British Journal of Nutrition (2017), **118**, 1052–1060
doi:10.1017/S0007114517003166

Underweight increases the risk of early death in tuberculosis patients

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(Submitted 17 May 2017 – Final revision received 5 August 2017 – Accepted 27 August 2017 – First published online 28 November 2017)

Abstract

Evidence regarding the association between BMI and mortality in tuberculosis (TB) patients is limited and inconsistent. We investigated the impact of BMI on TB-specific and non-TB-specific mortality with respect to different timing of death. All Taiwanese adults with TB in Taipei were included in a retrospective cohort study in 2012–2014. Multinomial Cox proportional hazards regression was used to evaluate the associations between BMI, cause-specific mortality and timing of death. Of 2410 eligible patients, 86·0 % (2061) were successfully treated, and TB-specific and non-TB-specific mortality occurred for 2·2 % (54) and 13·9 % (335), respectively. After controlling for potential confounders, underweight was significantly associated with a higher risk of all-cause mortality (adjusted hazard ratio (AHR) 1·57; 95 % CI 1·26, 1·95), whereas overweight was not. When cause-specific death was considered, underweight was associated with an increased risk of either TB-specific (AHR 1·85; 95 % CI 1·03, 3·33) or non-TB-specific death (AHR 1·52; 95 % CI 1·19, 1·95) during treatment. With joint consideration of cause-specific and timing of death, underweight only significantly increased the risk of TB-specific (AHR 2·23; 95 % CI 1·09, 4·59) and non-TB-specific mortality (AHR 1·81; 95 % CI 1·29, 2·55) within the first 8 weeks of treatment. This study suggests that underweight increases the risk of early death in TB patients during treatment.

Key words: Tuberculosis: BMI: Underweight: Mortality

Tuberculosis (TB) remains a common and deadly disease globally[1]. In 2015, there were an estimated 10·4 million incident cases of TB, and 1·8 million people died from the disease[2].

In Taiwan, of all notified infectious diseases, TB has been the most prevalent for decades[3]. Since 2006, Taiwan's Centers for Disease Control (CDC) has adopted a directly observed therapy, short course (DOTS) programme to achieve a successful treatment rate of 85 % and halve TB incidence by 2015. Since then, the success rate for TB treatment improved only slightly from 64·1 % in 2005 to 70·4 % in 2012. Mortality among TB patients accounted for 81·8 % of the unsuccessful cases of TB treatment[3].

BMI is a popular and useful tool to evaluate the nutritional status of an individual[4]. Nutrition disequilibrium (e.g. underweight or obesity) can impair the immune system (e.g. T cell suppression)[5] and could therefore affect the treatment outcome in TB patients. Although many studies have evaluated the risk factors for mortality in TB patients[6], the association between BMI and mortality in this population has not been studied extensively, and the existing evidence is inconsistent[4,7–12]. Some studies reported that lower BMI was significantly associated with a higher risk of mortality among TB patients[7–10,12], whereas another two found no such an association[4,11]. Moreover, one study found that overweight was a protective factor for mortality among TB patients[7].

According to the WHO, mortality in TB patients is defined as death for any reason during treatment[13]. However, a number of TB patients die of cerebrovascular disease or malignancy instead of TB. Although many studies have evaluated the factors associated with mortality in TB patients, few studies have determined the predictors of TB-specific or non-TB-specific mortality[6].

According to the CDC guidelines, TB patients should be administered effective drugs for at least 6 months[14]. The timing of death in TB patients varies during treatment; for example, many patients die within the first 8 weeks of treatment, whereas others die later[15]. Although few studies have examined the prognostic factors for TB with respect to the timing of death[6], a recent report found that predictors of mortality varied according to timing of death in TB patients[16].

Developing effective interventions to improve TB outcomes requires a better understanding of the factors associated

Abbreviations: AHR, adjusted hazard ratio; DOT, directly observed treatment; TB, tuberculosis.

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with cause-specific mortality and timing of death. Thus this population-based study aimed to investigate the impact of BMI on TB-specific and non-TB-specific mortality with respect to different timing of death.

