

## Original Article

# Increased meat consumption is associated with reduced tuberculosis treatment failure rate: A cohort study

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**Background and Objectives:** Information regarding the relationship between dietary meat intake and tuberculosis treatment outcomes among patients with tuberculosis is still limited. The aim of the present study was to investigate the relationship between meat consumption and tuberculosis treatment outcomes in patients with pulmonary tuberculosis. **Methods and Study Design:** A pulmonary tuberculosis cohort study including 2,261 patients with pulmonary tuberculosis was conducted in Linyi, Shandong Province, China from 2009 to 2013. Dietary data were collected using a semi-quantitative food frequency questionnaire. Treatment outcomes were assessed using a combination of sputum smear microscopy and chest computerized tomography. **Results:** In a multiple adjusted model, the higher quartile of total meat (OR=0.59, 95% CI, 0.38–0.91) was associated with a decreased failure rate of pulmonary tuberculosis treatment. In addition, higher consumption of chicken (OR=0.62; 95% CI, 0.44–0.87) and pork (OR=0.54; 95% CI, 0.31–0.95) was associated with a lower failure rate of tuberculosis treatment. **Conclusions:** Increased dietary intake of total meat, pork, and chicken are associated with a decreased failure rate of pulmonary tuberculosis treatment. A higher dietary meat intake may be beneficial in pulmonary tuberculosis treatment.

**Key Words:** tuberculosis (TB), meat, diet, food frequency questionnaire, China

## INTRODUCTION

Tuberculosis (TB) is an infectious respiratory disease caused by *Mycobacterium tuberculosis* (*M.tb*) and remains one of the top 10 causes of death worldwide. The WHO reported that there were 10 million new TB cases and 1.5 million deaths in 2019. The majority of these cases were concentrated in India and China.<sup>1</sup>

Several studies have indicated that TB and undernutrition interact in a two-way process.<sup>2-4</sup> Patients with TB are often malnourished, which usually manifests as protein energy malnutrition and micronutrient deficiencies. Severe malnutrition can further impair immune function, causing decreased total lymphocyte count and CD4/CD8 ratio and reducing the secretion of interleukin 2 and interferon gamma.<sup>4-6</sup> Diminished immune function increases susceptibility to *M.tb*, predisposing people to TB. The nutritional supplementation of patients with TB was demonstrated to increase weight and body mass index (BMI) as well as reduce mortality.<sup>5</sup> Several randomized controlled trials have indicated that dietary protein intake can improve the physical function and life quality of patients with pulmonary TB (PTB).<sup>7-9</sup> Additionally, micronutrient deficiency affects the effectiveness of TB treatment by delaying the elimination of bacilli from sputum in patients with PTB or decreasing the phagocytic activity of human macrophages.<sup>10-12</sup> Good nutritional status is essential for positive outcomes from TB treatment.<sup>13-16</sup>

Meat is a significant part of most people's the diet and

a crucial source of various nutrients, including high-quality animal protein, essential fatty acids, and various micronutrients.<sup>17,18</sup> According to the color of meat before it is cooked (red or white), meat is usually divided into red and white meat, which usually refers to livestock (e.g., lamb, beef, and pork) and poultry (e.g., chicken, duck, and goose), respectively.<sup>19</sup> White meat contains micronutrients, such as vitamin A, zinc, and iron, whereas red meat provides high-quality nutrients, such as zinc, iron, vitamins B-6 and B-12, and protein.<sup>19,20</sup> Meat may contribute to improving TB treatment by modulating immune response and increasing the intake of high-quality animal protein.<sup>10,18</sup> However, relevant studies have mainly focused on protein or the role of a single nutrient in supplementation for TB treatment.<sup>21,22</sup> The associations between meat consumption and TB treatment failure rate have received less attention and remain inconclusive in this regard. This study investigated the relationship be-

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tween meat intake and treatment outcomes among patients with TB.

