Obesity and Prevalence of Latent Tuberculosis: A Population-Based Survey

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ABSTRACT:

OBJECTIVE: Diminution in body weight is a known risk factor that increases the burden of active tuberculosis (TB). However, conflicting evidence exists for the effect of body weight on the risk of latent tuberculosis infection (LTBI). The objective of the present study is to examine the prevalence of LTBI at different body weights, evaluate the extent of association between body mass index (BMI) and LTBI and identify factors mediating this relationship in an adult population.

METHODS: We conducted a cross-sectional study to estimate the relationship between BMI and LTBI in participants from the US-National Health and Nutrition Examination Survey (NHANES; 2012, n = 5156; 514 with LTBI and 4642 controls).

RESULTS: The association between BMI and levels of cardiometabolic risk markers in both LTBI and control groups had a similar profile. When adjusted for age and sex, BMI was significantly inversely correlated with the prevalence of LTBI ($r = -0.147$, $P < .001$). Effect of BMI on the risk of LTBI was evaluated using multivariate logistic regression models adjusted for age, sex, diabetes, and level of education. In this model, increasing BMI was significantly associated with lower risk of LTBI (OR = 0.85; 95%CI: 0.77-0.96, $P < .01$).

CONCLUSION: This study further establishes an inverse relationship between BMI and prevalence of LTBI. Decreased BMI can be considered as a risk factor in LTBI, the reservoir for active TB cases.

KEYWORDS: Tuberculosis, obesity, body mass index, adults

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Introduction

Presently, tuberculosis (TB) is among the leading causes of death from a single infectious pathogen globally.[1] Although TB control has significantly improved over the past 2 decades, rendering the disease more preventable, TB is still responsible for more than a million deaths each year especially in low-income countries.[1,2] According to World Health Organization estimates, the number of TB incident cases in 2018 worldwide was 10.0 million, with more than 1.2 million deaths.[2] This burden, however, varies country to country by a number of individual- and population-related factors including age, sex, location, HIV infection, extent of drug-resistance, and country's sociodemographic and economic status.[1] Approximately 30% of persons exposed to *Mycobacterium tuberculosis* infection develop a state of persistent immune response to stimulation by the pathogen's antigen without evidence of clinically manifested TB and remain clinically asymptomatic (ie, with latent tuberculosis infection, LTBI).[3] However, 10% of the persons with LTBI will progress to active TB disease, presenting with clinical signs and symptoms.[4] Individuals with LTBI represent a reservoir for TB cases. The detection and management of LTBI is a component in the World Health Organization's "End TB Strategy" aiming to reduce worldwide TB incidence by 90% and TB mortality by 95% between 2016 and 2035.[5] Detection of active cases has been the primary public health response to TB. However, reducing the LTBI reservoir is fundamental in order to reach the ambitious goal of the "End TB Strategy."[6]

Several sociodemographic and metabolic risk factors have been proposed to influence the development of LTBI. Those included race, marital status, age, history of TB contact, urban residency, job category, and high (>7%) glycosylated hemoglobin (HbA1c).[7-11] Malnutrition[12] and the subsequent acute or chronic diminution in body weight[13-15] have also been proposed as factors that influence the development of TB. For example, an overall inverse relationship between TB and body mass index (BMI) has been depicted from studies carried out in diverse populations with a large variation in the average LTBI prevalence from Hong Kong, USA, Finland, and Norway.[15,16] Although the interplay between the 2 conditions is unclear, including whether low weight is a risk factor and/or an effect in LTBI, there is a general consensus that—at a population level—higher BMI is linked to lower prevalence of LTBI.[17]

Several lines of evidence support an association between BMI and the development of LTBI.[12-20] Cardiometabolic risk markers associated with obesity—such as fasting insulin, total cholesterol, LDL-cholesterol, HDL-cholesterol, and fasting triglycerides—are all linked to increased prevalence of diabetes mellitus.[16] Diabetes increases the risk of both LTBI and TB and has been associated with adverse treatment outcomes, including death.[21-23] Obesity upregulates cardiometabolic markers that both reduce T-helper-1 cytokine production in response to infection and impair the respiratory burst to expel the pathogens.[24] These observations suggest a utility for BMI and the related cardiometabolic risk markers in identifying subjects at risk of LTBI upon exposure to *M. tuberculosis*. The objective of the present study is to examine the prevalence of LTBI at different body weights, evaluate the extent of association between BMI and LTBI and identify factors mediating this relationship in an adult population.

