Major Article

Trends in the nontuberculous mycobacterial disease mortality rate in Japan: A nationwide observational study, 1997-2016

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Key points

This study assessed the national trends in mortality due to nontuberculous mycobacterial (NTM) disease in Japan from 1997 to 2016. The crude and age-adjusted NTM mortality rates increased during this period, particularly among females aged ≥80 years.

Key words: nontuberculous mycobacteria; trend analysis

Running title:

Trends in NTM mortality in Japan

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Abstract

Background: The incidence of nontuberculous mycobacterial (NTM) infections has been increasing worldwide, becoming a significant healthcare burden especially among elderly people. This study aimed to evaluate the trends in NTM-associated mortality in Japan.

Methods: This study used vital statistics data and data on all NTM-associated deaths (N=18,814) among individuals aged ≥40 years in Japan from 1997 to 2016. We calculated the crude and age-adjusted mortality rates by age and sex and used joinpoint regression to analyze trends and estimate the average annual percentage change (AAPC). We compared crude NTM- and tuberculosis (TB)-associated mortality rates by sex.

Results: The overall crude annual mortality rate increased from 0.63/100,000/year in 1997 to 1.93/100,000/year in 2016 and was the highest among individuals aged 80–84 years. The AAPC of the crude mortality rates among males of all ages and females aged 40–59 years were stable but increased among females aged 60–79 years (3.5%, 95% confidence interval [CI]: 2.8–4.3%) and ≥80 years (4.3%, 95% CI: 3.7–4.9%). Among males, the age-adjusted mortality rates did not show a significant trend, while among females, the rates increased over the study period (AAPC: 4.6%, 95% CI: 2.7–6.6%). In females, the crude NTM-associated mortality rate exceeded the TB mortality rate in 2014, 2015, and 2016.

Conclusions: NTM mortality increased in Japan between 1997 and 2016, especially among the elderly female population. Given the increasing NTM-associated mortality and susceptible aging population, public health authorities in Japan should pay greater attention to NTM infections.

Introduction

Nontuberculous mycobacteria (NTM) are mycobacteria other than *Mycobacterium tuberculosis* and special auxotrophs such as *Mycobacterium leprae,* and currently include more than 180 species [1]. NTM are ubiquitous environmental bacteria, that are present in soil and water sources [2]; among them, *Mycobacterium avium* complex (MAC), which includes *M. avium*, *M. intracellulare*, and *M. chimaera*, is the most common cause of NTM diseases worldwide, including Japan [3, 4]. Pathogenic NTM can infect humans as a result of ingestion, inhalation, and dermal contact from the environment, causing a wide variety of diseases [5]. Although NTM can invade lymph nodes, joints, skin, and soft tissues, they most frequently cause pulmonary lesions [5]. NTM pulmonary disease (NTM-PD) has two main presentations. The first presentation is a fibrocavitary disease, that occurs in patients with pre-existing pulmonary diseases, including chronic obstructive pulmonary disease or bronchiectasis. The second manifestation is a nodular bronchiectasis of the lingula and middle lobe, that tends to affect middle-aged and elderly women [6, 7].

The incidence of NTM infection has been increasing worldwide in recent years. During the past decade, the annual NTM disease incidence rates (per 100,000) in developed countries were as follows: 0.72–0.74 in France [8], 0.9–2.9 in the United Kingdom [9], 2.7–5.6 in the United States [10, 11], and 2.2–3.2 in Australia [12]. The increasing NTM disease incidence is placing a significant burden on healthcare systems [13, 14]. In Japan, which has a rapidly aging population, the reported incidence rates are higher than those of other developed countries. For instance, the annual incidence of NTM-PD in Nagasaki Prefecture was >10.0 per 100,000 population in 2008–2009 [15]. A large, laboratory-based study that used data from 4,710 Japanese institutions, revealed that the incidence rate of NTM-PD was 24.0 per 100,000 population in 2012–2013 [3]. Additionally, a national cross-sectional study based on health insurance claims data revealed an incidence rate of NTM-PD of 29.0 per 100,000

population in Japan in 2011, which was among the highest worldwide [16]. Another study, that included 551 medical facilities certified by the Japanese Respiratory Society, revealed an NTM-PD incidence rate of 14.7 per 100,000 population in Japan in 2014; this was a 2.6-fold increase since 2007 [17].

