

## Effect of Sex, Age, and Race on the Clinical Presentation of Tuberculosis: A 15-Year Population-Based Study

Xinyu Zhang, Aase B. Andersen, Troels Lillebaek, Zaza Kamper-Jørgensen, Vibeke Østergaard Thomsen, Karin Ladefoged, Carl F. Marrs, Lixin Zhang, and Zhenhua Yang\*

Department of Epidemiology, University of Michigan, Ann Arbor, Michigan; Department of Infectious Diseases, Odense University Hospital, Odense, Denmark; Department of Infectious Diseases, Copenhagen University Hospital, Copenhagen, Denmark; International Reference Laboratory of Mycobacteriology, Statens Serum Institut, Copenhagen, Denmark; Medical Department, Queen Ingrid's Hospital, Nuuk, Greenland

**Abstract.** Extrapulmonary tuberculosis (EPTB) is an important health problem that may cause serious morbidity and diagnostic challenges. We conducted a case-control study involving 5,684, approximately 99% of bacteriologically confirmed TB patients (including 1,925 EPTB cases) diagnosed in Denmark and Greenland during 1992–2007 to gain insight to the role of host factors in EPTB pathogenesis. Among patients from Somalia and Asia, persons 25–44 and 45–64 years of age were more likely to have EPTB than persons 15–24 years of age. In contrast, among persons from Greenland, the two oldest age groups were significantly less likely to have EPTB than the youngest age group. For all the age groups, the odds for having EPTB was significantly higher among patients from Somalia and Asia and significantly lower among the patients from Greenland than among patients from Denmark. Furthermore, the occurrence of specific types of EPTB significantly varied among different age groups or origins.

### INTRODUCTION

Tuberculosis (TB) is among the most widely spread and serious of all human infectious diseases, and there are more cases today than at any previous time in human history. One-third of the world's population is estimated to be infected by *Mycobacterium tuberculosis*, in whom active TB develops in nine million persons each year.<sup>1</sup> The estimate of global TB incidence increased from 6.6 million in 1990 to 9.4 million in 2008.<sup>2,3</sup> Moreover, during 1995–2002, the proportion of reported extrapulmonary TB (EPTB) cases among the global total incident cases of TB had increased from 4% to 19%.<sup>4</sup> Studies in industrialized countries, such as the United States, The Netherlands, England and Wales, and other countries in Europe, have shown temporary resurgence of TB because of immigration, or higher prevalence of TB and EPTB among persons of foreign origins, especially those from Africa and Asia.<sup>5–8</sup>

Host immune response is one of the determinants for the progression of infection of *M. tuberculosis* at extrapulmonary sites to clinically evident EPTB. A study has shown a significant higher proportion of EPTB cases among patients seropositive for human immunodeficiency virus (HIV) with lower CD4 cell counts.<sup>9</sup> Certain phenotypes of the tubercle bacilli may be linked to a higher risk of extrapulmonary dissemination, as indicated by studies involving mutant strains of *M. tuberculosis* in a rabbit model.<sup>10</sup> Thus, it seems that host factors concerning immune status and pathogen factors play an important role in extrapulmonary dissemination. Among all the extrapulmonary sites, lymph nodes, kidneys, bones, and brain are more likely to be affected.<sup>11</sup> Although it is true that the *a priori* possibility that a case of spondylitis in a TB-endemic country is in fact Potts disease may be high, this is not the case in most western countries where a number of differential diagnoses exist and a definitive diagnosis involving

biopsy is necessary. Therefore, compared with pulmonary TB, EPTB poses more challenges for diagnosis and monitoring of treatment because it involves relatively less accessible sites.<sup>12,13</sup> In general, the true prevalence of EPTB is therefore probably grossly underreported.