Methods

Study population and data source

This retrospective cohort study utilised TB surveillance data from Taipei, Taiwan. In Taipei, TB cases must be reported to the Taipei TB Prevention Center within 7 d of diagnosis. This study included Taiwanese adults (age ≥18 years) diagnosed with TB in Taipei during the period 2012–2014. TB was defined based on clinical and/or laboratory findings[17]. Clinical findings included symptoms (e.g. cough, wasting, prolonged fever) consistent with TB and exclusion of other differential diagnoses based on diagnostic evaluation[17]. Laboratory definitions included *M. tuberculosis* isolated from a clinical specimen or acid-fast bacilli (AFB) demonstrated in a clinical specimen from patients with clinical symptoms consistent with TB. This project was approved by the Institutional Review Board of Taipei City Hospitals (TCHIRB- 10505112-E).

Data collection

When TB patients are reported to the Taipei TB Prevention Center, trained case managers use a structured questionnaire to interview patients about their sociodemographic characteristics, clinical findings, and underlying diseases. Sociodemographic factors include age, sex, BMI, marital status, education level, smoking status, alcohol use and unemployment. TB patients in Taipei are required by law to be monitored until treatment success, death or lost to follow-up. For the purpose of monitoring treatment response, case managers followed up all TB cases by phone or in person once every other week.

Outcome variable

The outcome variable of interest was treatment outcome, which was categorised as successful treatment or mortality. Mortality was classified as TB-specific or non-TB-specific according to the cause of death. TB-specific death was defined as an underlying cause of death due to TB in the Taiwan Death Certification Registry (International Classification of Diseases (ICD)-9: A010–A018; ICD-10: A15–A19)[18]. Non-TB-specific death was defined as any underlying cause of death other than TB. By law, a death certificate must be registered according to ICD 9 or 10 within 30 d after a patient dies in Taiwan. Because trained medical registrars review all death certificates at the central office of the National Death Certification Registry, the cause-of-death coding in Taiwan is considered very accurate[19].

Mortality was also categorised as early or late according to the timing of death. Early death was defined as death within the first 8 weeks of TB treatment, and late death was defined as mortality later than 8 weeks after the start of TB treatment but before completion of such therapy[20].

Main explanatory variable

The main explanatory variable was BMI (kg/m^2), which was recorded when the case managers interviewed TB cases at the time of TB notification to the Taipei TB Prevention Department. According to the WHO International Classification of adult body weight, BMI was categorised as underweight (<18·5 kg/m^2), normal (18·5–24·9 kg/m^2) or overweight (≥25 kg/m^2)[21].

Control variables

Control variables included sociodemographic factors (education level, smoking status), clinical findings (AFB-smear status, TB culture, cavities on chest radiograph (CXR), pleural effusion, extrapulmonary TB), comorbidities (malignancy, diabetes mellitus, end-stage renal disease) and mode of TB treatment. Education level was categorised as uneducated, elementary school, high school, or university or higher. Smoking status was categorised as never, quit smoking and current smoker. The mode of TB treatment was classified as directly observed treatment (DOT) or self-administered treatment. DOT was defined as administration of antituberculosis medication directly supervised by trained public health observers[22].

Statistical analysis

First, the sociodemographic characteristics are presented according to BMI category. The two-sample t test was used for comparisons of continuous data between groups. Categorical data were analysed using the Pearson χ^2 test, where appropriate.

A Cox proportional hazards regression model was conducted using all-cause mortality *v.* treatment success as the outcome with BMI category as the main explanatory variable. The multinomial Cox proportional hazards regression analysis was used to identify the factors associated with cause-specific mortality (TB-specific *v.* non-TB-specific mortality) and timing of death (early *v.* late death). To investigate the factors associated with cause-specific mortality with respect to timing of death, the treatment outcome in TB patients was classified into five categories: TB-specific death within the first 8 weeks of treatment, TB-specific death later than 8 weeks of treatment, non-TB-specific death within the first 8 weeks of treatment, non-TB-specific death later than 8 weeks of treatment and treatment success. Then multinomial Cox proportional hazards regression analysis was conducted to determine the impact of BMI on TB-specific and non-TB-specific mortality with respect to different timing of death. Adjusted hazard ratios (AHR) and 95 % CI are reported, to indicate the strength and direction of associations. All data management and analyses were performed using the SAS 9.4 software package (SAS Institute).

