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Nutritional Risk Factors for Tuberculosis Among Adults in the United States, 1971–1992

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Abstract

The risk of developing tuberculosis (TB) may be related to nutritional status. To determine the impact of nutritional status on TB incidence, the authors analyzed data from the First National Health and Nutrition Examination Survey (NHANES I) Epidemiologic Follow-up Study (NHEFS). NHANES I collected information on a probability sample of the US population in 1971–1975. Adults were followed up in 1982–1992. Incident TB cases were ascertained through interviews, medical records, and death certificates. TB incidences were compared across different levels of nutritional status after controlling for potential confounding using proportional hazards regression appropriate to the complex sample design. TB incidence among adults with normal body mass index was 24.7 per 100,000 person-years (95% confidence interval (CI): 13.0, 36.3). In contrast, among persons who were underweight, overweight, and obese, estimated TB incidence rates were 260.2 (95% CI: 98.6, 421.8), 8.9 (95% CI: 2.2, 15.6), and 5.1 (95% CI: 0.0, 10.5) per 100,000 person-years, respectively. Adjusted hazard ratios were 12.43 (95% CI: 5.75, 26.95), 0.28 (95% CI: 0.13, 0.63), and 0.20 (95% CI: 0.07, 0.62), respectively, after controlling for demographic, socioeconomic, and medical characteristics. A low serum albumin level also increased the risk of TB, but low vitamin A, thiamine, riboflavin, and iron status did not. A population's nutritional profile is an important determinant of its TB incidence.

Keywords

body mass index; malnutrition; nutrition surveys; obesity; protein-energy malnutrition; subcutaneous fat; tuberculosis

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Protein-energy undernutrition impairs T-lymphocyte-mediated immunologic defenses, increasing the risk of specific infectious diseases (1–6). Among these, tuberculosis (TB) is a leading cause of morbidity and mortality, especially in middle- and low-income countries. An estimated 2 billion people worldwide are infected with *Mycobacterium tuberculosis*, and 1 billion people are undernourished (7, 8). According to the World Health Organization, the population attributable incidence of TB due to protein-energy undernutrition may exceed that due to human immunodeficiency virus (HIV) infection, smoking, or diabetes mellitus (9).

The bulk of evidence relating TB to undernutrition in humans comes from long-term historical trends inversely correlating TB incidence with economic development, ecologic comparisons between high- and low-income countries, and acute changes in TB incidence during famines, wars, economic crises, and natural disasters. In these situations, the effects of undernutrition cannot be disentangled from broader circumstances (10–16). Because TB causes anorexia and weight loss, cross-sectional and case-control studies cannot separate cause and effect. Cohort studies carried out among US Navy recruits and in Norway have demonstrated increased TB risk in thin persons (17–19). In a study in Philadelphia, Pennsylvania, men with low vitamin A and C levels had a higher TB incidence than men with adequate levels (20). In New York City, a clinical trial demonstrated that use of multivitamin-mineral supplements decreased TB incidence among family members of active TB cases (21). These studies date from the 1940s and 1950s. Since that time, the impact of specific nutrients on TB risk has not been adequately studied.

Mounting evidence suggests that obesity may decrease the risk of TB (22, 23). In China, a study of more than 42,000 elderly persons found that TB incidence was significantly lower in overweight persons than in normal-weight controls (23).

To determine the TB risk associated with nutritional status and to identify specific nutrients involved, we analyzed data from a population-based, 20-year follow-up study of adults in the United States.

MATERIALS AND METHODS

Study population and data sources

The First National Health and Nutrition Examination Survey (NHANES I), carried out during 1971–1975, collected extensive data on a probability sample of the civilian, noninstitutionalized US population aged 1–74 years in the 48 contiguous states, excepting reservation lands of American Indians (n = 23,808). Details of the complex survey design, plan, operation, and results have been published previously (24–27). Subjects were asked specifically about their TB history, and a representative subset had tuberculin skin tests. Subjects who had TB before NHANES I were excluded from analysis.

NHANES I provided the baseline sample for the NHANES I Epidemiologic Follow-up Study (NHEFS). Details on the plan, operation, and results of the NHEFS have been published previously (28–32). The NHEFS included all 14,407 adults aged 25–74 years at their NHANES I examination. They were followed up 4 times from 1982 to 1992 to identify

morbidity and mortality that could be related to their baseline characteristics. Follow-up data were obtained for 13,419 (93.1%) subjects from interviews, medical records, and death certificates: 13,155 (91.3%) subjects were interviewed at least once, 10,779 (74.8%) at least twice, and 8,949 (62.1%) at least thrice. Proxy informants were interviewed for deceased and incapacitated subjects. Respondents were asked about any overnight stays in hospitals and skilled nursing facilities; 11,025 (83.8% of 13,155) reported at least 1 stay in a health-care facility. Medical records were obtained for 10,765 (97.6% of 11,025) individuals and 48,737 facility stays; 2,487 (23.1%) persons had a single stay, 8,270 (76.8%) had ≥2 stays, and 6,825 (63.4%) had ≥3 stays. Death certificates were obtained for 4,482 (97.4%) of 4,604 deceased subjects (32.0% of the entire cohort of 14,407 subjects).

Outcome variables

Incident cases of TB were ascertained from interviews, medical records, and death certificates. The scripted interview did not ask about TB by name but included many questions probing for information about serious illnesses, health-care facility stays, and health-related conditions beyond those specified by name (28–31, 33). Key words and phrases were recorded verbatim, and the character strings were searched for “TB” or “tuberculosis.” For each mention, the full context was read so as to include only active TB. TB exposure, TB screening, and TB skin testing without active disease were not counted.

