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Dose–response relationship between body mass index and tuberculosis in China: a population-based cohort study

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ABSTRACT

Objectives This study aimed to describe and quantify the relationship between body mass index (BMI) and tuberculosis (TB) incidence.

Design A population-based prospective cohort study.

Setting Ten randomly selected communities in the southwestern mountainous region of China.

Participants Participants who had resided in study sites before screening for at least 6 months were eligible. Those who refused to participate or were temporary residents (who resided less than 6 months during three waves of screening) were excluded. The present research included 26 022 participants aged over 15 years for analyses.

Interventions The cohort study conducted three rounds of TB screening from 2013 to 2015. Face-to-face surveys for participants were carried out. TB symptoms positivity suspects underwent chest X-ray and sputum smear test for diagnosis.

Primary outcome measures The study outcome was the diagnosed active TB in the second and third rounds of screening.

Results During the follow-up of 2.25 years, 43 cases developed TB in 44 574.4 person-years. The negative log-linear relationship between BMI and TB incidence was fitted (adjusted R^2=0.76). Overweight or obese was associated with a lower risk of TB compared with normal weight (adjusted HR (aHR) 0.34, 95% CI 0.14 to 0.82). The inverse log-linear associations between continuous BMI and individual TB risk were evaluated. In subgroup analysis, the risk of TB reduced 78% in overweight or obese women (aHR 0.22, 95% CI 0.05 to 0.97), and a 64% reduction in the elderly (aHR 0.36, 95% CI 0.12 to 1.00) compared with those with normal weight, respectively.

Conclusions The study provided evidence for a negative association between BMI and TB development in Chinese adults. It suggests the inverse dose–response relationship between BMI and TB incidence, and implies an optimal cut-off point of BMI for screening strategy.

Strengths and limitations of this study

- This study described and quantified the relationship between body mass index (BMI) and tuberculosis (TB) incidence in China, one of the high TB burden countries.
- The large-scale cohort was a community population-based study. Well-designed prospective cohort, standardised measurement and defined screening protocol were strengths of the study.
- The large sample size and follow-up allowed us to analyse the population-level TB incidence, individual TB risk and its relationship with BMI by controlling confounders.
- The low baseline diabetes prevalence of the cohort profile was underpowered to show the BMI, diabetes and TB interaction.
- In a short time of cohort follow-up, several co-variates were self-reported by participants, which might bring limitations of underestimation and misreporting.

INTRODUCTION

Tuberculosis (TB) is an airborne communicable disease that causes a high public health burden.[1] The Chinese national survey in 2010 presented a high TB prevalence of 442 (417–469) per 100 000 persons. Nonetheless, it was a 65% decline in smear-positive TB prevalence from 1990 to 2010.[2] China is a high TB burden country. About 9% of the world's newly diagnosed pulmonary TB and an estimated 866 000 incident cases were from China. The estimated incidence rate (IR) was 61 (52–70) per 100 000 persons in 2019.[3]

Body mass index (BMI) was an efficient, convenient and measurable indicator for the body characteristics of the population. The association between BMI and TB incidence has been studied before. In 2010, a systemic review included six outdated cohort studies under different settings and TB burdens, which reported a homogeneous inverse relationship between BMI and TB incidence in the BMI range of 18.5–30 kg/m^2.[4]

Over the past decades, China has dramatically shifted in demographic and epidemiological profile, while disease spectrum and associated risks have changed simultaneously. The prevalence of obesity in 2014 was 61 and 27 times higher than those in 1975 among Chinese male and female adults, respectively.[5] The high BMI was ranked the top of

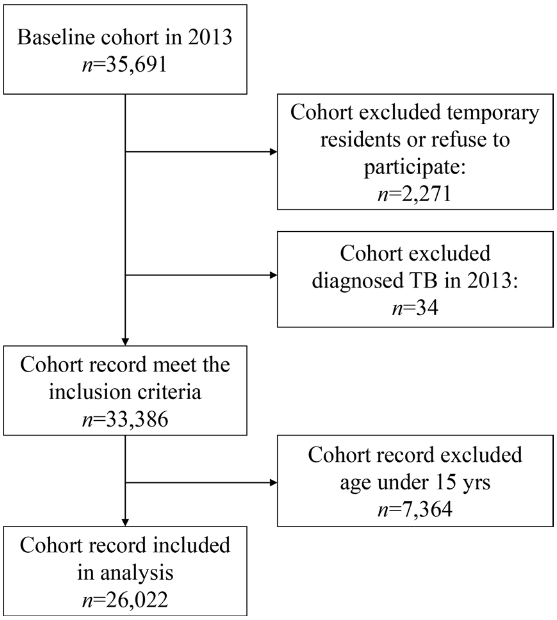

Figure 1 Diagram of the tuberculosis (TB) screening cohort in Yunnan, 2013–2015.

percentage changes in agestandardised summary exposure values from 1990 to 2017.[6] Thus, there is a need to explore the relationship between the dramatic change of primary exposure of BMI and the outcome of TB incidence.

Previous researches clarified risks that influenced the individuals infected with TB, such as male sex, elderly, diabetes mellitus (DM), underweight, cigarette smoking and indoor biomass fuel use in China.[7 8] However, the overall and stratified associations between BMI and the primary outcome of TB incidence are unsettled under a high TB burden setting. The present study aimed to examine the relationship between BMI and incidence of TB in a population-based TB screening cohort of China. The study also explored the association of BMI and individual TB risks, overall and in subgroups.

