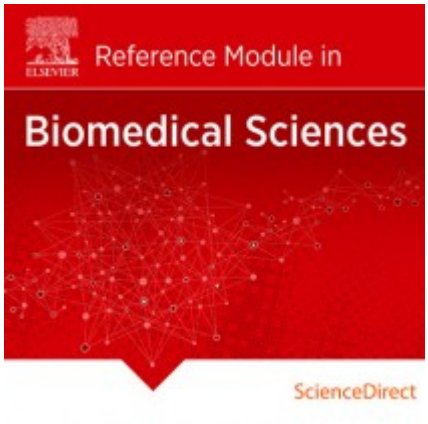

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Nutrition and Susceptibility to Tuberculosis☆

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Glossary

Cell-mediated immunity (CMI) The principle host defense against TB mediated primarily by T lymphocytes rather than antibodies.

Droplet nuclei Microscopic particles (1–5 mm in diameter) that can be expelled when a person coughs, sneezes, shouts or sings. The droplets produced by an infectious TB patient can carry tubercle bacilli and can remain suspended in the air for prolonged periods of time.

Undernutrition A type of malnutrition caused by the lack of food or failure of the body to absorb or assimilate nutrients properly.

Haematogenous re-seeding The process by which bacilli make their way back to the lung through the bloodstream where they infect all parts of the lung.

Bacillus of Calmette and Guerin (BCG) vaccine A tuberculosis vaccine used in many parts of the world containing an attenuated strain of tubercle bacillus developed by repeated culture on medium containing bile.

Undernutrition is an important risk factor for the development of tuberculosis (TB) both at the individual level and at the population level. Undernutrition profoundly affects cell-mediated immunity (CMI), and CMI is the principal host defense against TB. Although these concepts may be widely accepted, the relative and attributable risks of TB due to undernutrition are not well known. Moreover, the effects of specific nutrients have not been established. Recent evidence suggests that overweight and obesity may actually decrease the risk of developing TB. This article will summarize available evidence on the relationship between nutritional status and the risk of TB.

Understanding the link between undernutrition and susceptibility to TB is based on a conceptual model for the transmission and pathogenesis of TB. *Mycobacterium tuberculosis* is transmitted by the aerosol route when an individual who has pulmonary or tracheobronchial TB produces droplets containing viable *M. tuberculosis*. The moisture content of smaller droplets evaporates quickly and such "droplet nuclei" are the main vehicle for airborne transmission of TB. Of those who become infected, ~90% will remain free of TB, while ~10% will develop active TB disease at some time during their life. The risk of an infection progressing to active TB disease depends on the host's immune system and the microbe's virulence. The influence of nutritional status on host defenses is a central theme of this article.

Once the inhaled mycobacteria reach the alveoli, alveolar macrophages bind and internalize the bacilli, leading to the activation of these macrophages and to the production of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and other chemokines. These chemical messengers recruit macrophages and other immune response cells to the site of infection. As the inflammatory response progresses, the mycobacteria and infected macrophages are taken in the draining lymph to the hilar and mediastinal lymph nodes, and then via the thoracic duct into the blood stream, disseminating to potentially every organ or tissue in the body. Bacilli make their way back to the lung through the bloodstream where they infect all parts of the lung in a process known as hematogenous re-seeding which apparently occurs in all infected individuals. Blood-borne organisms establish "secondary" granulomas, in which the organisms may persist despite an active immune response, and which are often the sites of reactivation TB described below.

Mycobacterial antigens are presented to CD4+ (helper) and CD8+ (cytotoxic) T lymphocytes in the lymph nodes initiating the CMI. The population of TB-specific T lymphocytes expands and circulates to sites of active infection where they produce macrophage-activating cytokines such as interferon-gamma (IFN-γ). The combination of IFN-γ and TNF-α from phagocytes further activates macrophages to inhibit mycobacterial growth. During this period, the host begins to express evidence of a TB-specific T-lymphocyte-mediated immune response as manifested classically by a positive tuberculin (PPD) skin test. The process by which macrophages inhibit or destroy mycobacteria may also cause local tissue destruction and necrosis. Immunological feedback mechanisms modulate the intense inflammatory response to limit tissue damage while controlling the infection. Nevertheless, local tissue destruction in the lungs can lead to formation of cavities, characteristic of contagious, reactivation TB.