However, epidemiologic studies in industrialized countries and resource-limited countries with high burdens of TB found that younger populations, females, and persons of African or Asian origins had a higher risk for EPTB.<sup>6,14–16</sup> Moreover, different sexes, ethnicities, and ages were found to have different risk for having EPTB at a specific anatomic site.<sup>12,17–19</sup>

In Denmark during 1986–1999, the total number of TB cases increased by 77%, largely because of immigration from high-incidence countries, especially from Somalia.<sup>20</sup> In 2007, approximately 23% of the incident TB cases had EPTB.<sup>21</sup> Moreover, patients of foreign origins had most EPTB cases, and approximately two-thirds of all patients with EPTB were immigrants, approximately half from Somalia.<sup>20,22</sup> In addition, similar to the situation in Denmark, the incidence of TB in Greenland had doubled from 1990 to 1997.<sup>23</sup> This study was conducted to assess age, sex, and origin specific risk and categories of EPTB (involving a specific anatomic site) in a large cohort of TB patients that are believed to be diagnosed by using the same diagnostic standards.

### MATERIALS AND METHODS

**Study sample.** The study sample was composed of 5,684 TB patients, which represented approximately 99% of mycobacterial culture-confirmed non-pediatric TB cases ( $\geq 15$  years of age) diagnosed in Denmark during January 1, 1992–December 31, 2007. Of these 5,684 patients, 3,332 (58.7%) were males and 2,341 (41.3%) were females. The study sample consisted of 2,119 (37.3%) Danes, 1,090 (19.2%) Somalis, 795 (14.0%) Greenlanders, 654 (11.5%) Asians, and 1,026 (18.1%) patients of 112 other origins. The age of the study patients ranged between 15 and 96 years; 871 (15.3%) were 15–24 years old, 2,657 (46.7%) were 25–44 years old, 1,336 (23.5%) were 45–64 years old, and 820 (14.4%) were  $\geq 65$  years old.

\*Address correspondence to Zhenhua Yang, Department of Epidemiology, School of Public Health, University of Michigan, 1415 Washington Heights, 5124/SPH II, Ann Arbor, MI 48109-2029. E-mail: zhenhua@umich.edu

**Data collection.** Patient demographic and clinical information were obtained from the Danish National Tuberculosis Molecular Epidemiology Database that was available at the International Reference Laboratory of Mycobacteriology, Statens Serum Institut. In Denmark, there is a nationwide mandatory TB notification system. Physicians in hospitals and staff in the International Reference Laboratory of Mycobacteriology at Statens Serum Institut report TB cases to the Department of Epidemiology at Statens Serum Institut. The International Reference Laboratory of Mycobacteriology is the only laboratory in Denmark that performs mycobacterial culturing confirming TB diagnosis to assist in the national TB surveillance system. For the present study, a database without identifiers of the study subjects was used. This study was reviewed and approved by the health sciences institutional review board of the University of Michigan, the Danish National Ethical Committee, and the Danish Data Protection Agency.

**Study design and case definitions.** This study is a case-control study aiming at characterizing TB patients with different anatomic site involvement and identifying risk factors for having EPTB. On the basis of the origin of the specimens and clinical manifestations, the study patients were diagnosed as having pulmonary TB, extrapulmonary TB, or both. For this study, patients with TB exclusively in their lungs were classified as pulmonary TB (designated PTB). Patients with EPTB were categorized into two subgroups (EPTB alone and EPTB plus PTB) on the basis of whether they had TB exclusively at extrapulmonary tissue or organs or in pulmonary and extrapulmonary sites. These three groups were generated to compare the distribution of demographic characteristics between the PTB group and the EPTB alone group, and between the PTB group and the EPTB plus PTB group. In addition, patients with EPTB were grouped into seven categories, according to the classification of EPTB by the American Thoracic Society and the Centers for Disease Control and Prevention.<sup>11</sup> These seven categories (also called forms) include bone or/and joint TB, pleural TB, genitourinary TB, peritoneal TB, meningeal TB, lymphatic TB, and other. The distributions of the seven categories were compared between sexes, among different age groups, and between persons of different origins, respectively. Because of national legislation, we did not have access to HIV status of individual

patients, but because TB is an acquired immunodeficiency syndrome disease (AIDS)-defining disease, we knew the annual number of HIV-TB co-infected cases.

**Statistical analysis.** The chi-square test was used to test the difference in the distribution of the various demographic variables between the case and the control groups. The distribution of demographic characteristics was compared between the EPTB and the PTB group, and between the EPTB plus PTB group and the PTB group, respectively. To determine the associations between demographic characteristics and having EPTB alone or EPTB plus PTB, we calculated odds ratios and 95% confidence intervals by using the PTB group as the control group. We fit multivariate logistic regression models with interactions to test for interactions and control for confounders. In addition, we compared the distribution of PTB and the seven categories of EPTB between the two sexes, among the four age groups, and among the four origins groups, respectively, and adjusted for confounders by multiple regression analysis using the general linear model. All the statistical analyses were conducted by using SAS version 9.2 (SAS Institute, Cary, NC).