METHODS

Study design and participants

The study site was Dongchuan county of Yunnan province in the southwestern mountainous region of China. Dongchuan county is located 150 km away from the provincial capital; the population was 276 993 in 2015, healthcare accessibility was in the median level of the province.[9] The DM prevalence in Yunnan was 6.7% in adults, 6.2% in men and 7.2% in women, respectively.[10] The dietary investigation presented that livestock meat, fat and salt intake was more than the recommended nutrient intake, but insufficient intake of vegetables, fruits, eggs, milk and milk products.[11]

The study was a complicated, multistage sampling prospective TB screening cohort among communities; the detailed study design has been documented elsewhere.[12] In general, the cohort was based on three rounds of TB screening from June 2013 to December 2015 among 10 randomly sampled communities. The baseline investigation was conducted in 2013. Trained community health workers (CHWs) conducted home visits and face-to-face surveys for community residents who had resided in study sites before screening for at least 6 months. Of the 35 691 community residents visited by CHWs, 2271 who refused to participate or temporarily resided (resided less than 6 months) were excluded. The cohort enrolled 33 386 eligible participants. Standardised questionnaires comprised of suspected TB symptoms, demographic, comorbidity, epidemiological exposure and lifestyle were applied for baseline data collection. The participants' age under 15 years (n=7 364) or diagnosed active TB in baseline screening (n=34) were excluded for data analyses. Finally, the present research included 26 022 participants for analysis (figure 1). In the following years, the second and third rounds of screening were implemented by applying the same algorithm as the baseline survey. The participants in the fixed cohort were prospectively followed up until the occurrence of TB, death, moving out of the study field or the deadline in December of 2015.

Definition of key variables

BMI records in the baseline survey were the primary exposure of the study. CHWs measured the weight and height of participants. Individual BMI was the ratio of weight in kilograms as numerator divided by the square of height in metres as the denominator. According to the criteria of weight for adults ruled by the Ministry of Health of the People's Republic of China,[13] we categorised the continuous BMI into three groups: underweight (<18.5 kg/m^2), normal (18.5–24.0 kg/m^2), overweight or obese (≥24.0 kg/m^2).

Most of the participants' characteristics were self-reported when interviewed by CHWs at baseline investigation. The covariates included demographic, comorbidity, medical history and lifestyle information: sex (male, female), age, 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), annual family income per capita (<the median of 7200 Renminbi (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), and BCG vaccine scar in the arm (yes, no). Information on previously treated TB cases (yes, no) was matched and examined in the Tuberculosis Information Management System; known HIV or AIDS cases (yes, no) were reviewed in the local Center for Disease Control and Prevention database. Known DM cases (yes, no) were matched to the National Project of Basic Public Health Service personal health records for confirmation.

Table 1 The baseline characteristics of the cohort categorised by body mass index (BMI) in Yunnan, 2013–2015

	BMI category, kg/m^2			
	Underweight <18.5	Normal 18.5–24.0	Overweight or obese ≥24.0	Overall
Characteristics	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Total	2042 (7.9)	16 009 (61.5)	7971 (30.6)	26 022 (100.0)
Sex				
Male	838 (41.0)	7245 (45.3)	4313 (54.1)	12 396 (47.6)
Female	1204 (59.0)	8764 (54.7)	3658 (45.9)	13 626 (52.4)
Age (years)				
Mean (SD)	38.9 (21.4)	44.4 (17.1)	48.5 (14.7)	45.2 (17.0)
<65	1693 (82.9)	13 771 (86.0)	6765 (84.9)	22 229 (85.4)
≥65	349 (17.1)	2238 (14.0)	1206 (15.1)	3793 (14.6)
Ethnicity				
Han	1867 (91.4)	14 804 (92.5)	7436 (93.3)	24 107 (92.6)
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)
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)	15 126 (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)	11 638 (72.7)	6538 (82.0)	19 262 (74.0)
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)	12 975 (49.9)
Above the median	970 (47.5)	7948 (49.6)	4129 (51.8)	13 047 (50.1)
Previously treated TB				
No	2019 (98.9)	15 929 (99.5)	7936 (99.6)	25 884 (99.5)
Yes	23 (1.1)	80 (0.5)	35 (0.4)	138 (0.5)
Close contacts				
No	2039 (99.9)	15 990 (99.9)	7960 (99.9)	25 989 (99.9)
Yes	3 (0.1)	19 (0.1)	11 (0.1)	33 (0.1)
Known HIV/AIDS				
No	2040 (99.9)	15 995 (99.9)	7966 (99.9)	26 001 (99.9)
Yes	2 (0.1)	14 (0.1)	5 (0.1)	21 (0.1)
Known diabetes				
No	2021 (99.0)	15 693 (98.0)	7669 (96.2)	25 383 (97.5)
Yes	21 (1.0)	316 (2.0)	302 (3.8)	639 (2.5)
Chronic bronchitis				
No	1938 (94.9)	15 334 (95.8)	7565 (94.9)	24 837 (95.4)
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				
No	2032 (99.5)	15 978 (99.8)	7945 (99.7)	25 955 (99.7)

Continued

Table 1 Continued

Characteristics	BMI category, kg/m²			
	Underweight <18.5	Normal 18.5–24.0	Overweight or obese ≥24.0	Overall
	n (%)	n (%)	n (%)	n (%)
Yes	10 (0.5)	31 (0.2)	26 (0.3)	67 (0.3)
Smoking status				
Never	1689 (82.7)	12 178 (76.1)	5441 (68.3)	19 308 (74.2)
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				
Never	1778 (87.1)	12 884 (80.5)	5870 (73.6)	20 532 (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				
Yes	1265 (61.9)	9466 (59.1)	4570 (57.3)	15 301 (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)

TB, tuberculosis.

