Body mass index and its dose-response relationship with the incidence and risk of tuberculosis, a population-based cohort study

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Abstract

Background

Many pieces of evidence presented the body mass index (BMI) was inversely associated with tuberculosis (TB). BMI was radically changed during the past decades in China. The aim of the study was to evaluate the contemporary relationship between BMI and tuberculosis incident.

Methods

A population-based prospective cohort included 26 022 community participants was conducted. Three rounds of tuberculosis screening were implemented between June 2013 and December 2015. The main exposure was defined as baseline BMI, and was categorized into 3 levels: underweight (< 18.5 kg/m^2), normal (18.5 to 24.0 kg/m^2), overweight or obese (≥ 24.0 kg/m^2). The active tuberculosis incident in the second or third round screening was the study outcome. The dose-response relationship between BMI and tuberculosis incidence as well as tuberculosis risk were analyzed.

Results

During the followed up of 2.25 years, 43 cases developed tuberculosis in 44 574.4 person-years. The log-linear dose-response relationship between BMI and tuberculosis incidence was fitted (adjusted $R^2 = 0.95$). In multivariable Cox proportional regression, overweight and obese was associated with a lower risk of incident tuberculosis compared with normal weight (adjusted hazard ratio [aHR], 0.34; 95% confidence interval [CI] 0.14–0.82, $p < 0.01$), the inverse dose-response association between BMI and tuberculosis risk was characterized by restricted cubic spline. In subgroups analysis, the risk of tuberculosis reduced 78% in overweight or obese (aHR, 0.22; 95% CI 0.05–0.97, $p = 0.05$) and 64% (aHR, 0.36; 95% CI 0.12-1.00, $p = 0.05$) compared with normal weight among female and elderly.

Conclusion

Our study revealed that high BMI was a protective factor in tuberculosis development. Precise dose-response relationship between BMI and the incident tuberculosis, as well as the risk of tuberculosis progression in contemporary Chinese adulthood, will benefit to disease control policy.

Background

Tuberculosis (TB) is an airborne communicable disease that leads to a high burden of public health [1]. About 9% of the entire world newly diagnosed pulmonary tuberculosis (PTB) were from high burden countries of China, therefore gave an estimated incidence of 61 (95% CI: 52–70) pre 100 000 population as the country contributed 20% of the global population [2].

Body mass index (BMI) was an efficient, convenient, and measurable indicator for body characteristics in the population. The association between BMI and tuberculosis incidence was studied before. In 2010, a systemic review included 6 remote cohort studies presented homogeneous inverse relationships between BMI and tuberculosis incidence in the BMI range of 18.5–30 kg/m^2 under different settings and tuberculosis burden [3].

Over past decades, China had dramatic growth in the economy, accompanied by the demographic and epidemiological profile shift, disease spectrum, and risks have changed simultaneously. The prevalence of obesity in the year of 2014 was 61 or 27 times higher than it in 1975 among Chinese male or female adult [4]. The percentage changes in agestandardised summary exposure values (SEVs) were ranked the first for high BMI as a risk factor from 1990 to 2017 [5]. This dramatic change for the main exposure of BMI might have a nonnegligible impact on the outcome of the tuberculosis incident. Contemporary association for the BMI after adjusting the multiple demographic and epidemiological factors linked to the major outcome of tuberculosis incident are not established. Besides, the precise dose-response relationship between BMI and tuberculosis incidence as well as disease progress risk remains unclear in a high burden setting.

To address this knowledge gap, the present study aims to evaluate the relationship between BMI and incidence of tuberculosis based on a population-based tuberculosis screening cohort from 2013 to 2015 in China, yet to examine the dose-response relationship of BMI and tuberculosis risks, overall and in subgroups.

Methods

Data source and study population

The present cohort study was implemented between June 2013 and December 2015. The study site was Dongchuan county of Yunnan province in the southwestern mountainous region of China. It was a complex, multistage sampling prospective tuberculosis screening cohort among communities, the detailed study design has been documented elsewhere [6]. In general, three rounds of tuberculosis screening were implemented in the study time frame among randomly sampled communities. The cohort baseline investigation was conducted in 2013, home visits, and face-to-face surveys were carried out by trained community health workers (CHWs). Of the 35 691 community residents visited by CHWs, 2 271 refused to participate in the study, or temporary resident was not enrolled in the study. The cohort enrolled 33 386 eligible participants, standardized questionnaires comprised of suspected tuberculosis symptoms, demographic, comorbidity, or epidemiological exposure and lifestyle were applied for baseline data collection. These participants' age under 15 years (n = 7 364) or these diagnosed active tuberculosis in baseline screening (n = 34) were excluded. Finally, the present research included 26 022 participants for analysis (Fig. 1). The participants in the fixed cohort were prospectively followed up until the occurrence of tuberculosis, death, moved out of the study field, or to December 2015. The second and third round of tuberculosis screening was implemented in each year of 2014 and 2015, by applying the same algorithm with the baseline survey.

Measurement of BMI and covariates

BMI records in the baseline survey were the main exposure to this study. Individual BMI was calculated as the ratio of the weight in kilograms as numerator divided by the square of height in meters as the denominator. We categorized the continuous BMI into three groups: underweight (< 18.5 kg/m^2), normal (18.5 to 24.0 kg/m^2), overweight or obese (≥ 24.0 kg/m^2) according to criteria of weight for adults ruled by Ministry of Health of the People's Republic of China in 2013 [7].

Most of the participants' characteristics were self-reported when interviewed by CHWs at the baseline investigation. Covariates included demographic, comorbidity, medical history, and lifestyle information: sex (male, female), age (< 65 years, ≥ 65 years old), ethnicity (Han, other minority), education level (illiterate or semi-illiterate, primary school, secondary school, college and above, unknown), marital status (married, single, widowed/divorced/separated/other), family annual income per capital (< the median of 7200 RMB, ≥ the median of 7200 RMB), close contact to an index TB case (yes, no), chronic bronchitis (yes, no), pneumoconiosis (yes, no), smoking (never, former, current)and drinking habit (never, former, current), Bacillus Calmette-Guerin (BCG) vaccine scar in the arm (yes, no) were collected. Information of previously treated tuberculosis cases (yes, no) were examined by matching with the case report in Tuberculosis Information Management System (TBIMS), known human immunodeficiency virus or acquired immune deficiency syndrome (HIV/AIDS) cases (yes, no) were checked by local Center for Disease Control and Prevention (CDC) database. Known diabetes mellitus (DM) cases (yes, no) were matched to personal health records of the National Project of Basic Public Health Service (BPHS) for conformation.

Assessment of tuberculosis

The incident of tuberculosis and the time-to-incident was defined as the study outcome, those with followed up to December 2015, death, moved out of the study field, or refused to participate in second or third round screening were defined as censored data.

Tuberculosis diagnostic algorithm was: after home visit by CHWs, those tuberculosis symptoms positivity was defined as suspect, combined with those age over 65 years, close contact to an index case, previously treated tuberculosis, known DM and known HIV/AIDS cases underwent chest X-ray (CXR) and health examination. After that, those with abnormal radiography get further sputum smear test, three sputum samples (one at spot sputum, one at night and one on the next morning) were requested for laboratory diagnosis. Patients with a smear acid-fast bacilli positivity were diagnosed as laboratory-confirmed tuberculosis. Those abnormal radiographic with negative smear, their CXRs were reviewed by the diagnostic committee and were diagnosed as clinically diagnosed tuberculosis.