Results

Characteristics of patients with tuberculosis

A total of 2878 TB cases were reported to the Taipei TB Prevention Department in 2012–2014. Of these, ninety-two died before starting TB treatment, twenty-seven were lost to follow-up during treatment, twenty-eight was still on treatment at the time of this study, 212 had incomplete data and 109 had

British Journal of Nutrition

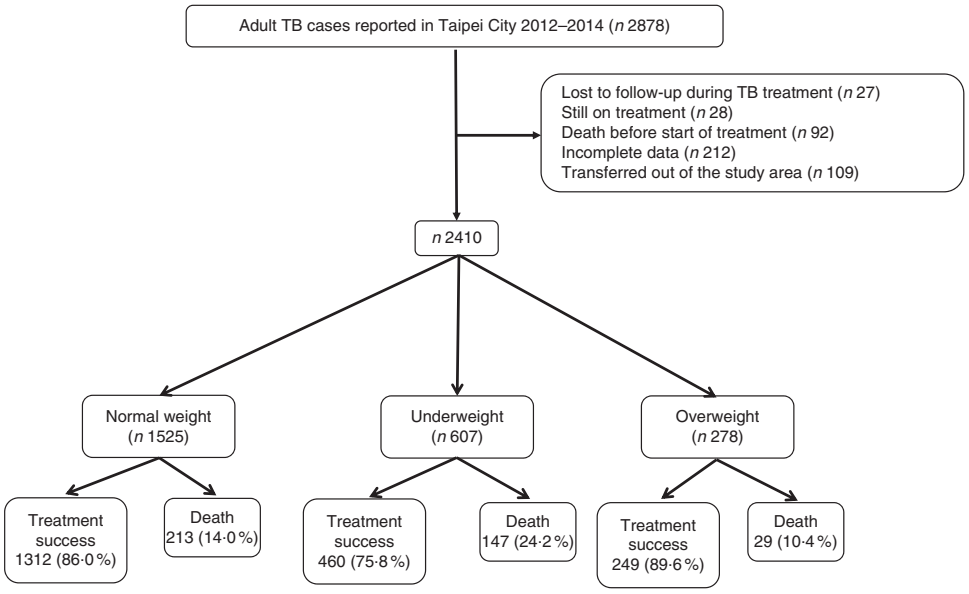

Fig. 1. Study population. TB, tuberculosis.

transferred out of Taipei city (Fig. 1). The remaining 2410 cases were included in the subsequent analysis; the mean age was 64·5 (SD 20·2) years, and 67·1 % were men (Table 1). According to the WHO BMI definition, 25·2, 63·3 and 11·5 % of the patients were classified as underweight, normal weight or overweight, respectively. During the study follow-up period, 145 (14·2 %) deaths occurred in normal weight patients, 99 (24·4 %) deaths occurred in underweight patients, and 19 (10·3 %) deaths occurred in overweight patients (Table 1). Table 1 also shows the distribution of mortality according to cause-specific and timing of death.

Associations between BMI and all-cause mortality

A Cox proportional hazards model was used to identify independent risk factors for all-cause mortality in TB patients (Table 2). After adjusting for age, sex, clinical findings and comorbidities, the risk of all-cause mortality was significantly higher in underweight patients (AHR 1·57; 95 % CI 1·26, 1·95; $P<0·001$) than in normal weight patients. Overweight was not significantly associated with all-cause mortality. Other risk factors for all-cause mortality included age ≥65 years (AHR 2·98; 95 % CI 2·10, 4·23), male sex (AHR 1·39; 95 % CI 1·08, 1·78), unemployment (AHR 2·30; 95 % CI 1·43, 3·68), end-stage renal disease (AHR 2·24; 95 % CI 1·54, 3·25), malignancy (AHR 2·68; 95 % CI 2·08, 3·46), AFB-smear positivity (AHR 1·56; 95 % CI 1·20, 1·95), TB-culture positivity (AHR 1·38; 95 % CI 1·01, 1·87) and pleural effusion on CXR (AHR 1·61; 95 % CI 1·23, 2·13). Also, factors associated with a lower risk of all-cause mortality included university or higher education (AHR 0·59; 95 % CI 0·40, 0·88) and DOT (AHR 0·62; 95 % CI 0·41, 0·91).

Association between BMI with tuberculosis-specific and non-tuberculosis-specific mortality

Table 3 shows the results of the multinomial Cox regression analysis of factors associated with TB-specific or non-TB-specific mortality. Underweight was significantly associated with a higher risk of TB-specific (AHR 1·85; 95 % CI 1·03, 3·33; $P=0·040$) and non-TB-specific mortality (AHR 1·52; 95 % CI 1·19, 1·95; $P<0·001$) during treatment. However, overweight was not significantly associated with TB-specific or non-TB-specific death during treatment.