## RESULTS

**Frequency of different categories of TB.** Of the 5,684 cases, 3,759 (66.1%) were placed into the PTB group, 1,449 (25.5%) were placed in the EPTB alone group, and the remaining 476 (8.4%) were placed in the combined EPTB plus PTB group. The most commonly observed category of EPTB was lymphatic TB ( $n = 808$ , 49.1%), followed by pleural TB ( $n = 224$ , 13.6%), bone or/and joint TB ( $n = 214$ , 13.0%), genitourinary TB ( $n = 151$ , 9.2%), peritoneal TB ( $n = 92$ , 5.6%), meningeal TB ( $n = 42$ , 2.6%), and others ( $n = 113$ , 6.9%). There were 251 study subjects having EPTB at an unknown anatomic site and 30 subjects with EPTB at multiple extrapulmonary sites.

**Characteristics of EPTB cases.** Comparison of demographic characteristics between the EPTB alone and the PTB groups, and between the EPTB plus PTB and the PTB groups, respectively, by chi-square analysis showed a significant difference in the distributions of age, sex, and origin between the EPTB alone and the PTB groups, and a significant difference in distributions of age and origin between the EPTB plus PTB and the PTB groups (Table 1). When the PTB group was

TABLE 1

Distribution of age, sex, and origin among 5,684 TB patients diagnosed in Denmark during January 1, 1992–December 31, 2007 by three disease categories (PTB, EPTB alone, and EPTB plus PTB)\*

Characteristic	PTB (n = 3,759)	EPTB alone (n = 1,449)	<i>P</i> †	EPTB plus PTB (n = 476)	<i>P</i> †
	No. (%)	No. (%)		No. (%)	
Age, years			< 0.01		< 0.01
15–24	534 (14.2)	248 (17.1)		89 (18.7)	
25–44	1,683 (44.8)	763 (52.7)		211 (44.3)	
45–64	1,022 (27.2)	229 (15.8)		85 (17.9)	
≥ 65	520 (13.8)	209 (14.4)		91 (19.1)	
Sex			< 0.01		0.25
M	2,342 (62.4)	680 (47.1)		310 (65.1)	
F	1,410 (37.6)	765 (52.9)		166 (34.9)	
Origin			< 0.01		< 0.01
Denmark	1,666 (53.3)	257 (22.7)		196 (49.4)	
Somalia	474 (15.2)	527 (46.5)		89 (22.4)	
Greenland	716 (22.9)	40 (3.5)		39 (9.8)	
Asia	271 (8.7)	310 (27.3)		73 (18.4)	

\*TB = tuberculosis; PTB = pulmonary TB; EPTB alone = extrapulmonary TB alone; EPTB plus PTB = concurrent pulmonary and extrapulmonary TB.

† Probability from Chi-square analysis.

used as the referent group, patients diagnosed with TB who were 15–24, 25–44 years, or  $\geq 65$  years of age; females; and Somali or Asian were significantly overrepresented among the EPTB alone group, and patients 15–24 or  $\geq 65$  years of age and those who were Somali or Asian were significantly overrepresented among the EPTB plus PTB group.

**Distribution of PTB and different categories of EPTB.** We compared the distributions of PTB and different categories of EPTB among 4,432 of the 5,684 study patients for whom information on disease site was available by sexes, among different age groups, and origin groups, and adjusted for confounders (Figure 1). The distributions of lymphatic TB, meningeal TB, and pleural TB differed significantly between male and female TB patients after adjusting for age and origin (Figure 1A). Compared with males, females had a significantly higher proportion of lymphatic TB (22.2% versus 15.5%;  $P < 0.01$ ), but a significantly lower proportion of meningeal TB (0.6% versus 1.3%;  $P < 0.01$ ) and pleural TB (3.03% versus 4.80%;  $P < 0.01$ ). However, for both sexes, the lymphatic system

was the most frequently affected among all the extrapulmonary sites, and meningeal TB was the least commonly seen form.