Medical records were abstracted by National Center for Health Statistics staff who had no knowledge of the present research. Trained personnel assigned *International Classification of Diseases*, Ninth Revision (ICD-9), codes on the basis of admission and discharge records. Death certificate data were obtained at both the individual level and the condition level, using multiple-cause methods to capture all information on each death certificate. Data from medical records and death certificates were searched for ICD-9 codes for TB (ICD-9 codes 010-018 and 137). TB exposure without disease (ICD-9 code V01.1), primary infection without disease (ICD-9 code 010.0), and tuberculin skin test positivity without disease (ICD-9 code 795.5) were excluded. To check the validity of the NHEFS-based population-estimated TB incidence, we compared it with actual reported incidence based on the Centers for Disease Control and Prevention’s National TB Surveillance System for this time period, taking into account the age structure of the cohort.

Nutritional status variables

Anthropometric indicators of nutritional status included body mass index (BMI), subcutaneous fat, and lean skeletal muscle. BMI (weight (kg)/height $(m)^2$) was categorized as low (<18.5), normal (18.5– <25), overweight (25– <30), or obese (≥30) (34, 35). Subcutaneous fat was based on the sum of the right triceps and subscapular skinfold thicknesses (36). Skeletal muscle was based on the cross-sectional area of the right mid-upper arm muscle (cm^2) using Frisancho’s method (37). Unlike the case for BMI, a fixed scale for classifying skinfold thickness and arm muscle area as low/normal/high has not been established. Therefore, we compared the mean skinfold thicknesses and arm muscle areas for persons who subsequently developed TB and those who did not. We also classified skinfold thickness and arm muscle area as low/normal/high on the basis of their sex-specific

population distributions, defining low as <5th percentile, high as >60th percentile, and normal as values between those cutpoints.

Hemoglobin was measured for all examinees, while a representative subsample of 11,348 people was tested for serum albumin, iron, iron-binding capacity, transferrin saturation, vitamin A, thiamine, riboflavin, and creatinine, plus urinary thiamine, riboflavin, and creatinine (38, 39). Vitamin D levels were not measured. Laboratory values were dichotomized as normal/abnormal on the basis of standard reference values for the population at that time (40).

Covariates

Of the characteristics measured at the NHANES I examination, we analyzed sex, age, race, Hispanic ethnicity, foreign birth, income, urban/rural residence, residence in a federally designated poverty area, and medical history of diabetes mellitus, anemia, and cancer.

Analytic methods

Data were analyzed with SAS 9.2 (SAS Institute Inc., Cary, North Carolina) and SUDAAN 10.0 (Research Triangle Institute, Research Triangle Park, North Carolina) software for population estimates, taking into account the complex sample design and sampling probabilities (27, 41). Statistical inferences are based on the population-estimated results. A P value less than 0.05 was considered significant, and all statistical tests were 2-sided.

TB incidences were compared among groups with different levels of baseline nutritional status. For continuous variables, the population-estimated distributions were compared using the t test or the Wilcoxon rank-sum test. For categorical measures of nutritional status, we compared cumulative TB incidence and incidence density per 100,000 person-years across levels of the nutritional indicator. For TB cases, follow-up time ended on the earliest date of diagnosis. Otherwise, follow-up time was censored on the date of the last observation. For each predictor variable, persons with normal values constituted the reference group. Groups were compared graphically by means of Kaplan-Meier plots and statistically by means of the log-rank test. Because BMI was correlated with both skinfold thickness and arm muscle area (BMI-skinfold thickness: $r = 0.72$ ($P < 0.0001$); BMI-arm muscle area: $r = 0.51$ ($P < 0.0001$)), these 3 anthropometric factors together were nearly collinear; skeletal muscle and subcutaneous adipose tissue are major components of body mass. Therefore, the adjusted hazard ratios for each were calculated in 3 separate main-effects models, each controlling for the same covariates.

We controlled for potential confounding with multivariable Cox proportional hazards regression incorporating the complex survey design and sampling weights. Predictor variables based on fewer than 5 actual TB cases were not included in the multivariable model. Control variables were examined for effect modification and confounding by means of stratified analysis using Mantel-Haenszel methods and by means of proportional hazards regression incorporating appropriate interaction terms, ensuring that each variable satisfied the proportional hazards assumption.

RESULTS

Of the 14,407 members of the NHEFS cohort, 218 were excluded because they had TB before NHANES I, leaving 14,189 in the analysis cohort. Their characteristics reflect the design-based oversampling of persons living in poverty areas, the elderly, and women of childbearing age (Table 1).

TB incidence

Of the 14,189 participants, 13,211 (93.1%) had usable follow-up data totaling 209,013 person-years and averaging 15.8 years in duration (standard deviation, 5.5; range, <1– 22). Sixty-one (0.43%) incident TB cases were detected (crude incidence = 28.3/100,000 person-years). Incorporating sampling weights and design specifications, the population-estimated cumulative incidence was 372,332 (95% confidence interval (CI): 244,787, 499,877) TB cases over a 20-year period (1973–1992). For comparison, the actual TB incidence in the national TB surveillance system for the 48 states was 380,578 cases for the same time period and age group (42, 43). The NHEFS-based population-estimated average annual TB incidence density was 22.8 per 100,000 person-years (95% CI: 15.0, 30.6) for the 20-year period 1973–1992. In national surveillance data, annual TB incidence in 1971 was 25.8 per 100,000 person-years, decreasing to 14.2 per 100,000 in 1992 (i.e., bracketing the NHEFS-based estimated annual average).