Elderly people are more susceptible to NTM disease, and advanced age is an important risk factor [10, 18]. Since Japan has one of the most rapidly aging populations in the world, it is possible that the mortality rate owing to NTM disease has been increasing. Although evaluating longitudinal national trends in NTM-associated mortality rates is essential for effective health policy administration, there have been no previous reports on the long-term trends in NTM-associated mortality rates in Japan. This study, therefore, aimed to examine current trends in NTM-associated mortality.

Materials and methods

Data source

Death certificates in Japan are comprehensively collected and saved as computerized files after being completed by medical doctors. The data files including patient's basic information are publicly available after anonymization. We examined the Japanese Vital Statistics data from 1997 to 2016, collected by the Japanese Ministry of Health, Labour and Welfare, which uses the *International Classification of Diseases, 10th revision* (ICD-10) to code the underlying causes of death [19]. NTM-associated mortality was defined using the ICD-10 codes A31 (A31.0, A31.1, A31.8, and A31.9), namely, "infection due to other mycobacteria," based on previous studies [20, 21]. Data on NTM-associated mortality analyzed in the present study were those recorded as the underlying cause of death in the death certificate, as performed in the previous study [21]. Data of patients aged ≥40 years were stratified by age and sex to calculate crude and age-adjusted mortality rates per 100,000 population. The age

was categorized as follows: 40–59 years, 60–79 years, and ≥80 years. All patients aged <40 years were excluded from the analysis owing to the small number of deaths in this age category. For comparison, we also examined tuberculosis (TB)-associated deaths among patients aged ≥40 years during the same period as the underlying cause of death (ICD–10 codes A15–A19).

Statistical analyses and data processing

To estimate the trends in crude and age-adjusted mortality rates, a joinpoint regression model was applied using the Joinpoint Regression Program, version 4.7.0.0, February 2019 (Statistical Research and Applications Branch, National Cancer Institute, USA). The annual percentage changes (APCs) between trend-change points were determined with 95% confidence intervals (CI). We used the direct age-standardization method to calculate age-adjusted rates of NTM-associated mortality using the Japanese population in 1997 as the standard population, expressed per 100,000 population, with 5-year age groups. To compare differences in mortality trends among population subgroups, we estimated the average annual percentage change (AAPC) for the entire period. A p-value <0.05 was defined as the level at which the slope was statistically significantly different from zero.

Ethics approval

This study used data published by the Japanese Ministry of Health, Labour and Welfare and the Statistics Bureau of the Ministry of Internal Affairs and Communications. Ethics approval was obtained by the institutional review board of Okayama University Hospital (No. 1910-009). The requirement for informed consent was waived, as the study was a retrospective analysis of routinely collected data.

Results

Number of NTM-associated deaths

In total, 18,791 NTM-associated deaths occurred over the 20-year study period. The annual number of deaths by sex is shown in **Fig. 1**. During the study period, the total number of deaths per year increased from 402 in 1997 to 1,487 in 2016. Although the number of NTM-associated deaths among males and females was similar in 1997 (183 and 219, respectively), the number of deaths among females were approximately double that of males in 2016 (478 and 1,009, respectively). The numbers of NTM-associated deaths by 5-year age groups are shown in **Fig. 2**. The number of NTM-associated deaths increased from 45 years of age, reaching its peak in both sexes in the 80–84-year age group.

Trends in the crude NTM mortality rates by age and sex

Fig. 3 summarizes the crude mortality rates of NTM-associated deaths among patients aged ≥40 years, by 20-year age groups and sex. The detailed results for each age group are provided in **Supplementary Table 1**. The overall crude annual mortality rate per 100,000 population increased from 0.63 in 1997 to 1.93 in 2016. The crude mortality rates were higher in both sexes of the older age groups. The results of the joinpoint regression analysis of the crude mortality rates by 20-year age groups are shown in **Table 1**. In males, AAPCs for the entire period of the crude mortality rates remained stable in all three age groups. Among females, although AAPCs in the 40–59-year age group were stable, those in the 60–79-year age group and ≥80-year age group showed continuous increases.