After adjusting for age and sex, distributions of the different categories of EPTB, except for genitourinary TB, differed significantly among TB patients from the four origin groups (Figure 1B). Among Danes and Greenlanders, pleural TB was the most commonly observed form of EPTB (6.3%). Among Somalis and Asians, lymphatic TB was the most frequently observed form of EPTB, accounting for 32.2% and 36.0% of the study subjects of the two origins, respectively. Moreover, bone or/and joint TB was observed at a relatively higher frequency among Somalis (10.37%) than among patients of other origins (Figure 1B). The distributions of the seven categories of EPTB were similar between the Danes and the Greenlanders diagnosed with TB. However the rate of PTB among all TB cases of Greenlandic origin was higher than that among all the TB cases of Danish origin. Among the Greenlanders diagnosed with TB, pleural TB was the most frequently seen form of EPTB (3.8%), followed by lymphatic TB (2.6%). In addition, the distribution of lymphatic TB, genitourinary TB, and pleural TB significantly differed among different age groups after adjustment for sex and origin (Figure 1C). Overall, lymphatic TB was the most frequently seen form of EPTB in all four age groups, and the frequency of genitourinary TB increased with age.

**Risk factors for EPTB.** Using the PTB group as the control group, we assessed the effect of age, sex, and origin on the odds of having EPTB alone or EPTB plus PTB compared with PTB by fitting two multivariate logistic regression models. In the first model, the EPTB alone group was the case group (Table 2). In the second model the EPTB plus PTB group was the case group (Table 3).

As shown in Table 2, females were more likely to have EPTB alone than males. There were significant interactions between age and origin with regard to their association with EPTB alone. Among patients of Somali and Asian origins, persons 25–44 and 45–64 years of age had a significantly higher odds for having EPTB alone than persons 15–24 years of age. In contrast, among Greenlanders, the odds for having EPTB was significantly lower in persons 25–44 and 45–64 years of age than in persons 15–24 years of age. For all age groups, Somalis and Asians had increased odds for having EPTB alone and Greenlanders had a significantly reduced odds when compared with Danes.

No interactions were found among the three demographic variables regarding their effect on having EPTB plus PTB. Compared with persons 15–24 years of age, persons 25–44 and 45–64 years of age were less likely to have EPTB plus PTB (Table 3). Being female was an independent protective factor for having EPTB plus PTB. Compared with Danes, Somalis and Asians were more likely to have EPTB plus PTB, and Greenlanders had significantly lower odds.

In addition, considering the possibility that different specific types of EPTB may have different sets of risk factors as shown in an earlier study by Rieder and others,<sup>8</sup> we fit two multivariate logistic regression models with lymphatic TB and other forms of EPTB alone as the outcome variables, respectively, with PTB group as the reference, given that lymphatic TB accounted for the largest proportion of our EPTB alone sample. The same risk factors were found for lymphatic TB and all other EPTB alone. We also conducted the same analyses to compare risk factors for having pleural TB plus PTB and