Methods

Study population

Data were collected from the US National Health and Nutrition Examination Survey (NHANES), a cross-sectional survey of the noninstitutionalized civilian US resident population. The survey is designed to collect information on the health and wellness as well as nutrition status of the populations. The NHANES survey is conducted by the National Center for Health Statistics (NCHS), CDC. The survey examines a nationally representative sample of approximately 5000 individuals of all age groups each year from counties across the USA (15 of which are visited each year). All of the study methods have been approved by the NCHS research ethics review board. All participants provided informed consent and were selected by using a complex multistage sampling design.[25] This survey includes an in-home health interview and a physical examination in a mobile examination center (MEC) in addition to a follow-up telephone interview. The present study included data from the 2011/2012 cycles of NHANES. This cycle includes QuantiFERON®-TB Gold-In-Tube (QFT-GIT) to measure LTBI.[26] Detailed methods of the NHANES survey construction and sampling strategy have been previously described.[27,28] This survey cycle was a stratified, multistage, probability random sample designed to represent the noninstitutionalized house-dwelling US civilian population. In this analysis, we included all eligible participants from the 2011/2012 cycle of NHANES who were adults (>18 years), completed the interview and health examination, had valid QFTGIT (positive/negative) and weight and height data. The total number of participants included in the present study was 5156 subjects (male:female ratio of 1:1.06). The study participants were further divided to controls (n = 4642) and LTBI (n = 514) subgroups.

Study measures, metabolic markers, sociodemographic factors, and other covariates

Body mass index (kg/m^2) was assessed as previously described.[28] We used the international classification of adult underweight, normal weight, overweight, and obesity according to BMI ranges as defined by the World Health Organization (WHO)[18] where the cut-off points were ⩽18.50, 18.50 to 24.99, 25.00 to 29.99, and ⩾30.00 kg/m^2, respectively. Assessment for the status of LTBI was carried out by QFT-GIT, analyzed according to manufacturer instructions (QuantiFERON®-TB Gold [QFT®] ELISA; QIAGEN, Germantown, MD, USA—www.quantiferon.com). Results were interpreted according to guidelines from the Centers for Disease Control and Prevention (CDC) for using interferon-gamma release assays (IGRAs).[29] Individuals with indeterminate QFTGIT results and those who self-reported they had ever been told by a health care professional to had TB were excluded. Samples for QFT-GIT testing were processed at a Clinical Laboratory Improvement Act-certified laboratory as previously described.[30]

A number of metabolic markers were measured including cardiometabolic risk factors (apolipoprotein [Apo] B1 [g/L], LDL-C [mmol/L], HDL-C [mmol/L], T-Chol [mmol/L], T-Chol:HDL-C ratio, triglycerides [mmol/L], and HbA1c [%]); and systolic and diastolic blood pressure (mmHg). Diabetes status was defined as a self-reported (information on use of insulin and oral diabetes agents) or HbA1c ⩾ 6.5%.[31] Individuals who have already been diagnosed as hypertensive, diabetic, or those who were using antihypertensive drugs were included.[32-34] Insulin resistance (IR) was approximated using the homeostatic model assessment (HOMA-IR) formula (glucose [mmol/L] × insulin [μIU/mL] ÷ 22.5).[35,36] Liver functions were evaluated in both survey studies using serum enzyme markers of alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, lactate dehydrogenase, and γ-glutamyl transferase. Furthermore, a number of serum micronutrients and minerals were measured and captured in the present study including vitamin B12 (pmol/L), red blood cells (RBC), folate (nmol/L), folic acid (nmol/L), folate (nmol/L), sodium (mmol/L), potassium (mmol/L), and calcium (mmol/L). Sociodemographic information was captured through responses to questionnaires given during the structured interview portion of the survey and included: age, gender, race, education, history of injection drug use, and ratio of family income to poverty. Race was categorized into 4 main subgroups: White, African Americans, Asian (ie, Korean, Filipino, Japanese, Chinese, South Asian, Southeast Asian, Arab, and West Asian), and Hispanic and Other (ie, Latin American or mixed race). Ratio of family income to poverty was assessed as determined by the Department of Health and Human Services to be used as a measure of poverty.[37] Self-reported smoking status was categorized into smokers (daily/occasional) and non-smokers.[38]

Statistical analysis

All analyses were stratified by LTBI status and survey weights were excluded from the analysis. Frequency distributions and means (±standard deviation, SD) were used to describe baseline characteristics. Differences between groups (controls and LTBI for the entire study population and at different BMI ranges) for examined sociodemographic characteristics and levels of biomarkers and cardiometabolic risk factors were determined using *t*-test and χ^2 tests for continuous and categorical variables, respectively. Fisher's exact test was used for categorical data analysis where there were small sample sizes. Bivariate Pearson correlation adjusted for age, sex, and ethnicity was used to explore the association between BMI and cardiometabolic risk markers in the control and LTBI groups. Correlational analysis between BMI and LTBI or BMI and the cardiometabolic risk markers was carried to estimate Pearson correlation coefficient (*r*). Partial correlation was used to adjust the analysis for age, sex, and ethnicity. Multivariable logistic regression models were used to estimate odds ratios (OR) and 95% confidence intervals (CI) between BMI and LTBI adjusted for potential confounders. Covariates included in multivariable models as confounders were chosen from observed bivariate associations between BMI and LTBI. The degree of missing data was assessed for each variable and was considered for multivariable regression model inclusion. If a variable had >80% missing data, it was not included in the regression model. There was no statistically significant difference between the proportion of missing data and LTBI status, thus data were considered missing at random. All analyses were conducted using SPSS (IBM SPSS Statistics, Version 21.0. Armonk, NY, USA).