Trends in the age-adjusted NTM mortality rates by age and sex

The overall trends in age-adjusted NTM mortality rates by sex are shown in **Fig. 4**, and the

results of the joinpoint regression analysis by sex are shown in **Table 2.** The overall age-adjusted NTM mortality rates increased significantly over the study period.

Comparison of trends in the crude TB-associated and NTM-associated mortality rates

Fig. 5 shows the comparison of trends in the crude annual mortality rate of TB-associated deaths and NTM-associated deaths per 100,000 population, in all age groups combined. While the crude TB mortality rate decreased from 4.25/100,000 in 1997 to 2.44/100,000 in 2016, the crude NTM mortality rate increased from 0.63/100,000 in 1997 to 1.93/100,000 in 2016. While the crude TB mortality rate decreased in males, it remained higher than the NTM mortality rate. Conversely, in females, the crude NTM mortality exceeded the TB mortality rate during 2014–2016 and continued to increase.

Discussion

This study showed that the absolute number of deaths associated with NTM infections increased in Japan between 1997 and 2016; the overall crude annual mortality rate per 100,000 population increased from 0.63 to 1.93. Notably, our study showed significant differences in NTM mortality rates and NTM mortality trends, that is, dramatic increases in the number of deaths, especially in the older female population; this persisted even after age adjustment. Considering the increase in the aging population worldwide, the high NTM-associated mortality rate in the elderly may increase the socioeconomic burden on health services.

Increased NTM-associated mortality rates can be explained by the increased incidence of NTM disease in Japan. The number of newly diagnosed cases of NTM-PD has increased, with the incidence rate of 14.7 cases per 100,000 person-years in 2014; this increased from 5.7 cases per 100,000 person-years reported in 2007 [17]. Several factors may be contributing

to the increasing incidence of NTM disease, including increased awareness of NTM among healthcare practitioners, improved laboratory techniques for NTM identification, changes in host factors such as advanced age and various immunocompromising conditions, increased pathogenicity in the organisms, and changes in environmental factors [22, 23]. Among them, the increasing life-span among individuals of both sexes over the past 20 years is a prominent contributor in Japan, where the population aged over 65 years increased from 15.7% of the total population in 1997 to 27.3% in 2016. Considering the fact that NTM typically affects older individuals [10, 18], an increased number of the aged population must be an important contributing factor. Agricultural activities have been associated with NTM transmission [24], but we could not assess whether agricultural activities affected NTM mortality rates in this study owing to a lack of data.

In our study, the female population experienced a greater increase in mortality rates than the male population over the study period. Differences in NTM disease according to sex have varied among studies, but there are several possible explanations for the difference observed in the trend. First, a recent large population-based study in Korea reported that the overall ratio of female-to-male patients with NTM infection was 1.57, and the incidence of NTM infection in 2016 was approximately 2.5-fold higher in females than in males [25]. Additionally, it showed an age-adjusted mortality rate ratio of 2.16 among individuals with NTM disease relative to the general population [25]. Given these results, it is not surprising that in our study, females aged ≥80 years had a higher NTM mortality rate than in other sex and age groups in our study. Second, nearly 90% of pulmonary NTM in Japan is caused by MAC, and the prevalence of MAC infection occurs predominantly in the female elderly population [3]. Although the prognosis of MAC infection is considered to be relatively good, a recent systematic review by Diel *et al.* [26] reported that the 5-year all-cause mortality rate among individuals with MAC lung disease was as high as 27%. Third, *M. abscessus* complex

comprises a group of rapidly growing, multidrug-resistant NTM, with a relatively poor prognosis compared to other NTM infections [27]. The rate of *M. abscessus* complex infections is high among elderly females [27], and is reported to have increased approximately 5-fold from 1 case in 2001 to 5 cases per 1,000,000 person-years in 2014 [17]. This increase may have contributed to the increased mortality rate in the elderly female population.

Sex hormones may play an important role in postmenopausal women as a causative factor for NTM infection [28]. It is known that low serum estradiol levels are strongly related to MAC lung disease in middle-aged or elderly women, and that compared to uninfected controls, women with MAC lung disease have lower serum dehydroepiandrosterone sulfate levels [28, 29]. Chan *et al*. [30] reported that an abnormal expression of sex hormones, adipokines, and/or TGF-beta may explain why women of low weight and older age are more susceptible to NTM lung disease. Although these studies suggested that lower levels of sex hormones, especially estrogen, may result in an increased occurrence of NTM disease in elderly women, further investigation of these hormonal effects on immune function in NTM infection is required.