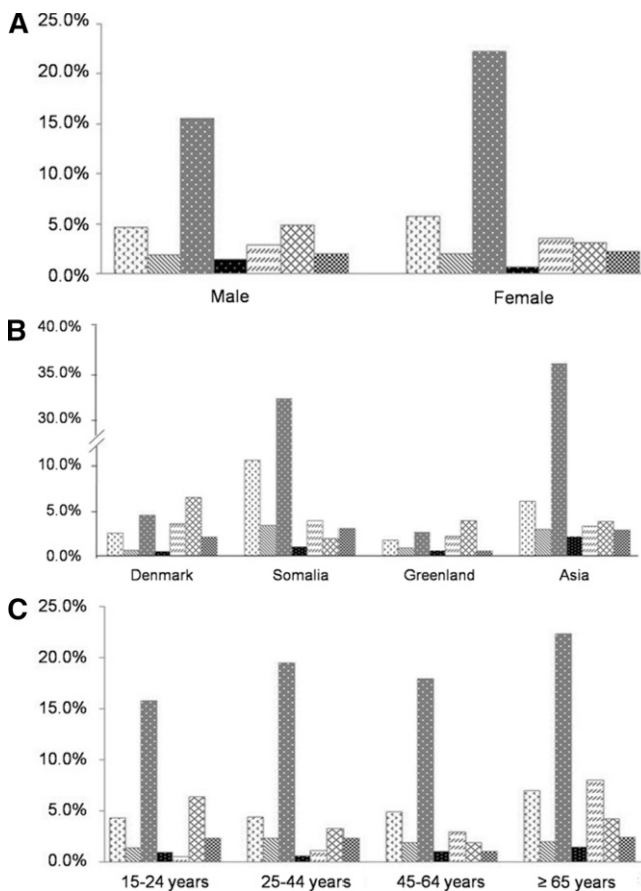


FIGURE 1. Distributions of different categories of extrapulmonary tuberculosis among 4,432 tuberculosis (TB) patients diagnosed in Denmark during 1992–2007 by **A**, sex, **B**, origin, and **C**, age, adjusting for other two of the three variables. Representations of different bars are as follows: bone and/or joint TB, peritoneal TB, lymphatic TB, meningeal TB, genitourinary TB, pleural TB, and other categories. Proportions of pulmonary TB were 67.3% among males and 61.1% among females; 80.4%, 44.6%, 88.2%, and 43.5% among Danes, Somalis, Greenlanders, and Asians, respectively; and 68.6%, 66.6%, 68.6%, and 52.9% among persons 15–24, 25–44, 45–64, and  $\geq 65$  years of age, respectively.

TABLE 2  
Multivariate logistic regression model determining independent risk factors and effect modifiers for having EPTB-alone (n = 4,258)

Characteristic	OR	95% CI	P‡	Characteristic	OR	95% CI	P‡	Characteristic	OR	95% CI	P‡
Danes				15–24 years				Male	1		
15–24 years	1			Danes	1			Female†	1.67	1.42–1.96	< 0.01
25–44 years	0.50	0.26–0.95	0.03	Somalis	4.40	2.37–8.17	< 0.01				
45–64 years	0.55	0.29–1.03	0.06	Greenlanders	0.78	0.35–1.74	0.55				
≥ 65 years	2.44	1.34–4.44	< 0.01	Asians	5.02	2.56–9.85	< 0.01				
Somalis				25–44 years							
15–24 years	1			Danes	1						
25–44 years	1.79	1.34–2.39	< 0.01	Somalis	15.85	11.24–22.35	< 0.01				
45–64 years	3.73	1.91–7.27	< 0.01	Greenlanders	0.45	0.27–0.91	0.02				
≥ 65 years	2.20	0.87–5.61	0.10	Asians	16.65	11.34–24.43	< 0.01				
Greenlanders				45–64 years							
15–24 years	1			Danes	1						
25–44 years	0.32	0.15–0.68	< 0.01	Somalis	30.11	15.2–59.67	< 0.01				
45–64 years	0.23	0.09–0.62	< 0.01	Greenlanders	0.33	0.14–0.78	0.01				
≥ 65 years	1.06	0.35–3.14	0.92	Asians	16.24	10.03–26.31	< 0.01				
Asians				≥ 65 years							
15–24 years	1			Danes	1						
25–44 years	1.65	1.07–2.54	0.02	Somalis	3.98	1.58–10.01	< 0.01				
45–64 years	1.76	1.04–3	0.04	Greenlanders	0.34	0.13–0.88	0.03				
≥ 65 years	0.47	0.22–0.98	0.04	Asians	0.97	0.5–1.89	0.92				

\* EPTB alone = extrapulmonary tuberculosis alone; PTB = pulmonary TB; OR = odds ratio; CI = confidence interval; PTB was used as the control.

† The sex association was not modified by either origin or age of the study subjects.

‡ Probability from Chi-square analysis.

the other EPTB plus PTB group; similar results were found for pleural TB plus PTB or the other EPTB plus PTB group.

## DISCUSSION

EPTB is a significant health problem worldwide because of difficulties in its diagnosis and in monitoring its treatment. Although probably underreported, its burden is believed to be increasing, especially among HIV-infected patients and AIDS patients.<sup>13,24,25</sup> This study was conducted to assess age-, sex-, and origin-specific risk and categories of EPTB in a large cohort of 5,684 TB patients diagnosed in Denmark during 1992–2007. Access to diagnosis and health care was essentially the same over time for all patient groups. Therefore, the study offered a unique opportunity for studying host factors by determining relative differences in disease patterns among ethnic groups living in Denmark and Greenland.