Outcomes

The incidence of TB and time-to-incident were defined as the study outcome. Participants followed up to December 2015, death, moving out of the study field, or refusing to participate in the second or third round screening were defined as censored data.

The TB diagnostic process followed the China National Tuberculosis Programme. The TB diagnostic algorithm was: after a home visit by CHWs, TB symptoms positivity was defined as suspects, then suspects underwent chest X-ray (CXR) and health examination. Conventionally, those with abnormal radiographs get sputum smear test (three sputum samples) for laboratory diagnosis. Patients with a smear acid-fast bacilli positivity were diagnosed with laboratory-confirmed TB. People with abnormal radiographs and negative smears, whose CXRs were reviewed by the diagnostic committee, were defined as clinically diagnosed TB.

Statistical analyses

We described the cohort characteristics by the proportions in BMI categories. We computed the person-years and TB IR in all participants by BMI level and other covariates. The IR ratio and 95% CI were calculated to compare the incidence between groups.

We applied the Kaplan-Meier analysis and log-rank test to compare the cumulative hazard of time to TB incidence in three BMI levels. Denary logarithm-transferred TB incidence was regressed with the averaged BMI in six groups (BMI <18.5, 18.5–20.4, 20.5–22.4, 22.5–23.9, 24–27.9 and ≥28 kg/m²), then the determination coefficient R^2 and adjusted R^2 were used to evaluate the model.

We used stepwise multivariate Cox proportional hazard regression models to estimate the HR and the corresponding 95% CI of factors; normal weight of BMI was set as the reference level. We corrected the effect of DM by introducing it as a covariate in a different COX regression. We performed the linear trend test for BMI by including the ordinal BMI in the multivariate model. We examined the dose–response association between continuous BMI and predicted linear cumulative hazard of TB, overall and risk subgroups. The potential non-linear association was evaluated by the restricted cubic spline (RCS) regression. RCS knots were fixed as the continuous BMI quartiles (25%, 50% and 75%). The association between BMI and TB development was evaluated in stratifications of gender and age by adjusting the confounders.

The study complied with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.[14]

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

Patient and public involvement

There was no patient or public involvement.

RESULTS

Population characteristics and follow-up of the cohort

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

Table 2 Follow-up and the tuberculosis (TB) incidence by associated factors in the cohort in Yunnan, 2013–2015

Characteristics	Number of participants in cohort n (%)	Person-years	Number of cases n	Incidence rate (per 100 000) (95% CI)	Incidence rate ratio (95% CI)	P value*
All	26 022 (100.0)	44 574.4	43	96.5 (69.8 to 129.9)		
Sex						
Male	12 396 (47.6)	21 231.7	26	122.5 (80.0 to 179.4)	Ref	
Female	13 626 (52.4)	23 342.7	17	72.8 (42.4 to 116.6)	0.59 (0.31 to 1.12)	0.11
Age (years)						
<65	22 229 (85.4)	39 227.5	13	33.1 (17.6 to 56.7)		
≥65	3793 (14.6)	5346.9	30	561.1 (378.6 to 801.0)	17.41 (8.70 to 34.83)	<0.01
Ethnicity						
Han	24 107 (92.6)	41 304.6	36	87.2 (61.0 to 120.7)	Ref	
Other minority	1915 (7.4)	3269.8	7	214.1 (86.1 to 441.1)	2.27 (0.94 to 5.50)	0.07
Education level						
Illiterate or semi-illiterate	2048 (7.9)	3134	14	446.7 (244.2 to 749.5)	Ref	
Primary school	4671 (18.0)	7686.4	13	169.1 (90.1 to 289.2)	0.38 (0.17 to 0.85)	0.02
Secondary school	15 126 (58.1)	26 416.3	13	49.2 (26.2 to 84.2)	0.11 (0.05 to 0.25)	<0.01
College and above	4123 (15.8)	7248.5	3	41.4 (8.5 to 121.0)	0.08 (0.02 to 0.32)	<0.01
Unknown	54 (0.2)	89.2	0	0 (0.0 to 4133.7)	–	
Marital status						
Married	19 262 (74.0)	33 163.6	26	78.4 (51.2 to 114.9)	Ref	
Single	4179 (16.1)	7280.2	3	41.2 (8.5 to 120.4)	0.42 (0.10 to 1.67)	0.22
Widowed/divorced/ separated/other	2581 (9.9)	4130.7	14	338.9 (185.3 to 568.7)	4.23 (2.12 to 8.45)	<0.01
Family annual income per capita (median=7200 RMB)						
Below the median	12 975 (49.9)	22 547.9	20	88.7 (54.2 to 137.0)	Ref	
Above the median	13 047 (50.1)	22 026.5	23	104.4 (66.2 to 156.7)	1.18 (0.63 to 2.23)	0.6
Previously treated TB						
No	25 884 (99.5)	44 368.3	38	85.6 (60.6 to 117.6)		
Yes	138 (0.5)	206.2	5	2425.3 (787.5 to 5659.8)	25.01 (8.84 to 70.78)	<0.01
Close contacts						
No	25 989 (99.9)	44 518.7	43	96.6 (70.1 to 130.5)		
Yes	33 (0.1)	55.7	0	0 (0.0 to 6624.0)	–	
Known HIV/AIDS						
No	26 001 (99.9)	44 547.2	43	96.5 (69.9 to 130.0)		
Yes	21 (0.1)	27.3	0	0 (0.0 to 13 532.2)	–	
Known diabetes						
No	25 383 (97.5)	43 657.4	41	93.9 (67.4 to 127.4)	Ref	
Yes	639 (2.5)	917.1	2	218.1 (26.4 to 787.8)	1.56 (0.28 to 8.76)	0.62
Chronic bronchitis						
No	24 837 (95.4)	42 653.9	41	96.1 (69.0 to 130.4)	Ref	
Yes	919 (3.5)	1455.1	2	137.4 (16.6 to 496.5)	0.96 (0.17 to 5.39)	0.96
Unknown	266 (1.0)	465.4	0	0 (0.0 to 792.6)	–	
Pneumoconiosis						
No	25 955 (99.7)	44 475.3	42	94.4 (68.1 to 127.6)	Ref	
Yes	67 (0.3)	99.1	1	1009.2 (25.6 to 5622.8)	4.07 (0.27 to 61.44)	0.31
Smoking status						
Never	19 308 (74.2)	32 995.7	28	84.9 (56.4 to 122.6)	Ref	