Association between BMI and early or late death during tuberculosis treatment

Table 4 shows the results of the multinomial Cox regression analysis of factors associated with early or late death during TB treatment. After controlling for potential confounders, underweight was significantly associated with a higher risk of early death (AHR 1·87; 95 % CI 1·38, 2·55; $P<0·001$), but not late death. Moreover, overweight was not significantly associated with early or late death during TB treatment.

Association between BMI and cause-specific mortality with respect to the timing of death

Table 5 shows the results of the multinomial Cox regression analysis for the association between BMI and cause-specific mortality in relation to the timing of death. After adjusting for age, sex, clinical findings, and comorbidities, underweight was significantly associated with a higher risk of TB-specific (AHR 2·23; 95 % CI 1·09, 4·59; $P=0·029$) and non-TB-specific mortality (AHR 1·81; 95 % CI 1·29, 2·55; $P<0·001$) within the first 8 weeks of treatment, but not significantly associated with TB-specific or non-TB-specific mortality later than 8 weeks after treatment initiation. Also, overweight was not significantly associated with TB-specific or non-TB-specific death within or later than 8 weeks after treatment initiation.

Discussion

In this cohort study of 2410 Taiwanese adults with TB in 2012–2014, overall mortality was 14·0 %. After controlling for potential confounders, underweight was significantly associated with a

Table 1. Characteristics of tuberculosis patients; by BMI category
(Numbers and percentages; mean values and standard deviations)

	BMI (kg/m^2)						
	Normal (18·5–24·9) (*n* 1525)		Underweight (<18·5) (*n* 607)		Overweight (≥25) (*n* 278)		
Characteristics	*n*	%	*n*	%	*n*	%	*P*
Age (years)							<0·001
Mean	63·6		67·6		63·0		
SD	19·9		21·3		18·2		
18–64	722	47·3	228	37·6	145	52·2	<0·001
≥65	803	52·7	379	62·4	133	47·8	
Sex							0·159
Female	492	32·3	218	35·9	84	30·2	
Male	1033	67·7	389	64·1	194	69·8	
Marital status							0·02
Unmarried	293	19·2	142	23·4	45	16·2	
Married	1212	79·5	462	76·1	227	81·7	
Unknown	20	1·3	3	0·5	6	2·1	
Education level							0·192
No education	115	7·5	53	8·7	29	10·4	
Elementary school	325	21·3	140	23·1	60	21·6	
High school	577	37·8	205	33·8	111	39·9	
University or higher	472	31·0	187	30·8	73	26·3	
Unknown	36	2·4	22	3·6	5	1·8	
Unemployment							<0·001
No	422	27·7	112	18·5	81	29·1	
Yes	1103	72·3	495	81·5	197	70·9	
Smoking status							0·442
Never smoker	1208	79·2	498	82·0	224	80·6	
Former smoker	99	6·5	40	6·6	15	5·4	
Current smoker	218	14·3	69	11·4	39	14·0	
Any alcohol use							0·082
No	1411	92·5	576	94·9	254	91·4	
Yes	114	7·5	31	5·1	24	8·6	
DM							<0·001
No	1265	83·0	554	91·3	194	69·8	
Yes	260	17·0	53	8·7	84	30·2	
ESRD							0·148
No	1482	97·2	586	96·5	264	95·0	
Yes	43	2·8	21	3·5	14	5·0	
Malignancy							0·028
No	1401	91·9	552	90·9	267	96·0	
Yes	124	8·1	55	9·1	11	4·0	
History of TB							0·006
No	1471	96·5	570	93·9	272	97·8	
Yes	54	3·5	37	6·1	6	2·2	
AFB-smear positivity							<0·001
No	958	62·8	314	51·7	178	64·0	
Yes	567	37·2	293	48·3	100	36·0	
TB-culture positivity							<0·001
No	434	28·5	125	20·6	85	30·6	
Yes	1091	71·5	482	79·4	193	69·4	
Cavity on CXR							0·03
No	1332	87·3	511	84·2	251	90·3	
Yes	193	12·7	96	15·8	27	9·7	
Pleural effusion							0·791
No	1348	88·4	531	87·5	247	88·9	
Yes	177	11·6	76	12·5	31	11·1	
Extrapulmonary TB							<0·001
No	1405	92·1	577	95·1	244	87·8	
Yes	120	7·9	30	4·9	34	12·2	
DOT							0·08
No	102	6·7	46	7·6	10	3·6	
Yes	1423	93·3	561	92·4	268	96·4	
Cause-specific mortality							<0·001
TB-specific death	26	1·7	25	4·1	3	1·1	
Non-TB-specific death	187	12·3	122	20·1	26	9·3	
Timing of death							<0·001
Early death	102	6·7	87	14·3	17	6·1	
Late death	111	7·3	60	9·9	12	4·3	