In the large majority of people, the adaptive immune response controls the infection without overt symptoms or other clinical manifestations of TB disease. In a small minority of individuals, estimated to be $<5\%$, the immune response will not control the infection, and the infection progresses to active TB disease known as "progressive primary TB." The risk of progression, however, is much greater in persons with immune systems weakened by undernutrition, HIV infection, immunosuppressive medications, and extremes of age. In persons whose immune systems successfully control the primary infection, mycobacteria may remain viable

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within granulomas for years or decades. Among individuals with a positive tuberculin skin test and no history of active TB disease, the risk of developing reactivation TB disease over the individual's lifetime is also estimated to be ~5%, but increases greatly in persons with weakened immune systems.

While there is little evidence of increased risk of primary *infection*, the risk of progression from infection to *disease* increases substantially in undernourished individuals. This is likely due to the adverse effects of undernutrition on CMI which is essential for control of mycobacterial growth. Protein undernutrition clearly compromises CMI. Experimental animal studies have demonstrated that even modest protein deprivation impairs host responses to BCG vaccination and tuberculin skin test responsiveness after aerosol exposure to *M. tuberculosis*. Protein repletion rapidly restores these responses. Protein from the diet and from somatic stores is crucial for many aspects of host defense against TB as described above. Essential amino acids play important physiological roles apart from serving as building blocks for protein synthesis. Other macronutrients may also influence the immune system, especially fatty acids, including n-6 and n-3 polyunsaturated fatty acids (PUFA). n-3 PUFA have a direct influence on immune cell membrane composition and function, as well as on the production of eicosanoids and other inflammatory mediators. High intakes of long chain n-3 PUFA dampen inflammatory responses and ameliorate chronic inflammatory conditions such as rheumatoid arthritis, potentially at the cost of increasing susceptibility to infection including TB (see below).The balance n-3 and n-6 PUFA may be a key determinant of their effects on the immune system and disease resistance.

Recent findings suggest that chronic excess caloric intake may actually decrease the risk of TB. A 2009 study from China demonstrated that persons who were overweight and obese had ~1/4th to ~1/5th the risk of developing TB, respectively, compared with persons having normal body mass index. These findings are consistent with other studies which are described below. The mechanisms by which excessive body mass decreases TB incidence are ripe for investigation. Recent research demonstrates that adipose tissue may be a reservoir for non-replicating *M. tuberculosis*, and that such bacilli accumulate triacylglycerol in intracytoplasmic lipid bodies. A triacylglycerol synthase-encoding gene (*tgs1*) in *M. tuberculosis is* a member of the DosR regulon that may control the development of a non-replicating "persister" phenotype in the mycobacteria. Induction of the isocitrate lyase gene, *icl1*, in these mycobacteria allows a shift to utilization of lipids as a source of carbon and energy. Indeed, Roth speculated that obesity may have provided an evolutionary advantage during TB epidemics in the past, predisposing to obesity the modern day descendents of the survivors. Taken together, these recent data suggest the presence of a non-replicating bacterial population which persists especially in adipose tissue. Such mycobacteria may stop replicating or replicate more slowly, decreasing the probability of active TB disease.

Micronutrient deficiencies, for example, vitamin A, may affect resistance to TB by altering the function of the respiratory mucosa and the integrity of pulmonary epithelial tissues. Vitamins of the B complex and vitamin C play important roles in B-cell mediated humoral immune responses, but at present there is less evidence for their role in CMI. Vitamin B_{12} may be an exception to this generalization; B_{12} repletion in patients with pernicious anemia has been shown to reverse skin test anergy. The antioxidant functions of vitamin C, vitamin E, selenium, and glutathione have critical roles in protection against oxidative stresses, including reactive oxygen intermediates that play effector roles in cellular immunity as described below. Vitamin E may have other effects on both cellular and humoral limbs of the immune system as well, especially in relation to n-3 PUFA. At least one trial of vitamin E supplementation showed a benefit on clinically relevant measures of T-cell function. However, high doses of vitamin E may have adverse effects.

Vitamin D may have a role in anti-TB immunity through activation of macrophages. Induction of a cell-surface receptor for the vitamin D metabolite, 25-hydroxycholecalciferol, as well as the hydroxylase which forms 1,25-dihydroxycholecalciferol, appear to be part of the mechanism that helps these cells destroy the pathogen. These vitamin D effects are linked with production of the endogenous antibiotic peptide, cathelicidin. Research has confirmed an antimycobacterial role of vitamin D in stimulating macrophage killing of M. tuberculosis. However several randomized controlled clinical trials of vitamin D supplementation have not shown a meaningful effect on TB treatment outcomes. It may be that vitamin D is more important in susceptibility to TB infection, or in progression from infection to disease, than in host response to TB disease. In a randomized controlled trial of vitamin D supplementation in Mongolian school children, the vitamin D group had a lower frequency than the placebo group of tuberculin skin test conversion from negative to positive, and this effect was more pronounced comparing children with normal vs low serum vitamin D levels.