Anthropometric indicators of nutritional status

Mean BMI, skinfold thickness, and arm muscle area were significantly lower in persons who subsequently developed TB than in those who did not, except for arm muscle area among females (Table 2). For each measure, there was an inverse gradient with TB incidence (Table 3). TB incidence among participants with BMI <18.5, representing approximately 3% of the population, was 260.2 per 100,000 person-years (95% CI: 98.6, 421.8), 11.7-fold higher than that among participants with normal BMI (24.7/100,000 person-years, 95% CI: 13.0, 36.3). In contrast, TB incidence was 2.8-fold lower (8.9/100,000 person-years, 95% CI: 2.2, 15.6) among those who were overweight and 4.8-fold lower (5.1/100,000 person-years, 95% CI: 0.0, 10.5) among those who were obese.

BMI does not distinguish between muscle, adipose tissue, bone, viscera, and water. To differentiate the effects of muscle from the effects of adipose tissue, we examined TB incidence by skinfold thickness, arm muscle area, and the interaction between the two. Mean skinfold thickness was 14.7 mm lower and arm muscle area was 4.7 cm^2 lower among persons who developed TB than among those who did not (Table 2). Both fat and muscle were inversely associated with TB incidence. As skinfold thickness increased from low to normal to high, the TB incidence rate decreased from 170.6 per 100,000 person-years (95% CI: 59.6, 281.5) to 22.4 (95% CI: 10.6, 34.2) to 7.5 (95% CI: 1.9, 13.0). The pattern was similar with arm muscle area, but with a smaller amplitude (Table 3).

Subcutaneous fat and skeletal muscle had a synergistic effect. In the subset of people with both low skinfold thickness and low arm muscle area, TB incidence was 572.7 per 100,000 person-years (95% CI: 134.2, 1,011.2), more than 20-fold greater than the incidence in

people with normal skinfold thickness and arm muscle area (Table 3). Among people with low values for either variable but not both, the risk of TB increased 3.0- to 5.5-fold. In contrast, among people whose arm muscle area and skinfold thickness were high, TB risk was significantly lower than among people with normal values (Table 3).

Kaplan-Meier plots (Figure 1 and Web Figure 1 (http://aje.oxfordjournals.org/)) display the TB incidence in undernourished, adequately nourished, and overweight groups over time. Undernourished participants developed TB significantly more quickly and obese participants developed TB significantly more slowly than those with normal nutritional status ($P < 0.0001$, log-rank test).

Hemoglobin, serum proteins, and serum and urinary micronutrients

Compared with participants who did not develop TB, population-estimated mean hemoglobin levels (14.1 g/dL (95% CI: 13.7, 14.6) vs. 14.6 g/dL (95% CI: 14.5, 14.7); $P = 0.04$) and serum albumin levels (4.1 g/dL (95% CI: 3.9, 4.3) vs. 4.4 g/dL (95% CI: 4.4, 4.4); $P = 0.006$) were significantly lower among persons who later developed TB (Table 2). An abnormally low hemoglobin level (i.e., anemia) was observed in 2.5% of the population, but their TB incidence was not elevated. Hypoalbuminemia was observed in only 0.7% of the population, but their TB risk was 12.9-fold higher (95% CI: 2.5, 67.1) than among people with normal albumin levels (Table 3). Serum vitamin A, iron status, and urinary excretion of thiamine and riboflavin were not significantly associated with TB risk.

Multivariable analysis

Based on multivariable proportional hazards regression for complex sample surveys, the population-estimated hazard of developing TB for persons with low BMI was 12.4-fold (95% CI: 5.7, 26.9) greater than that for persons with normal BMI, after controlling for age, sex, race, Hispanic ethnicity, immigration, urban/rural residence, income, residence in a designated poverty area, excess alcohol consumption, smoking, and diabetes mellitus (Table 4). In contrast, among people who were overweight, it was nearly 4-fold lower (adjusted hazard ratio = 0.28, 95% CI: 0.13, 0.63); among people who were obese, it was 5-fold lower (adjusted hazard ratio = 0.20, 95% CI: 0.07, 0.62). Similarly, low skinfold thickness and low arm muscle area increased the hazard of developing TB 9.2-fold (95% CI: 3.2, 26.0) and 5.6-fold (95% CI: 2.2, 14.3), respectively. Anemia and iron status were not predictors of TB risk. There were too few TB cases among persons with low vitamin A, thiamine, riboflavin, or albumin levels to include those variables. Otherwise, only male sex, increasing age, smoking, and diabetes mellitus increased TB risk.

Internal validation

To exclude the possibility that the observed association between TB and nutrition was due to the risk of becoming infected rather than (or in addition to) the risk of developing active disease, we analyzed nutritional status and TB incidence in relation to tuberculin skin test results. Of 1,470 persons tested, tuberculin skin tests were negative in 948 (64.5%); 249 (16.9%) had induration of 1–9 mm, and 273 (18.6%) had induration of ≥10 mm. There was no difference in the distribution of tuberculin skin test results by BMI.

If undernutrition led to hospitalization or death, the observed risk may have increased due to increased ascertainment of TB from medical records or death certificates rather than an actual increased risk of TB. However, the proportions of persons with 1 or more stays at a health-care facility were identical (71.9%) in people with low BMI and people with normal BMI, and the proportion was higher among overweight (76.8%) and obese (78.6%) people —opposite the relation between TB incidence and BMI. Mortality was higher in people who were overweight (34.7%) and obese (38.0%) than in people with normal BMI (27.1%).