Despite the current increase in NTM incidence and mortality, the appropriate regimen and length of treatment for NTM-PD have not been established [31]. The management of NTM-PD is a challenge, as it requires prolonged use of combinations of multiple drugs such as macrolides, rifampin, and ethambutol, which have significant potential for toxicity and drug-drug interactions [32]. The decision to start treatment must be made based on the potential risks and benefits of therapy in individual patients. Based on recent studies [15, 33, 34], advanced age, male gender, low body mass index (<18.5 kg/m^2), underlying respiratory diseases (especially chronic pulmonary aspergillosis), particular radiographic findings (cavitary or nodular bronchiectasis), malignancy (pulmonary or extrapulmonary), chronic

heart or liver disease, anemia, hypoalbuminemia, and an erythrocyte sedimentation rate of >50 mm/h are indicators of poor prognosis. Considering these risk factors, the quality of life, and a patient-centered approach, rather than solely expecting microbiologic eradication [35], clinicians should determine whether to initiate treatment. Considering the increasing mortality rate in the elderly population, especially in women, decisions regarding the initiation and discontinuation of NTM treatment may become more challenging and open to question in the future.

We previously conducted similar research on trends in the incidence and mortality rate of TB in Japan from 1997 to 2016 [36]; this showed a decrease in the TB mortality rate over the 20-year period. Of note, our current study revealed that in females, the crude NTM mortality rate exceeded the crude TB mortality rate in 2014, 2015, and 2016. These results suggest that NTM has become a more serious threat than TB, especially among aged women. Therefore, we believe that healthcare and political measures to combat NTM infection should be taken urgently in Japan.

A strength of the present study is that it is the first to use the national database for the purpose of trend analysis for NTM-associated mortality in Japan, using joinpoint regression analysis. However, the study has several limitations owing to the nature of the data and the methods used. First, since the underlying causes of death were analyzed from death certificates, NTM-associated death rates may have been underestimated. Second, this study obtained data by selecting the causes of death from the nosological classifications provided in ICD-10; thus, it was impossible to determine whether the recorded cause of death was accurate. For example, the diagnosis of NTM lung disease is made by at least two isolations of an identical NTM organism from sputum or a single detection of NTM in invasive examinations, such as bronchoscopy or lung biopsy [37]. Thus, the diagnosis of NTM death can be inappropriately made and recorded. Finally, owing to the absence of clinical data, we could not determine the

infectious foci of NTM, perform in-depth analyses at a species level, or determine the prognosis of NTM infections. Moreover, data on comorbidities were not available from the death certificate, and the effect of immunocompromised states associated with NTM infection may have been underestimated. Since our study did not include ICD-10 code B20.0 (HIV disease resulting in mycobacterial infection and HIV disease resulting in tuberculosis), NTM-associated deaths related to HIV infection were not included in the analysis. However, other immunosuppressive conditions, which may have predisposed patients to NTM infections, were not excluded in this study. Despite these limitations, the present study evaluated the Japanese national NTM-associated mortality trends over a 20-year period. The findings of this study are useful for future policy decision making.

In conclusion, we identified an overall increasing trend of NTM-associated mortality, especially among the elderly female population in Japan over a 20-year period. In addition to the increasing size of the elderly population, we assume that an increased awareness of the disease among clinicians and technical advancements in bacterial identification may have contributed to the observed increase in NTM-associated mortality. Given the increased mortality and a susceptible aging population, NTM infections warrant greater attention from public healthcare providers to improve understanding on clinical care and healthcare planning.

Conflicts of interest

The authors declare no conflicts of interest in association with the present study.

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Respir Crit Care Med **2007**; 175: 367-416.

1   **Figure legends**

2   Fig. 1. Nontuberculous mycobacteria-associated deaths by year and sex, 1997–2016

3   Fig. 2. Age and sex distribution of nontuberculous mycobacteria-associated deaths,

4   1997–2016

5   Fig. 3. Crude nontuberculous mycobacteria-associated annual mortality rate (per

6   100,000 population) by age and sex, 1997–2016

7   Fig. 4. Age-adjusted nontuberculous mycobacteria-associated annual mortality rate (per

8   100,000 population) by sex, 1997–2016

9   Fig. 5. Comparison of crude tuberculosis and nontuberculous mycobacteria-associated

10   annual mortality rate, 1997–2016

11

12   Supplementary Table 1. Crude nontuberculous mycobacteria-associated annual

13   mortality rate (per 100,000 population) by age and sex, 1997–2016.