DM, diabetes mellitus; ESRD, end-stage renal disease; TB, tuberculosis; AFB, acid-fast bacilli; CXR, chest radiograph; DOT, directly observed treatment.

Table 2. Univariate and multivariate analyses of risk factors for all-cause mortality in tuberculosis (TB) patients; Taipei; Taiwan (2012–2014) (Numbers and percentages; hazard ratios (HR), adjusted hazard ratios (AHR) and 95 % confidence intervals)

		All-cause mortality		Univariate analysis		Multivariate analysis	
Variables	Number of patients	*n*	%	HR	95 % CI	AHR	95 % CI
BMI (kg/m^2)							
Normal (18·5–24·9)	1525	213	14·0	1		1	
Underweight (<18·5)	607	147	24·2	1·86***	1·51, 2·29	1·57***	1·26, 1·95
Overweight (≥25)	278	29	10·4	0·74	0·50, 1·09	0·81	0·54, 1·19
Age (years)							
18–64	1095	48	4·4	1		1	
≥65	1315	341	25·9	6·56***	4·85, 8·87	2·98***	2·10, 4·23
Sex							
Female	794	95	12·0	1		1	
Male	1616	294	18·2	1·53***	1·22, 1·93	1·39**	1·08, 1·78
Marital status							
Unmarried	480	30	6·3	1		1	
Married	1901	355	18·7	3·19***	2·20, 4·63	1·32	0·89, 1·97
Unknown	29	4	13·8	2·33	0·82, 6·62	1·14	0·39, 3·29
Education level							
No education	197	46	23·4	1		1	
Elementary school	525	129	24·6	1·05	0·75, 1·47	1·02	0·72, 1·44
High school	893	127	14·2	0·58**	0·41, 0·81	0·76	0·53, 1·08
University or higher	732	63	8·6	0·35***	0·24, 0·52	0·59*	0·40, 0·88
Unknown	63	24	38·1	1·70*	1·04, 2·78	1·30	0·78, 2·16
Unemployment							
No	615	21	3·4	1		1	
Yes	1795	368	20·5	6·46***	4·16, 10·03	2·30***	1·43, 3·68
Smoking status							
Never smoking	1930	329	17·1	1		1	
Quit smoking	154	28	18·2	1·05	0·71, 1·54	0·83	0·56, 1·23
Current smoking	326	32	9·8	0·54***	0·37, 0·77	0·80	0·54, 1·19
Any alcohol use							
No	2241	375	16·7	1		1	
Yes	169	14	8·3	0·45**	0·27, 0·77	0·72	0·41, 1·27
DM							
No	2013	318	15·8	1		1	
Yes	397	71	17·9	1·11	0·86, 1·44	1·09	0·84, 1·42
ESRD							
No	2332	357	15·3	1		1	
Yes	78	32	41·0	3·00***	2·09, 4·30	2·24***	1·54, 3·25
Malignancy							
No	2220	311	14·0	1		1	
Yes	190	78	41·1	3·48***	2·71, 4·46	2·68***	2·08, 3·46
TB relapse							
No	2313	370	16·0	1		1	
Yes	97	19	19·6	1·17	0·74, 1·85	1·10	0·69, 1·76
Acid-fast bacilli smear							
Negative	1450	189	13·0	1		1	
Positive	960	200	20·8	1·65***	1·35, 2·02	1·56***	1·25, 1·94
TB culture							
Negative	644	64	9·9	1		1	
Positive	1766	325	18·4	1·95***	1·49, 2·55	1·38*	1·01, 1·87
Cavities on CXR							
No	2094	349	16·7	1		1	
Yes	316	40	12·7	0·73	0·52, 1·02	0·77	0·55, 1·08
Pleural effusion on CXR							
No	2126	321	15·1	1		1	
Yes	284	68	23·9	1·68***	1·29, 2·18	1·61***	1·23, 2·13
Extrapulmonary TB							
No	2226	370	16·6	1		1	
Yes	184	19	10·3	0·54**	0·34, 0·86	0·87	0·54, 1·42
DOT							
No	158	28	17·7	1		1	
Yes	2252	361	16·0	0·81	0·55, 1·19	0·62*	0·42, 0·91