Continued

Table 2 Continued

Characteristics	Number of participants in cohort n (%)	Person-years	Number of cases n	Incidence rate (per 100 000) (95% CI)	Incidence rate ratio (95% CI)	P value*
Former	822 (3.2)	1318.3	1	75.9 (1.9 to 422.7)	0.34 (0.02 to 5.23)	0.44
Current	5892 (22.6)	10260.4	14	136.4 (74.6 to 228.9)	1.57 (0.79 to 3.11)	0.19
Alcohol use						
Never	20532 (78.9)	35082	27	77 (50.7 to 112.0)	Ref	
Former	1066 (4.1)	1772.5	5	282.1 (91.6 to 658.3)	3.26 (1.13 to 9.43)	0.03
Current	4424 (17.0)	7719.9	11	142.5 (71.1 to 255.0)	1.79 (0.84 to 3.79)	0.13
BCG scar						
Yes	15301 (58.8)	26975.3	11	40.8 (20.4 to 73.0)	Ref	
No	9127 (35.1)	14772.3	29	196.3 (131.5 to 281.9)	5 (2.38 to 10.51)	<0.01
Unknown	1594 (6.1)	2826.8	3	106.1 (21.9 to 310.1)	2.14 (0.49 to 9.31)	0.31

*Incidence rate ratio comparison between groups.

The follow-up time of the cohort was 2.25 years (27 months) in three rounds of screening. Overall, 43 cases developed TB in the observed 44 574.4 person-years. Hence, the TB incidence was 96.5 per 100 000 person-years (95% CI 69.8 to 129.9). The median time-to-incident was 1.64 years (20 months). TB incidence was significantly higher among those aged over 65 years compared with under 65 years (p<0.01), lower education level compared with higher education level (p<0.01), widowed/divorced/separated/other compared with married (p<0.01), previously treated TB compared with no previous TB (p<0.01), former drinker compared with no drinking people (p=0.03), and people without BCG scar compared with those with scar (p<0.01, table 2).

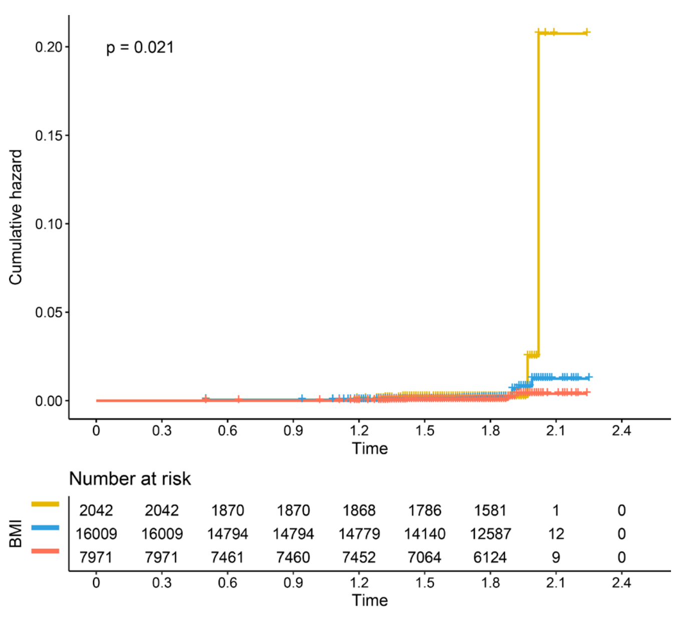

Figure 2 Kaplan-Meier plot of cumulative hazard of tuberculosis by body mass index (BMI) in Yunnan, 2013–2015. The yellow line (underweight) represents lower BMI (<18.5 kg/m^2), the blue line (normal) represents the BMI between 18.5 and 24 kg/m^2, orange line (overweight) represents BMI over 24 kg/m^2. The time to events or censor was defined by years.

Dose–response relationship of BMI and TB incidence

The Kaplan-Meier univariate analysis showed that the cumulative hazard of developing TB was different in BMI levels (p=0.021). Lower BMI had a shorter time of developing TB (figure 2).

The IRs of TB were 173.2 (95% CI 63.6 to 376.9), 113.2 (95% CI 76.9 to 160.7), and 43.7 (95% CI 16.0 to 95.1) per 100 000 person-years in the underweight, normal-weight, and overweight or obese groups, respectively (table 3).

An inverse logarithmic-linear dose–response relationship between BMI and TB incidence was fitted. Logarithmic-transferred TB incidence was regressed with linear BMI change (R^2=0.81, adjusted R^2=0.76). In the BMI range between 17.5 and 30.1 kg/m^2, the slope and intercept of the trend line corresponded to a 7.91% reduction in TB incidence with each 1-unit BMI increment (figure 3).

