (%)	Attributable TB cases §
Angola	112,000	25	35.5	39,742
Bangladesh	361,000	15	24.8	89,571
Brazil	96,000	2.5	5.2	5005
Cambodia	47,000	16	26.0	12,237
CAR	26,000	60	56.9	14,793
China	833,000	8.6	15.9	132,529
Congo	20,000	40	46.8	9362
DPRK	132,000	48	51.4	67,798
DRC	278,000	Data not available		
Ethiopia	157,000	21	31.6	49,613
India	2,640,000	15	24.8	655,038
Indonesia	845,000	8.3	15.4	130,473
Kenya	140,000	29	38.9	54,530
Lesotho	14,000	13	22.2	3114
Liberia	15,000	37	44.9	6731
Mozambique	110,000	28	38.1	41,931
Myanmar	174,000	11	19.5	33,903
Namibia	12,000	27	37.3	4472
Nigeria	440,000	13	22.2	97,854
Pakistan	570,000	20	30.6	174,167
PNG	38,000	Data not available		
Philippines	599,000	13	22.2	133,215
Russian Federation	73,000	2.5	5.2	3806
Sierra Leone	23,000	26	36.4	8369
South Africa	360,000	6.2	12.0	43,210
Thailand	105,000	7.8	14.6	15,379
URT	137,000	31	40.5	55,549
Viet Nam	170,000	9.3	17.0	28,874
Zambia	59,000	47	50.8	29,993
Zimbabwe	29,000	51	52.9	15,334

Source: Global TB report 2020 * Based on Food and Agriculture Organization (FAO) estimates of prevalence of undernourishment cited in Global TB Report 2020 [1]. Abbreviations: CAR = Central African Republic; DPRK = Democratic People's Republic of Korea; DRC = Democratic Republic of the Congo; PAF = Population Attributable Fraction; RR = Relative Risk; PNG = Papua New Guinea; URT = United Republic of Tanzania.
Note: It is not possible to compute margins of error around prevalence of undernourishment estimates.

were higher in the African countries than the Asian countries.

Table 2 shows the prevalence of undernutrition, the corrected estimates of PAF and number of attributable cases. The median (IQR) of prevalence of undernutrition was 11.2% (8.0, 14.4), that of the PAF related to undernutrition was 19.7% (15.0, 24.0), and 24% (2.07 million) of incident cases in all the 30 high burden countries were attributable to undernutrition. The prevalence of undernutrition was higher in the Asian countries compared to prevalence of undernourishment with a few exceptions and ranged from 12.3% in Philippines to 23.6% in India (the highest globally). In the African countries, the prevalence of undernutrition was lower than prevalence of undernourishment without exception and ranged from 4.7% in South Africa to the highest of 15.9% in DRC. In South Africa and Zimbabwe it was lower by 24% and 84% than the prevalence of undernourishment estimates respectively. When the PAFs were recomputed replacing undernourishment with undernutrition, the median (IQR) PAF was 19.7 % (15.0, 24.0) with a range of 3% in Russia to 34.2% in India. The PAFs of undernutrition in African countries ranged from 9% in South Africa to 26% in DRC and in Asian countries from 10% in China to 34% in India. The three countries with the highest PAF of undernutrition globally were India, Bangladesh and Vietnam. Among the African countries, the number of attributable cases declined by a median (IQR) of 50% (35, 57). The overall increase in attributable cases in Myanmar, Bangladesh, India, Indonesia and Vietnam was 25%, 29%, 38%, 43%, and 65% respectively; an overall median (IQR) increase of 16.7% (10, 35.7) in Asian countries. The number of cases attributable to undernutrition was 1.7 million in Asian countries and 0.37 million in African countries.

Table 3 shows the PAFs corrected using prevalence of undernutrition and revised RR of 4.49 (95%CI: 2.28, 8.86). The median (IQR) PAF attributable to undernutrition in 30 high TB burden countries was 28% (21.8, 33.4). An estimated 32.9% (95% CI: 10.1, 60.1) or 2.84 million of 8.62 million incident cases in the selected countries were attributable to undernutrition. The revised PAF of undernutrition ranged from 5.9% in Russia to a maximum of 44.5% in India. The estimated number of cases attributable to undernutrition computed with a higher RR of undernutrition was 2.3 millions in Asia and 0.45 millions in Africa.