DM, diabetes mellitus; ESRD, end-stage renal disease; CXR, chest radiograph; DOT, directly observed treatment.
* $P<0·05$, ** $P<0·01$, *** $P<0·001$.

Table 3. Associations of BMI with tuberculosis (TB)-specific and non-TB-specific death† (Adjusted hazard ratios (AHR) and 95 % confidence intervals)

	TB-specific death‡		Non-TB-specific death‡	
Variables	AHR	95 % CI	AHR	95 % CI
BMI (kg/m^2) (normal weight)				
Underweight	1·85*	1·03, 3·33	1·52***	1·19, 1·95
Overweight	0·76	0·22, 2·56	0·81	0·54, 1·23
Age ≥65 years	13·86**	2·40, 80·02	2·55***	1·72, 3·78
Male sex	1·14	0·59, 2·22	1·42**	1·09, 1·85
Married status	1·21	0·33, 4·46	1·31	0·86, 2·01
Education level				
No education	1		1	
Elementary school	0·67	0·24, 1·89	1·07	0·73, 1·55
High school	1·03	0·41, 2·61	0·71	0·49, 1·05
University or higher	0·99	0·35, 2·81	0·53**	0·34, 0·83
Unknown	0·74	0·13, 4·18	1·39	0·79, 2·44
Smoking status				
Never smoker	1		1	
Former smoker	0·92	0·33, 2·62	0·81	0·52, 1·26
Current smoker	0·54	0·12, 2·38	0·83	0·55, 1·24
Any alcohol use			0·80	0·46, 1·38
Unemployment	2·22	0·50, 9·92	2·29**	1·35, 3·88
HIV infection				
DM	0·64	0·26, 1·54	1·17	0·88, 1·55
ESRD	1·68	0·55, 5·13	2·32***	1·53, 3·52
Malignancy	1·42	0·65, 3·15	2·94***	2·23, 3·89
History of TB disease	1·64	0·57, 4·71	1·02	0·60, 1·72
AFB-smear positivity	2·45**	1·31, 4·58	1·45**	1·14, 1·84
TB-culture positivity	1·75	0·69, 4·42	1·32	0·95, 1·84
Cavity on CXR	1·23	0·57, 2·65	0·70	0·48, 1·03
Pleural effusion	2·39*	1·23, 4·66	1·49*	1·09, 2·04
Extrapulmonary TB	2·17	0·68, 6·89	0·75	0·42, 1·32
DOT	0·42	0·17, 1·01	0·67	0·41, 1·10

DM, diabetes mellitus; ESRD, end-stage renal disease; AFB, acid-fast bacilli; CXR, chest radiograph; DOT, directly observed treatment.
* $P<0·05$, ** $P<0·01$, *** $P<0·001$.
† Reference is successfully treated individuals.
‡ Adjusted for BMI, age, sex, marital status, education level, unemployment, alcohol use, diabetes mellitus, end-stage renal disease, malignancy, TB relapse, AFB smear, TB culture, cavities on CXR, extrapulmonary TB and directly observed treatment.

higher risk of all-cause mortality, whereas overweight was not. When cause-specific death was considered, underweight was associated with an increased risk of either TB-specific or non-TB-specific mortality during TB treatment. When considering both cause-specific mortality and timing of death, underweight only significantly increased the risk of TB-specific and non-TB-specific mortality within the first 8 weeks of treatment, but was not significantly associated with a higher risk of mortality later than 8 weeks after treatment initiation.