Dietary mineral deficiencies also affect CMI. Zinc deficiency interferes with T cell replication and maturation leading to lymphopenia. Zinc deficiency is also associated with elevated glucocorticoid levels that suppress cell-mediated immunity. Iron plays a critical role in support of CMI, however, iron is also critical to the replication of mycobacteria and other pathogens. Mycobacteria have evolved intense iron-scavenging mechanisms, and iron deficiency may have worse consequences for the microbe than the host. Thus, the impact of iron on susceptibility to TB is difficult to predict.

Despite the seemingly clear pathways through which nutrition affects CMI and resistance to TB, the evidence in humans linking undernutrition to TB risk is indirect and surprisingly weak from the perspective of scientific rigor. The bulk of evidence in humans comes from a large body of uncontrolled observations during famines, wars, and natural disasters, as well as ecological studies comparing low-income with affluent countries. In these complex circumstances, the effects of undernutrition cannot be disentangled from the effects of poor housing, overcrowding, lack of medical care, poor hygiene, social disruption, and poverty. Although much of this observational evidence is scientifically weak, it constitutes a large body of repeated observations supporting a strong relationship between undernutrition and TB. In addition, the decline in TB in the past century in developed countries often is ascribed to improvements in living conditions, especially nutrition, a concept championed in seminal work by Thomas

McKeown. The remainder of this article summarizes the evidence from observations in human populations and from experimental animal models with relevance to human TB.

Early research on the interaction of nutrition and TB was exhaustively reviewed in the classic text by Scrimshaw, Taylor, and Gordon. The studies in humans were either ecological or uncontrolled observational studies. For example, studies of the sharp increases in TB morbidity and mortality in France and Germany during the two World Wars, or in the Warsaw ghetto during World War II, do not isolate the effects of undernutrition from the impact of extreme crowding, social and environmental degradation, lack of medical services, and catastrophic social circumstances. While highly suggestive, the impact of starvation on TB morbidity and mortality independent of other circumstances cannot be isolated in these studies.

Three ecological studies present compelling evidence that undernutrition, isolated to some extent from other confounding circumstances, plays a direct role in TB morbidity and mortality. During World War I, neutral Denmark exported the bulk of its meat, fish, poultry, and dairy products to support the war effort elsewhere so the local diet lacked these protein-, vitamin-, and mineral-rich foods. During that period, TB rates increased similar to the warring countries. In 1918, however, Germany blockaded Denmark making exports impossible, creating a local surplus of these foods. TB rates in Denmark plummeted while rates in the neighboring countries continued to increase unabated. The second study involves the Trondheim, Norway, Naval Training School, where an extremely high rate of TB among recruits in the early 20th century was ascribed to crowding, poor housing, and unhygienic conditions. TB rates did not decrease after improved housing and hygiene were provided. On the other hand, when the diet was fortified with milk, margarine, cod liver oil, whole wheat bread, and fresh fruits and vegetables, TB morbidity promptly declined to the prevailing level for young adults of that area. After WWII, Leyton reported on British and Russian prisoners of war (POW) held in the same German POW camps, sharing the same living conditions and diet, except the British received Red Cross food supplements amounting to 30 g protein and 1000 kcal per day. In a subsequent radiographic survey, the TB rate among the British POW was only 1.2% while the rate in Russian POW was 15%–19%. In the malnourished prisoners, TB was more severe, the onset was more rapid, and patients died rapidly with large pulmonary cavities and massive tissue breakdown. Granuloma formation was poor in the malnourished prisoners, supporting the idea there was a deficit of CMI in this group.

Protein–energy undernutrition compromises CMI and may exacerbate TB, however, TB itself can adversely affect nutritional status. Understanding the temporal relationship between the onset of undernutrition and the development of TB is crucial to correctly assess any possible cause–effect relationship. Cross-sectional and case–control studies generally suffer from the same flaw: Patients with and without TB disease are compared in terms of their concurrent nutritional status. While these studies demonstrate substantial macro- and micronutrient deficits in TB patients, they are not useful in determining the effect of undernutrition on susceptibility to TB because TB causes undernutrition. The intrinsic uncertainty over the chronological sequence of cause and effect in case–control and cross–sectional studies becomes intractable.