Tables 2 and 3 also show the impact of corrected and revised estimate on the number of cases attributable to undernutrition in India, the country with the highest burden of TB as well as prevalence of undernutrition. According to current estimates a quarter of the cases in India may be related to undernutrition (0.67 millions). Using a correction of PAF based on prevalence of undernutrition, this figure rises to one-third of incident cases (0.9 million), while using a revised RR it is nearly half of incident cases (1.2 millions). Fig. 3 describes the TB incidence in all 30 high burden countries, the current, corrected and the revised figures (in thousands).

6. Discussion

We noted and addressed a methodological issue affecting the validity of the 2010 and 2020 estimates attributable to undernutrition and undernourishment, respectively. The terms undernutrition and undernourishment were used interchangeably. The PAF of undernutrition in the 2010 estimate thus used the prevalence of undernourishment (rather than prevalence of low BMI or undernutrition). The recent estimate of PAF of undernourishment used RR of undernutrition (there is no RR for TB available for the exposure of undernourishment).

We present for the first time, methodologically corrected estimates of the PAF of TB related to undernutrition, using both the prevalence and RR of the same risk factor of undernutrition. We also reported the number of cases attributable to undernutrition in high TB burden countries. Overall, the median PAF of undernutrition was 19.7%

Table 2

Population Attributable Fraction for Tuberculosis related to Undernutrition and attributable TB cases in high burden countries using prevalence of undernutrition based on anthropometry* and Relative Risk of 3.2 (95% CI: 3.1, 3.3).

High TB burden Countries	Incident TB cases	Prevalence of undernutrition based on anthropometry [%, (95% CIs)] *	PAF for undernutrition# [%, (95% CIs)]	Attributable TB cases [(95% CIs)] §
Angola	112,000	13.5 (7.2, 21.10)	22.9 (10.4, 33.2)	25,647 (11,643, 37,169)
Bangladesh	361,000	21.5 (16.80, 26.70)	32.1 (24.9, 38.6)	115,922 (89,725, 139,401)
Brazil	96,000	27.0 (18.0, 39.0)	5.6 (3, 8.3)	5.383 (2,915, 7,954)
Cambodia	47,000	13.6 (8.90, 19.10)	23 (14, 31)	10,824 (6,561, 14,587)
CAR	26,000	14.8 (8.9, 21.6)	24.6 (13.6, 33.8)	6,386 (3,537, 8,792)
China	833,000	5.3 (3.9, 6.9)	10.4 (7, 14)	86,985 (58,014, 116,427)
Congo	20,000	13.1 (8.9, 19.1)	22.4 (13.2, 30.5)	4,474 (2,636, 6,096)
DPRK	132,000	6.6 (3.1, 12.2)	12.7 (2.8, 21.5)	16,736 (3,749, 28,335)
DRC	278,000	15.9 (10.0, 22.5)	25.9 (15.5, 34.8)	72,044 (42,969, 96,746)
Ethiopia	157,000	15.8 (10.5, 21.9)	25.8 (16.2, 34.1)	40,497 (25,494, 53,498)
India	2,640,000	23.6 (19.9, 27.6)	34.2 (28.6, 39.3)	902,446 (755,413, 1,038,631)
Indonesia	845,000	12.9 (9.3, 16.9)	22.1 (15.2, 28.5)	186,798 (128,076, 241,175)
Kenya	140,000	11.8 (7.6, 16.9)	20.6 (11.9, 28.4)	28,854 (16,696, 39,745)
Lesotho	14,000	7.9 (4.9, 11.6)	14.8 (7.8, 21.4)	2,073 (1,097, 2,991)
Liberia	15,000	8.3 (4.9, 12.50)	15.4 (7.6, 22.7)	2,316 (1,145, 3,398)
Mozambique	110,000	11.1 (7.1, 15.9)	19.6 (11.2, 27.2)	21,590 (12,374, 29,918)
Myanmar	174,000	14.6 (10.4, 19.5)	24.3 (16.4, 31.4)	42,302 (28,545, 54,711)
Namibia	12,000	9.7 (6.1, 14.1)	17.6 (9.7, 24.8)	2,110 (1,161, 2,981)
Nigeria	440,000	10.3 (7.3, 13.9)	18.5 (12, 24.6)	81,285 (52,777, 108,162)
Pakistan	570,000	15.0 (10.8, 19.9)	24.8 (17, 31.9)	141,429 (96,812, 181,693)
PNG	38,000	2.3 (1.0, 4.4)	4.8 (0.7, 8.9)	1,830 (281, 3,400)
Philippines	599,000	12.3 (84, 16.7)	21.3 (13.6, 28.3)	127,569 (81,626, 169,541)
Russian Federation	73,000	1.8 (1.1, 2.6)	3.8 (1.9, 5.8)	2,781 (1,409, 4,233)
Sierra Leone	23,000	10.3 (6.4, 14.9)	18.5 (10.2, 26)	4,249 (2,347, 5,977)
South Africa	360,000	4.7 (3.2, 6.4)	9.4 (5.7, 13.1)	33,736 (20,360, 47,290)
Thailand	105,000	8.6 (5.6, 12.3)	15.9 (9.1, 22.4)	16,705 (9,512, 23,472)
URT	137,000	11.0 (7.5, 15.1)	19.5 (12.2, 26.2)	26,694 (16,717, 35,923)
Viet Nam	170,000	17.7 (13.6, 22.1)	28 (21.1, 34.3)	47,645 (35,943, 58,342)
Zambia	59,000	11.2 (7.0, 16.0)	19.8 (11.2, 27.5)	11,664 (6,623, 16,202)
Zimbabwe	29,000	7.9 (5.0, 11.4)	14.8 (8.1, 21.1)	4,294 (2,360, 6,124)

