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A consistent log-linear relationship between tuberculosis incidence and body mass index

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Background Low weight for height is an established risk factor for tuberculosis (TB), and recent studies suggest that overweight is a protective factor. No previous systematic review has been done to explore the consistency and establish the gradient of this apparent 'dose–response' relationship.

Methods A systematic literature review was carried out to identify cohort studies that collected data on weight and height at baseline and that used a diagnosis of active TB as the study outcome. Weight-for-height measures used in the original studies were transformed into body mass index (BMI). Exponential trend lines were fitted to each data set.

Results Six studies were included. In all of them, there was a log-linear inverse relationship between TB incidence and BMI, within the BMI range 18.5–30 kg/m^2. The average slope gave a reduction in TB incidence of 13.8% [95% confidence interval 13.4−14.2] per unit increase in BMI. The dose–response relationship was less certain at BMI <18.5 and >30 kg/m^2.

Conclusion There is a strong and consistent log-linear relationship between TB incidence and BMI across a variety of settings with different levels of TB burden. More research is required to test the relationship at very low and very high BMI levels, to establish the biological mechanism linking BMI with risk of TB and to establish the potential impact on the global TB epidemic of changing nutritional status of populations.

Keywords Tuberculosis, nutrition, body mass index, review

Introduction

Malnutrition is associated with an increased risk of progression from tuberculosis (TB) infection to active disease, because of the negative impact of micro- and macronutrient deficiencies on the cell-mediated immune system.[1,2] Population nutritional status, with its link to poverty, socio-economic development and environmental change, is therefore an important social determinant of TB incidence.[3] No previous systematic review has been done to determine the strength of the association between nutrition status and the risk of TB, and the potential impact of changed population nutrition status has not been considered in previous attempts to model future TB incidence trends.[4–6]

Two recent narrative reviews of the association between nutrition and TB[1,2] have highlighted the methodological challenge to correctly ascertain the temporal association between nutrition status and TB. Because TB leads to weight loss and a range of changes to macro- and micronutrient status,[1] cross-sectional and case–control studies that measure

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nutrition status at the time of TB diagnosis are likely to produce spurious associations or overestimate the strength of any causal relationship between nutrition status and risk of TB. Therefore, only cohort studies (or case–control studies nested in cohorts that have established baseline nutrition status before onset of disease) can produce reliable estimates of the strength of the association. Numerous studies have shown associations between a range of nutritional deficiencies (protein-energy, vitamins A, D, C and E, zinc and selenium) and TB.[1,2] However, most of these associations were found in studies with a cross-sectional design. One nutritional indicator that has been used as an exposure measure in several cohort studies on the association between nutrition and TB is the body mass index (BMI), or equivalent weight-for-height measures.[1,2]

We conducted a systematic review of cohort studies of the association between BMI and incidence of active TB, and investigated the dose–response relationship between TB incidences over the full range of BMI from those who are underweight to those who are obese.

Methods

We searched systematically for cohort studies that reported data on weight and height at baseline, that ascertained disease status at baseline and that used a diagnosis of active TB as the study outcome. Cross-sectional studies and case–control studies were excluded. We also excluded studies that had TB mortality as outcome, since any association between nutrition and risk of TB death is compounded also by the risk of fatal outcome of active disease.

We searched PubMed (until December 2008 and not excluding any paper based on language), as well as a private collection of TB publications (a collection of journal articles, reports and books on TB, including selected material dating back to the beginning of the 20th century), which includes over 16 000 articles and was last updated in 2008. The keywords used were: tuberculosis and either nutrition, malnutrition, body-mass-index, BMI, weight or wasting. The email list 'TB-Related News and Journal Items Weekly Update' (prepared by the Centers for Disease Control and Prevention, Atlanta, USA) was monitored weekly from January 2007 to December 2008. Finally, the reference lists of two recent systematic reviews of the association between malnutrition and TB[1,2] were searched. In total, 96 full papers were reviewed in detail. We identified six studies that fulfilled the inclusion criteria and all of them were included in the analysis. Study characteristics are summarized in Table 1.