Statistical analysis

We compared the proportions in BMI groups by the chi-square test. We computed the person-years and incident rate (IR) of tuberculosis in all participants, by BMI level and other covariates. Incident rate ratio (IRR) and 95% CI were calculated to compare incidence between groups.

We applied the Kaplan-Meier analysis and Log-Rank test to compare the cumulative hazard of time to tuberculosis incidents in different BMI levels. Denary logarithm transferred tuberculosis incidence was regressed with the average BMI in three levels by the linear regression model, the determination coefficient of R^2 and adjusted R^2 were used to evaluate the log-linear model. Cox proportional hazard regression models were fitted to estimate the hazard ratio (HR) of variables with the corresponding 95% CI, BMI categorization of normal weight was set as the reference level. We adjusted for covariates in multivariate analysis, the bidirectional stepwise variable selection strategy was applied, the parameter for the criterion of inclusion was p-value ≤ 0.05, and exclusion was p-value ≥ 0.1. After variable selection, we adjusted the categorical factors to control confounder: sex, age, ethnicity, marital status, previously treated tuberculosis, smoking status, and alcohol use. The linear trend test for BMI was performed by replacing BMI as an ordinal variable includes in the multivariate model. DM might correlate with both BMI and tuberculosis, we corrected DM in a different Cox regression model.

We examined the dose-response association between BMI and predicted linear cumulative hazard of tuberculosis for the Cox regression model adjusted for age, sex, ethnicity, marital status, previously treated TB, smoking status, alcohol use, known DM, and continuous BMI, overall and in risk subgroups. The relationship was evaluated with restricted cubic spline regression (RCS), the spline knots were the quartiles (25%, 50%, and 75%) of continuous BMI.

Subgroup analysis for gender and age were applied after adjusting the covariates. The interaction effect between BMI and gender or age was examined. The effect was defined as an added term of cross-product the BMI level and gender or age in the multivariable Cox regression model after controlling other confounders.

All statistical analysis was performed by R software 3.5.2 (http://www.Rproject.org). The level of $p < 0.05$ was set as statistical significance.

Table 1
The baseline characteristics of the cohort categorized by body mass index.

Characteristics	BMI category, kg/m^2				
	Underweight < 18.5	Normal 18.5 to 24.0	Overweight and obese ≥ 24.0	Overall	p-value
	n (%)	n (%)	n (%)	n (%)	
Total	2042 (7.9%)	16009 (61.5%)	7971 (30.6%)	26022 (100.0%)	
Sex					< 0.01
Male	838 (41.0%)	7245 (45.3%)	4313 (54.1%)	12396 (47.6%)	
Female	1204 (59.0%)	8764 (54.7%)	3658 (45.9%)	13626 (52.4%)	
Age (years)					< 0.01
Mean (SD)	38.9 (21.4)	44.4 (17.1)	48.5 (14.7)	45.2 (17.0)	
Median	34	43	48	44	
< 65	1693 (82.9%)	13771 (86.0%)	6765 (84.9%)	22229 (85.4%)	
≥ 65	349 (17.1%)	2238 (14.0%)	1206 (15.1%)	3793 (14.6%)	
Ethnicity					
Han	1867 (91.4%)	14804 (92.5%)	7436 (93.3%)	24107 (92.6%)	< 0.01
Other minority	175 (8.6%)	1205 (7.5%)	535 (6.7%)	1915 (7.4%)	
Education level					
Illiterate or semi-illiterate	155 (7.6%)	1190 (7.4%)	703 (8.8%)	2048 (7.9%)	< 0.01
Primary school	292 (14.3%)	2749 (17.2%)	1630 (20.4%)	4671 (18.0%)	
Secondary school	1249 (61.2%)	9432 (58.9%)	4445 (55.8%)	15126 (58.1%)	
College and above	339 (16.6%)	2603 (16.3%)	1181 (14.8%)	4123 (15.8%)	
Unknown	7 (0.3%)	35 (0.2%)	12 (0.2%)	54 (0.2%)	
Marital status					
Married	1086 (53.2%)	11638 (72.7%)	6538 (82.0%)	19262 (74.0%)	< 0.01
Single	785 (38.4%)	2759 (17.2%)	635 (8.0%)	4179 (16.1%)	
Widowed/divorced/separated/other	171 (8.4%)	1612 (10.1%)	798 (10.0%)	2581 (9.9%)	
Family annual income per capita (Median = 7200 RMB)					
Below the median	1072 (52.5%)	8061 (50.4%)	3842 (48.2%)	12975 (49.9%)	< 0.01
Above the median	970 (47.5%)	7948 (49.6%)	4129 (51.8%)	13047 (50.1%)	
Previously treated TB					
No	2019 (98.9%)	15929 (99.5%)	7936 (99.6%)	25884 (99.5%)	< 0.01

Abbreviations: BMI, Body mass index; SD, Standard deviation; HIV, Human immunodeficiency virus; AIDS, Acquired immune deficiency syndrome; BCG, Bacillus Calmette-Guerin vaccine

Characteristics	BMI category, kg/m²				
	Underweight < 18.5	Normal 18.5 to 24.0	Overweight and obese ≥ 24.0	Overall	p-value
	n (%)	n (%)	n (%)	n (%)	
Yes	23 (1.1%)	80 (0.5%)	35 (0.4%)	138 (0.5%)	
Close contacts					
No	2039 (99.9%)	15990 (99.9%)	7960 (99.9%)	25989 (99.9%)	< 0.01
Yes	3 (0.1%)	19 (0.1%)	11 (0.1%)	33 (0.1%)	
Known HIV/AIDS					
No	2040 (99.9%)	15995 (99.9%)	7966 (99.9%)	26001 (99.9%)	0.82
Yes	2 (0.1%)	14 (0.1%)	5 (0.1%)	21 (0.1%)	
Known diabetes					
No	2021 (99.0%)	15693 (98.0%)	7669 (96.2%)	25383 (97.5%)	0.68
Yes	21 (1.0%)	316 (2.0%)	302 (3.8%)	639 (2.5%)	
Chronic bronchitis					
No	1938 (94.9%)	15334 (95.8%)	7565 (94.9%)	24837 (95.4%)	< 0.01
Yes	88 (4.3%)	480 (3.0%)	351 (4.4%)	919 (3.5%)	
Unknown	16 (0.8%)	195 (1.2%)	55 (0.7%)	266 (1.0%)	
Pneumoconiosis					< 0.01
No	2032 (99.5%)	15978 (99.8%)	7945 (99.7%)	25955 (99.7%)	
Yes	10 (0.5%)	31 (0.2%)	26 (0.3%)	67 (0.3%)	
Smoking status					
Never	1689 (82.7%)	12178 (76.1%)	5441 (68.3%)	19308 (74.2%)	0.02
Former	57 (2.8%)	485 (3.0%)	280 (3.5%)	822 (3.2%)	
Current	296 (14.5%)	3346 (20.9%)	2250 (28.2%)	5892 (22.6%)	
Alcohol use					< 0.01
Never	1778 (87.1%)	12884 (80.5%)	5870 (73.6%)	20532 (78.9%)	
Former	76 (3.7%)	594 (3.7%)	396 (5.0%)	1066 (4.1%)	
Current	188 (9.2%)	2531 (15.8%)	1705 (21.4%)	4424 (17.0%)	
BCG scar					< 0.01
Yes	1265 (61.9%)	9466 (59.1%)	4570 (57.3%)	15301 (58.8%)	
No	660 (32.3%)	5571 (34.8%)	2896 (36.3%)	9127 (35.1%)	
Unknown	117 (5.7%)	972 (6.1%)	505 (6.3%)	1594 (6.1%)	

Abbreviations: BMI, Body mass index; SD, Standard deviation; HIV, Human immunodeficiency virus; AIDS, Acquired immune deficiency syndrome; BCG, Bacillus Calmette-Guerin vaccine

Table 2
Follow up and the tuberculosis incident by associated factors in the cohort.