The association of BMI with TB outcome was inconsistent in previous reports[4,7–12]. Four studies found that lower BMI was significantly associated with a higher risk of mortality among TB patients[8–10,12], with one study reporting that greater BMI (per unit increase) was significantly associated with a lower risk of mortality[8]. In contrast, another two studies found no differences in the risk of mortality based on BMI (<18·5 *v.* ≥18·5 kg/m^2)[4,11]. Moreover, Hanrahan *et al.*[7] found that underweight significantly increased the risk of mortality among patients with HIV and TB coinfections, whereas obesity and overweight were protective. The present study found that overweight was not significantly associated with the risk of mortality, but underweight was significantly associated with a higher risk of either TB-specific or non-TB-specific mortality during treatment. Furthermore, the main impact of underweight on mortality occurred within the first 8 weeks of TB treatment. The findings in this study indicated that underweight was an independent risk for TB-specific and non-TB-specific mortality, particularly within 8 weeks after the start of TB treatment.

Although underweight was significantly associated with a higher risk of TB-specific and non-TB-specific mortality within the first 8 weeks of TB treatment, the association was NS after the initial 8 weeks of TB treatment. Higher early mortality among underweight TB patients may be due to lower immunity and more severe TB infection in this population. Underweight can suppress lymphocyte stimulation and reduce secretion of Th1 cytokines (e.g. IL-2, TNF-α and interferon-γ)[23], which could cause more severe TB infection. In malnourished animals, macrophages produce more transforming growth factor β, which further suppresses T cells and causes severe TB disease[24,25]. Animal studies have also shown that malnourished mice have an impaired immune system (e.g. reduction of reactive N intermediates) in response to *Mycobacterium* infection[26]. Moreover, malnourished animals have higher bacterial burdens with TB infection and die earlier of infection[26].

This study showed that overweight TB patients had a lower risk of all-cause mortality than normal weight patients (10·4 *v.* 14·0 %), although this was not statistically significant. Although this association of interest has not been extensively studied,

British Journal of Nutrition

Table 4. Associations of BMI with early and late death in tuberculosis (TB) patients†
(Adjusted hazard ratios (AHR) and 95 % confidence intervals)

	Early death‡		Late death‡	
Variables	AHR	95 % CI	AHR	95 % CI
BMI (kg/m^2) (normal weight)				
Underweight	1·87***	1·38, 2·55	1·26	0·90, 1·76
Overweight	1·04	0·61, 1·76	0·60	0·34, 1·09
Age ≥65 years	2·60***	1·56, 4·32	3·54***	1·95, 6·41
Male sex	1·33	0·95, 1·85	1·47*	1·02, 2·11
Married status	2·28*	1·16, 4·45	0·82	0·48, 1·41
Education level				
No education	1		1	
Elementary school	0·84	0·53, 1·33	1·31	0·76, 2·26
High school	0·64	0·40, 1·01	0·93	0·53, 1·62
University or higher	0·50*	0·29, 0·85	0·76	0·40, 1·43
Unknown	0·84	0·40, 1·73	2·02	0·94, 4·31
Smoking status				
Never smoker	1		1	
Former smoker	0·80	0·44, 1·45	0·81	0·44, 1·47
Current smoker	0·84	0·49, 1·44	0·73	0·42, 1·29
Any alcohol use	0·62	0·27, 1·43	0·87	0·42, 1·79
Unemployment	2·60**	1·27, 5·31	2·00*	1·00, 4·01
DM	0·97	0·66, 1·43	1·25	0·86, 1·83
ESRD	1·51	0·79, 2·87	3·15***	1·85, 5·36
Malignancy	2·30***	1·60, 3·31	3·46***	2·34, 5·12
History of TB disease	1·00	0·50, 1·96	1·28	0·65, 2·52
AFB-smear positivity	2·23***	1·63, 3·06	1·05	0·74, 1·49
TB-culture positivity	1·79*	1·10, 2·91	1·11	0·72, 1·73
Cavity on CXR	0·94	0·61, 1·44	0·56*	0·32, 0·99
Pleural effusion	2·00***	1·37, 2·91	1·29	0·83, 1·99
Extrapulmonary TB	1·38	0·72, 2·66	0·55	0·26, 1·15
DOT	0·32***	0·20, 0·51	3·20	0·97, 10·62

DM, diabetes mellitus; ESRD, end-stage renal disease; AFB, acid-fast bacilli; CXR, chest radiograph; DOT, directly observed treatment.
* $P<0·05$; ** $P<0·01$; *** $P<0·001$.
† Reference is successfully treated individuals.
‡ Adjusted for BMI, age, sex, marital status, education level, unemployment, alcohol use, diabetes mellitus, end-stage renal disease, malignancy, TB relapse, AFB smear, TB culture, cavities on CXR, extrapulmonary TB and directly observed treatment.