In two studies,[7,8] TB incidence was reported for different baseline weight-for-height categories, defined as the percentage below or above median weight within each specified height (Table 2). The authors provided the median weight and the limits of weight in pounds corresponding to each weight-for-height category within each respective height range (one range per inch, except open ranges for $\leqslant 63$ inches and $\geqslant 74$ inches in the study by Edwards *et al*.[8]). We used this information to calculate the corresponding BMI for each upper cut-off point in each height range (1 inch $= 0.0254$ m, and 1 pound $= 0.4536$ kg). The average BMI was then calculated for each weight-for-height category across the height ranges (Table 1). In four studies, the analyses relied on the reported baseline BMI (Table 2).

If not provided in the original paper, confidence intervals (CIs) for the incidence rate were calculated based on reported number of events and reported number of person-years of observation. We fitted exponential trend lines to each data set and made pair-wise comparisons (using *t*-tests) of the rates of decline among all of the data sets, and carried out an analysis of covariance without an interaction term.

Results

TB incidence for different BMI levels from each study and the fitted exponential trend line are shown in Figure 1. We found a log-linear inverse dose–response relationship between BMI and TB incidence, within the BMI range 18.5–30 kg/m^2 in all studies (Figure 1). The *t*-tests for difference in slope gave *P*-values ranging from 0.089 to 0.855. The average slope was equivalent to a reduction in TB incidence of 13.8% (95% CI 13.4−14.2) per unit increase in BMI.

Two studies reported the incidence of TB for BMI <18.5 kg/m^2. Three studies reported incidence separately for obese people (BMI >30 kg/m^2: two of them found a lower TB risk for obese people than overweight people (BMI 25–30 kg/m^2); one study showed the reverse relationship.

Discussion

In the BMI range 18.5–30 kg/m^2, we found a remarkably consistent inverse logarithmic relationship between BMI and TB incidence, across studies that had been carried out over the past 50 years in diverse study populations with a large variation in average TB incidence, and which had controlled for various sets of confounders. In other words, across all these studies TB incidence increased exponentially as BMI decreased. The dose–response relationship was more uncertain at BMI levels <18.5 kg/m^2 and there were only two studies reporting data on incidence for people with BMI <18.5 kg/m^2. No study reported incidence separately for those with severe malnutrition (BMI <16 kg/m^2). The dose–response relationship was also less certain for BMI $\geqslant 30$ kg/m^2.

Table 1 Study characteristics

Study	Country	Subjects	Study period	Average follow-up time (years)	Type of TB and mode of ascertainment	Confounders controlled for
Palmer *et al.*[7]	USA	68 754 male navy recruits, 17–21 years old	1949–55	4	All types of active TB, ascertained from annual X-ray and tuberculin screening, contact investigations, and review hospital admission records	Age, sex, tuberculin reactivity[a]
Edwards *et al.*[8]	USA	823 199 male navy recruits, 17–21 years old	1958–67	4	As above	As above[a]
Hemilä *et al.*[9]	Finland	26 975 male smokers participating in a trial on the effect of vitamin supplementation on risk of cancer	1985–93	7 (median)	All types of active TB, ascertained from the national register of hospital discharges	Age, residency, marital status, education, smoking, alcohol intake and vitamin intake[b]
Tverdal[10]	Norway	1 717 655 persons >14 years of age participating in the national Mass Radiography Service	1963–82	12	All new cases of active TB	Age and sex[c]
Leung *et al.*[11]	Hong Kong	42 116 persons ⩾65 years of age enrolled at health centres for the elderly	2000–05	5	All new cases of active TB, ascertained from medical records at health centres, public health records of the TB and Chest Service	Age, sex, smoking, alcohol use, marital status, education level, housing, work-status, diabetes and several other medical conditions[b]
Cegielski *et al.*[d]	USA	13 211 adults aged 25–74 years, population sample included in NHANES	1971–92	11 (median)	All new cases of active TB	Age, sex, ethnicity, urban residency, alcohol use, diabetes, cancer and immigration[b]