DISCUSSION

Protein-energy nutrition was strongly associated with TB incidence in US adults during the period 1973–1992, independent of demographic, socioeconomic, and medical factors. Persons with low BMI, little subcutaneous fat, or low skeletal muscle had 5.5- to 12.5-fold higher risks of TB than persons with normal nutritional status. One-third of TB cases occurring among US adults during this 20-year period arose from this small (≤5%) fraction of the population. Low levels of serum albumin and serum transferrin, both markers of protein nutritional status, were strongly associated with an increased risk of TB. We did not include NHANES I dietary measures of nutritional status in this report because specific nutrient intakes were based on a single 24-hour dietary recall, which is not an adequate baseline measurement for a long-term follow-up study. With that caveat, however, it was interesting in this context that protein intake less than 50% of normal was the only dietary measure strongly associated with increased TB incidence (data not shown) (44–46). Thus, the consistency of the evidence suggests that protein undernutrition is important in host defenses against TB. Amino acids play key physiologic roles as precursors of molecules that are important to host defense, such as tryptophan (niacin, serotonin), arginine (nitric oxide), and methionine (*S*-adenosylmethionine). When energy intake and reserves are inadequate, somatic and dietary proteins are prioritized for energy. The negative impact of protein undernutrition on cell-mediated immunity is well-documented (1–7, 10, 11). In populations where protein insufficiency is common, it may contribute substantially to TB incidence. However, nutrition-related deficits in cell-mediated immunity are rapidly reversible with appropriate nutrient intake (47, 48).

Persons who were overweight, had thick fat, or had large muscles (approximately 40% of the population) had only one-third to one-fifth the risk of TB as people with normal values for these measures, consistent with previous studies (17–19, 23). Adipose tissue may be a reservoir for nonreplicating *M. tuberculosis* (49, 50). Such bacilli accumulate triglycerides in cytoplasmic lipid bodies and proliferate slowly in vitro (51, 52). A molecular genetic basis for these phenotypic characteristics has been identified (53–58). Thus, the decreased incidence of TB associated with increased BMI, especially with increased adipose tissue, may be related to development of a nonreplicating “persister” phenotype of *M. tuberculosis* in a lipid-rich environment. If these observations are confirmed, policies regarding isoniazid preventive treatment could be revisited, because the potential benefit would be much lower among obese persons with low risk of developing active TB. Given the prevalence of obesity in the United States, the cost savings to TB control programs could be substantial, because the majority of persons being treated in public TB control programs are being treated for latent infection, not active TB disease.

This analysis had important limitations, especially the potential for biased ascertainment of TB incidence. Because follow-up interviews did not ask specifically about TB, the data may not have captured every incident case of TB, especially cases not resulting in hospitalization or death. This potential bias, however, does not explain the observed association. First, the NHEFS-based estimated TB incidence was remarkably close to actual TB incidence according to national surveillance data, reflecting internal and external validity and lending credibility to the results (42, 43). The US TB surveillance system has been shown to be highly complete (59–63). Second, ascertainment of TB incidence was neither biased toward underweight persons nor biased against overweight persons. Third, in the 1970s, hospitalization of TB patients was the norm; the practice decreased gradually over time. The proportion of TB patients hospitalized was very high throughout the 1970s, gradually trending downward to approximately 50% by the late 1990s (64–73). Twenty-one of the 61 TB cases were ascertained through interviews, not ICD-9 codes.

Misclassification may have resulted from the use of ICD-9 codes, but in this study ICD-9 codes were assigned by trained National Center for Health Statistics staff, not by each facility's billing department. We further mitigated this potential source of error by excluding ICD-9 codes for primary TB infection, TB exposure, and tuberculin skin test positivity in the absence of active TB.

A second limitation is the fact that the nutritional status of the US population has changed. Even though obesity was not widespread in the 1970s, many people are skeptical that undernutrition was ever a substantial problem in the United States. Indeed, only 2.2% of the cohort had low BMI. Nevertheless, the historical record speaks for itself (74–78). Large-scale nutrition surveys conducted in the 1960s found such widespread hunger and malnutrition among impoverished groups in the United States (79–85) that in a 1969 address to Congress, President Richard Nixon stated, "In the past few years, we have awakened to the distressing fact that despite our material abundance and agricultural wealth … there can be no doubt that hunger and malnutrition exist in America, and that some millions are affected" (86). The 1969 White House Conference on Food, Nutrition, and Hunger was a turning point (79–81), leading to large-scale government initiatives to combat undernutrition in the 1970s: food stamps; Aid to Families with Dependent Children (AFDC); the Supplemental Nutrition Program for Women, Infants, and Children (WIC); school breakfast programs; and Meals on Wheels for the elderly (79–82, 87). Undernutrition was mitigated in the United States only after these programs had been implemented throughout the 1970s. NHANES I itself was implemented to monitor the impact of these programs; hence, people living in poverty and people at high risk of undernutrition were heavily oversampled in NHANES I.

In addition to an increase in obesity, the incidence of diabetes mellitus has increased, the prevalence of smoking has decreased, and TB incidence among US-born persons has decreased, so the majority of TB cases now occur among foreign-born persons. The HIV epidemic also began in the 1980s. Apart from specific measures of nutritional status, diabetes and smoking were strong risk factors for TB in these data. While overweight persons in general had a lower risk of developing TB, the risk among overweight persons with diabetes was still elevated. HIV infection caused much TB morbidity from the

mid-1980s through the late 1990s, when highly effective antiretroviral treatment became widely available. In the NHEFS cohort, 22 persons were identified as having HIV infection based on ICD-9 codes in the follow-up data, but none of them had TB. Thus, there were too few HIV-infected persons to control for HIV infection.

Because the population's nutritional profile has changed, the results presented here do not reflect the population attributable risk after 1992, but they remain valid estimates of TB risk relative to nutritional indicators measured on a fixed scale, such as BMI categories and standard laboratory criteria. In addition, risk ratios based on absolute measures of nutritional status may be used to estimate attributable risk in populations with known, corresponding measures of nutritional status.