Table 1. Trends in the annual crude mortality rate due to non-tuberculosis mycobacteria-associated per 100,000 population aged ≥40 years by sex and age group, 1997–2016

Age group (years)	Period 1		Period 2		Average APC (%), (95% CI)	
	Years	APC (%)	Years	APC (%)		
Male						
40–59	1997–2016	−1.1			−1.1 (−3.3 to 1.1)	
60–79	1997–2001	7.7	2001–2016	−0.5	1.1 (−0.7 to 3.0)	
≥80	1997–2000	17.9	2000–2016	−0.1	2.5 (−0.5 to 5.6)	
Female						
40–59	1997–2016	1.5			1.5 (−0.9 to 3.9)	
60–79	1997–2016	3.5	*		3.5 (2.8 to 4.3)	*
≥80	1997–2016	4.3	*		4.3 (3.7 to 4.9)	*

* Significantly different from zero ($p < 0.05$)

Abbreviations: APC, annual percentage change; CI, confidence interval

Within each sex and age group, periods were separated as Period 1 and Period 2 when the trend changes were statistically detected in the Joinpoint regression analysis during the study period.

Table 2. Trends in the age-adjusted nontuberculous mycobacteria-associated mortality rate per 100,000 population aged ≥40 years, 1997–2016

	Period 1			Period 2			Entire study period	
	Years	APC (%)		Years	APC (%)		Average APC (%), (95% CI)	
Total	1997–2000	10.4	*	2000–2016	1.7	*	3.1 (2.0 to 4.1)	*
Male	1997–2000	11.4		2000–2016	−0.6		1.2 (–0.7 to 3.2)	
Female	1997–1999	16.1		1999–2016	3.3	*	4.6 (2.7 to 6.6)	*

* Significantly different from zero ($p < 0.05$)

Abbreviations: APC, annual percentage change; CI, confidence interval

Within each sex and age group, periods were separated as Period 1 and Period 2 when the trend changes were statistically detected in the Joinpoint regression analysis during the study period.

Figure 1

Fig. 1 Nontuberculous mycobacteria-associated deaths by year and sex, 1997–2016
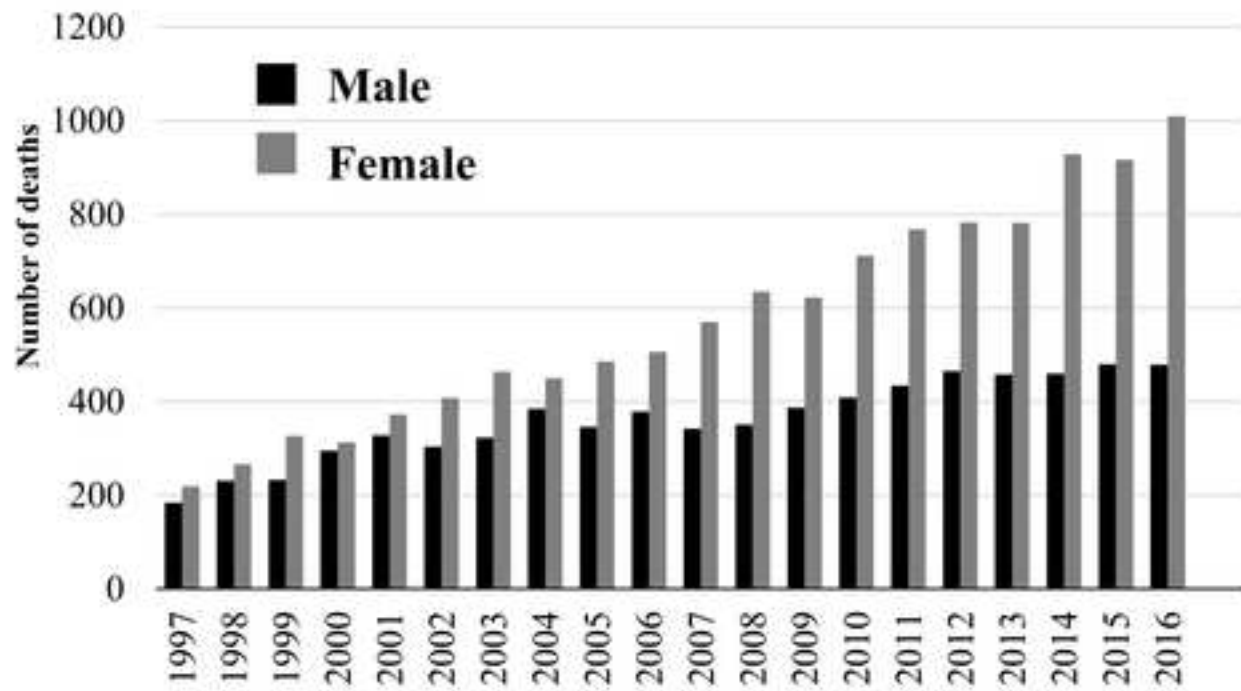
Figure 2