[a]Both studies included only men aged 17–21 years. Both studies investigated tuberculin reactivity at baseline, and found no association between weight-for-height and tuberculin reactivity. The cohorts included both tuberculin reactors and non-reactors, and tuberculin reactivity did not confound or modify the effect of weight-for-height on TB incidence.
[b]Through multivariate analysis.
[c]Through stratified analysis (age and sex).
[d]Unpublished manuscript: Cegielski JP. Kohlmeier L, Cornoni-Huntley J. Relative and population attributable risks of tuberculosis due to under- and overnutrition.

Table 2 Definitions of weight-for-height categories, and incidence by weight-for-height band

Original weight-for-height category	Percentage of study sample	Average BMI corresponding to upper weight-for-height cut-off (kg/m^2)	Corresponding BMI range (kg/m^2)	Assumed average BMI within range (kg/m^2)	Incidence per 100 000 and year (95% CI)
Palmer *et al.*					
⩾15% less than median	11	19.2	⩽19.2	18.5	75.1 (43.7–106.5)
10–14% less than median	16	20.4	19.3–20.4	19.8	67.3 (42.8–91.8)
5–9% less than median	21	21.5	20.5–21.5	21	35.2 (19.8–50.7)
±4% of median	32	23.7	21.6–23.7	22.6	29.7 (18.3–41.1)
⩾5% above median	21		>23.7	25	18.9 (7.7–30.0)
Edwards *et al.*					
⩾10% less than median	18	19.6	⩽19.6	18.5	79.1 (64.7–93.6)
±9% of median	59	23.9	19.7–23.9	21.8	46.5 (40.4–52.6)
⩾10% above median	24		>23.9	25	22.5 (15.8–29.1)
Hemilä *et al.* BMI (kg/m^2)					
<23	19			21	116.0 (79–153)
23–27	42			25	55.2 (38.1–72.3)
>27	39			29	32.7 (19.0–46.3)
Tverdal BMI (kg/m^2)					
<21	17			18.5	16.7 (15.3–18.0)
21–22.9	21			22	11.2 (10.2–12.1)
23–24.9	22			24	8.3 (7.4–9.1)
25–26.9	17			26	6.2 (5.4–7.0)
27–28.9	11			28	4.1 (3.3–4.9)
29–30.9	6			30	2.8 (1.8–3.7)
>31	6			32	3.1 (2.1–4.0)
Leung *et al.* BMI (kg/m^2)					
<18.5	5			17	599 (425–847)
18.5–22.9	31			20.75	291 (251–335)
23–24.9	23			24	218 (163–294)
25–29.9	35			27.5	163 (122–218)
>30	6			31.5	102 (47–218)
Cegielski *et al.* BMI (kg/m^2)					
<18.5	5			17.5	175.9 (88.1–138.8)
18.5–25	35			22.2	31.5 (9.8–12.7)
25–30	40			27.2	15.3 (6.7–9.9)
>30	20			34.2	8.5 (6.2–13.2)

The main limitation of this review is the small number of cohort studies that has been performed over the past half century. Publication bias is possible but not likely to be severe since these types of studies are by necessity large, and it would be unlikely they would go entirely unpublished or missed both by our review as well as previous literature reviews.[1,2] All studies relied on baseline BMI estimates only, but BMI tends to change only slightly over time.[12] Another clear limitation is that all the studies have been carried out in high-income countries, and generalization to low-income countries, where the TB burden is presently highest, should therefore be with some caution. Furthermore, three of the studies included only men as study subjects (two of them restricted to navy recruits, and one to male smokers). One study included only elderly people. Only two studies used a study population that represented the