This study had important strengths. First, NHANES I and NHEFS have been documented extensively, with assessments of internal and external validity (24–32, 88–92). Second, standardized, validated indicators of nutritional status were based on body measurements and laboratory data. Third, multivariable statistical methods were based on the complex study design (27, 44). Fourth, to our knowledge, this is the only longitudinal cohort study of nutritional status and incident TB based on a nationally representative sample. Few observational studies have measured nutritional status and TB incidence among individuals in the appropriate temporal sequence, and none have excluded previous TB to ensure that only incident cases were included among the outcomes. In only 1 other study have investigators controlled for known risk factors using multivariable methods (23). Fifth, we separated the risks of TB in relation to adipose tissue, somatic protein, and individual micronutrients. Three older cohort studies demonstrated an association between TB incidence and weight-height indices, but they focused on "body build" as the operative concept rather than nutritional status (17–19, 93). However, both fat mass and muscle mass vary with nutritional intake and physical activity.

The absence of association with iron status could not have been predicted. Iron is critical to the immune response but also to the metabolism and replication of *Mycobacterium*. Data are insufficient to predict whether iron deficiency favors the microbe more than the host.

The absence of an association with vitamin A was not surprising, because vitamin A protects against infection mainly through epithelial integrity and humoral, not cellular, immune responses (94). Overt vitamin A deficiency was uncommon in the study cohort. Vitamin D has been associated with cellular immune defenses against TB, but vitamin D levels were not measured.

This study has implications beyond TB incidence in the US population. Changes in the prevalence of undernutrition in groups at risk for TB may affect TB incidence, as modeled by Lönnroth et al. (9, 22) and as noted by other investigators (95–97). Economic contractions and surging commodity food prices may affect TB incidence if they affect the nutritional status of populations; consider the popular term "belt-tightening" to describe economic hardship. Even modest nutritional deficits adversely affect cell-mediated immunity. Where undernutrition and TB are prevalent, the attributable proportion of TB cases may be substantial. In 1988, the US Surgeon General cited undernutrition as the

leading cause of acquired immune system dysfunction worldwide (87). Most importantly, immune function is rapidly restored with nutritional repletion, suggesting that the provision of nutritional support to families and contacts of persons with TB may decrease TB incidence, in addition to the numerous other benefits of adequate nutrition.

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Abbreviations

BMI	body mass index
CI	confidence interval
HIV	human immunodeficiency virus
ICD-9	*International Classification of Diseases*, Ninth Revision
NHANES I	First National Health and Nutrition Examination Survey
NHEFS	NHANES I Epidemiologic Follow-up Study
TB	tuberculosis

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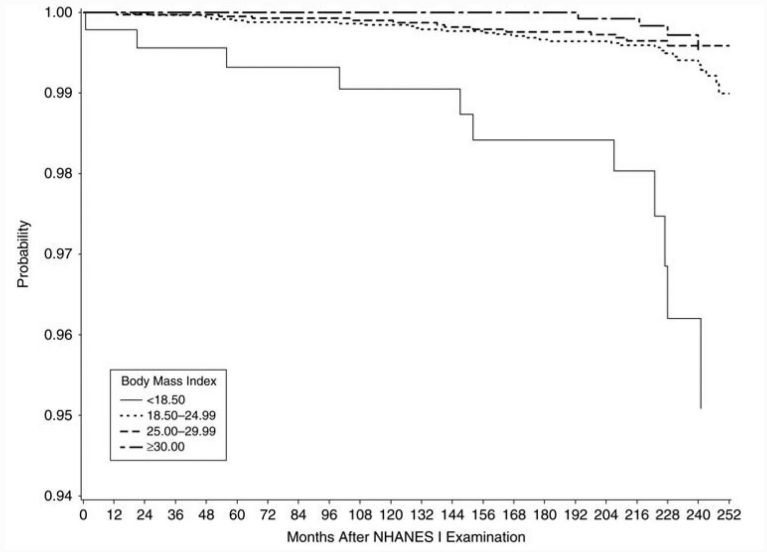

Figure 1.

Kaplan-Meier plot of the probability of remaining free of tuberculosis according to body mass index (weight (kg)/height $(m)^2$), First National Health and Nutrition Examination Survey (NHANES I) Epidemiologic Follow-up Study, 1971–1992.

Table 1

Characteristics (Population-estimated Percentage) of Participants Who Later Developed Tuberculosis (n = 61) and Those Who Did Not (n = 14,128), NHANES I Epidemiologic Follow-up Study, 1971–1992[a]

Characteristic	Persons Who Later Developed Tuberculosis		Persons Who Did Not Develop Tuberculosis		*P* Value
	%	95% CI	%	95% CI	
Male sex	40.1	20.8, 59.4	52.7	51.5, 54.0	0.2
Age group, years					0.1
25–34	12.6	0, 28.6	26.3	25.2, 27.4	
35–44	13.9	1.5, 28.6	21.4	20.4, 22.4	
45–54	37.5	17.5, 57.5	21.9	21.0, 22.9	
55–64	14.3	0, 29.8	18.1	17.0, 19.2	
≥65	21.8	11.6, 32.0	12.2	11.1, 13.4	
Race					0.5
White	85.2	75.2, 95.2	89.2	87.9, 90.6	
Black	12.5	3.2, 21.9	9.7	8.4, 11.0	
Other	2.2	0, 5.9	1.1	0.8, 1.4	
Hispanic ethnicity	4.7	0, 9.5	4.2	3.1, 5.4	0.9
Residence in an urban area					0.8
Urban	59.9	42.7, 77.1	55.0	51.6, 58.3	
Suburban	8.8	0, 17.7	12.6	10.5, 14.7	
Rural	31.3	13.4, 49.2	32.4	29.6, 35.2	
Residence in a designated poverty area[b]	32.3	16.0, 48.7	18.9	14.0, 23.9	0.07
Immigrant to the United States	6.3	0, 13.2	8.1	7.2, 9.0	0.6
Annual income[c,d]					0.05
<$10,000	61.6	45.0, 78.1	49.3	46.8, 51.8	
$10,000-$20,000	18.8	6.3, 31.4	38.4	36.7, 40.2	
>$20,000	19.6	5.6, 33.6	12.3	10.8, 13.8	
Alcohol					
Alcohol consumption of >7 drinks/week[d]	23.5	6.1, 40.9	19.6	18.0, 21.1	0.6
Current smoking[d]	79.0	65.5, 92.5	61.0	59.7, 62.4	0.03
Medical history					
Anemia	31.3	13.2, 49.4	21.2	20.3, 22.1	0.2
Diabetes	12.9	1.8, 24.0	3.8	3.4, 4.3	0.005
Body mass index[e]					<0.0001
Low (<18.5)	31.7	15.3, 48.1	3.1	2.8, 3.5	
Normal (18.5–<25)	51.6	34.1, 69.1	47.0	45.7, 48.3	
Overweight (25–<30)	13.3	5.1, 21.6	34.0	33.0, 35.1	
Obese (≥30)	3.4	0, 7.1	15.8	14.9, 16.7	