Results

Characteristics of the control and LTBI groups

A total of 5156 respondents were examined in the present study. The prevalence of LTBI was approximately 10% (n = 514). In the underweight, normal weight, overweight, and obese subgroups, the prevalence of LTBI was 10.6%, 10.2%, 10.6%, and 9.1%, respectively. There was no difference in LTBI prevalence within each weight subgroup. Baseline sociodemographic characteristics and levels of biomarkers and cardiometabolic risk factors of the study population, stratified by LTBI status, are shown in Table 1. Individuals with LTBI were, on average, older than control counterparts ($P < .001$) and subjects with older age were significantly more prevalent in the LTBI group compared to controls ($P < .001$). The control group was predominantly Whites (39.1%) whereas in subjects with LTBI, Black, and Asians were more prevalent, constituting >50% of the group. There was a higher percentage of subjects with less than grade 12 education in the LTBI compared to controls and lower percentage of those with post-secondary education. The ratio of family income to poverty was significantly lower in the LTBI group than controls ($P = .036$). Approximately 1.7-fold significantly higher ($P < .001$) prevalence of diabetes was noted in the LTBI group than controls. In the present study diabetes was defined as self-reported or participants with Hb1Ac ⩾ 6.5%. No significant differences were shown between LTBI and control group in the examined cardiometabolic risk markers except for the levels of fasting triglycerides that was significantly higher in the LTBI than controls (1.44 ± 0.85 vs 1.42 ± 1.06, $P < .001$). Insulin resistance (HOMA-IR) was significantly higher in the LTBI group than controls (31.1 ± 83.9 vs 22.1 ± 26.9; $P = .0423$). Levels of micronutrients such as vitamin B12 and folate and activities of liver enzymes such as alanine aminotransferase and γ-glutamyl transferase were all significantly higher in the LTBI group compared to controls. Levels of RBC folate and serum folic acid were significantly lower in the LTBI group than in controls.

Characteristics of the study population stratified by BMI

Sociodemographic characteristics and levels of cardiometabolic risk markers in LTBI and controls, stratified by the different BMI ranges, are shown in Table 2. Overall, there was a higher percentage of males and persons of older age in the LTBI group than controls in all BMI subgroups. In both normal weight and overweight subgroups, there was a significantly higher percentage of Whites in the control group (LTBI OR for Whites = 0.56; 95%CI: 0.47-0.67; $P < .001$) but more Asians in the LTBI group (LTBI OR for Asians = 4.59; 95%CI: 3.59-5.88; $P < .001$). In contrast, in the obese subgroup, there was a higher percentage of Blacks in the LTBI group (LTBI OR for Blacks = 1.21; 95%CI: 0.89-1.72; $P = .141$) but more Whites in the control obese subgroup (LTBI OR for Whites = 0.35; 95%CI: 0.23-0.54; $P < .001$). LTBI groups had lower education levels (using highest education as a reference category; LTBI OR for lower education = 1.67; 95%CI: 1.39-2.01; $P < .001$). Although all BMI subgroups showed a lower ratio of family income to poverty compared to controls, this difference was only significant in the obese subgroup ($P = .0167$). Prevalence of diabetes ranged from 1.6- to 8.3-fold higher in the LTBI group than in controls, across all the BMI subgroups. The highest prevalence of diabetes was noted in the obese subgroups compared to other BMI ranges. Differences in the cardiometabolic risk markers between LTBI and controls were principally noted in the normal weight and overweight subgroups. This was particularly apparent in the increased levels of triglycerides, cholesterol (T-Chol:HDL-C), fasting glucose, and HbA1C levels in the LTBI group and the HDL in the control group of normal weight and overweight subgroups.

Table 1. Sociodemographic characteristics and levels of potential cardiometabolic risk factors stratified by presence or absence of latent tuberculosis infection, U.S. National Health and Nutrition Examination Survey (NHANES), 2011/2012.