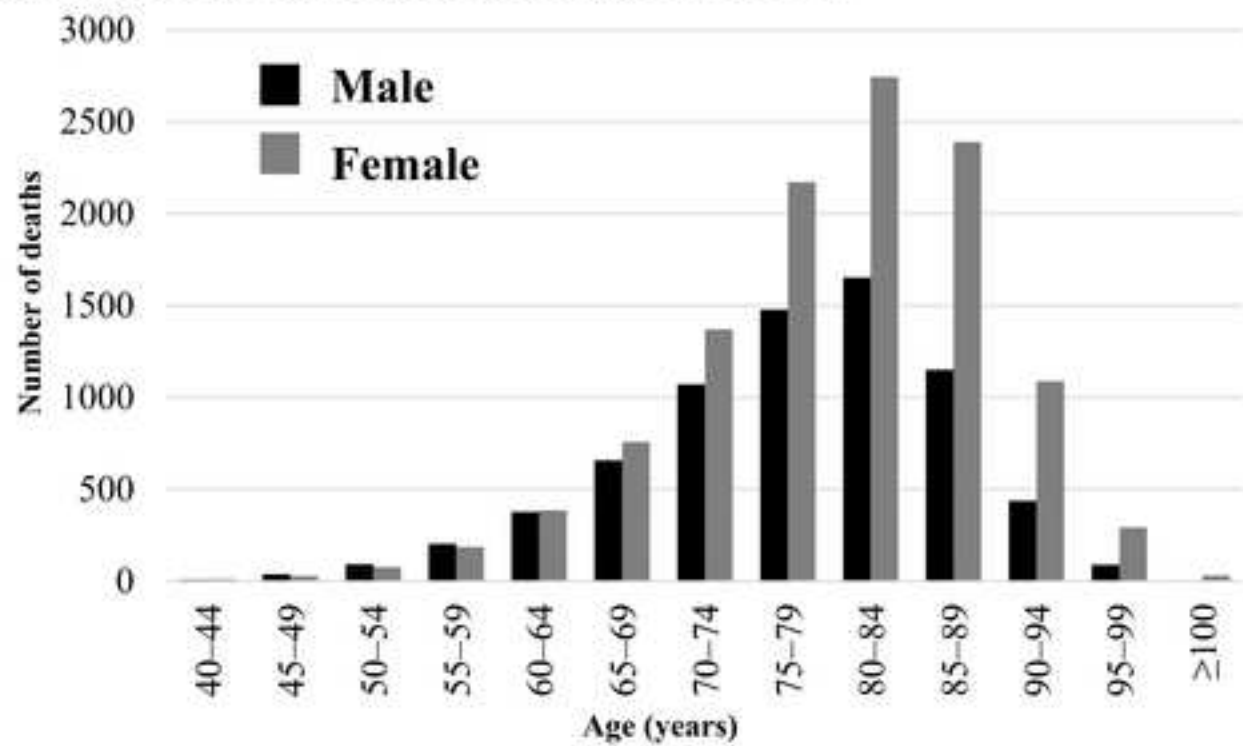Fig. 2 Age and sex distribution of nontuberculous mycobacteria-associated deaths, 1997–2016