The major findings of this study were 1) one-third (1,925 of 5,684) of the patients had EPTB; 2) the distribution of a given

anatomic site involvement significantly varied according to the age and origin of the patients; 3) for all the age groups, the odds for having EPTB was significantly higher among the Somali and Asian patients and significantly lower among Greenlandic patients than Danish patients; and 4) among Somali and Asian patients, those 25–44 and 45–64 years of age were more likely to have EPTB alone than persons 15–24 years of age; in contrast, among Greenlanders, the two oldest age groups were significantly less likely to have EPTB alone than the youngest age group.

The proportion (30.7%) of EPTB among all the TB cases found in this study is comparable with the range reported previously in some industrialized countries. EPTB was found to account for 21.6%, 27%, and 38% of all TB cases in studies conducted in Germany,<sup>26</sup> the United States,<sup>6</sup> and The Netherlands, respectively.<sup>7</sup> In these studies, the proportions of immigrants were 32.1%, 43% and > 50%, respectively. Given that a higher proportion were immigrants (62.6%) in the present study than in any of the previous studies mentioned, the observed rate of EPTB seems to be lower than expected, especially because the present study did not include any pediatric TB, unlike the previous studies.

The finding that Asians and Somalis diagnosed with TB had a higher proportion of EPTB (58.5% and 56.5%, respectively) than Danes (21.4%) in our study is consistent with results of previous reports.<sup>7,27,28</sup> However, compared with a study conducted in Minnesota, United States, in which > 70% of Somali immigrants had EPTB,<sup>14</sup> our study found a lower proportion (56.5%) of EPTB among Somalis. In this study, > 90% of Asian patients originated from World Health Organization-defined high-burden countries.<sup>29</sup> Several previous studies have reported EPTB among TB cases in persons of Asian origin.<sup>28,30,31</sup> However, the present study is the first extensive study of EPTB involving a large sample of patients of Greenlandic origin. Previous studies have found the distribution of different categories of EPTB among immigrants,<sup>5,7,14</sup> but few studies have determined the sex-, age-, and origin-specific distribution

TABLE 3  
Multivariate logistic regression model determining independent risk factors for having EPTB plus PTB (n = 3,522)

Characteristics	OR	95% CI	P†
Age, years			
15–24	1		
25–44	0.72	0.53–0.98	0.04
45–64	0.55	0.38–0.80	< 0.01
≥ 65	1.18	0.81–1.72	0.39
Origin			
Denmark	1		
Somalia	1.52	1.12–2.08	0.01
Greenland	0.50	0.34–0.71	< 0.01
Asia	2.22	1.63–3.04	< 0.01
Sex			
M	1		
F	0.79	0.63–1.00	0.05

\* EPTB plus PTB = concurrent pulmonary and extrapulmonary tuberculosis; PTB = pulmonary TB; OR = odds ratio; CI = confidence interval; PTB was used as the control.

† Probability from Chi-square analysis.

of different categories of EPTB and adjusted for other demographic characteristics. This adjustment was possible in the current study because of the use of a large study sample. Our finding that the tropism of TB infection distribution of different anatomic site involvement significantly varied among age and origin groups has important implications for understanding the pathogenesis of EPTB.

Several demographic characteristics were identified as risk factors for EPTB. The association between sex and having EPTB alone is consistent with the findings from previous studies.<sup>5,6,16,26</sup> However, our observation that females had a significantly decreased likelihood of having EPTB plus PTB is new. The observed different effects of sex on having EPTB alone and having EPTB plus PTB are intriguing and warrant further investigations to gain a better understanding of the reasons for the observed variation in the sex effect between EPTB alone and EPTB plus PTB.