## METHODS

### *Ethics*

The study was approved by the Medical Ethics Committee of Qingdao Municipal Center for Disease Control and Prevention and it complied with the Declaration of Helsinki. The study was registered in the Chinese Clinical Trial Registry (ChiCTR-OCC-10000994). Informed consent was obtained from all participants.

### *Study design and population*

This population-based pulmonary TB cohort study was conducted between 2009 and 2013 in Linyi, Shandong Province, China, and participants were recruited from local TB clinics.

The inclusion criteria were as follows, patients who: (1) were newly diagnosed with PTB (according to the Chinese national guidelines on TB prevention and control,<sup>23</sup> PTB diagnoses were mainly based on sputum smear examination combined with comprehensive analysis of chest images and clinical signs), (2) adults (age  $\geq 18$  years), and (3) had agreed to sign the consent form. The exclusion criteria were as follows: patients with (1) extrapulmonary TB or drug-resistant TB; (2) serious liver or kidney diseases, congestive heart failure, skeletal diseases, acquired immunodeficiency syndrome, or malignant tumors; (3) cognitive dysfunction or mental disorders; or (4) diseases that impair eating.

### *Interpretation of treatment options and outcomes*

The treatment regimen was selected on the basis of the recommendations of the Chinese national guidelines on TB prevention and control.<sup>23</sup> All confirmed TB cases received a 6-month standardized regimen in two phases: a 2-month reinforcement phase and a 4-month consolidation phase. Isoniazid, rifampicin, ethambutol, and pyrazinamide were given in the intensive phase, whereas ethambutol and pyrazinamide were withdrawn during the continuation phase. Patients were hospitalized for treatment in the first month after diagnosis, and discharged patients received periodic review. Patients usually bought meals that were typical for their dietary habits during treatment. According to the aforementioned national guidelines and the revised TB treatment definitions and reporting framework organized by the WHO, the treatment was considered successful if the patient was cured or completed the prescribed course. The criteria for cured TB were as follows: the results of two consecutive sputum smears in a positive patient found negative in sputum smear microscopy, one of which should be obtained at the end of treatment, and no active lesions detected by computed tomography scan.<sup>23,24</sup> Failed treatment referred to a positive sputum smear test for smear-positive PTB patients at the end of the 6-month treatment period or a positive sputum smear test of smear-negative PTB patients during the treatment process.

### *Biochemical measurements and covariates*

A mercury sphygmomanometer and standard stethoscope were used to measure the blood pressure of each patient.

Blood samples were taken by cubital venipuncture between 8 and 10 Am after 10–12 h of fasting. A fully automatic biochemical analyzer was used to detect the contents of hemoglobin, triglycerides, total cholesterol and aspartate aminotransferase (AST) in each patient. Weight and height were measured by our project members. Next, body mass index (BMI, kg/m<sup>2</sup>) was calculated; BMI thresholds of  $<18.5$ , 18.5–23.9, and  $\geq 24$  represented the underweight, normal weight, and overweight and obese Chinese population, respectively.<sup>25</sup> Participants were interviewed by trained staff using a standardized face-to-face questionnaire.

Patients self-reported information on their gender, age, educational level, marital status (single, married, widowed, or divorced), occupation, and patients' behavioral habits (including smoking, drinking, and regular exercise). Educational level was presented in five categories: none, primary school, junior high school, senior high school, and college diploma or higher.