CHARACTERISTIC	CONTROLS (N = 4642)		LTBI (N = 514)		*P*[b]
	N	%[a] OR MEAN ± SD	N	%[a] OR MEAN ± SD	
Males (%)	2259	48.7	236	45.7	
Age (years)	4642	46.1 ± 18.5	514	55.8 ± 15.7	<.001
Age group (years)					
18-30	1196	25.8	38	7.4	<.001
31-50	1552	33.4	137	26.7	
51-70	1328	28.6	249	48.4	
>70	566	12.2	90	17.5	
Ethnicity (%)					
White	1816	39.1	73	14.2	<.001
Black	1218	26.2	122	23.8	
Asian	564	12.2	143	27.8	
Hispanic and other	262	5.9	105	2.2	
Highest level of education (%)					
Less than grade 12	927	19.9	190	36.5	<.001
High-school graduate	923	19.8	104	20.0	
Post-secondary graduate	2530	54.4	215	41.3	
Ratio of family income to poverty	4282	2.42 ± 1.6	454	2.19 ± 1.5	.036
History of intravenous drug use (%)	61	1.3	9	1.7	
Smoking status (%)					
Daily/occasional	872	18.8	102	19.6	.003
Non-smoker	972	20.9	138	26.5	
Diabetes (%)—self-reported or HbA1c ⩾ 6.5%[c]	653	14.1	127	24.4	<.001
Cardiometabolic risk markers					
Systolic blood pressure (mmHg)	4276	123 ± 18	477	126 ± 19	
Diastolic blood pressure (mmHg)	4276	71 ± 13	477	71 ± 13	
Triglycerides, fasting (mmol/L)	2258	1.42 ± 1.06	239	1.44 ± 0.85	<.001
Total cholesterol (mmol/L)	4553	4.95 ± 1.08	503	5.04 ± 1.04	
LDL-C (mmol/L)	2216	2.92 ± 0.91	237	2.93 ± 0.89	
HDL-C (mmol/L)	4553	1.36 ± 0.38	503	1.32 ± 0.37	
Total cholesterol:HDL-C ratio	4553	3.87 ± 1.29	504	4.05 ± 1.30	
Insulin, fasting (pmol/L)	2174	81.6 ± 72.0	232	84.1 ± 69.9	
Glucose, fasting (mmol/L)	2284	5.93 ± 1.87	244	6.32 ± 2.05	

(Continued)

Table 1. (Continued)

CHARACTERISTIC	CONTROLS (N = 4642)		LTBI (N = 514)		P^b
	N	%[a] OR MEAN ± SD	N	%[a] OR MEAN ± SD	
HOMA-IR	2172	22.1 ± 26.9	234	31.1 ± 83.9	.0423
HbA1c (%)	4630	5.73 ± 1.10	514	6.03 ± 1.23	
Apolipoprotein B, fasting (g/L)	2259	0.89 ± 0.25	239	0.90 ± 0.23	
Obesity					
Body mass index (kg/m^2)	4642	28.7 ± 7.0	514	28.5 ± 6.7	
Underweight: BMI: <18.5 kg/m^2 (%)	101	2.18	12	2.33	
Normal weight: BMI: 18.5-24.9 kg/m^2 (%)	1422	30.63	162	31.46	
Overweight: BMI: 25-29.9 kg/m^2 (%)	1488	32.06	177	34.37	
Obese: BMI: >30 kg/m^2 (%)	1631	35.13	163	31.66	
Vitamins and minerals					
Vitamin B12 (pmol/L)	4266	464 ± 363	493	470 ± 313	<.001
RBC folate (nmol/L)	4603	1099 ± 509	511	1072 ± 450	<.001
Folic acid, serum (nmol/L)	4499	2.51 ± 10.4	499	2.04 ± 5.61	<.001
Serum folate (nmol/L)	4495	45.7 ± 28.2	498	46.4 ± 23.5	.023
Sodium (mmol/L)	4523	139 ± 2	501	139 ± 3	
Potassium (mmol/L)	4522	3.93 ± 0.35	501	3.95 ± 0.35	
Calcium (mmol/L)	4523	2.35 ± 0.09	501	2.33 ± 0.10	
Liver enzyme markers					
Alanine aminotransferase (U/L)	4522	24.6 ± 26.6	500	25.2 ± 20.9	<.001
Alkaline phosphatase (U/L)	4523	67.5 ± 24.3	501	69.8 ± 23.2	
Aspartate aminotransferase (U/L)	4520	25.5 ± 16.7	500	26.5 ± 17.3	
γ-Glutamyl transferase (U/L)	4522	27.1 ± 38.1	501	27.9 ± 30.6	<.001
Lactate dehydrogenase (U/L)	4520	128.0 ± 27.8	500	129.4 ± 27.1	

Abbreviations: LTBI, latent tuberculosis infection; LDL-C, low-density lipoprotein; HDL-C, high-density lipoprotein; HOMA-IR, homeostatic model assessment insulin resistance; HbA1c (%), glycosylated hemoglobin; RBC, red blood cells.
[a]Percentages are for unweighted frequency.
[b]Significant difference between control and LTBI cases was carried out by χ^2 test or Student's *t*-test. Only significant differences are shown.
[c]Diabetes is defined as Hb1Ac ⩾ 6.5% or self-reported cases as per survey questionnaire.

However, there was a statistically significant difference between the means of the different BMI subgroups in both LTBI and control groups for the examined cardiometabolic risk markers (P_{trend}: .021 to <.001). Levels of vitamin B12 were significantly lower in the LTBI underweight subgroup compared to their control counterparts (P = .037). Despite the significant difference between RBC folate and serum folic acid between the entire LTBI and control groups, there was no significant difference in their levels between LTBI and control groups in each of the BMI subcategories. However, there was a trend toward increased RBC folate and decreased serum folic acid in both study groups as the BMI increases (P_{trend} < .001). Except for the alkaline phosphatase levels in the obese subgroups that was higher in the LTBI than controls (P = .038), liver enzymes did not show significant differences at the different BMI subgroups between LTBI and controls.