*Source for age standardized BMI < 18.5 kg/m^2 in both sexes reported in Global Health Observatory database on BMI (accessible at https://www.who.int/data/gho/data/themes/topics/topic-details/GHO/body-mass-index); #PAF calculated using a RR of 3.2(95%CI: 3, 3.3);

Abbreviations: CAR = Central African Republic; DPRK = Democratic People's Republic of Korea; DRC = Democratic Republic of the Congo; PAF = Population Attributable Fraction; RR = Relative Risk; PNG = Papua New Guinea; URT = United Republic of Tanzania.

§ Attributable cases using prevalence of undernutrition and RR of 3.2.;

compared to the median PAF of 28.3% of undernourishment. In 30 high TB burden countries, 24% or 2.07 million out of 8.62 million incident cases in these countries were attributable to undernutrition. In most Asian countries like India, prevalence of undernourishment is less than prevalence of undernutrition and it underestimates the numbers who are underweight. On the other hand, the FAO estimates of undernourishment overestimate the proportion of people who are underweight in Africa. Overall undernutrition assumes an even greater imperative in the light of the COVID-19 pandemic, as food prices soar, as estimates suggest a doubling of the number of people experiencing acute hunger with serious implications for the TB epidemic [1,24].

After correction of the estimates, although the overall proportion of cases attributable to undernutrition increased only marginally, undernutrition emerged as the leading risk factor for TB in Asia. For example, the PAF based on prevalence of undernourishment for India was 24.8% while that based on prevalence of undernutrition was 34%. Using the correct estimates of prevalence of undernutrition did not alter the global burden of cases attributable to undernutrition (1.96 million to 2.07 million). However it helped identify specific high TB burden countries like India and other Asian countries with low prevalence of HIV, where undernutrition is the major risk factor for TB and where TB prevention efforts may benefit significantly from public health measures to address undernutrition. Shifting the population distribution of BMI in adults towards a desirable BMI level could have a marked impact on TB incidence, as indicated by a *meta*-analysis and modeling studies [7,19].

On replacing the RR of 3.2 with 4.49 for the revised estimates, the PAF of undernutrition increased to a median PAF of 28%. As a result, the number of cases attributable to undernutrition increases to 2.84 million of the total 8.62 million (32.9%) incident TB cases. This suggests that one-third of TB cases in 30 high TB burden countries could be attributable to undernutrition, and therefore could be potentially eliminated if undernutrition was addressed. This represents an absolute increase of 0.88 million cases or a relative increase of nearly 45% of incident cases attributable to undernutrition, compared to current estimates.

6.1. Strengths and limitations

Our study provides a valid estimate of the impact of undernutrition on the TB epidemic in 30 high TB burden countries for the year 2020. The use of the metric of undernutrition rather than undernourishment has implications for various National TB control programs. The prevalence of undernourishment determined by FAO does not allow disaggregated analysis to identify vulnerable populations in a country but use of prevalence of undernutrition easily available from periodic demographic and health surveys can identify these [25]. Our revised RR for undernutrition is more robust as it is based on a cohort study with nationally representative sample with many confounders adjusted for and based on a recent cohort from a high TB burden country with low HIV prevalence [10,20].