Characteristic	Persons Who Later Developed Tuberculosis		Persons Who Did Not Develop Tuberculosis		*P* Value
	%	95% CI	%	95% CI	
Skinfold thickness[f]					<0.0001
Low	32.6	13.7, 51.6	4.8	4.3, 5.3	
Normal	54.3	33.6, 75.0	55.3	53.9, 56.6	
High	13.1	4.1, 22.0	39.9	38.6, 41.3	
Mid-upper arm muscle area[f]					<0.0001
Low	24.0	8.6, 39.5	4.9	4.5, 5.4	
Normal	60.0	42.0, 78.1	55.1	53.7, 56.4	
High	15.9	6.4, 25.5	40.0	38.6, 41.4	
Anemia[g]	11.4	0.1, 22.7	12.8	11.6, 14.1	0.8
Hypoalbuminemia[h]	11.2	0, 29.2	0.5	0.4, 0.7	<0.0001
Iron deficiency[i]					Indeterminate
Unlikely	90.5	82.7, 98.4	89.0	88.1, 89.9	
Possible	9.5	1.6, 17.3	9.1	8.4, 9.8	
Probable	0	0	1.9	1.5, 2.2	
Low serum vitamin A level,[j] µg/L					Indeterminate
<20	0	0	0.1	0.1, 0.2	
<30	4.0	0, 9.4	1.5	1.2, 1.7	0.13
Low thiamine excretion	0.9	0, 2.7	0.2	0.1, 0.4	0.2
Low riboflavin excretion	0	0	0.8	0.6, 1.0	Indeterminate

Abbreviations: CI, confidence interval; NHANES I, First National Health and Nutrition Examination Survey; NHEFS, NHANES I Epidemiologic Follow-up Study.

[a]Data shown are population-estimated percentages for categorical variables incorporating survey design specifications (adjusted weights, stratification, multistage cluster sampling). Of 14,407 persons in the entire NHEFS cohort, 218 with a history of tuberculosis prior to the NHANES I baseline medical examination were excluded, leaving 14,189 persons in the analysis cohort.

[b]Data on residence in a federally designated poverty area was recorded for the main Nutrition Survey (n = 11,348), carried out in 1971–1974 and comprised of 65 primary sampling units, but not the Augmentation Survey (n = 3,059), carried out in 1974–1975 and comprised of 35 additional primary sampling units. Both components, separately and together, were based on nationally representative samples.

[c]An income of $10,000 in 1973 dollars is equivalent to an income of $38,783 in 2000 dollars and $49,111 in 2010 dollars (http://data.bls.gov/ cgi-bin/cpicalc.pl).

[d]Data on income were missing for 3.8% of NHEFS cohort participants, data on alcohol consumption were missing for 13.5%, and data on smoking were missing for 9.2%.

[e]Weight (kg)/height (m)2.

[f]Skinfold thickness and arm muscle a “Low” was defined as <5th percentile, “hi rea were classifi gh” as >60th perc ed as low, normal, or high on the basis of their sex-specific population distributions. entile, and “normal” as values between those cutpoints.

[g]Anemia was defined as a hemoglobin level less than 1 1.5 g/dL in females and less than 13.0 g/dL in males.

[h]Hypoalbuminemia was defined as a s erum albumin lev el less than 3.5 g/dL.

[i]Iron status and the likelihood of iron d as follows. “Iron deficiency probable” was “iron deficiency possible” was defined as abnormalities. eficiency were ba defined as low s any 2 of these 3 sed on serum iron level, percent transferrin saturation, and total iron-binding capacity, erum iron

level and low percent transferrin saturation and high iron-binding capacity; abnormalities; and “iron deficiency unlikely” was defined as only 1 or none of these abnormalities.

[j]Different criteria for vitamin A deficiency have been proposed for clinical purposes (<20 μg/L or <70 μmol/L) and epidemiologic purposes (<30 μg/L or <105 μmol/L).