Table 2. Sociodemographic characteristics and levels of potential cardiometabolic risk factors stratified by presence or absence of latent tuberculosis infection and by body mass index, U.S. National Health and Nutrition Examination Survey (NHANES), 2011/2012.

CHARACTERISTIC	UNDERWEIGHT (BMI: <18.5 KG/M²)			NORMAL WEIGHT (BMI: 18.5-24.9 KG/M²)			OVERWEIGHT (BMI: 25-29.9 KG/M²)			OBESE (BMI: >30 KG/M²)			CONTROL P_{TREND}[b]	TB P_{TREND}[b]
	CONTROL (N = 101)	LTBI (N = 12)	P[b]	CONTROL (N = 1422)	LTBI (N = 162)	P[b]	CONTROL (N = 1488)	LTBI (N = 177)	P[b]	CONTROL (N = 1631)	LTBI (N = 163)	P[b]		
Males (%)[a]	33.7	58.3		48.4	61.1	.002	54.6	62.1	.056	44.5	48.8		<.001	.050
Age (years)	36.8 ± 20.4	59.8 ± 22.6	.005	42.8 ± 19.5	53.4 ± 16.8	<.001	48.1 ± 18.1	57.1 ± 14.5	<.001	47.6 ± 17.2	56.3 ± 14.9	<.001	<.001	
Age group in years (%)														
18-30	59.4	16.7	.004	35.6	11.1	<.001	20.8	5.2	<.001	20.1	5.4	<.001	<.001	.0161
31-50	14.8	16.7		29.9	29.0		35.5	25.3		35.8	26.3			
51-70	13.9	16.7		22.5	44.4		29.3	49.4		33.71	53.3			
>70	11.9	50.0		12.0	15.4		14.4	20.1		10.4	15.0			
Ethnicity (%)														
White	33.7	25.0		24.8	11.7	<.001	40.8	13.0	<.001	37.0	17.1	<.001	<.001	<.001
Black	23.8	33.3		12.4	21.0		22.6	19.8		34.9	30.5			
Asian	25.7	33.3		15.0	45.7		9.4	31.1		3.7	6.7			
Hispanic and other	15.1			31.5	10.5		20.1	35.8		14.2				
Highest level of education (%)														
Less than grade 12	17.8	50.0		11.0	26.9	.002	20.4	36.2	<.001	21.6	43.9	<.001	.002	.031
High-school graduate	16.8	8.3		10.3	16.7		19.3	22.6		23.3	22.0			
Post-secondary graduate	46.5	41.7		37.0	51.2		53.0	40.7		51.8	33.5			
Ratio of family income to poverty	1.92 ± 1.56	1.82 ± 1.74		2.50 ± 1.72	2.41 ± 1.68		2.51 ± 1.67	2.25 ± 1.62		2.30 ± 1.63	1.94 ± 1.42	.0167		
History of intravenous drug use (%)	0.0	0.0		0.4	1.9		1.6	1.1		1.7	2.4		.024	
Smoking status (%)														
Daily/occasional	26.7	25.0		13.6	21.0		16.5	20.3		17.7	17.8		<.001	
Non-smoker	13.9	25.0		10.2	24.1		23.4	27.1		22.8	29.3			
Diabetes (%)[c]	2.0	16.7	.009	4.3	16.7	<.001	11.5	19.8	<.001	23.3	38.4	<.001	<.001	<.001
Cardiometabolic risk markers														
Systolic blood pressure (mmHg)	115 ± 24	150 ± 41	.021	120 ± 19	125 ± 21	.006	123 ± 18	124 ± 17		126 ± 17	128 ± 16		<.001	<.001
Diastolic blood pressure (mmHg)	67 ± 10	71 ± 21		69 ± 12	70 ± 12		71 ± 12	70 ± 13		73 ± 13	72 ± 14		<.001	
Triglycerides, fasting (mmol/L)	1.00 ± 0.6	1.26 ± 1.0		1.28 ± 0.9	1.56 ± 1.4	.016	1.73 ± 1.4	2.0 ± 1.4	.020	1.95 ± 1.7	1.87 ± 1.3		<.001	.018
Total cholesterol (mmol/L)	4.48 ± 0.9	4.63 ± 1.0		4.82 ± 1.1	4.96 ± 1.1		5.01 ± 1.1	5.2 ± 1.1		5.0 ± 1.1	5.0 ± 1.0		<.001	
LDL-C (mmol/L)	2.47 ± 0.6	2.10 ± 0.5		2.79 ± 0.9	2.91 ± 0.8		3.0 ± 0.9	2.9 ± 0.8		3.0 ± 0.92	3.0 ± 1.0		<.001	

(Continued)

Table 2. (Continued)