Our study has certain limitations. PAF is a static measure and some of the impact of addressing undernutrition is still not captured in these estimates [26]. In the case of transmissible diseases like TB, the prevention of progression to active disease by improved nutrition will also decrease the onward transmission of infection and prevent secondary cases. Measures like the transmission PAF may capture this impact [27]. We have not accounted for the interactions between undernutrition and other risk factors like HIV, diabetes, where a low BMI is also a risk factor for active TB [28], and the risk of TB is significantly higher for patients

Table 3
Population Attributable Fraction for Tuberculosis related to undernutrition and attributable cases in high burden countries using prevalence of undernutrition based on anthropometry and Relative Risk of 4.49 (2.28, 8.86).

High TB burden Countries	Incident TB cases	Prevalence of undernutrition based on anthropometry * [%, (95% CIs)]	PAF with revised RR§ [%, (95% CIs)]	Attributable TB cases due to undernutrition estimated with revised RR≠ [(95% CIs)]
Angola	112,000	13.5 (7.2, 21.10)	32.0 (5.6,65.2)	35,869 (6271,73067)
Bangladesh	361,000	21.5 (16.80,26.70)	42.9 (14.5,70.4)	154,756 (52210,254096)
Brazil	96,000	2.7 (1.80,3.90)	8.6 (1.6,2.5)	8267 (1513,24430)
Cambodia	47,000	13.6 (8.90,19.10)	32.2 (7.7,63.0)	15,128 (3600,29595)
CAR	26,000	14.8 (8.9,21.6)	34.1 (7.5,65.9)	8855 (1937,17128)
China	833,000	5.3 (3.9,6.9)	15.6 (3.7,38.0)	130,029 (30702,316860)
Congo	20,000	13.1 (8.9,19.1)	31.4 (7.2,62.4)	6275 (1440,12472)
DPRK	132,000	6.6 (3.1,12.2)	18.7 (1.5,50.8)	24,713 (1943,67064)
DRC	278,000	15.9 (10.0,22.5)	35.7 (8.6,66.6)	99,212 (23761,185848)
Ethiopia	157,000	15.8 (10.5,21.9)	35.5 (9.0,66.1)	55,802 (14156,103834)
India	2,640,000	23.6 (19.9,27.6)	45.2 (17.0,71.0)	1,192,346 (448963,1874920)
Indonesia	845,000	12.9 (9.3,16.9)	31.0 (8.4,60.2)	262,326 (70712,508230)
Kenya	140,000	11.8 (7.6,16.9)	29.2 (6.5,60.0)	40,837 (9063,83952)
Lesotho	14,000	7.9 (4.9,11.6)	21.6 (4.2,50.7)	3026 (583,7092)
Liberia	15,000	8.3 (4.9,12.50)	22.5 (4.1,52.5)	3369 (608,7879)
Mozambique	110,000	11.1 (7.1,15.9)	27.9 (6.1,58.5)	30,714 (6694,64387)
Myanmar	174,000	14.6 (10.4,19.5)	33.8 (9.1,63.4)	58,733 (15864,110332)
Namibia	12,000	9.7 (6.1,14.1)	25.3 (5.2,55.5)	3035 (623,6664)
Nigeria	440,000	10.3 (7.3,13.9)	26.4 (6.5,55.2)	116,344 (28660,242829)
Pakistan	570,000	15.0 (10.8,19.9)	34.4 (9.5,63.9)	195,862 (53971,364071)
PNG	38,000	20.3 (1.0,4.4)	7.4 (0.04,27.1)	2824 (144,10290)
Philippines	599,000	12.3 (84,16.7)	30.0 (7.5,59.8)	179,905 (44705,358595)
Russian Federation	73,000	1.8 (1.1, 2.6)	5.9 (1.0,18.9)	4315 (727,13774)
Sierra Leone	23,000	10.3 (6.4, 14.9)	26.4 (5.5,57.0)	6082 (1263,13114)
South Africa	360,000	4.7 (3.2,6.4)	14.1 (3.0,36.4)	50,730 (10704,130904)
Thailand	105,000	8.6 (5.6,12.3)	23.1 (4.9,52.1)	24,239 (5088,54707)
URT	137,000	11.0 (7.5,15.1)	27.7 (6.6,57.3)	38,004 (9088,78524)
Viet Nam	170,000	17.7 (13.6,22.1)	38.2 (12.1,66.4)	64,914 (20942,112843)
Zambia	59,000	11.2 (7.0,16.0)	28.1 (6.1, 58.9)	16,581 (3582,34724)
Zimbabwe	29,000	7.9 (5.0, 11.4)	21.6 (4.3,50.3)	6268(1256, 14583)