Characteristics	Number of participants in cohort	Person-years	Number of cases	Incident rate (per 100 000)		Incident rate ratio		*p*-value
	n (%)		n	(95% CI)		(95% CI)		
All								
	26022	44574.4	43	96.5	(69.8-129.9)			
Sex								
Male	12396 (47.6%)	21231.7	26	122.5	(80.0-179.4)	ref		
Female	13626 (52.4%)	23342.7	17	72.8	(42.4-116.6)	0.59	(0.31–1.12)	0.11
Age (years)								
< 65	22229 (85.4%)	39227.5	13	33.1	(17.6–56.7)			
≥ 65	3793 (14.6%)	5346.9	30	561.1	(378.6–801.0)	17.41	(8.70-34.83)	< 0.01
Ethnicity								
Han	24107 (92.6%)	41304.6	36	87.2	(61.0-120.7)	ref		
Other minority	1915 (7.4%)	3269.8	7	214.1	(86.1-441.1)	2.27	(0.94–5.50)	0.07
Education level								
Illiterate or semi-illiterate	2048 (7.9%)	3134.0	14	446.7	(244.2-749.5)	ref		
Primary school	4671 (18.0%)	7686.4	13	169.1	(90.1-289.2)	0.38	(0.17–0.85)	0.02
Secondary school	15126 (58.1%)	26416.3	13	49.2	(26.2–84.2)	0.11	(0.05–0.25)	< 0.01
College and above	4123 (15.8%)	7248.5	3	41.4	(8.5–121.0)	0.08	(0.02–0.32)	< 0.01
Unknown	54 (0.2%)	89.2	0	0.0	(0.0-4133.7)	-		
Marital status								
Married	19262 (74.0%)	33163.6	26	78.4	(51.2-114.9)	ref		
Single	4179 (16.1%)	7280.2	3	41.2	(8.5-120.4)	0.42	(0.10–1.67)	0.22
Widowed/divorced/separated/other	2581 (9.9%)	4130.7	14	338.9	(185.3-568.7)	4.23	(2.12–8.45)	< 0.01
Family annual income per capita (Median = 7200 RMB)								
Below the median	12975 (49.9%)	22547.9	20	88.7	(54.2–137.0)	ref		
Above the median	13047 (50.1%)	22026.5	23	104.4	(66.2-156.7)	1.18	(0.63–2.23)	0.60
Previously treated TB								
No	25884 (99.5%)	44368.3	38	85.6	(60.6-117.6)			
Yes	138 (0.5%)	206.2	5	2425.3	(787.5-5659.8)	25.01	(8.84–70.78)	< 0.01

Abbreviations: CI, Confidence interval; HIV, Human immunodeficiency virus; AIDS, Acquired immune deficiency syndrome; BCG, Bacillus Calmette-Guerin vaccine

Characteristics	Number of participants in cohort	Person-years	Number of cases	Incident rate (per 100 000)		Incident rate ratio		*p*-value
	n (%)		n	(95% CI)		(95% CI)		
Close contacts								
No	25989 (99.9%)	44518.7	43	96.6	(70.1-130.5)			
Yes	33 (0.1%)	55.7	0	0.0	(0.0-6624.0)	-		
Known HIV/AIDS								
No	26001 (99.9%)	44547.2	43	96.5	(69.9–130.0)			
Yes	21 (0.1%)	27.3	0	0.0	(0.0-13532.2)	-		
Known diabetes								
No	25383 (97.5%)	43657.4	41	93.9	(67.4-127.4)	ref		
Yes	639 (2.5%)	917.1	2	218.1	(26.4-787.8)	1.56	(0.28–8.76)	0.62
Chronic bronchitis								
No	24837 (95.4%)	42653.9	41	96.1	(69.0-130.4)	ref		
Yes	919 (3.5%)	1455.1	2	137.4	(16.6-496.5)	0.96	(0.17–5.39)	0.96
Unknown	266 (1.0%)	465.4	0	0.0	(0.0-792.6)	-		
Pneumoconiosis								
No	25955 (99.7%)	44475.3	42	94.4	(68.1-127.6)	ref		
Yes	67 (0.3%)	99.1	1	1009.2	(25.6-5622.8)	4.07	(0.27–61.44)	0.31
Smoking status								
Never	19308 (74.2%)	32995.7	28	84.9	(56.4-122.6)	ref		
Former	822 (3.2%)	1318.3	1	75.9	(1.9-422.7)	0.34	(0.02–5.23)	0.44
Current	5892 (22.6%)	10260.4	14	136.4	(74.6-228.9)	1.57	(0.79–3.11)	0.19
Alcohol use								
Never	20532 (78.9%)	35082.0	27	77.0	(50.7–112.0)	ref		
Former	1066 (4.1%)	1772.5	5	282.1	(91.6-658.3)	3.26	(1.13–9.43)	0.03
Current	4424 (17.0%)	7719.9	11	142.5	(71.1–255.0)	1.79	(0.84–3.79)	0.13
BCG scar								
Yes	15301 (58.8%)	26975.3	11	40.8	(20.4–73.0)	ref		
No	9127 (35.1%)	14772.3	29	196.3	(131.5-281.9)	5.00	(2.38–10.51)	< 0.01
Unknown	1594 (6.1%)	2826.8	3	106.1	(21.9-310.1)	2.14	(0.49–9.31)	0.31

Abbreviations: CI, Confidence interval; HIV, Human immunodeficiency virus; AIDS, Acquired immune deficiency syndrome; BCG, Bacillus Calmette-Guerin vaccine

Table 3
Body mass index and risks of tuberculosis in the cohort.

	BMI category, kg/m^2					
	Underweight		**Normal**		**Overweight and obese**	
	< 18.5		**18.5 to 24.0**		**≥ 24.0**	
Mean (95% *CI*), kg/m^2	17.5	(17.4–17.5)	21.4	(21.3–21.4)	26.3	(26.2–26.3)
Person-years	3464.8		27382.0		13727.7	
Number of cases	6		31		6	
Incidence rate (per 100 000, 95% *CI*)	173.2	(63.6-376.9)	113.2	(76.9-160.7)	43.7	(16.0-95.1)
Incident rate ratio (95% *CI*)	1.39	(0.53–3.65)	ref		0.35[†]	(0.13–0.92)
cHR (95% *CI*)	1.55	(0.65–3.71)	ref		0.36[†]	(0.15–0.87)
Age-adjusted *HR* (95% *CI*)[a]	1.26	(0.52–3.03)	ref		0.34[†]	(0.14–0.82)
Multivariable adjusted *HR* (95% *CI*)[b]	1.26	(0.52–3.06)	ref		0.34[†]	(0.14–0.82)
Corrected with DM *HR* (95% *CI*)[c]	1.25	(0.52–3.04)	ref		0.34[†]	(0.14–0.83)

Abbreviations: BMI, Body mass index; CI, Confidence interval; HR, Hazard ratio, cHR, crude Hazard ratio; DM, Diabetes mellitus

[a] Age-adjusted *HR*: category with aged 65 years.