CHARACTERISTIC	UNDERWEIGHT (BMI: <18.5 KG/M²)			NORMAL WEIGHT (BMI: 18.5-24.9 KG/M²)			OVERWEIGHT (BMI: 25-29.9 KG/M²)			OBESE (BMI: >30 KG/M²)			CONTROL P_{TREND}[b]	TB P_{TREND}[b]
	CONTROL (N = 101)	LTBI (N = 12)	P[b]	CONTROL (N = 1422)	LTBI (N = 162)	P[b]	CONTROL (N = 1488)	LTBI (N = 177)	P[b]	CONTROL (N = 1631)	LTBI (N = 163)	P[b]		
HDL-C (mmol/L)	1.59 ± 0.41	1.48 ± 0.41		1.50 ± 0.39	1.43 ± 0.40	.049	1.36 ± 0.4	1.29 ± 0.3	.036	1.23 ± 0.31	1.23 ± 0.33		<.001	<.001
Total cholesterol:HDL-C ratio	2.91 ± 0.71	3.32 ± 1.15		3.38 ± 1.0	3.71 ± 1.29	.003	3.93 ± 1.3	4.2 ± 1.2	.007	4.3 ± 1.37	4.28 ± 1.25		<.001	<.001
Insulin, fasting (pmol/L)	45.3 ± 37.7	38.2 ± 15.1		47.1 ± 30.6	55.2 ± 43.4		75.9 ± 78.1	78.9 ± 51.5		118 ± 75	120 ± 90.6		<.001	.023
Glucose, fasting (mmol/L)	5.26 ± 0.72	5.68 ± 0.49		5.52 ± 1.52	5.72 ± 1.19		5.81 ± 1.6	6.26 ± 1.6	.018	6.44 ± 2.24	6.98 ± 2.8		<.001	.001
HOMA-IR	10.6 ± 8.85	9.75 ± 4.16		11.9 ± 10.6	14.9 ± 15.8		20.3 ± 30.9	23.3 ± 22.3		35.1 ± 28.5	38.2 ± 36.1		<.001	.015
HbA1c (%)	5.26 ± 0.40	5.54 ± 0.45		5.50 ± 0.91	5.87 ± 1.29	<.001	5.68 ± 1.0	5.93 ± 1.1	.004	6.01 ± 1.29	6.33 ± 1.32	.003	<.001	.001
Apolipoprotein B, fasting (g/L)	0.74 ± 0.19	0.62 ± 0.14		0.81 ± 0.23	0.89 ± 0.22	.037	0.91 ± 0.25	0.91 ± 0.21		0.94 ± 0.24	0.94 ± 0.25		<.001	.021
Vitamins and minerals														
Vitamin B12 (pmol/L)	494 ± 226	389 ± 130	.037	482 ± 376	486 ± 311		457 ± 329	443 ± 248		453 ± 386	488 ± 379			
RBC folate (nmol/L)	959 ± 609	874 ± 392		1042 ± 440	1006 ± 391		1116 ± 514	1032 ± 412		1140 ± 547	1197 ± 520		<.001	<.001
Folic acid, serum (nmol/L)	3.35 ± 9.39	5.41 ± 15.3		3.12 ± 14.8	2.02 ± 4.81		2.48 ± 9.0	2.37 ± 7.09		1.96 ± 6.3	1.46 ± 2.28		<.001	<.001
Serum folate (nmol/L)	45.8 ± 29.2	41.7 ± 28.1		47.7 ± 30.4	45.9 ± 21.9		46.5 ± 28.8	47.9 ± 25.5		43.1 ± 25.4	45.4 ± 22.4		<.001	
Sodium (mmol/L)	139 ± 2.40	139 ± 1.82		139 ± 2.21	139 ± 3.8		139 ± 2.22	139 ± 1.82		139 ± 2.23	139 ± 2.12			
Potassium (mmol/L)	3.85 ± 0.41	3.70 ± 0.35		3.91 ± 0.34	3.93 ± 0.38		3.95 ± 0.33	3.97 ± 0.33		3.95 ± 0.35	3.96 ± 0.36			
Calcium (mmol/L)	2.37 ± 0.10	2.32 ± 0.08		2.36 ± 0.08	2.34 ± 0.11		2.35 ± 0.10	2.35 ± 0.08		2.34 ± 0.09	2.32 ± 0.10		<.001	.035
Liver enzyme markers														
Alanine aminotransferase (U/L)	17.7 ± 11.3	19.2 ± 8.9		21.1 ± 17.9	24.1 ± 24.6		24.3 ± 15.6	24.2 ± 12.9		28.2 ± 38.5	27.7 ± 24.5		<.001	
Alkaline phosphatase (U/L)	60.6 ± 22.1	67.3 ± 21.1		63.3 ± 21.6	64.5 ± 18.9		66.9 ± 21.4	68.6 ± 25.3		72.1 ± 28.1	76.2 ± 23.3	.038	<.001	<.001
Aspartate aminotransferase (U/L)	24.9 ± 23.3	40.2 ± 59.8		24.8 ± 15.1	26.9 ± 19.9		25.3 ± 11.9	25.2 ± 10.5		26.3 ± 20.9	26.4 ± 14.0			.046
γ-Glutamyl transferase (U/L)	21.5 ± 55.5	20.1 ± 17.7		22.5 ± 43.7	24.6 ± 30.8		27.8 ± 34.3	25.9 ± 23.7		30.8 ± 34.2	33.7 ± 36.5		<.001	.026
Lactate dehydrogenase (U/L)	120 ± 29	140 ± 51		124 ± 28	127 ± 27		126 ± 25.6	128 ± 26.7		132 ± 29	132 ± 25		<.001	

Abbreviations: LTBI, latent tuberculosis infection; LDL-C, low-density lipoprotein; HDL-C, high-density lipoprotein; HOMA-IR, homeostatic model assessment insulin resistance; HbA1c (%), glycosylated hemoglobin; RBC, red blood cells.