*Source for age standardized BMI < 18.5 kg/m^2 in both sexes reported in Global Health Observatory database on BMI (accessible at https://www.who.int/data/gho/data/themes/topics/topic-details/GHO/body-mass-index);
Abbreviations: CAR = Central African Republic; DPRK = Democratic People's Republic of Korea; DRC = Democratic Republic of the Congo; PAF = Population Attributable Fraction; RR = Relative Risk; PNG = Papua New Guinea; URT = United Republic of Tanzania.
≠ Revised RR as per the latest evidence [10].

with diabetes who have a low BMI [29]. The association between undernutrition and incident TB in these estimates is an ecologic association and it cannot be confirmed whether the incident cases are actually occurring in those who have undernutrition. The estimates of low BMI in countries do not entirely capture the burden of undernutrition in the community. In India, for example, according to the National Family Health Survey-4, the prevalence of low BMI in adults is 23.6%, but a much higher proportion of children suffer from undernutrition; 38% of children under-five had stunting and 36% were underweight [30]. The wide confidence intervals around the RR attributable to undernutrition are due to paucity of cohort studies in populations with undernutrition. Finally our analysis is based on the criterion of a BMI <18.5 kg/m^2 to define undernutrition in adults. A reconsideration of the BMI cut-offs used to define undernutrition on a global scale, has been proposed by the major clinical nutrition societies under the Global Leadership Initiative on Malnutrition (GLIM) [31]. According to this consensus, the one of the criteria to define undernutrition should be a BMI <20 kg/m^2. This revised cut-off for undernutrition would impact on the estimates of PAF and attributable incident cases related to undernutrition. The estimates of PAF and attributable incident cases of TB using this cutoff would require estimates of the population prevalence of BMI < 20 kg/m^2 as well as the risk ratio for a BMI < 20 kg/m^2; neither of which are not currently available.

7. Conclusion

The estimation of PAF related to undernutrition rather than undernourishment is methodologically valid and operationally relevant and should be the basis of future such estimations. We report that with corrected and revised estimates of PAF of undernutrition, 24%–33% of the 8.62 million TB cases in high burden countries may be attributable to undernutrition. The PAF of undernutrition at sub-national levels can provide actionable data for TB control efforts by identifying specific vulnerable populations with higher prevalence and PAFs of undernutrition. Undernutrition is the leading driver of TB globally and in the highest TB burden countries of Asia, and should be the focus of multisectoral efforts to reduce TB incidence in line with the goals of the END TB strategy.

8. Contributors

AB, MB AnB and AK conceptualized the study, AB and AnB did the data curation, formal analysis and visualization. AB and MB wrote the original draft; all authors were involved in reviewing and editing the versions thereafter.

9. Data sharing

All empirical data used in this study are made either publicly available, in the supplementary material or available from public domain.

10. Ethics and Consent

Not applicable: This research includes analysis of already available global health data in public domain. Authors did not approach any human participants for this study.

Fig. 3. Number of cases of tuberculosis (in thousands) based on current, corrected and revised population attributable fraction (PAF) related to undernourishment and undernutrition in 30 high TB burden countries. TB incidence: Reported incidence in the Global TB Report 2020. Current: Number of cases of TB based on prevalence of undernourishment (by Food and Agriculture Organization) and relative risk of 3.2 as per the Global TB Report 2020. Corrected: Number of cases of TB based on prevalence of undernutrition (Global Health Observatory) and relative risk of 3.2. Revised: Number of cases of TB based on prevalence of undernutrition (Global Health Observatory figures) and revised relative risk of 4.49.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

Authors acknowledge the data visualization and graphs done by Mr. Aman Bhargava, a student of Bachelors in Design at Srishti Manipal Institute of Art, Design and Technology, Bangalore

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