Dose–response relationship of BMI and TB risk

The multivariable Cox proportional regression presented overweight or obese associated with a lower incident TB hazard than normal weight (adjusted HR (aHR) 0.34, 95% CI 0.14 to 0.82, p<0.01). Underweight related to a higher hazard but statistically insignificant (aHR 1.26, 95% CI 0.52 to 3.06, p=0.60). The BMI linear trend was significant. Accompanied by BMI level upgraded, TB hazard reduced, 48% (aHR 0.52, 95% CI 0.31 to 0.85, p<0.01). After the correction for DM status, the association between BMI and TB risk was unchanged (table 3).

RCS regressions were fitted to present the negative relationship between continuous BMI and individual linear cumulative hazards of TB (figures 4 and 5). The pooled

Table 3 Body mass index (BMI) and risks of tuberculosis (TB) in the cohort in Yunnan, 2013–2015

	BMI category, kg/m²		
	Underweight	Normal	Overweight or obese
	<18.5	18.5–24.0	≥24.0
Mean (95% CI), kg/m²	17.5 (17.4 to 17.5)	21.4 (21.3 to 21.4)	26.3 (26.2 to 26.3)
Person-years	3464.8	27 382	13 727.7
Number of cases	6	31	6
Incidence rate (per 100 000, 95% CI)	173.2 (63.6 to 376.9)	113.2 (76.9 to 160.7)	43.7 (16.0 to 95.1)
Incidence rate ratio (95% CI)	1.39 (0.53 to 3.65)	Ref	0.35* (0.13 to 0.92)
cHR (95% CI)	1.55 (0.65 to 3.71)	Ref	0.36* (0.15 to 0.87)
Age-adjusted HR (95% CI)*	1.26 (0.52 to 3.03)	Ref	0.34* (0.14 to 0.82)
Multivariable-adjusted HR (95% CI)†	1.26 (0.52 to 3.06)	Ref	0.34* (0.14 to 0.82)
Corrected with DM HR (95% CI)‡	1.25 (0.52 to 3.04)	Ref	0.34* (0.14 to 0.83)

*P<0.01.
*Category with age 65 years.
†Adjusted with covariates: age, sex, ethnicity, marital status, previous treated TB, smoking status, alcohol use, all variables were adjusted as categorical variable.
‡Adjusted with covariates: age, sex, ethnicity, marital status, previously treated TB, smoking status, alcohol use and known diabetes; all variables were adjusted as categorical variables.
cHR, crude HR; DM, diabetes mellitus.

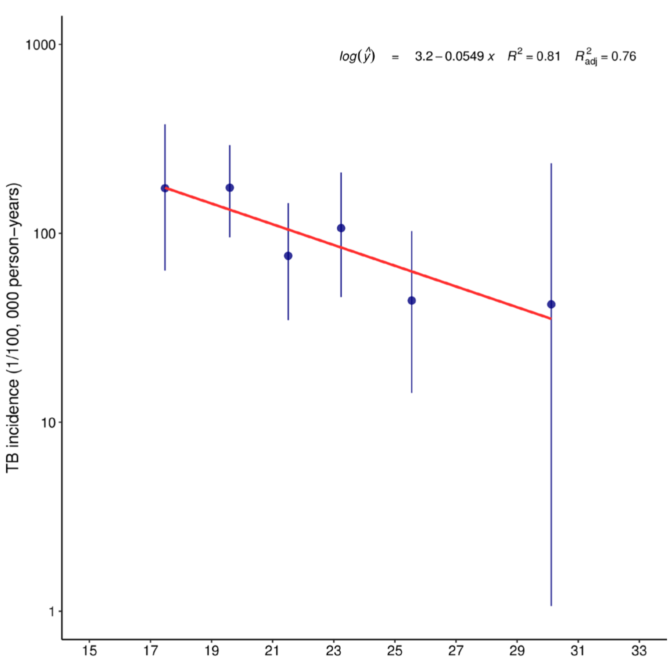

Figure 3 Dose–response relationship of the association between body mass index (BMI) and the incidence of tuberculosis (TB) in Yunnan, 2013–2015. TB incidence was transformed by denary logarithm, then regressed with the mean BMI in six categories. Blue points and ranges represent the TB incidence and 95% CI by the averaged BMI in six categories (averaged BMI: 17.5, 19.6, 21.5, 23.2, 25.5 and 30.1 kg/m² in BMI <18.5, 18.5–20.4, 20.5–22.4, 22.5–23.9, 24–27.9, ≥28 kg/m² groups, respectively); the red line represents the log-linear dose–response relationship between BMI and TB incidence.

or stratified risks of TB were approximated negative log-linear associated with BMI.

Subgroup analysis according to gender and age

TB incidence was inversely related to BMI among men (table 4). The risk of TB showed a 78% reduction in overweight or obese (aHR 0.22, 95% CI 0.05 to 0.97, p=0.05) compared with normal-weight women. While stratified by age under or above 65 years, TB incidence was inversely related to BMI in both groups. The hazard of TB presented a 64% reduction in overweight or obese (aHR 0.36 95% CI 0.12 to 1.00, p=0.05) compared with normal weight among the elderly.

DISCUSSION

This prospective population-based cohort study estimated the inverse log-linear dose–response association of BMI and TB incidence in Chinese adults. The cohort study clarified BMI had a strong association with TB development. There was two-thirds reduction of disease risk for overweight or obese compared with the normal-weight population; likewise, the protective effect was presented in a subpopulation of women and the elderly. Additionally, consistent inverse relationships were precisely illustrated between continuous BMI and individual risk of TB.