Another interesting and new observation in our study is that for all age groups, the odds for having EPTB was significantly higher among Somali and Asian patients and significantly lower among the Greenlandic patients than among the Danish patients. During the 20th century, a resurgence of TB was observed in many countries in Europe, including Denmark, partly caused by increased immigration from countries with a high burden of TB.<sup>5,32-34</sup> The association between immigration and increased prevalence of either TB or EPTB has been reported. However, the previously reported odds ratios for having EPTB among immigrants (1.5–5.1) were much lower than what was found among two age groups in the present study.<sup>5,6,28,35</sup>

To our knowledge, an age effect on patient origin and EPTB association has not been reported. A remarkable age modification of origin and EPTB association was observed in this study, as shown by the odds ratios for the comparison between Somalis and Danes. Moreover, EPTB developed in some immigrants after many years of residence in Denmark, which would imply that environmental factors might have a less important role in determining the likelihood of having EPTB than the host factors, including genetic background and immune status. It was particularly interesting to observe a significantly lower risk of having EPTB among Greenlanders diagnosed with TB than among Danes across all age groups, given the social and political links between Greenland and Denmark and well-documented TB transmission between Greenland and Denmark.<sup>36</sup> Approximately 85% of the population in Greenland is Inuit. The ethnicity/genetic constitution of Inuits is more related to the Asian/Mongolian phenotype than the Caucasian phenotype. The TB burden in Greenland is comparable with that in many parts of Asia (130 per 100,000 inhabitants). The difference in disease presentation found in this study among patients from Greenland compared with other high-burden regions such as Asia and Somalia further add to the hypothesis of host factors playing an important role. However, existence of certain Arctic *M. tuberculosis* clones with less affinity for extrapulmonary locations cannot be ruled out by this study.

Studies conducted in different populations showed inconsistent results regarding an age effect. One study that compared EPTB cases with PTB cases reported that being younger was a potential risk factor for having EPTB.<sup>15</sup> Another study reported no significant effect of age on the risk of EPTB, but the adjusted risk ratios also demonstrated a bimodal distribution.<sup>16</sup> The observation that a certain age or origin

group had different odds of having EPTB alone and EPTB plus PTB further suggested the difference between these two groups. This finding also indicates the future direction for studies to find determinant factors for having EPTB with and without pulmonary involvement.

Our study had several limitations. Information about several host factors that have been reported to be associated with the clinical presentations of TB infection, including HIV/AIDS status<sup>6,16,27,35</sup> and socioeconomic and life style factors (such as smoking)<sup>16</sup> was not recorded in the surveillance data that we used for the current study. In addition, Yang and others reported a significant association between infection with strains belonging to Beijing family of *M. tuberculosis* and EPTB.<sup>37</sup> Information about the genetic lineage of the study isolates was also not available for our study. Thus, any analysis on effect of these host and microbial factors or adjustment for their effect was not possible. Therefore, the observed effects of age, sex, and origin may be a reflection of a combination of effects of various host and microbial factors that were not included in the present study. However, considering that the prevalence of HIV/AIDS among TB patients was 2% by 2007, which was relatively low, we assume that the effect of HIV/AIDS on the study findings was limited.<sup>38</sup> Furthermore, the fact that few Beijing strains have been circulating in Denmark and Greenland may limit the effect of microbial factors on the study findings.

In conclusion, age, sex, and origin play an important role in the pathogenesis of *Mycobacterium tuberculosis* infection and affect the risk and clinical presentation of EPTB. This study generated knowledge that has important clinical and public health implications.

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Authors' addresses: Xinyu Zhang, Carl F. Marrs, Lixin Zhang, and Zhenhua Yang, Department of Epidemiology, University of Michigan, Ann Arbor, MI, E-mails: xinyuz@umich.edu, cfmarrs@umich.edu, lxzhang@umich.edu, and zhenhua@umich.edu. Aase B. Andersen, Department of Infectious Diseases, Odense University Hospital, Odense, Denmark, E-mail: bengaard@dadlnet.dk. Troels Lillebaek, Department of Infectious Diseases, Copenhagen University Hospital, Copenhagen, Denmark, E-mail: lillebaek@dadlnet.dk. Zaza Kamper-Jørgensen and Vibeke Østergaard Thomsen, International Reference Laboratory of Mycobacteriology, Statens Serum Institut, Copenhagen, Denmark, E-mails: zkj@ssi.dk and vot@ssi.dk. Karin Ladefoged, Medical Department, Queen Ingrid's Hospital, Nuuk, Greenland, E-mail: kala@peqgik.gl.

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