[b] Multivariable adjusted *HR*: after variable selection, adjusted with covariates: age, sex, ethnicity, marital status, previously treated TB, smoking status, alcohol use, all variables were adjusted as categorical variable.

[c] Corrected with DM *HR*: adjusted with covariates: age, sex, ethnicity, marital status, previously treated TB, smoking status, alcohol use and known diabetes, all variables were adjusted as categorical variable.

[†] $p < 0.01$

Table 4
Subgroup analysis for the association between body mass index and risks of tuberculosis in the cohort.

Covariates	BMI groups	Person-years	Number of cases	Incidence rate		aHR		p-value	Interaction
			n	(95% CI)		(95% CI)			p-value[c]
Sex[a]									
Male	Underweight	1408.3	5	355.0	(115.3-828.6)	1.69	(0.59–4.82)	0.33	ref
	Normal	12370.7	17	137.4	(80.1–220.0)	ref			
	Overweight	7452.7	4	53.7	(14.6-137.4)	0.44	(0.15–1.31)	0.14	ref
Female	Underweight	2056.5	1	48.6	(1.2-270.9)	0.38	(0.05–2.93)	0.35	0.25
	Normal	15011.2	14	93.3	(51.0-156.5)	ref			
	Overweight	6274.9	2	31.9	(3.9-115.1)	0.22	(0.05–0.97)	0.05	0.52
Age (years)[b]									
< 65	Underweight	2981.1	2	67.1	(8.1-242.3)	1.79	(0.37–8.65)	0.47	ref
	Normal	24229.7	9	37.1	(17.0-70.5)	ref			
	Overweight	12016.6	2	16.6	(2.0-60.1)	0.42	(0.09-2.00)	0.28	ref
≥ 65	Underweight	483.7	4	827.0	(225.3-2117.6)	1.20	(0.41–3.54)	0.74	0.54
	Normal	3152.3	22	697.9	(437.4-1056.7)	ref			
	Overweight	1711.0	4	233.8	(63.7-598.6)	0.36	(0.12-1.00)	0.05	0.87

Abbreviations: BMI, Body mass index; CI, Confidence interval; aHR, adjusted Hazard ratio

[a] Adjusted with covariates: age, ethnicity, marital status, previously treated TB, smoking status, alcohol use, all variables were adjusted as categorical variable.

[b] Adjusted with covariates: sex, ethnicity, marital status, previously treated TB, smoking status, alcohol use, all variables were adjusted as categorical variable.

[c] *P*-Value for interaction by subgroup; estimated from the product term of factors.

Results

Baseline characteristics and follow-up of the cohort

This study included 26 022 participants and followed up to outcomes. The underweight, normal weight and overweight or obese participants occupied the proportion of 7.9%, 61.5%, and 30.6% at baseline, respectively. The median age was 44 years and the male to female ratio was 1 to 1.1 (Table 1).

The followed-up time of the cohort was 2.25 years (27 months) in three rounds of screening. Overall, the number of 43 cases developed tuberculosis in 44 574.4 observed person-years, the tuberculosis incidence rate was 96.5 per 100 000 person-years (95% CI 69.8-129.9). Median times to incident tuberculosis was 1.64 years (20 months). Tuberculosis incidence was significantly higher in those aged over 65 years, lower education level, widowed/divorced/separated/other, previously treated tuberculosis, former drinker, and persons without BCG scar (Table 2).

Dose-response relationship of BMI and tuberculosis incident

The Kaplan-Meier univariate analysis showed that the cumulative hazard of developing tuberculosis was different by BMI levels (the overall Log-Rank test $p = 0.021$). Lower BMI had a shorter time of developing tuberculosis (Fig. 2).

For the cohort participants, the incidence rate of tuberculosis was 173.2 (95% CI 63.6-376.9), 113.2 (95% CI 76.9-160.7), and 43.7 (95% CI 16.0-95.1) per 100 000 person-years in underweight, normal weight and overweight or obese respectively (Table 3).

Inverse logarithmic-linear dose-response relationship between BMI and tuberculosis incidence was fitted. The logarithmic transferred TB incidence and linear BMI change were regressed (R^2 = 0.98, adjusted R^2 = 0.95), the intercept and slope were 3.46 and − 0.068 respectively (Fig. 3).

Dose-response relationship of BMI and tuberculosis risk

After adjusting the covariates, the multivariable Cox proportional regression presented that overweight and obese was associated with a lower hazard of incident tuberculosis compared with normal weight (aHR, 0.34; 95% CI 0.14–0.82, $p < 0.01$), underweight related to a higher hazard but statistical non-significant (aHR, 1.26; 95% CI 0.52–3.06, $p = 0.60$). The BMI linear trend was significant and an estimated 48% reduction for tuberculosis hazard along with BMI increased (aHR, 0.52; 95% CI 0.31–0.85, $p < 0.01$). After correction with DM status, the association between BMI and tuberculosis risk remained unchanged (Table 3).

Overall and in subgroups, restricted cubic spline regressions were fitted to present dose-response relationship between continuous BMI and linear cumulative hazards of tuberculosis (Figs. 4 and 5). Approximated negative linear or cubic polynomial relationship between the pooled or stratified risks of tuberculosis and BMI, except the subgroups of those single or former drinkers, showed a U-shaped curve.

Subgroups analysis according to gender and age

Across different subgroups of sex, tuberculosis incidence inversely related to BMI in male induvial. The risk of tuberculosis showed a 78% reduction in overweight or obese (aHR, 0.22; 95% CI 0.05–0.97, $p = 0.05$) compared with normal weight among females (Table 4). While stratified by age under or above 65, tuberculosis incidence inversely related to BMI in both populations. The hazard of tuberculosis presented a 64% reduction in overweight or obese (aHR, 0.36; 95% CI 0.12-1.00, $p = 0.05$) compared with normal weight among the elderly. There was no evidence of interaction effect for BMI by sex or age.

Discussion

In this prospective population-based cohort study, we estimated the inverse log-linear dose-response association of BMI and the tuberculosis incidence in contemporary Chinese adults. The cohort study clarified the higher BMI was a strong predictor for tuberculosis development, a two-third reduction of tuberculosis risk for overweight and obese compared with normal weight population, protective effect yet presented in sub-population of female and elderly. Additionally, consistent inverse relationships were precisely illustrated between the successive BMI and the risk of tuberculosis overall and stratified.

The log-linear inverse association between the BMI and tuberculosis incidence was consistent with the result of the previous systemic review [3]. Though five out of six cohort studies included in this systemic review were performed in the last century, and all 6 studies were carried out in high-income counties. Likewise, large population-based cohorts reported by Cegielski et al in the US [8] and Pealing et al in the UK [9] stated the inverse association in low disease burden and high-income setting. Our study was implemented in the high burden site of a middle-income country, this inverse association remained unchanged to these reports far distance from recent in lower TB burden settings.