After intestinal bypass surgery for morbid obesity, patients experience rapid weight loss and malabsorption due to their short-circuited bowels. In several case series, the postoperative incidence of TB was 10- to 100-fold higher than historical or population comparison groups. Similarly, partial gastrectomy for ulcer disease was shown to predispose men to TB, especially among men whose weight was $<85\%$ of ideal.

Two cross-sectional studies on vitamin D metabolism in relation to TB have focused on the molecular and cellular mechanisms of the interaction rather than on the direction of causality. Cells recovered by bronchoalveolar lavage (BAL) and peripheral blood mononuclear cells from TB patients both produced $1,25(OH)_2D3$, the amount correlating with the number of CD8+ T lymphocytes but not with other cell types. CD4+ T lymphocytes in BAL fluid from TB patients expressed specific receptors for $1,25(OH)_2$ vitamin D3 but not 25(OH)D3. Since $1,25(OH)_2D3$ can improve the capacity of macrophages to kill mycobacteria, these results support the conclusion that cellular interactions mediated in part by $1,25(OH)_2D3$ may be important in resistance to TB.

The unique strength of cohort studies is nutritional status is measured prior to the onset of TB. Only two cohort studies have examined the relationship between micronutrients and TB incidence. In the 1940s, Getz and coworkers enrolled a cohort of 1100 men who were free of TB at baseline, and followed them for up to 5 years with serial clinical, radiographic, and laboratory examinations. Plasma vitamin A levels were low in 13 of 16 men (81%) who developed TB compared to 318 of 1058 (30%) of those who did not. Similarly, plasma vitamin C levels were low in 100% of the subjects who developed active TB compared to 117 of 1013 (11%) of those who did not. Exposure to TB did not differ between the groups. In a Finnish study on cancer prevention, investigators randomized 26,975 healthy male smokers aged 50–69 years to supplementation with tocopherol, beta-carotene, both, or neither. The subjects were followed for a mean of 6.7 years. In $>173,000$ person-years of follow-up, 167 cases of TB were detected. Higher intakes of fruits and vegetables were associated with lower risk of TB (the adjusted relative risk of TB was 0.4; 95% confidence interval, 0.24–0.69). This study is noteworthy for its size and data quality, however, detecting TB through hospital discharges selects TB patients who were sick enough to require hospital admission. Lower dietary intakes of key nutrients may have been associated with higher rates of hospitalization rather than (or in addition to) higher rates of TB.

As part of the long-term follow-up of participants in large-scale BCG vaccine trials in Georgia and Alabama, Comstock and Palmer reported the incidence of TB was 2.2 times higher in children with 0–4 mm subcutaneous fat than in children with 10 mm subcutaneous fat. Cegielski examined the relationship between undernutrition, as determined in the first National Health and Nutrition Examination Survey (NHANES-1), and TB incidence as ascertained in the NHANES-1 Epidemiological Follow-up Study. NHANES-1 was a cross-sectional survey based on a representative sample of the US population from 1971 to 1975. In the Follow-up Study, the adult subjects of NHANES-1, aged 25–74 years at baseline, were followed up until 1992. Having body mass index

(BMI), average skin-fold thickness, or mid-upper arm cross-sectional muscle area in the lowest decile of the population increased the adjusted hazard of TB from 6- to 10-fold, controlling for other known risk factors for TB.