### *Dietary assessment*

After the patients completed 2 months of intensive therapy, the researchers asked them about their dietary intake over the 2-month period. On the base of the 2002 national health and dietary survey, a semi-quantitative food frequency questionnaire (FFQ) was used for assessing patients and asking them about their diet.<sup>26</sup> The FFQ enquired about five meat items. The red meat items included beef, pork and lamb,<sup>27</sup> and the white meat items mainly included chicken and duck. A standard serving size for each item was first determined, which was used as a basis for confirming the intake of each item. The frequency of meat intake was classified as follows: never/rarely, 1–2 times per month, once per week, 2–3 times per week, 4–5 times per week, once per day, and 2–3 times per day. The frequency of food intake was transformed into daily levels, and the amount of each food consumed (grams/day) was calculated through multiplication of the daily frequency by the portion sizes. Food models, pictures, and related tools (e.g., bowls and plates) served as visual aids, which helped participants to accurately recall and estimate food portion sizes and facilitated the surveyors in checking and evaluating food portions.

### *Statistical analysis*

SPSS version 22.0 was used for statistical analysis. Quantitative data that did not conform to a normal distribution were described using median and interquartile range. Frequencies and percentages were used to describe using the distributions of categorical variables. The Mann–Whitney U test and a chi-squared test were used for quantitative and qualitative variables, respectively, to compare distributions of demographics, behavioral factors, and other characteristics between the two groups. Intakes of total meat, red meat, and white meat were categorized into quartiles according to the distribution in the study population, and the lowest consumption category was used as a reference.

A binary logistic regression model was established to appraise the associations between total meat, specific types of meats, and the failure rate of TB treatment. A basic model (crude model) was unadjusted, whereas

model 1 was only adjusted for age and sex. In model 2, three variables (marital status, education, and BMI) were considered confounding factors, which exhibited a statistical difference between the two groups in the univariate analysis. Studies have indicated that age, sex, smoking status, drinking habits, occupation, regular exercise, and the total intake of energy, fruit and vegetables, fish, offal, eggs, dairy, vitamin A, vitamin C, magnesium (Mg), and zinc (Zn) are potential confounding factors.<sup>28-37</sup> Thus, these factors were adjusted for in model 2.

The linearity between the continuous independent variables and dependent variables was tested using the Box–Tidwell procedure. Multicollinearity among the independent variables was evaluated using the variance inflation factor of linear regression analysis, the values for which were lower than 10, indicating that no strong multicollinearity was present. In the logistic regression model, the median values of each category of meat were taken as the continuous variables to test for linear trends. The results of logistic regression were summarized with ORs and their corresponding 95% CI (confidence interval, CI). All tests involved double-sided inspection, and  $p < 0.05$  or  $p < 0.01$  was considered statistically significant.

## RESULTS

This study conducted a post-hoc analysis, for which 2,716 confirmed patients with PTB were recruited between 2009 and 2013. As presented in Figure 1, among those patients with TB, we excluded individuals who refused to participate in the study ( $n=97$ ), who met the exclusion criteria ( $n=212$ ), who lacked meat intake data, and who had incomplete or abnormal dietary meat intakes ( $n=146$ ). Finally, a total of 2,261 respondents (1,763 men and 498 women) who provided basic meat dietary information remained in the present study for the final analysis.

The demographic characteristics of the cases are presented in Table 1. Treatment was successful for 2,079 patients and unsuccessful for 182 patients. BMI ( $p < 0.01$ ), educational level ( $p = 0.043$ ), and marital status ( $p = 0.01$ ) were significantly different between the treatment success

and failure groups. The distributions of sex, age, smoking status, drinking habits, occupation, and regular exercise did not differ considerably between the two groups. Furthermore, hematological parameters were not significantly different between the treatment success and failure groups.

Table 2 reveals that compared with the treatment failure group, patients in the treatment success group had higher intakes of total meat (28.57 g/d vs 20.95 g/d), red meat (16.66 g/d vs 14.29 g/d), and white meat (6.67 g/d vs 5.00 g/d). Multivariable-adjusted ORs of the failure rate of TB treatment across quartiles of meat consumption are presented in Table 3. In the crude model and model 1, the higher quartile intakes of total meat, red meat, and white meat were significantly negatively correlated with the failure rate of TB treatment. When multiple potential confounders were considered, a significant association was found between a higher consumption of total and red meat and a lower risk of TB treatment failure. Compared with those in the corresponding lowest quartile, patients in the highest quartile for intakes of total meat (OR [95% CI]: 0.59 [0.38–0.91]) and red meat (OR [95% CI]: 0.58 [0.37–0.92]) had a lower TB treatment failure rate. By contrast, no association was found between higher white meat consumption and the failure rate of TB treatment (OR [95% CI]: 0.68 [0.41–1.11],  $p$  for trend = 0.058).