Table 2

Characteristics (Population-estimated Mean and Median Values) of Participants Who Later Developed Tuberculosis (n = 61) and Those Who Did Not (n = 14,128), NHANES I Epidemiologic Follow-up Study, 1971–1992[a]

Characteristic	Persons Who Later Developed Tuberculosis		Persons Who Did Not Develop Tuberculosis		*P* Value
	Mean or Median	95% CI	Mean or Median	95% CI	
Mean body mass index[b]					
Total	21.6	20.5, 22.7	25.5	25.5, 25.7	<0.0001
Men	20.9	19.6, 22.1	25.8	25.7, 26.0	<0.0001
Women	22.7	20.5, 24.9	25.4	25.3, 25.6	0.01
Mean skinfold thickness, mm					
Total	22.1	18.0, 26.3	36.8	36.3, 37.3	<0.0001
Men	16.0	12.3, 19.6	29.1	28.6, 29.5	<0.0001
Women	31.4	24.5, 38.3	43.8	43.2, 44.4	0.0006
Mean mid-upper arm muscle area, cm^2					
Total	46.9	43.2, 50.7	51.6	51.1, 52.1	0.02
Men	51.5	48.5, 54.4	63.7	63.3, 64.2	<0.0001
Women	40.2	35.6, 40.9	40.8	40.4, 41.2	0.8
Mean hemoglobin level, g/dL					
Total	14.1	13.7, 14.6	14.6	14.5, 14.7	0.04
Men	14.7	14.2, 15.2	15.5	15.4, 15.6	0.001
Women	13.3	12.9, 13.8	13.7	13.6, 13.8	0.06
Mean serum albumin level, g/dL	4.1	3.9, 4.3	4.4	4.4, 4.4	0.006
Mean serum vitamin A level, μg/L	64.3	55.2, 73.4	59.9	59.0, 60.8	0.30
Median urinary thiamine level, μg/g creatinine	346	254, 576	302	284, 323	0.12
Median urinary riboflavin level, μg/g creatinine	286	175, 460	255	246, 266	0.29

Abbreviations: CI, confidence interval; NHANES I, First National Health and Nutrition Examination Survey; NHEFS, NHANES I Epidemiologic Follow-up Study.

[a]Data shown are population-estimated mean and median values (as indicated) incorporating survey design specifications (adjusted weights, stratification, multistage cluster sampling). Of 14,407 persons in the entire NHEFS cohort, 218 with a history of tuberculosis prior to the NHANES I baseline medical examination were excluded, leaving 14,189 persons in the analysis cohort.

[b]Weight (kg)/height $(m)^2$.

Table 3

Population-estimated Incidence of Tuberculosis According to Anthropometric and Laboratory Measures of Nutritional Status Among US Adults, NHANES I Epidemiologic Follow-up Study, 1971–1992

Nutritional Status Indicator	Crude Frequency of TB in NHEFS Cohort		Crude Distribution of Subjects in Each Category of NHEFS Cohort[a]		No. of TB Cases, in Thousands (Population Estimate)		Incidence Density/100,000 Person-Years (Population Estimate)		Hazard Ratio	95% CI
	No. of Cases	% of Category Total	No. of Subjects	% of NHEFS Total	No. of Cases	95% CI	No. of Cases	95% CI		
Total	61	0.43	14,189	100	372.0	245, 500	22.8	15.0, 30.6		
Body mass index[b]										
<18.5	11	2.17	508	3.8	118.0	45, 191	260.2	98.6, 421.8	11.7	5.3, 25.9
18.5–25	32	0.48	6,639	46.8	192.0	101, 282	24.7	13.0, 36.3	1	Reference
25–30	14	0.30	4,647	32.8	50.0	12, 87	8.9	2.2, 15.6	0.37	0.17, 0.82
>30	4	0.17	2,388	16.8	13.0	0, 26	5.1	0.0, 10.5	0.22	0.07, 0.69
SFT,[c] mm										
Low	14	1.83	767	5.42	121.5	44.1, 198.9	170.6	59.6, 281.5	8.04	3.10, 20.87
Normal	34	0.43	7,846	55.44	202.2	96.2, 308.6	22.4	10.6, 34.2	1	Reference
High	13	0.23	5,538	39.14	48.7	12.6, 84.8	7.5	1.9, 13.0	0.34	0.14, 0.85
AMA,[c] cm^2										
Low	13	1.55	839	5.92	89.5	32.1, 146.9	120.4	41.6, 199.1	5.09	2.00, 12.94
Normal	35	0.45	7,751	54.70	223.4	118.1, 328.7	24.8	13.0, 36.6	1	Reference
High	13	0.23	5,580	39.20	59.4	16.5, 102.3	9.1	2.5, 15.6	0.36	0.17, 0.79
Both SFT and AMA										
SFT low, AMA low	7	5.07	138	0.98	59.6	18.0, 101.2	572.7	134.2, 1,011.2	27.87	10.26, 75.68
SFT low, AMA normal	7	1.35	519	3.67	61.8	0, 133.0	119.4	0, 239.7	2.98	0.63, 14.12
SFT low, AMA high	0	0	110	0.78	0		0		0	
SFT normal, AMA low	6	1.11	540	3.82	29.9	0, 69.6	63.8	0, 128.1	5.54	1.34, 22.91
SFT normal, AMA normal	22	0.44	4,984	35.23	133.7	53.2, 214.3	23.2	9.1, 37.2	1	Reference
SFT normal, AMA high	6	0.26	2,321	16.41	38.6	0, 77.5	13.8	0, 27.7	0.46	0.13, 1.66
SFT high, AMA low	0	0	161	1.14	0		0		0	