Most recently, studies presented the BMI related to the tuberculosis development. Population-based observational studies revealed that lower BMI was related to tuberculosis. Researches of the cross-sectional prevalence investigation and followed up cohort among elderly in China, Zhang et al and Cheng et al [10, 11] reported that a significantly higher risk or hazard of tuberculosis in the underweight group (adjusted odds ratio [aOR], 1.55; 95% CI, 1.09–2.22) and (aHR, 2.33; 95% CI 1.32–4.12) respectively, compared with normal-weight among those age over 65 years in China. However, our study reported a non-significant association for underweight and tuberculosis in general adult and elderly sub-population. This discrepancy might be trigger by the difference proportion and distribution of baseline demographic and socioeconomic factors, meanwhile, this previous elderly cohort study reported a large proportion of loss-to-follow might overestimate the risk.

Besides, many shreds of evidence presented overweight or obesity was associated with a lower risk of tuberculosis. Yen et al [12] reported in a Taiwan cohort that by comparing with normal weight group, the overweight (aOR, 0.67; 95% CI, 0.49–0.91) and obesity (aOR, 0.43; 95% CI, 028-0.67) was a protective factor to tuberculosis incident. Kim et al [13] reported a consistent inverse association between BMI and tuberculosis, this followed up research also presented that overweight (aHR, 0.45; 95% CI, 0.40–0.50) and obesity (aHR, 0.40; 95% CI, 0.30–0.54) as a protective predictor of tuberculosis. Although there was a slight difference in hazard or risk ratio for tuberculosis development among studies, regarding the cutoff points for BMI categorization and the definition for overweight or obesity was different across study sites and countries, all these researches revealed the identical direction of association with our study. These unanimous results from systemic review and multi-population observational studies, with addition to this cohort among Chinese adulthood, showed the strong and constant evidence of the inverse association between BMI and tuberculosis incidence.

The highlight of the present study was that we quantified the dose-response relationship between BMI and the disease incident, as well as the risk of tuberculosis progression. Our research established the association between successive BMI and TB incident, which was more accurate and solid compared with previous discrete BMI levels. Under the high burden of 96.5 per 100 000 person-years incident setting, the logarithmic TB incidence decreased response to the linear increment of BMI. The results suggested that the tiny improvement of population nutrition status would have a great public health impact that significantly decreased the TB incident, especially among nutritionally vulnerable populations such as BMI under 18.5 kg/m^2. For instance, the BMI increased from 18 to 19 kg/m^2, the TB incidence declined 24.8 per 100 000 person-years in population. This suggests that the nutrition-improvement food distribution program for the targeted population might be a beneficial strategy for these high burden regions. This also implied that the increment of main exposure BMI during decades might play a crucial role in the overall 28% decline of tuberculosis prevalence between 1990 and 2010 in China [14].

There was another contribution to this study. We had got a better understanding of the logarithmic predicted individual tuberculosis risk declined accompanied by BMI linear increment, despite subgroups such as single person or former drinker presented U-shaped curve. The BMI value of 22.5 kg/m^2 was on the log-linear x-axis (with slope and intercept of zero) that corresponded to an exponential tuberculosis hazard of 1. This implied the cutoff point of BMI on tuberculosis hazard was 22.5 kg/m^2, the value was the threshold of hazardous-protective effect for tuberculosis progression among the general community population. The potential benefit of this novel insight was that while implementing the tuberculosis active case finding (ACF) screening, we speculated the screening strategy could possibly yield if sub-population of BMI under 22.5 kg/m^2 was set as one of the targeted populations [6, 15]. Notwithstanding, the discussion about the universal BMI category was inappropriate. Disease morbidity-, disease mortality-, or population-specific BMI categorization was reasonable [16], many studies confirmed a lower BMI cutoff point for Chinese adults to define fat, overweight or obese while considering comorbidities, progression or sub-population [17–20]. The generalization of this finding should be cautious because the cohort sample was unrepresentative to other regions, more evidence was needed to confirm the cutoff point of BMI and the yield of screening.

DM was a well-known risk factor for tuberculosis, BMI also had a strong relation with DM. Although in the present study the association between known DM and TB was no-significant in the DM corrected model, the reduction of TB risk associated with BMI remains unchanged after including DM status. A systemic review of 3 cohorts examined DM associated with an increased risk of TB (relative risk, 3.11; 95% CI 2.27–4.26) [21]. Kuo et al [22] reported type 2 diabetes (T2DM) significantly increase 31% tuberculosis risk (aHR, 1.31; 95% CI 1.23–1.39) after adjusting sex, age, and comorbidities. Lee et al [23] then revealed DM patients with poor glycemic control had a higher hazard of TB (aHR, 2.21; 95% CI 1.63–2.99) after adjusting covariates and BMI. Lin et al [24] stated causal mediation between factors of BMI, DM, and TB. Obesity decreased tuberculosis hazard in 2 cohorts followed up over 7 years, obesity had a slight hazard effect on tuberculosis mediated by DM but had a strong protective effect not mediated through DM. A feasible explanation for this argument and inconsistent was that the prevalence of DM in the present cohort was 2.5%, which was substantially lower than 9.7% of total diabetes prevalence among China adults [25]. The evidence was insufficient of DM as a risk factor or its interaction effect with BMI for tuberculosis incidence in lower prevalence during the short-term observation.

The biological mechanism of BMI effect on tuberculosis incident was complicated. The population nutrition status was characterized mainly by the indicator of BMI. Nutrition, immune function, and infection were complex related and in dynamic interact patterns. The malnutrition linked to the cell-mediated immunity (CMI) system that was profoundly affected the host defense against *Mycobacterium tuberculosis*, result in the tuberculosis infection or immunity. Malnourished mice caused chronic Protein-energy malnutrition (PEM) suffered a higher bacterial burden and the efficacy of BCG vaccination was reduced [26]. A review stated that PEM impairs CMI and worsens the infections, conversely, the infection can lead rapidly to weight loss, malnutrition, and immunologic dysfunction, moreover, PEM is partly due to food deprivation [27]. Thus, the direction and interact or causal relationship between malnutrition and tuberculosis still scarcely understood, many unknown variables affect the relationship. Another possible interpretation was that the difference in genetic susceptibility of obesity among hosts leads to the association. Obesity-associated gene *FTO* (fat mass and obesity-associated, Gene ID: 79068) and its genetic polymorphisms rs9939609, rs8050136 within the *FTO* associated with obesity. The significant association between the genetic polymorphism rs9939609 and tuberculosis risk was found, that compared with the common genotype TT, individuals carrying AA had a tuberculosis risk (aOR, 3.77; 95% CI: 2.26–6.28) [28].

The strengthening of our research is that this population-based prospective study included a large number of community participants in the southwestern mountainous region of China. The cohort estimated steady tuberculosis incidence under relatively high disease burden setting in Chinese adulthood, which could supply solid evidence for tuberculosis control policymaker in the area. Moreover, this well-designed cohort study quantified log-linear inverse dose-response relationship between BMI and tuberculosis incidence, yet estimated the dose-response association between BMI and individual risk progress to tuberculosis. Additionally, the overall and stratification analysis was performed after adjusting the confounders. The protective effect of the higher BMI presented in the general population and subgroup of females and the elderly might contribute to TB control policy.