In a related vein, three massive studies focused on "body build" as a risk factor for TB incidence. Palmer et al reported on the relationship between TB incidence and naturally acquired delayed-type tuberculin sensitivity among nearly all US Navy recruits from 1949 to 1951. Of 68,754 subjects with follow up data, 8704 (12.7%) had tuberculin sensitivity recorded as >0 mm induration. During 4 years of follow-up, 109 developed TB: 28 among those with 0 mm skin test reactions, 29 among those with 1–9 mm reactions, and 57 among those with 10 mm or greater reactions. Later, these investigators related the risk of TB to the recruits' height and weight data on a stratified random sample of 1138 subjects. TB incidence was 75/105 for those 15% or more below the median weight for height, decreasing to 19/105 for those at least 5% overweight for height. Edwards et al extended this study to more than 823,000 Navy recruits and found that TB developed 3-fold more often in young men 10% or more below their ideal body weight compared with those 10% or more above their ideal body weight. Rather than attribute these results to nutritional status, the authors concluded that there was an association between "body build" and risk of TB disease. The relationship between body build and TB was reviewed by Snider in 1987. One study stands out. Norway screened 42%–85% of the population older than age 14 years for TB with radiography from 1963 to 1975. Height and weight were measured accurately for approximately 80% of those screened. As reported by Tverdal et al, more than 1.7 million Norwegians were followed up via the national notification system through 1982 (i.e., 8–19 years of follow-up; mean, 12.1 years). A total of 2531 incident cases of TB were identified. The incidence of pulmonary TB declined logarithmically with increasing BMI for both sexes, all age groups, and at all durations of follow-up. The age-adjusted incidence of pulmonary TB was five times higher in the lowest BMI category than in the highest. Even though the study was based on BMI, Tverdal argued that the observed relationship was a function of body build. Comstock suggested body build may influence susceptibility to TB because of differences in pulmonary mechanics, but no data supporting this hypothesis exist. Interpreting the findings in terms of unknown factors associated with body build rather than the most obvious explanation, that is, nutritional status, ignores the fundamental relationship between body weight, caloric intake, and energy expenditure. A more nuanced view may be that body habitus is a function of genetic endowment and of nutrient intake/physical activity, each of which affects the incidence of TB in complex ways.

A unique study of the effect of micronutrient supplementation on TB incidence was reported by Downes in 1949. In a controlled trial among the families of black TB patients in the Harlem ghetto of New York City, 194 of 218 families under public health supervision were examined and divided into two groups matched for family size. The families were allocated alternately to receive vitamin and mineral supplements versus no supplements. The two groups were similar in terms of prior attack rates and mortality from TB, prevalence of TB at the start of the study, sputum smear positivity among the index cases, and relation of the index case to the rest of the family. In addition, the groups were similar in terms of their economic status, crowding, and eating habits. After 5 years of follow-up, the risk of TB in the control group was 2.8-fold higher than the supplemented group. However, there was substantial noncompliance with the supplements. Compared with those who actually took the vitamin supplements throughout the observation period, the risk of TB in the control group was 5.9-fold higher. Therefore, vitamin supplementation substantially reduced the risk of TB among family contacts of active TB cases.

The effects of undernutrition on the immune response to mycobacterial proteins closely related to the CMI required for resistance to infection with *M. tuberculosis*, namely delayed-type hypersensitivity (DTH) responses, have been studied following BCG vaccination. Satyanarayana et al. showed that milder grades of undernutrition did not affect the tuberculin skin test response 6 months after immunization with BCG, but children with kwashiorkor were skin test negative. Chandra and Newberne demonstrated that the DTH skin test response to tuberculin was reduced in protein–energy undernourished children and adults. Among TB patients, PPD skin test reactivity was directly proportional to serum transferrin level, a sensitive indicator of protein undernutrition. Similarly, malnourished individuals did not develop skin test responses to tuberculin as often or as large after BCG vaccination as did well-nourished children. Importantly, this defect has been demonstrated even in modest protein–energy undernutrition.

Experimental animal models allow investigators to elucidate the causal links between nutritional deficiencies, immune system function, and TB in ways not possible in human studies. The link between diet, antimycobacterial immunity, and resistance to TB has been investigated in a highly relevant guinea pig model of low-dose pulmonary TB that mimics the pathogenesis of TB in humans. Moderate, chronic deficiencies of protein and other nutrients (e.g., zinc, vitamin D) induced in guinea pigs had many of the metabolic hallmarks of human dietary deficiencies. Groups of BCG-vaccinated and nonvaccinated guinea pigs were given different diet treatments and then challenged with an aerosol containing a low dose of virulent *M. tuberculosis*. Antigen-specific immune responses in vitro and in vivo were assessed several weeks later and the ability of the guinea pigs to control the infection was determined quantitatively by culture of viable mycobacteria from the lungs and spleens.

Moderate, chronic protein deficiency (modeled by a 10% ovalbumin-based diet) over several weeks resulted in a dramatic loss of CMI in infected guinea pigs. Protein deprived animals had much smaller DTH reactions and their T lymphocytes proliferated poorly to PPD in vitro and produced significantly less interleukin (IL)-2, IFNγ. Macrophages from protein malnourished guinea pigs produced less TNFα in response to infection with virulent *M. tuberculosis*. Protein-deficient guinea pigs were unable to form mature, well-circumscribed granulomas in the lung. BCG-induced protection was diminished by protein deficiency. Protein undernutrition altered the numbers of CD4+ and CD8+ T cells in the spleen and bronchotracheal lymph nodes draining the infected lung. Thus, protein deficiency was accompanied by impairment of the normal trafficking of T lymphocytes that would be required for the formation of protective granulomas due, perhaps, to diet-induced changes in the production or function of chemokines, or by perturbations in the expression of adhesion molecules on T cells or endothelial cells.