[a]Percentages shown are for unweighted frequency.

[b]Significant difference between control and LTBI cases was carried out by χ^2 test or Student's *t*-test. Only significant differences are shown.

[c]Diabetes is defined as Hb1Ac ⩾ 6.5% or self-reported cases as per survey questionnaire.

Table 3. Correlation between body mass index and levels of potential cardiometabolic risk factors stratified by presence or absence of latent tuberculosis infection, U.S. National Health and Nutrition Examination Survey (NHANES), 2011/2012.[a]

RISK MARKER	CONTROLS		LTBI	
	R	*P*[b]	*R*	*P*[b]
Systolic blood pressure (mmHg)	0.138	<.001	−0.014	
Diastolic blood pressure (mmHg)	0.145	<.001	0.021	
Triglycerides, fasting (mmol/L)	0.213	<.001	0.211	.002
Total cholesterol (mmol/L)	0.003		−0.062	
LDL-C (mmol/L)	0.065	.006	−0.027	
HDL-C (mmol/L)	−0.338	<.001	−0.315	<.001
Total cholesterol:HDL-C ratio	0.299	<.001	0.257	<.001
Insulin, fasting (pmol/L)	0.470	<.001	0.368	<.001
Glucose, fasting (mmol/L)	0.224	<.001	0.218	.002
HOMA-IR	0.399	<.001	0.372	<.001
HbA1c (%)	0.212	<.001	0.254	<.001
Apolipoprotein B, fasting (g/L)	0.165	<.001	0.067	

Abbreviations: LTBI, latent tuberculosis infection; LDL-C, low-density lipoprotein; HDL-C, high-density lipoprotein; HOMA-IR, homeostatic model assessment insulin resistance; HbA1c (%), glycosylated hemoglobin.
[a]Correlation coefficients between BMI and the cardiometabolic risk markers were adjusted for age, sex, and ethnicity.
[b]Only significant values are shown.

Relationship between BMI and LTBI

In a partial correlation analysis between BMI and LTBI, BMI was inversely correlated with the prevalence of LTBI ($r = -0.134$, $P < .01$); this inverse correlation increased when data were adjusted for age and sex ($r = -0.147$, $P < .001$). Association between BMI and levels of cardiometabolic risk markers in the study population stratified by LTBI is shown in Table 3. When adjusted for age, sex, and ethnicity, both control and LTBI groups exhibited a similar profile of correlation between BMI and cardiometabolic risk markers. In general, increasing BMI was significantly associated with elevated levels of cardiometabolic risk markers such as fasting insulin, HOMA-IR, total cholesterol:HDL-C ratio, fasting glucose, fasting triglycerides, HbA1c, and LDL-C and with lower levels of HDL-C. Multivariate logistic regression models used to estimate OR adjusted for potential confounders (and 95%CI) for LTBI with increasing BMI is shown in Table 4. Age, sex, diabetes, and level of education were the main confounders in the association between increasing BMI and lower prevalence of LTBI. When adjusted for age, sex, and diabetes, OR for LTBI was 0.88 (95%CI: 0.79-0.98; $P = .026$). When this model was further adjusted for the level of education, the OR decreased to 0.85 (95%CI: 0.77-0.96, $P = .01$). The addition of smoking, injection drug use, and ethnicity to the model did not affect the odds of LTBI associated with increasing BMI.

Discussion

Our analyses of NHANES data from 2011/2012 reveal an inverse relationship between BMI and prevalence of LTBI when adjusted for age and sex. These results are consistent with previous reports substantiating such an inverse relationship that appears to be continuous across BMI categories, from underweight through to obesity.[15,16] As an example of the inverse relationship seen between BMI and TB incidence, a cohort of >65-years-old individuals who were followed for 5 years in Hong Kong, a hazard ratio was noted of 0.9 (95%CI: 0.87-0.93) for TB per unit increase in BMI.[39] This TB risk reduction with increasing BMI has been, however, specific for pulmonary TB but not for the extrapulmonary disease. When the effect of BMI was evaluated on all-cause and causes-specific mortality, a similar inverse association between obesity and TB has been observed both globally[40] and regionally, eg, in India.[41]

Although the exact mechanism for the inverse relationship between obesity and TB is yet to be fully understood, it was postulated that nutritional factors[14,42] and the related adiposity[43] may influence the capacity of the immune system to combat TB and other infections.[14] The role of cytokine-mediated innate immunity in host protection against *M. tuberculosis* infection has been demonstrated in numerous experimental models of infection and established a critical role for interferon-γ (IFN-γ), tumor necrosis factor-α (TNF-α), and interleukins (ILs) in

Table 4. Odds for having presence or absence of latent tuberculosis infection with increased body mass index using multivariate logistic regression, U.S. National Health and Nutrition Examination Survey (NHANES), 2011/2012.