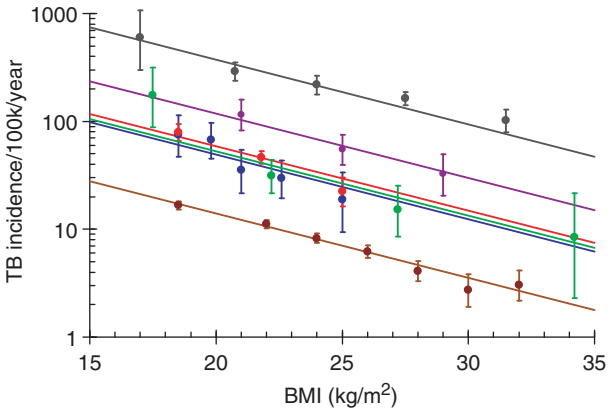

Figure 1 Dose–response relationship in the reviewed cohort studies on the association between BMI and TB incidence. The lines are: black, Leung[4] (0.089); purple, Hemila[10] (0.855); red, Edwards[9] (0.206); green, Cegielski (0.531); blue, Palmer[8] (0.367); brown, Tverdal[11] (0.493). Numbers in brackets give the significance levels for differences from the fitted lines based on the deviance calculated using binomial errors

general population. None of the older studies, and few of the more recent ones, attempted to control for some important confounders, such as smoking, diabetes, alcohol abuse, silicosis, crowded living conditions, etc. HIV was not controlled for in any of the studies, though HIV was non-existent or the prevalence was very low in all of the study settings. Socio-economic status was partly controlled for in three studies only. Despite these variations in study setting and sample, and despite different potential for residual confounding, the dose–response relationship was remarkably stable. It was present also in the studies that used a population sample, and that controlled for several important confounders.

Our findings suggest that BMI is a good predictor of relative TB risk, but do not shed any further light on the mechanisms through which nutritional status influences risk of TB. Since BMI is a crude measure of nutritional status, it may be questioned if it can be treated as a causal factor in and by itself, which can be used to estimate population-attributable fraction and to model impact of population nutritional status on future TB incidence trends. To further assess its utility in this respect, we have evaluated the available data according to the standard criteria for causality in epidemiology.[13,14]

Association and strength of association

We found a strong association between BMI and TB incidence in all reviewed studies.

Temporality

In this review we included cohort studies that had ascertained BMI at baseline among people who were initially free from active TB disease. The direction of the association is therefore unquestionable.

Dose–response relationship

We found a consistent and homogeneous dose–response across all reviewed studies.

Consistency

There was a similar strength of the association across the reviewed studies. The findings in this review are also consistent with a recent analysis of BMI and cause-specific mortality across 57 prospective studies with a total cohort of about 900 000 individuals that reported a strong inverse dose–response relationship between BMI and death due to TB.[12] It is also consistent with a recent cohort study[15] of the association between BMI and TB mortality in India.

Plausibility of biological pathways

It is well known that nutritional status influences the functioning of the cell-mediated immune system. Though the exact pathways are not fully understood, there is no doubt that several nutritional factors also influence the capacity of the cell-mediated immune system to fight TB bacilli.[1,2] Low BMI (<18.5 kg/m^2) is an established indicator for energy deficiency,[16] but an imprecise indicator of micronutrient status. Our findings are therefore most strongly supported by the evidence on role of energy deficiency for TB and other infections.[1]

Exclusion of confounding and alternative explanations

As discussed above, confounding was controlled for to various extents in the reviewed studies. Residual confounding is likely in several studies, but it was unlikely that it would annul the strong and consistent dose–response relationship.