Macrophages from TB patients are known to produce suppressive factors for T cells, including transforming growth factor-beta (TGF-β). Alveolar macrophages effectively down regulate T cell activation in an attempt to mitigate potentially damaging pulmonary inflammation in response to inhaled antigens.Alveolar macrophages from protein-deficient guinea pigs exerted a 10-fold greater suppression of T cells compared to cells from normally nourished animals, perhaps due to the greater levels of TGFβ produced by these cells. Recombinant human TGF-β injected daily into guinea pigs infected with virulent *M. tuberculosis* suppressed T cell functions and impaired bacillary control in a manner similar to dietary protein deficiency. Thus, macrophages from protein-deprived guinea pigs appear to be more suppressive for T lymphocyte functions, and this suppression may be mediated, in part, by overproduction of TGF-β.

One of the most important findings from this model is that the profound loss of T cell-mediated resistance that accompanies chronic dietary protein deprivation was substantially and rapidly reversible. Protein-deficient, BCG-vaccinated guinea pigs given a normal diet beginning on the day of pulmonary challenge with *M. tuberculosis* displayed DTH reactivity and control of bacillary growth within a few weeks that were indistinguishable from those in BCG-vaccinated animals that had never been protein deficient. Similar results were observed in protein-malnourished mice. Using a high-dose, intravenous challenge model, Chan and colleagues observed many of the same T cell defects that have been reported in low protein guinea pigs, including inability to control the virulent infection, impaired granuloma formation, and recovery of resistance following refeeding with an adequate diet. These studies confirm the fundamental nature of the effects of protein deprivation on susceptibility to TB even when host species, and infection dose and route are altered.

Recently, the guinea pig and mouse models of low-dose, pulmonary TB have been used to demonstrate the significant effects of dietary n-3 PUFA on TB resistance. Guinea pigs fed a diet enriched in fish oil or transgenic *fat*-1 mice producing n-3 PUFA endogenously were more susceptible to infection with virulent *M. tuberculosis*. Immune cells from *fat-1* mice or cells from wild-type mice cultured in medium containing n-3 PUFA produced less TNFα, IL-6, and IL-1β, and exhibited reduced oxidative burst and impaired phagosome-lysosome fusion. These n-3 PUFA-enriched macrophages were significantly impaired in their ability to control *M. tuberculosis* over several days of culture.

This article has reviewed and critiqued published studies in human populations and in relevant animal models covering the in vivo evidence relating the risk of TB due to nutritional status and nutritional factors. Although TB is clearly related to undernutrition, the risk relative to specific levels and types of protein-energy deficiency and micronutrient deficiencies remain to be defined. Analysis of the NHANES-1 Epidemiological Follow-up Study provides plausible estimates of a 6- to 10-fold increase in relative risk among undernourished adults as well as a substantially decreased risk in overweight and obese individuals. Severe protein-energy deficiencies may increase the relative risk more than mild or moderate undernutrition, but severe undernutrition affects fewer people, even in low-income countries, except during famines, war, natural disasters, etc. Mild to moderate protein-energy or micronutrient deficiencies affect more people at risk for TB, so prevention efforts should target those groups as well. The population attributable risk of TB due to undernutrition may be substantial, especially in populations where both TB infection and undernutrition are prevalent. Undernourished individuals have an increased likelihood of primary or latent infection progressing to active disease. In populations with substantial latent TB infection, the occurrence of undernutrition may be an important determinant of the incidence of reactivation TB. In many developing countries, the risk of becoming infected with TB is as high as 1% –2% per year of life. The United Nations Food and Agriculture Organization estimates that one billion people are undernourished. When combined with an estimate of two billion people latently infected with *M. tuberculosis*, even modest decreases in resistance affecting such large numbers of people may result in substantial increases in TB incidence. The potential public health impact of undernutrition on the global incidence of TB was summarized in a US Surgeon General's Report on Nutrition and Health, which emphasized that undernutrition was the leading cause of acquired, correctable immune system dysfunction throughout the world. Population groups at highest risk for poor nutrition are also at high risk for TB; poverty is the common denominator.

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