MODEL ADJUSTMENT[a]	OR[a]	95%CI	*P*[b]
No LTBI	1	Ref	—
Crude	0.94	0.84-1.04	
Age	0.89	0.80-0.98	.038
Diabetes	0.90	0.82-0.97	.049
Age and sex	0.89	0.80-0.99	.048
Age and diabetes	0.87	0.79-0.97	.019
Age, sex, and diabetes	0.88	0.79-0.98	.026
Age, sex, diabetes, and education	0.85	0.77-0.96	.010

Abbreviations: LTBI, latent tuberculosis infection. ORs are in a descending order within the adjusted models.
[a]Multivariate logistic regression models were used to estimate adjusted odds ratios (OR) and 95% confidence intervals (CI) between BMI and LTBI.
[b]Only significant values are shown.

controlling infection.[44] Adipocyte and the immune cells within the adipose tissue secrete elevated levels of these inflammatory mediators[45] to influence insulin sensitivity, inflammation, and innate and adaptive immune responses.[43]

When the relationship between LTBI and obesity was adjusted for age, sex, and diabetes, we noted a significant lowering in the odds of LTBI (OR = 0.87, 95%CI: 0.79-0.97; *P* = .019). It was proposed that prolonged persistence of *M. tuberculosis* (ie, LTBI) may result in alerted levels of cardiometabolic risk markers.[46] Such an altered metabolic profile is known to result in increased synthesis of cytokines and acute phase reactants such as C-reactive protein (CRP) in normal individuals[47] and in TB patients[48] leading to a lower proliferation rates of T-cell subsets and modification of their functions.[49,50] There is a possibility for a particular metabolic profile to arise in LTBI patients to prevent the emergence of TB and may result in weight lowering. This, together with the observation that the economic status of the control group was higher than the LTBI group, both should be considered in developing LTBI apart from the findings of the serologic or metabolic profiles observed in this study population.

An increased risk of LTBI has been observed in underweight subjects.[13,15,20,35] This may be explained by the theory that malnutrition predisposes to increased vulnerability to LTBI and TB through mechanisms related to compromised immune and thymic function.[51-53] Low plasma leptin, eg, in the malnourished state, was linked to impairment of the immune response.[54] This is in contrast to the high leptin concentrations known to occur in obesity as a result of the increased fat mass.[43] Leptin promotes proliferation and activation of T lymphocytes upon mitogen stimulation.[55] The general consensus is, therefore, that leptin may serve as a protective factor against infections,[56,57] a proposition that may explain observations showing that low body weight is associated with risk of TB, disease severity, and unfavorable response to treatment.[58] Furthermore, higher mortality among underweight TB patients was also proposed to be due to decreased immunity and a greater severity of TB infection. Being underweight reduces the number of lymphocyte,[14] leading to a higher risk of TB infection and/or increased disease severity in underweight patients. Taken together, animal models infected with *M. tuberculosis* showed that malnourishment result in impairment of the immune system, higher bacterial burden, and early death following infection.[59]

The present report has several limitations. We only considered BMI as an indicator of obesity. Waist circumference and waist-to-hip ratio could have been also included. However, these factors would have prevented categorizing the degree of obesity to the extent generated when using BMI as an indicator. Another limitation is that we did not consider the interaction between LTBI, obesity, and metabolic syndrome-related morbidities other than diabetes (eg, cardiovascular or kidney diseases) given the well-established interaction and convergence between the increasing BMI and these chronic conditions.[60] Self-report of diabetes is problematic since up to 30% of diabetes in the US is undiagnosed.[31] This level is presumed even higher among immigrants and the economically marginalized. The actual versus reported prevalence of diabetes may have affected the impact of confounders in the present study. Most importantly, the inverse relationship between obesity and LTBI observed here reflects an association between the 2 conditions but should not be construed as an inference of causality. We did not explore other factors contributing to increases or decreases in BMI that may also have independent effects on LTBI prevalence such as the role and effect of malnutrition,[14,42] adiposity,[43] synthesis of pro-inflammatory cytokines,[44] plasma leptin,[55] and tuberculosis reporting rate in country of origin.

In conclusion, the present study evaluated the relation of LTBI risk with BMI and demonstrated an inverse association between BMI and risk of having LTBI in a model adjusted for age and sex. This underscores an epidemiologic inverse association of body weight with the development of LTBI, and by extension, a potential inverse association of body weight with the subsequent development of TB. The inverse relationships between prevalence of obesity and incidence of LTBI and between having diabetes mellitus (in which obesity is a risk factor) and developing TB itself underscore a need to examine further the relationship between obesity and all forms of TB infection.

Author Contribution

AB conceived the study idea and design, data acquisition, analysis and interpretation, and wrote the manuscript. CJL assisted in data analysis. All authors critically reviewed the manuscript, approved the final draft and agreed to be accountable for all aspects of the work.

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