However, there were a few limitations to the study. First, this study followed up over two years and conducted three rounds of screening due to the limited funding and resource. Accordingly, we could not observe all the tuberculosis incidents in a long period, the short-term followed up period plus the low prevalence of comorbidities at baseline (such as known DM, known HIV/AIDS, Chronic bronchitis, Pneumoconiosis) might lead to these factors insignificant associated with tuberculosis development. A systemic review showed that in the first 2 years after latent tuberculosis infection (LTBI) status, 65% of the LTBI cases progressed to active tuberculosis in a total follow up time of 20 years [29]. This cohort could capture most of the LTBI development to tuberculosis, but there were still 35% infected individual could not reach end-point of disease progression due to the short-term follow up. Second, the study did not get LTBI status in the baseline population, how the BMI effect on LTBI progression to active TB was still unsolved. Though there was evidence that the lower BMI did not increase the LTBI risk [30], overweight or obesity was a risk factor associated with LTBI status [31]. Further study should be conducted to clarify this interesting contradiction of BMI playing a different role in LTBI status and TB development. Additionally, several covariates were self-reported by participants such as smoking and drinking habit, the exposure level without accurate measurement would be imprecise to estimate the association.

Conclusion

Collectively, the study revealed the inverse log-linear dose-response relationship between BMI and incident tuberculosis, likewise the association between BMI and risk of tuberculosis progression in contemporary Chinese adulthood. Overweight and obesity was the protective factor of TB development in the general population and subgroups of female or elderly.

Abbreviations

BMI:body mass index; TB:tuberculosis; PTB:pulmonary tuberculosis; aHR:adjusted hazard ratio; CI:confidence interval; SEVs:summary exposure values; CHWs:community health workers; BCG:Bacillus Calmette-Guerin; TBIMS:Tuberculosis Information Management System; HIV/AIDS:human immunodeficiency virus or acquired immune deficiency syndrome; CDC:Center for Disease Control and Prevention; DM:diabetes mellitus; BPHS:National Project of Basic Public Health Service; CXR:chest X-ray; IR:incident rate; IRR:incident rate ratio; RCS:restricted cubic spline; IRB:Institutional Review Board; aOR:adjusted odds ratio; ACF:active case finding; T2DM:type 2 diabetes; CMI:cell-mediated immunity; PEM:protein-energy malnutrition; LTBI:latent tuberculosis infection.

Declarations

Ethical Approval

This study was reviewed and approved by the Institutional Review Board (IRB) of the Chinese Center for Disease Control and Prevention (No. 201820). All participants gave written consent to enroll and participate in this study. The study was not included personal identification and all data in analyses was anonymized.

Competing Interests

The authors declare that they have no competing interests.

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Authors’ Contributions

JC, SZ and LX conceived and designed the study. JC, SZ, JH, KL, YQ, RY, LL and YY collected the data. JC performed the statistical analysis. JC and LX prepared the manuscript. All authors read and approved the final manuscript.

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Consent for publication

Not applicable.

Availability of Data and Material

We do not wish to share our data. Data is available upon reasonable request to the corresponding author.

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Figures

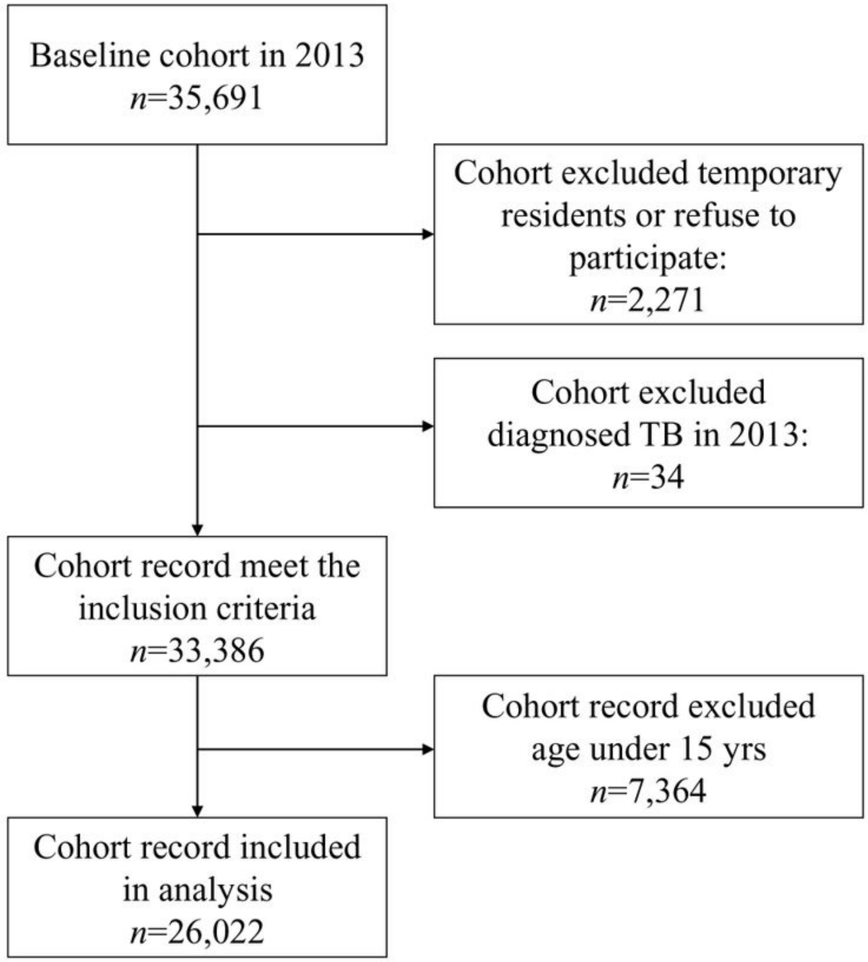

Figure 1

Diagram of the tuberculosis screening cohort between 2013 and 2015. Abbreviations: TB, tuberculosis