We performed further analysis on the association of regular or low consumption of specific categories of meat and treatment outcomes. As presented in Table 4, the significant association between higher intakes of chicken (OR = 0.62; 95% CI, 0.44–0.87) and pork (OR = 0.54; 95% CI, 0.31–0.95) and a lower TB treatment failure rate was still clearly seen after multiple confounding factors were controlled for. No significant associations were observed between the consumption of duck, beef, and lamb and the failure rate of TB treatment either in the crude or adjusted models.

## DISCUSSION

In this population-based cohort study, we observed that

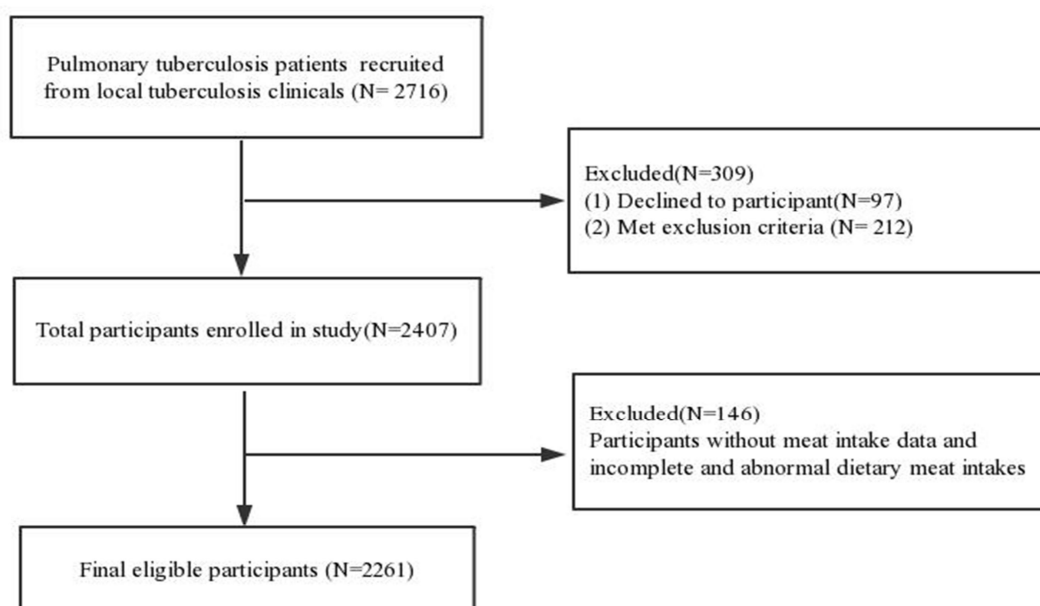


Figure 1. Flow chart of the study.