Nutritional Status Indicator	Crude Frequency of TB in NHEFS Cohort		Crude Distribution of Subjects in Each Category of NHEFS Cohort[a]		No. of TB Cases, in Thousands (Population Estimate)		Incidence Density/100,000 Person-Years (Population Estimate)		Hazard Ratio	95% CI
	No. of Cases	% of Category Total	No. of Subjects	% of NHEFS Total	No. of Cases	95% CI	No. of Cases	95% CI		
SFT high, AMA normal	6	0.26	2,246	15.88	27.8	0, 59.4	10.3	0, 20.6	0.59	0.23, 1.49
SFT high, AMA high	7	0.22	3,129	22.12	20.8	4.0, 37.6	5.7	1.1, 10.3	0.25	0.09, 0.67
Blood hemoglobin level										
Low (anemia)[d]	10	0.48	2,087	15.32	42.2	0, 84.4	20.7	0, 41.5	0.88	0.29, 2.66
Normal	49	0.42	11,533	84.68	327.0	205.3, 448.6	23.7	14.8, 32.7	1	Reference
Serum albumin level										
Low (hypoalbuminemia)[e]	3	1.86	155	1.39	44.8	0, 117.7	408.7	0, 1,085.2	12.96	2.50, 67.10
Normal	50	0.45	11,013	98.61	323.2	190.1, 456.3	264.4	89.2, 439.6	1	Reference
Iron status[f]										
Deficiency unlikely	44	0.48	9,258	87.8	325.3	181.1, 469.4	30.8	17.0, 44.5	1	Reference
Deficiency possible	7	0.67	1,046	9.9	34.0	5.5, 62.6	32.1	4.9, 59.3	1.04	0.29, 1.34
Deficiency likely	0	0	235	2.2	0		0		Undefined	Undefined
Serum vitamin A level, µmol/L										
<105	3	1.46	205	1.9	14.6	0, 34.1	80.9	0, 189.8	2.80	0.70, 11.40
>105	48	0.45	10,584	98.10	348.5	199.0, 498.1	29.6	16.8, 42.4	1	Reference
Low thiamine excretion	1	4.0	25	0.2	3.3	0, 9.9	123.2	0, 381.0	3.70	0.50, 28.80
Low riboflavin excretion	0	0	95	0.9	0		0		Undefined	Undefined

Abbreviations: AMA, arm muscle area; CI, confidence interval; NHANES I, First National Health and Nutrition Examination Survey; NHEFS, NHANES I Epidemiologic Follow-up Study; SFT, skinfold thickness; TB, tuberculosis.

[a] Excludes 218 subjects with a prior history of TB before NHANES I.

[b] Weight (kg)/height $(m)^2$.

[c] SFT and AMA were classified as low, normal, or high on the basis of their sex-specific population distributions. “Low” was defined as <5th percentile, “high” as >60th percentile, and “normal” as values between those cutpoints.

[d] Anemia was defined as a hemoglobin level less than 11.5 g/dL in females and less than 13.0 g/dL in males.

[e] Hypoalbuminemia was defined as a serum albumin level less than 3.5 g/dL.

[f] The likelihood of iron deficiency was based on serum iron level, percent transferrin saturation, and total iron-binding capacity, as follows. "Iron deficiency probable" was defined as low serum iron level and low percent transferrin saturation and high iron-binding capacity; "iron deficiency possible" was defined as any 2 of these 3 abnormalities; and "iron deficiency unlikely" was defined as only 1 or none of these abnormalities.

Table 4

Population-estimated Adjusted Hazard Ratios for the Relation of Tuberculosis Incidence With Selected Measures of Nutritional Status and Other Risk Factors Among US Adults, NHANES I Epidemiologic Follow-up Study, 1973–1992[a]

Characteristic	Adjusted Hazard Ratio	95% Confidence Interval
Sex		
Female	0.35	0.14, 0.86
Male	1	Reference
Age group, years		
25–34	1	Reference
Each 10-year increment	1.62	1.16, 2.26
Race		
White	1	Reference
Nonwhite	1.60	0.93, 2.76
Annual income[b]		
<$10,000	2.17	0.89, 5.25
$10,000-$20,000	1.10	0.49, 2.45
>$20,000	1	Reference
Current smoking		
Yes	2.01	1.01, 4.03
No	1	Reference
Body mass index[c]		
<18.5	12.43	5.75, 26.95
18.5-<25	1	Reference
25-<30	0.28	0.13, 0.63
>30	0.20	0.07, 0.62
Skinfold thickness[d]		
Low	9.19	3.25, 25.98
Normal	1	Reference
High	0.30	0.12, 0.73
Cross-sectional arm muscle area[d]		
Low	5.56	2.16, 14.30
Normal	1	Reference
High	0.31	0.15, 0.65
Diabetes mellitus	7.58	2.94, 9.49
Anemia[e]		
Yes	0.69	0.22, 2.13
No	1	Reference
Hypoalbuminemia[f]		

Characteristic	Adjusted Hazard Ratio	95% Confidence Interval
Yes	0.93	0.36, 2.41
No	1	Reference
Iron status[g]		
Iron deficiency unlikely	1	Reference
Iron deficiency possible	0.82	0.30, 2.21

Abbreviation: NHANES I, First National Health and Nutrition Examination Survey.

[a]Results were based on multivariable Cox proportional hazards regression analysis for complex survey data. Terms were included in the final model if they were statistically significant at the $P < 0.05$ level or if they had a substantial (>10%) effect on the hazard ratio for tuberculosis incidence.

[b]An income of $10,000 in 1973 dollars is equivalent to an income of $38,783 in 2000 dollars and $49,111 in 2010 dollars (http://data.bls.gov/cgi-bin/cpicalc.pl).

[c]Weight (kg)/height $(m)^2$.

[d]Skinfold thickness and arm muscle area were classified as low, normal, or high on the basis of their sex-specific population distributions. “Low’ was defined as <5th percentile, “high” as >60th percentile, and “normal’ as values between those cutpoints.

[e]Anemia was defined as a hemoglobin level less than 11.5 g/dL in females and less than 13.0 g/dL in males.

[f]Hypoalbuminemia was defined as a serum albumin level less than 3.5 g/dL.

[g]Iron status and the likelihood of iron deficiency were based on serum iron level, percent transferrin saturation, and total iron-binding capacity, as follows. “Iron deficiency probable” was defined as low serum iron level and low percent transferrin saturation and high iron-binding capacity; “iron deficiency possible” was defined as any 2 of these 3 abnormalities; and “iron deficiency unlikely” was defined as only 1 or none of these abnormalities.