The strengths of our research were that this population-based prospective study included a large number of community participants in the southwestern mountainous region of China. The study presented TB incidence under a high disease burden setting in Chinese adults. Moreover, this well-designed cohort study provided evidence

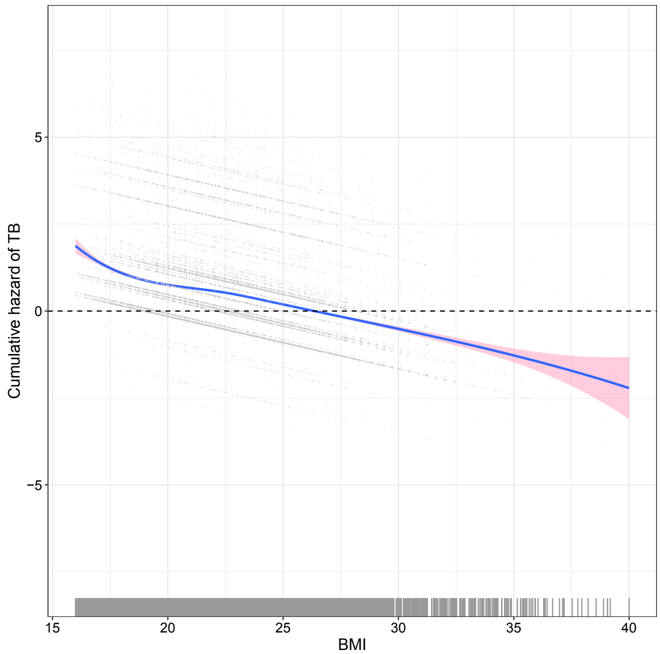

Figure 4 Dose–response curves for the body mass index (BMI) and cumulative hazard of tuberculosis (TB) in Yunnan, 2013–2015. The blue line and pink area represent the non-linear relationship (95% CI) of predicted log-linear cumulative hazard of TB and BMI using the restricted cubic spline regression, the spline knots of BMI were the quartiles (25%, 50% and 75%) of the continuous variable. The grey line on x-axis indicated the continuous BMI value, the grey dots indicated the predicted log-linear cumulative hazards. 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.

of log-linear inverse dose–response relationship between BMI and TB incidence in population level, also the dose–response association between BMI and individual risk. Furthermore, the overall and stratified analyses were performed after adjusting confounders. The protective effect of the higher BMI, presented in the general population, subgroups of women and the elderly might contribute to TB control policy.

However, there were a few limitations to the study. First, the limited funding and resource led to only 2 years' follow-up and conducting three rounds of screening. So we could not observe all TB incidence in an extended period. Second, the cohort DM prevalence (2.5%) was lower than 9.7% in China and 6.7% in Yunnan around 2010; thus, the study failed to analyse the modified effect of DM on BMI, and was insufficient to identify the interaction and mediation between BMI, DM and TB. Third, the BMI was measured at a single point in the baseline. BMI could change over time, and the dynamic BMI might influence TB in the follow-up. Furthermore, several covariates were self-reported by participants, such as smoking and drinking habits; therefore, the association would be imprecise without accurate measurement. Other limitations included a small sample size for some subpopulations, and the low prevalence of comorbidities in the baseline led to the insignificant association. The false-negative and underestimation of TB diagnosis would occur due to not using CT and culture in limited-resource settings. The food intake and dietary information was absent in the baseline survey; therefore, we could not quantify the energy–BMI–TB interaction here. Further studies are needed to better understand the role of BMI in the occurrence of TB.

The finding of the log-linear inverse association between BMI and TB incidence was consistent with a previous systemic review.[4] Five out of six cohort studies included in the systemic review were performed in the last century, while all six studies were carried out in high-income countries. Likewise, population-based cohorts reported by Cegielski *et al* in the USA[15] and Pealing *et al* in the UK[16] stated the inverse association in low disease burden and high-income settings. Our study was implemented in the high burden site and middle-income country, though the inverse association remained unchanged.

Most recently, observational studies reported low BMI related to TB development. In researches of cross-sectional prevalence investigation and follow-up cohort among those aged over 65 years in China, Zhang *et al* and Cheng *et al*[8 17] reported the significant higher risk (OR 1.55, 95% CI 1.09 to 2.22) or hazard (HR 2.33, 95% CI 1.32 to 4.12) of TB in the underweight group compared with the normal-weight group. However, our study reported an insignificant association for underweight in the general adult and subpopulation. This discrepancy might be explained by the differential distribution of baseline demographic and socioeconomic factors. In addition, the previous cohort in the elderly reported a large proportion of loss to follow-up, which might overestimate the risk of underweight among the elderly.

Moreover, the evidence presented that overweight or obesity was associated with low risk of TB. All these researches presented the identical direction of the association. Yen *et al*[18] reported that in a Taiwan cohort, compared with the normal-weight group, overweight (OR 0.67, 95% CI 0.49 to 0.91) and obesity (OR 0.43, 95% CI 028 to 0.67) were protective factors to disease incidence. Kim *et al*[19] reported a consistent inverse association between BMI and TB. The follow-up research presented that overweight (HR 0.45, 95% CI 0.40 to 0.50) and obesity (HR 0.40, 95% CI 0.30 to 0.54) were protective predictors. Although the cut-off points for BMI and the definition for overweight or obesity differed across study sites and countries, various studies showed a slight difference in HR or risk ratio (RR) for TB development. These unanimous conclusions of the systemic review and multipopulation observational studies showed strong and constant evidence of the inverse association between BMI and TB incidence.