**Table 1.** The baseline characteristics of study subjects in this cohort (n=2261)

	Treatment outcomes		p-value <sup>†</sup>
	Successful	Failed	
Number of subjects (%)	2079 (91.9)	182 (8.1)	
Sex (%)			0.096
Men	1630 (78.4)	133 (73.1)	
Women	449 (21.6)	49 (26.9)	
Age, years	54 (36, 65)	55 (40, 67)	0.280
Education completed (%)			0.043
None	534 (25.7)	58 (31.9)	
Primary School	672 (32.3)	55 (30.2)	
Junior high school	640 (30.8)	52 (28.6)	
Senior high school	179 (8.6)	8 (4.4)	
Diploma or higher	54 (2.6)	9 (4.9)	
Marital status (%)			0.010
Single	310 (14.9)	25 (13.7)	
Married	1652(79.5)	140 (76.9)	
Widowed	112 (5.4)	14 (7.7)	
Divorced	5 (0.2)	3 (1.6)	
Occupation (%)			0.653
Unskilled farmer or worker	2009 (96.6)	177 (97.3)	
Student	17 (0.8)	1 (0.5)	
Professional	32 (1.5)	4 (2.2)	
Retired	7 (0.3)	0 (0.0)	
Other	14 (0.7)	0 (0.0)	
BMI (kg/m <sup>2</sup> ) (%)			<0.010
<18.5	388 (18.7)	48 (26.4)	
18.5 to <23.9	1483 (71.3)	108 (59.3)	
≥24	208 (10.0)	26 (14.3)	
Smoking (%)			0.900
No	1487 (71.5)	131 (72.0)	
Yes	592 (28.5)	51 (28.0)	
Drinking (%)			0.331
No	1424 (68.5)	131 (72.0)	
Yes	655 (31.5)	51 (28.0)	
Regular exercise (%)			0.079
No	956 (46.0)	96 (52.7)	
Yes	1123 (54.0)	86 (72.3)	
SBP (mmHg) <sup>‡</sup>	120 (110, 125)	120 (110, 125)	0.877
DBP (mmHg) <sup>‡</sup>	80 (70, 80)	80 (70, 80)	0.073
Glucose (mmol/L) <sup>‡</sup>	5.0 (4.5, 5.6)	5.2 (4.6, 5.7)	0.110
Hemoglobin (g/L) <sup>‡</sup>	135 (124, 144)	133 (120, 146)	0.668
Triglycerides (mmol/L) <sup>‡</sup>	1.01 (0.76, 1.29)	1.08 (0.83, 1.39)	0.079
Total cholesterol (mmol/L) <sup>‡</sup>	4.26 (3.67, 4.92)	4.29 (3.65, 5.10)	0.522
AST (U/L) <sup>‡</sup>	21 (14, 33)	21 (15, 30)	0.982

BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; AST: aspartate aminotransferase.

Categorical variables are presented as n (%) while non-normal continuous variables are presented as median (25th, and 75th percentiles).

<sup>†</sup>p values derived from chi-squared tests for categorical variables and Mann-Whitney U tests for non-normal continuous variables.

<sup>‡</sup>SBP: the numbers of patients in successful treatment group and failed treatment group were 2037 and 175; DBP: the numbers of patients in two groups were 2037 and 175; Glucose: the number of patients were 2079 and 182. Hemoglobin: the number of patients were 1988 and 173; Triglycerides: the number of patients were 2014 and 181; Total cholesterol: the number of patients were 2005 and 181; AST: the number of patients were 2031 and 182.

**Table 2.** The comparison of daily meat intake between the successful treatment and failed treatment groups (Median values and interquartile ranges)<sup>†</sup>

	Treatment outcomes		p-value <sup>‡</sup>
	Successful (2079)	Failed (182)	
Total meat (g/d)	28.6 (14.3, 57.1)	21.0 (9.54, 45.6)	<0.001
Total red meat (g/d)	16.7 (7.14, 42.9)	14.3 (6.67, 30.1)	0.001
Total white meat (g/d)	6.67 (3.33, 14.3)	5.00 (1.67, 14.3)	0.022

<sup>†</sup>Non-normal continuous variables are presented as median values and interquartile ranges.

<sup>‡</sup>p values derived from Mann-Whitney U tests for non-normal continuous variables.