Reversibility following interventions

The studies reviewed in the present study do not provide any evidence on reversibility. However, extensive evidence demonstrates deficiencies of cell-mediated immune function are rapidly reversed upon nutritional rehabilitation. Furthermore, historical evidence and ecological analyses show that TB incidence has both increased during time of food insecurity and high prevalence of starvation, and then decreased rapidly when food security has improved.[1,17]

Undernutrition has been an established risk factor for TB for decades, but two novel aspects of this association are brought out by our analysis. First is quantification of the association—the consistent logarithmic shape and magnitude of the association at different levels of BMI, as well as the variance across different study methodologies and populations. Secondly, the dose–response relationship continues above a BMI of 25 kg/m^2. In other words, being overweight may reduce the risk of TB. From the viewpoint of biological plausibility, it would seem reasonable

to assume that the salutary effect on immunity of increasing BMI would be seen up to a BMI level regarded as normal in a healthy person, but not beyond that level, particularly since it is known that diabetes is associated with overweight[18] as well as with an increasing risk of TB.[19,20] This finding therefore raises additional questions about the possible biological mechanisms involved. It has previously been speculated that 'body build' in itself somehow influences risk of TB,[21] perhaps through the impact on lung physiology, but no published empirical data are available to support this hypothesis.[22] Does overweight influence the virulence of mycobacteria indirectly? A recent study found that mycobacteria with lipid bodies do not replicate as rapidly as mycobacteria without such lipid bodies.[23] It is not known if this phenomenon is associated with micro- or macronutrient status of the host. If it is, could overweight indirectly influence the capacity of mycobacteria to replicate? Another study found that mycobacteria can persist without replication in fatty tissues.[24] Could more fat tissue be associated with higher likelihood of mycobacteria remaining dormant?

If BMI is causally linked to the risk of TB in the way that the data presented here suggest, then promoting adequate nutrition and weight gain in undernourished populations, and shifting the overall BMI distribution in a population to higher values, would reduce TB incidence. Such an effect of improved nutrition has been suggested from analyses of the causes of TB incidence decline in Europe in the 20th century, though that analysis was not based on data on changing BMI in populations.[1,17] A shift in the distribution that resulted in increased prevalence of overweight would further reduce TB incidence if the shift were to occur among people who are or may become TB infected. Such a shift would have negative consequences for other important public health conditions. However, a recent systematic review found that mortality among overweight people (BMI 25–30 kg/m^2) was not higher than for those with normal BMI (18.5–25 kg/m^2).[25] The large collaborative prospective study mentioned above[13] found a U-shaped dose–response relationship where the overall mortality was higher among overweight people compared with those having a BMI of 22.5–25 kg/m^2, but not higher than those with BMI 18.5–22.5 kg/m^2. Though it would be inadvisable at this point to promote raising BMI to >25 kg/m^2 as a means to reduce risk of TB, our analysis should contribute to the debate about how healthy weight-for-height bands should be defined.

Our findings also raise questions about the indication for preventive treatment of TB; among those who are overweight and obese such treatment may be less beneficial than among people who have normal weight for height, whereas the indications might be especially strong among those who are undernourished.

In conclusion, we have found a strong and consistent inverse logarithmic relationship between BMI and risk of active TB, and provide a tentative quantification of this relationship that can serve as a basis—together with data on BMI distribution in different subpopulations—for analyses of the potential impact on the global TB epidemic of changing nutritional status of populations. However, more research is required to test if this dose–response relationship is the same in low-income countries, and at very low and very high BMI levels. For the exploration of the dose–response relationship at very low BMI levels, the inclusion of TB as an outcome in ongoing or planned large cohort studies in low-income countries with high prevalence of undernutrition, would be valuable. Further research is also needed to establish the biological mechanism linking BMI with risk of TB.

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KEY MESSAGES

- Across a wide variety of epidemiological settings, the risk of TB increases by about 14% for each unit reduction in body mass index (BMI).
- This applies to BMI ranging from 30 to 18.5 kg/m^2, while the relationship at <18 kg/m^2 and >30 kg/m^2 is less certain.
- Consequently, people who are overweight have lower risk of TB than people with normal weight for height.

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