The highlight of the present study was that it provided specific evidence of a quantified dose–response relationship between BMI and the disease incidence and the individual risk of TB progression. Under the high burden of

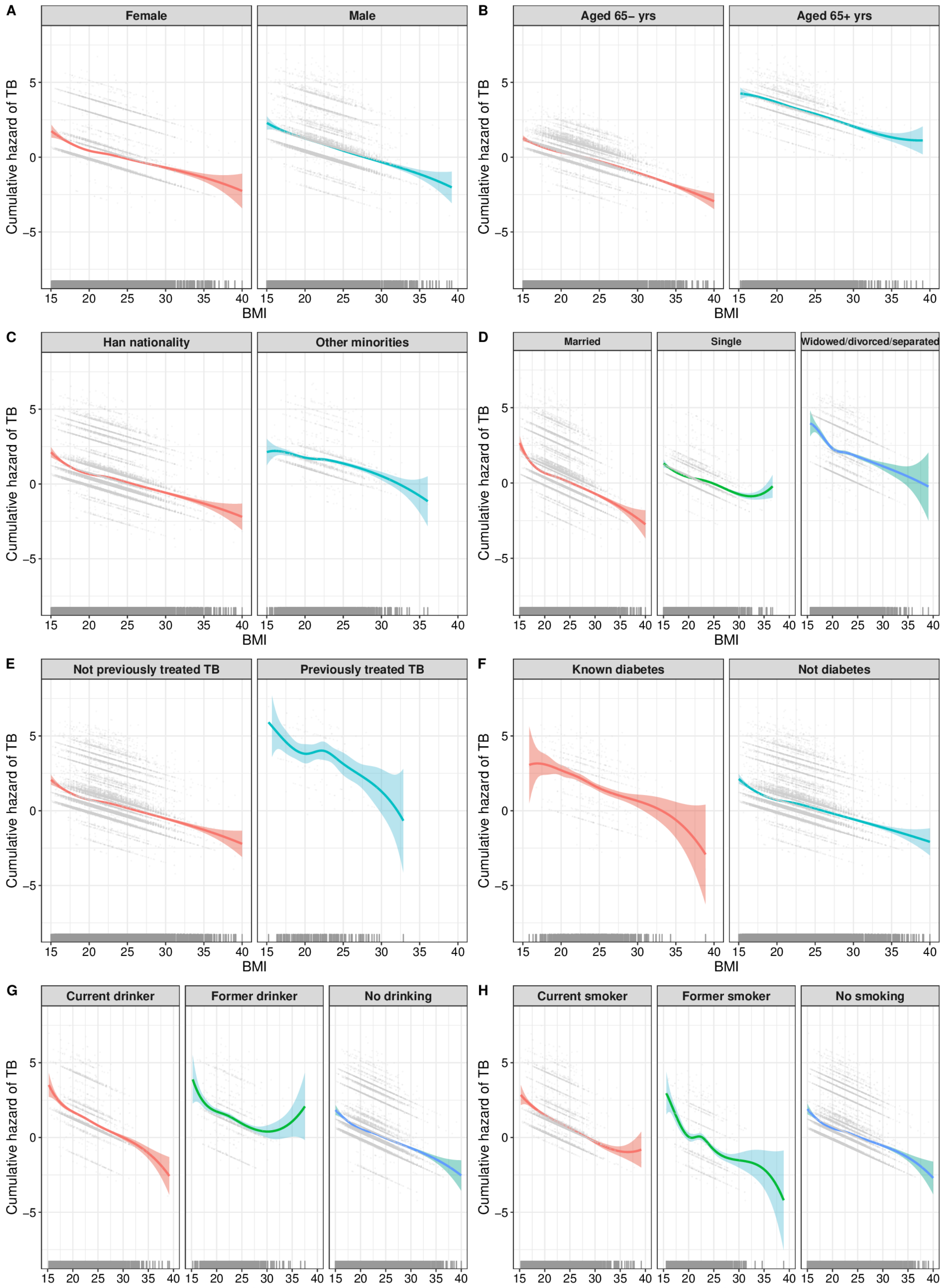

Figure 5 Dose–response curves for the body mass index (BMI) and cumulative hazard of tuberculosis (TB) stratified by predictors in Yunnan, 2013–2015. Panels represent different categories of predictors in the model and its non-linear relationship between predicted log-linear cumulative hazard of TB and BMI using the restricted cubic spline regression, the spline knots of BMI were the quartiles (25%, 50% and 75%) of the continuous variable. The grey line on x-axis indicated the continuous BMI value, the grey dots indicated the predicted log-linear cumulative hazards. 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.

Table 4 Subgroup analysis for the association between body mass index (BMI) and risks of tuberculosis (TB) in the cohort in Yunnan, 2013–2015

Covariates	BMI groups	Person-years	Number of cases n	Incidence rate (95% CI)	aHR (95% CI)	P value
Sex*						
Male	Underweight	1408.3	5	355 (115.3 to 828.6)	1.69 (0.59 to 4.82)	0.33
	Normal	12 370.7	17	137.4 (80.1 to 220.0)	Ref	
	Overweight	7452.7	4	53.7 (14.6 to 137.4)	0.44 (0.15 to 1.31)	0.14
Female	Underweight	2056.5	1	48.6 (1.2 to 270.9)	0.38 (0.05 to 2.93)	0.35
	Normal	15 011.2	14	93.3 (51.0 to 156.5)	Ref	
	Overweight	6274.9	2	31.9 (3.9 to 115.1)	0.22 (0.05 to 0.97)	0.05
Age (years)†						
<65	Underweight	2981.1	2	67.1 (8.1 to 242.3)	1.79 (0.37 to 8.65)	0.47
	Normal	24 229.7	9	37.1 (17.0 to 70.5)	Ref	
	Overweight	12 016.6	2	16.6 (2.0 to 60.1)	0.42 (0.09 to 2.00)	0.28
≥65	Underweight	483.7	4	827 (225.3 to 2117.6)	1.2 (0.41 to 3.54)	0.74
	Normal	3152.3	22	697.9 (437.4 to 1056.7)	Ref	
	Overweight	1711	4	233.8 (63.7 to 598.6)	0.36 (0.12 to 1.00)	0.05

*Adjusted with covariates: age, ethnicity, marital status, previously treated TB, smoking status, alcohol use; all variables were adjusted as categorical variables.
†Adjusted with covariates: sex, ethnicity, marital status, previously treated TB, smoking status, alcohol use; all variables were adjusted as categorical variables.
aHR, adjusted HR.