**Table 3.** The association of meat intake with the failure rate of tuberculosis treatment

Meat items	Cases	Crude model <sup>‡</sup>	Model 1 <sup>§</sup>	Model 2 <sup>¶</sup>
	Successful/Failed (n/n)	OR (95% CI) <sup>†</sup>	OR (95% CI) <sup>†</sup>	OR (95% CI) <sup>†</sup>
Total meat (g/d)				
<14.28	500/64	Reference	Reference	Reference
14.28 to <28.57	482/42	0.68 (0.45, 1.02)	0.70 (0.46, 1.05)	0.74 (0.48, 1.13)
28.57 to <57.14	606/41	0.53 (0.35, 0.80)**	0.54 (0.36, 0.82)**	0.59 (0.38, 0.91)*
≥57.14	491/35	0.56 (0.36, 0.86)**	0.56 (0.37, 0.87)**	0.63(0.37, 1.07)
<i>p</i> for trend <sup>††</sup>		0.028	0.030	0.143
Total red meat (g/d)				
<7.14	521/62	Reference	Reference	Reference
7.14 to <15.65	502/47	0.79 (0.53, 1.17)	0.81 (0.55, 1.21)	0.89 (0.59, 1.35)
15.65 to <42.86	491/33	0.56 (0.36, 0.88)*	0.51 (0.37, 0.88)*	0.58 (0.37, 0.92)*
≥42.86	565/40	0.59 (0.39, 0.90)*	0.67 (0.40, 0.92)*	0.67 (0.41, 1.08)
<i>p</i> for trend <sup>††</sup>		0.026	0.029	0.107
Total white meat (g/d)				
<3.33	506/53	Reference	Reference	Reference
3.33 to <6.67	609/63	0.99(0.67, 1.45)	1.02 (0.70, 1.51)	1.06 (0.71, 1.58)
6.67 to <14.28	226/20	0.85(0.49, 1.45)	0.87 (0.51, 1.49)	0.91 (0.52, 1.59)
≥14.28	738/46	0.60 (0.39, 0.90)*	0.61 (0.41, 0.93)*	0.68 (0.41, 1.11)
<i>p</i> for trend <sup>††</sup>		0.005	0.006	0.058

<sup>†</sup>OR (95% CI): odds ratio (95% confidence interval).

<sup>‡</sup>Crude model unadjusted.

<sup>§</sup>Model 1 adjusted for age and sex.

<sup>¶</sup>Model 2 adjusted for age, sex, smoking, drinking, BMI, education completed, marital status, occupation, regular exercise, the intake of total energy, total fruit and vegetables, fish, eggs, dairy, offal, vitamin A, vitamin C, Mg and Zn.

<sup>††</sup>Tests for linear trend were carried out by logistic regression, using a median value of each exposure intake category as a single.

\**p*<0.05, \*\**p*<0.01.

**Table 4.** Association of the specific types of white and red meat consumption with the failure rate of tuberculosis treatment

Meat Items	Crude model <sup>§††</sup>		Model 2 <sup>¶††</sup>	
	OR (95% CI) <sup>‡</sup>	<i>p</i> -value	OR (95% CI) <sup>‡</sup>	<i>p</i> -value
Total white meat				
Chicken	0.59 (0.43, 0.80)**	0.001	0.62 (0.44, 0.87)**	0.007
Duck	0.70 (0.34, 1.46)	0.340	0.77 (0.36, 1.68)	0.516
Total red meat				
Pork	0.59 (0.35, 0.99)*	0.045	0.54 (0.31, 0.95)*	0.032
Beef	0.75 (0.44, 1.30)	0.314	0.72 (0.41, 1.28)	0.270
Lamb	0.83 (0.50, 1.38)	0.478	0.84 (0.49, 1.42)	0.508

<sup>‡</sup>OR (95% CI): odds ratio (95% confidence interval).

<sup>§</sup>Crude model unadjusted.

<sup>¶</sup>Model 2 adjusted for age, sex, smoking, drinking, BMI, education completed, marital status, occupation, regular exercise, the intake of total energy, total fruit and vegetables, offal, fish, eggs, dairy, vitamin A, vitamin C, Mg and Zn.