Table 5. Multinomial regression for the association between BMI and cause-specific mortality in relation to timing of death in tuberculosis (TB) patients†
(Adjusted hazard ratios (AHR) and 95 % confidence intervals)

	TB-specific mortality‡				Non-TB-specific mortality‡			
	Early death		Late death		Early death		Late death	
Variables	AHR	95 % CI	AHR	95 % CI	AHR	95 % CI	AHR	95 % CI
BMI (kg/m^2) (normal weight)								
Underweight	2·23*	1·09, 4·59	1·24	0·41, 3·74	1·81***	1·29, 2·55	1·25	0·88, 1·79
Overweight	1·21	0·33, 4·35	–		1·01	0·56, 1·81	0·66	0·36, 1·19

* $P<0·05$, *** $P<0·001$.
† Reference is successfully treated individuals.
‡ Variables included: age, sex, clinical findings and comorbidities.

a prior study found that overweight or obesity was protective against mortality in patients with HIV–TB co-infection[7]. Patients with TB who experience a mild or moderate increase in BMI may consume more protein and energy on a daily basis, which could result in more robust immune function and reduce mortality. However, more studies are needed to evaluate the impact of overweight or obesity on all-cause and cause-specific mortality as well as timing of death in TB patients.

This study found that DOT was significantly associated with a lower risk of mortality after controlling for BMI and other potential confounders. In Taipei's DOTS programme, each DOT observer monitors five to fifteen TB patients on average[3]. DOT observers interview patients regarding their TB symptoms and complications of treatment under the supervision of public health nurses. When TB patients on DOT have, for example, worsened dyspnea, the public health nurses contact doctors to arrange hospital visits. DOT has been recommended for TB patients to improve their adherence to treatment[27]. Our study suggests that DOT programme should be applied to all TB patients to further reduce mortality.

The strength of this study is that all eligible TB patients were included in the analysis; therefore, the sample size was not based on the considerations of statistical power. However, some limitations should be considered when interpreting the findings of this citywide population-based study. First, in this retrospective cohort study, some important patient information (e.g. intravenous drug use, chronic lung disease and psychiatric disorders) was not available. Second, 25·4 % of the TB cases were identified based on clinical diagnosis rather than by AFB smear or culture, which could have resulted in over-diagnosis of TB. However, this is less likely in this study because the Taipei TB Control Department holds an expert committee monthly to discuss the uncertain diagnosis of TB cases[3]. Third, the information regarding BMI among TB patients were self-reported, and therefore subject to recall bias. Moreover, this study only measured BMI at baseline. As BMI can change during TB treatment[28], more studies are needed to determine the time-varying effect of BMI on mortality in TB patients. Finally, the external validity of our findings may be a concern because all the participants were Taiwanese. The generalisability of our results to other non-Asian ethnic groups thus requires further verification. Nevertheless, our findings suggest new avenues for future research.

Conclusions

In the present study, mortality was high in TB patients in Taipei, Taiwan, in 2012–2014. After controlling for other covariates, underweight was significantly associated with an increased risk of all-cause mortality during TB treatment, whereas overweight was not. For cause-specific mortality, underweight was associated with an increased risk of either TB-specific or non-TB-specific mortality during treatment. With the simultaneous consideration of cause-specific mortality and timing of death, underweight only significantly increased the risk of TB-specific and non-TB-specific mortality within the first 8 weeks of treatment, but was not significantly associated with a higher risk of mortality after the initial 8 weeks of treatment. The findings in this study indicate that underweight increases the risk of early death in TB patients during the treatment.

Acknowledgements

The authors are grateful to registered nurses Jen-Chieh Hsiao and Miao-Yun Chen for interviewing the subjects and reviewing their medical records.

This study was funded.

Y.-F. Y., F.-I. T., B.-L. H., Y.-J. L. substantially contributed to the conception and design of the study, data analysis, data interpretation and the drafting of the manuscript. Y.-F. Y. substantially contributed to data acquisition and interpretation of the results. Y.-F. Y., F.-I. T., B.-L. H., Y.-J. L. all approved the final version of the manuscript.

The authors declare that there are no conflicts of interest.

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