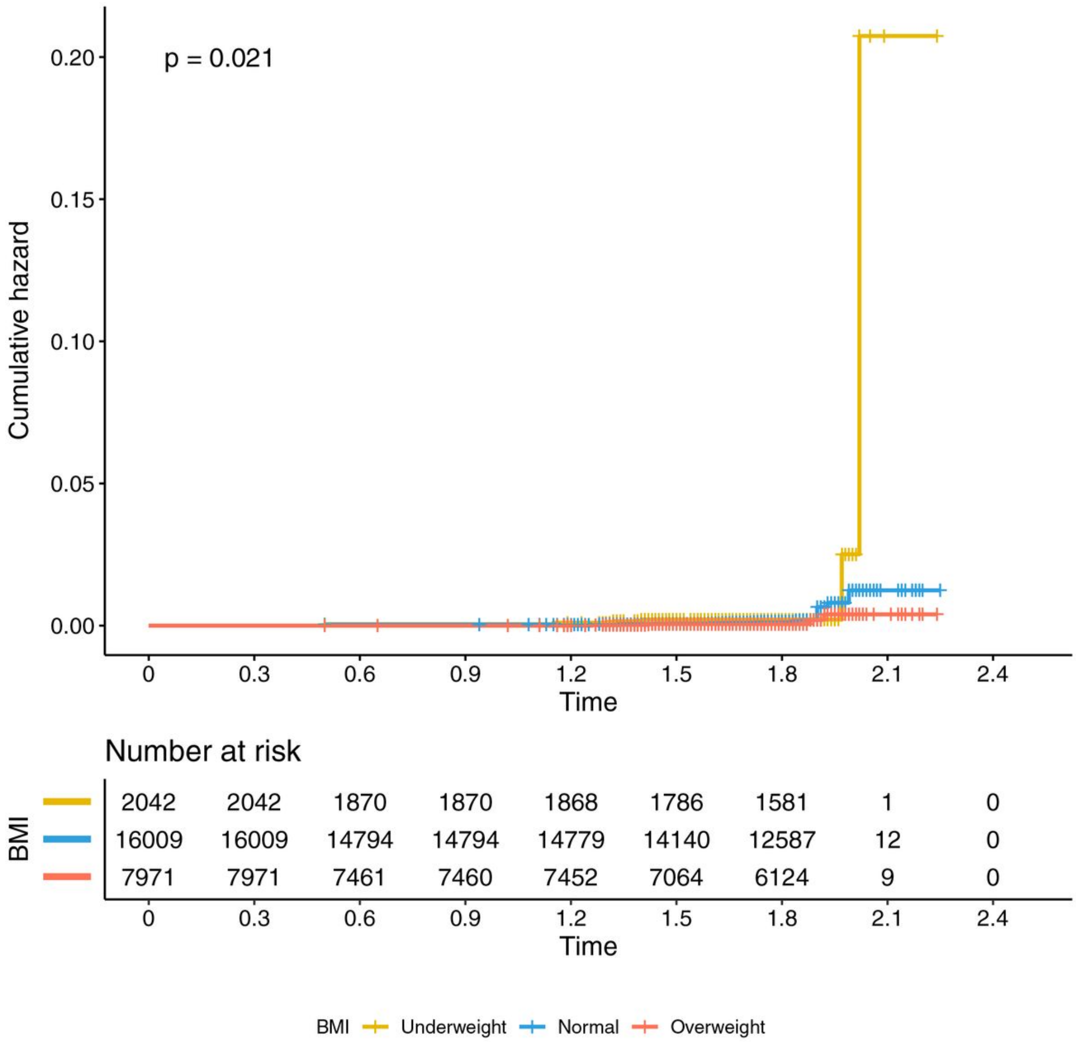

Figure 2

Kaplan-Meier plot of cumulative hazard of tuberculosis by body mass index. The yellow line (Underweight) represents lower BMI (18.5<kg/m2), the blue line (Normal) represents the BMI between 18.5 and 24 kg/m2, orange line (Overweight) represent BMI over 24 kg/m2. The time to events or censor was defined by years. Abbreviations: TB, tuberculosis; BMI, body mass index

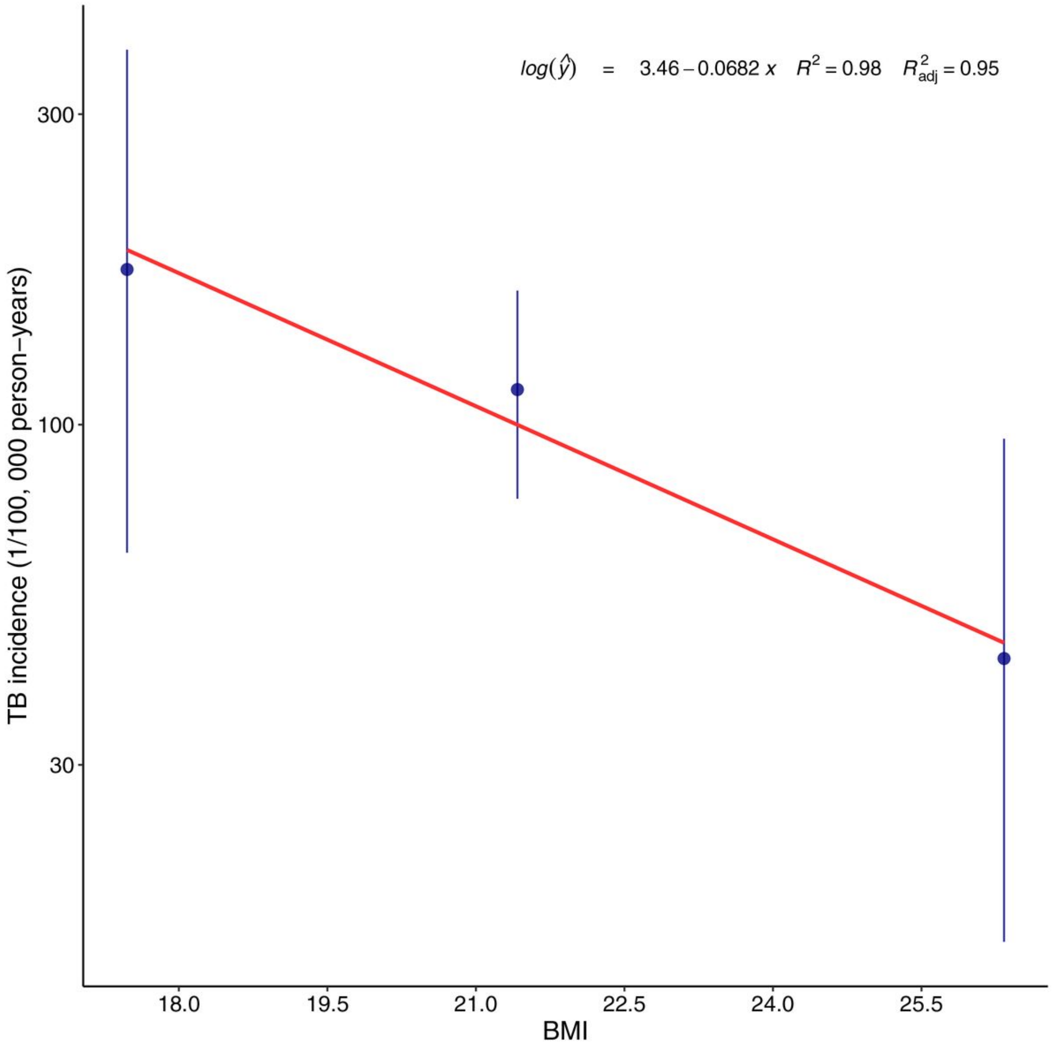

Figure 3

Dose-response relationship of the association between body mass index and the incidence of tuberculosis. TB incidence was transformed with denary logarithm, then regressed with a mean BMI of three categories. Blue points and ranges represent the TB incidence and 95% CI by the average BMI in three categories (17.5 kg/m2, 21.4 kg/m2 and 26.3 kg/m2 in underweight, normal and overweight groups respectively), the red line represents the log-linear dose-response relationship between BMI and TB incidence. Abbreviations: TB, tuberculosis; BMI, body mass index; CI, confidence interval;