<sup>††</sup>The little consumption group was used as the reference group.

\**p*<0.05, \*\**p*<0.01.

higher dietary meat intake contributed to a lower risk of TB treatment failure. This study also revealed that increased consumption of chicken and pork was associated with decreased risk of TB treatment failure.

Relevant research has mainly revealed the relationship of TB treatment with high-energy and protein dietary supplements, high-energy oral nutritional supplements,<sup>7</sup> or specific micronutrients supplements.<sup>21,22,33,37,38</sup> However, few studies have explored the relationship between meat intake and the effectiveness of TB treatment. A case-control study conducted among Asian immigrants considered that a vegetarian diet lacking meat and fish reduced immunity and increased the activation of mycobacteria, thereby increasing the risk of TB.<sup>39</sup> Similarly, another case-control study demonstrated that vegans had significantly higher rates of TB infection compared with those on a mixed diet that included fish, chicken, and

meat.<sup>40</sup> A cohort study conducted in China indicated that compared with patients with PTB with a high meat intake, patients with a low intake had a higher risk of TB treatment failure, which is consistent with our research results.<sup>41</sup> Our research indicates that an increased meat intake could increase the success rate of TB treatment. The protein intake of patients with TB is usually insufficient, which affects their protein metabolism and slows the healing of lesions.<sup>42</sup> Adequate protein supplementation could increase the number of anti-TB drug carriers and the concentration of anti-TB drugs in the blood, promoting the conversion of sputum and improving therapeutic effects.<sup>43</sup> Thus, a diet sufficiently rich in protein-rich meat intake is essential for improving the effectiveness of treatment.

Meat can provide valuable nutrients and has a higher bioavailability.<sup>19,20</sup> A cross-sectional study revealed that

compared with non-consumers, meat consumers had higher intakes of Zn, niacin, and vitamin B-12, and the intake of Fe in people with high meat intakes was higher than that in people with low meat intakes.<sup>44</sup> Epidemiological evidence suggests that white meat (e.g., chicken and fish) and red meat (e.g., pork) could promote health.<sup>20,45-47</sup> Although it remains unclear how the intake of meat modulates the therapeutic effects of TB, the various nutrients in meat may play a regulatory role. Studies have indicated that the cholesterol contained in pork may affect the phagocytic function of macrophages by affecting their membrane fluidity, and furthermore, cholesterol can promote the sterilization rate of sputum culture in patients with PTB.<sup>48</sup> Chicken is rich in vitamins A and B, minerals, and other nutrients, that exert active effects during TB treatment.<sup>49</sup> Those positive effects include increasing the phagocytic activity of human macrophages, inhibiting the growth of toxic *M.tb*, affecting the production and activity of cytokines and lymphocytes, and accelerating the removal of bacilli from sputum in patients with PTB.<sup>10,12,18,50</sup> Therefore, the components of meat have potential roles in improving the outcomes of TB treatment.

We acknowledge that this study had some limitations. First, dietary intakes were self-reported, inevitably resulting in misreporting caused by recall bias. Second, the nutritional content of meat may vary depending on its cooking and processing methods, which may affect patients' absorption of meat nutrients. Third, this research was conducted in Linyi City, Shandong Province, which is an inland city; thus, the dietary meat intake habits of patients with TB may have differed slightly from those of patients living in coastal cities.

Despite these limitations, the current survey had some merits. First, its population-based design and large sample size provided stronger evidence for the relationship between meat intake and TB treatment outcomes. Second, this is among the first published reports on associations between total white meat consumption, total red meat consumption, specific types of meat consumption, and TB treatment outcomes. Third, we provided food models, pictures, and related tools to reduce recall bias.

### Conclusion

The results of the present study indicate that increased dietary intakes of total meat and individual meat types (particularly chicken and pork) are associated with the increased success rate among patients with TB treatment.

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### AUTHOR DISCLOSURES

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