96.5 per 100 000 person-years settings, the logarithmic TB incidence decreased responding to the linear increment of BMI. The results suggested that the tiny improvement of the population's nutrition status would have a remarkable public health impact. The nutritional advancement could significantly decrease the TB incidence, especially among vulnerable undernourished populations with BMI under 18.5 kg/m^2 in low/middle-income countries. The study also implied that the increment of primary exposure of BMI might play a crucial role in the overall 28% decline of TB prevalence between 1990 and 2010 in China.[2]

Another contribution of this study was that the results might support using a lower BMI cut-off point in China. The study better understood the logarithmic-predicted individual TB risk decline with BMI linear increment. The BMI value of 22.5 kg/m^2 was on the log-linear x-axis (with slope and intercept of zero), corresponding to an exponential hazard of 1. It implied the cut-off point of BMI on TB hazard was 22.5 kg/m^2. This value was the threshold of the hazardous-protective effect on TB progression among the general community population. The potential benefit of this novel insight was this cut-off value implemented in the TB active case finding screening. Thus, a screening strategy could yield if the BMI under 22.5 kg/m^2 was set to the targeted population.[12 20] Notwithstanding this, discussions about the universal BMI category were inappropriate. Morbidity-specific, mortality-specific and population-specific BMI categorisations were reasonable.[21] Many studies confirmed a lower BMI cut-off point for Chinese adults to define overweight or obese while considering comorbidities, prognosis or subpopulation.[22–25] However, the generalisation of this finding should be treated with caution because the cohort sample was unrepresentative for other regions; more evidence was needed to confirm the cut-off value of BMI and the yield of screening.

DM was a well-known risk factor for TB; BMI also had a solid relation to DM. Although the association between known DM and TB was not significant in the present study, the relationship of BMI and TB remains unchanged after including DM status. A systematic review of three cohorts examined DM associated with an increased risk of TB (RR 3.11, 95% CI 2.27 to 4.26).[26] Kuo *et al*[27] reported DM significantly increased 31% TB risk (HR 1.31, 95% CI 1.23 to 1.39). Lee *et al*[28] revealed patients with DM with poor glycaemic control had a higher hazard of TB (HR 2.21, 95% CI 1.63 to 2.99). Lin *et al*[29] stated causal mediation between BMI, DM and TB. A feasible explanation for this argument and inconsistency was that the prevalence of DM in the present cohort was 2.5%, which was substantially lower than 9.7% of diabetes prevalence among Chinese adults.[30] The data and evidence were insufficient to show the BMI–DM interaction during the short-term observation in this study.

The biological mechanism of BMI's effect on TB incidence was complicated. Population's nutrition status was characterised mainly by the indicator of BMI. Nutrition, immune function and infection were complexly related to dynamic interaction patterns. Malnutrition was linked to disabling the cell-mediated immunity (CMI) system, which profoundly affected the host defence against *Mycobacterium tuberculosis*, resulting in TB infection or immunity. Malnourished mice caused chronic protein-energy malnutrition (PEM) and suffered a higher bacterial burden while the efficacy of BCG vaccination was reduced.[31] A review stated that PEM impairs CMI and worsens the infections; conversely, the infection could lead to rapid weight loss, malnutrition and immunological dysfunction. Moreover, PEM was partly due to food deprivation.[32] Thus, the direction and interaction of the causal relationship between malnutrition and TB are still scarcely understood. Many unknown variables affect the relationship. The biological explanation and mechanism of lower TB risk in obese or overweight individuals might be due to an increased capacity to have access to high-energy dense foods. The above PEM–CMI–infections negative feedback loop was interrupted, leading to high host defence against *M. tuberculosis* and less the probability of infection. Another possible interpretation was that the difference in genetic susceptibility of obesity among hosts led to the association. Obesity-associated gene *FTO* (fat mass and obesity associated, Gene ID: 79068) and its genetic polymorphisms rs9939609, rs8050136 within the *FTO* were associated with obesity. The significant association between genetic polymorphism rs9939609 and TB risk was presented. By comparing with the common genotype TT, individuals carrying AA had a higher TB risk (OR 3.77, 95% CI 2.26 to 6.28).[33]

CONCLUSION

Collectively, the study suggested the inverse log-linear dose–response relationship between BMI and TB incidence; likewise, it implied the inverse association between BMI and the risk of individual TB development in Chinese adults. Overweight or obesity was negatively associated with TB development in the general population and subgroups of women and the elderly. The study provided evidence that recent TB incidence decline could be partially attributed to the dramatic changes of BMI in China. The finding suggested an implication for policymakers: the active TB case finding strategy in the community population should prioritise the individuals with BMI lower than 22.5 kg/m^2. Moreover, it implied moderate improvement of BMI in high TB burden area would impact TB incidence.

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Contributors 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. LX is responsible for the overall content as guarantor. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Ethics approval This study involves human participants and 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 enrol and participate in this study. The study did not include personal identification and all data in the analyses were anonymised.

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Data availability statement Data are available upon reasonable request. All data relevant to the study are included in the article or uploaded as supplemental information. All relevant data in this study are freely available in the manuscript as submitted and are included in summary tables and the Results section of the manuscript. The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

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