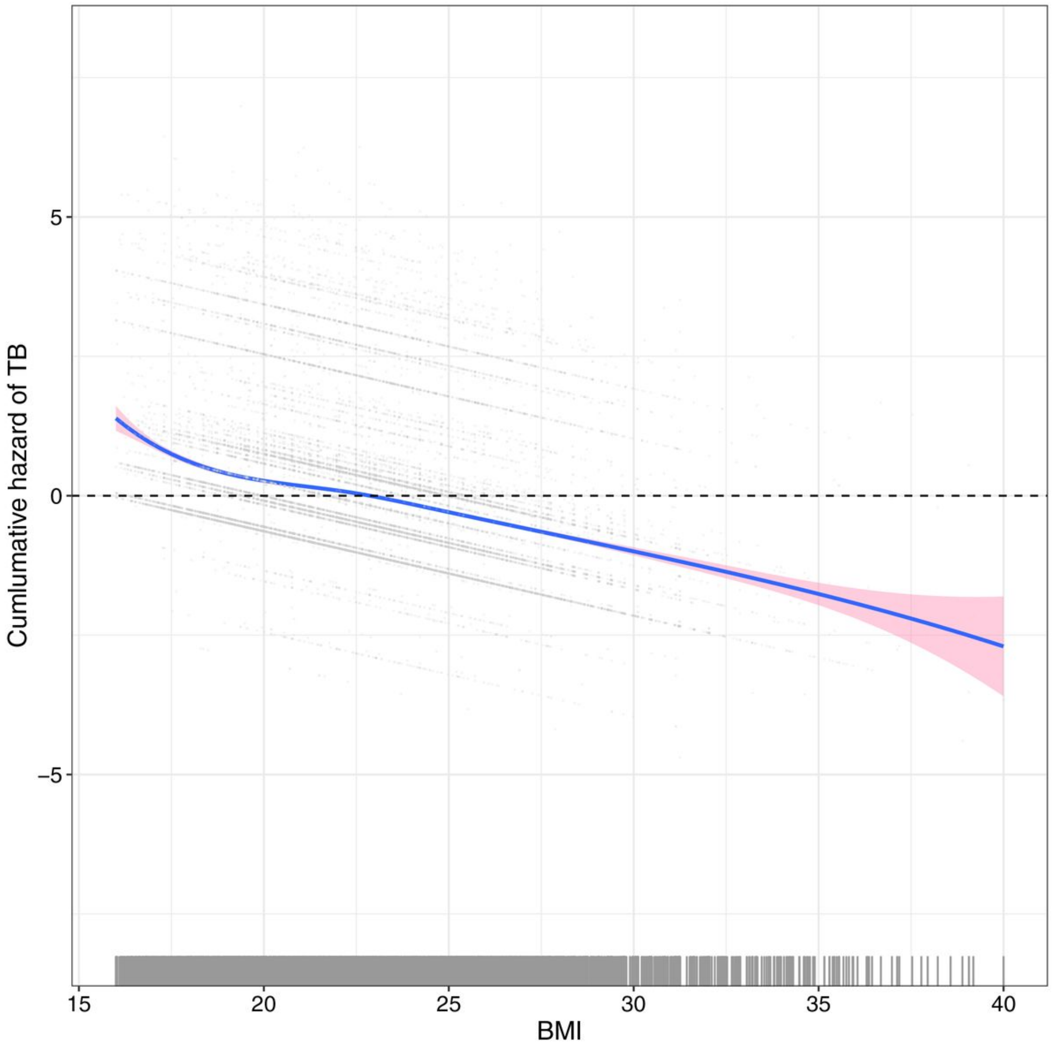

Figure 4

Dose-response curves for the body mass index and logarithmic cumulative hazard of tuberculosis in Cox proportional hazards model. The blue line and pink area represent the non-linear relationship of predicted log-linear cumulative hazard of TB and BMI using the restricted cubic spline regression, the spline knots of BMI were the quartiles (25%, 50%, and 75%) of the continuous variable. The Cox model adjusted for age, sex, ethnicity, marital status, previously treated TB, smoking status, alcohol use, known diabetes, and BMI. All variables were adjusted as categorical variables except continuous BMI. Abbreviations: TB, tuberculosis; BMI, body mass index

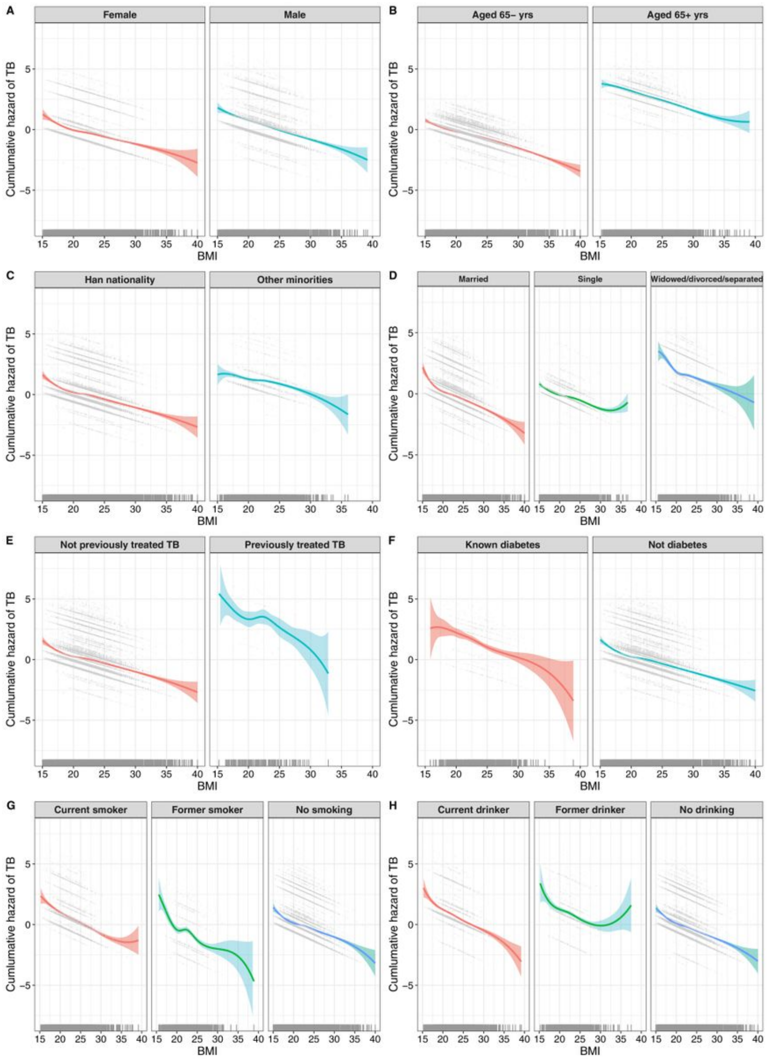

Figure 5

Dose-response curves for the body mass index and logarithmic cumulative hazard of tuberculosis in Cox proportional hazards model stratified by predictors. Panels represent different categories of predictors in the model and its non-linear relationship between predicted log-linear cumulative hazard of TB and BMI using the restricted cubic spline regression, the spline knots of BMI were the quartiles (25%, 50%, and 75%) of the continuous variable. The Cox proportional hazards model adjusted for age, sex, ethnicity, marital status, previously treated TB, smoking status, alcohol use, known diabetes, and BMI. All variables were adjusted as categorical variables except continuous BMI. (A)Sex, (B)Age, (C)Ethnicity, (D)Marital status; (E)Previously treated TB, (F)Known diabetes, (G)Smoking status, (H)Alcohol use Abbreviations: TB, tuberculosis; BMI, body mass index