Figure 3

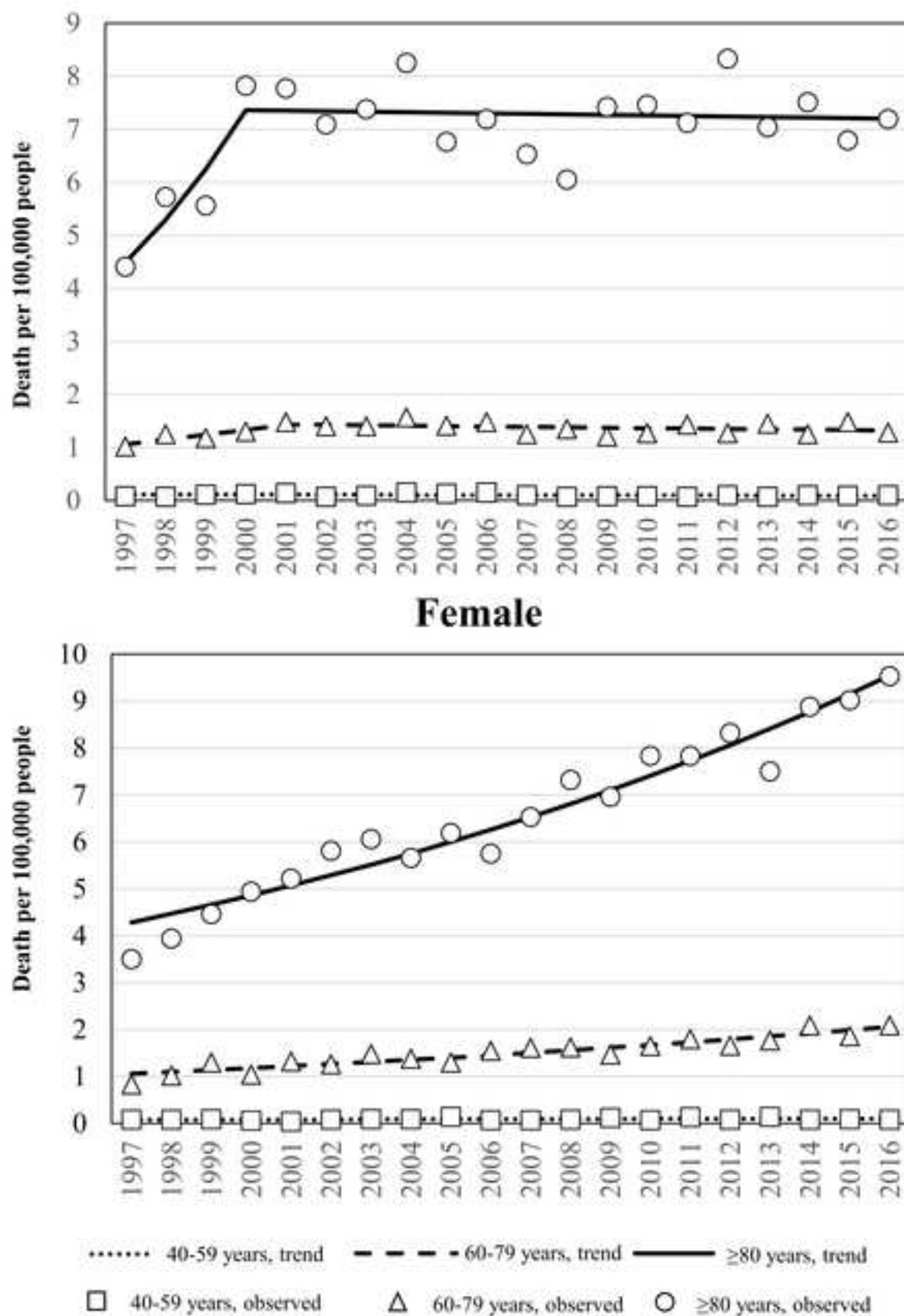Fig. 3 Crude nontuberculous mycobacteria-associated annual mortality rate (per 100,000 population) by age and sex, 1997–2016

Figure 4

Fig. 4 Age-adjusted nontuberculous mycobacteria-associated annual mortality rate (per 100,000 population) by sex, 1997–2016
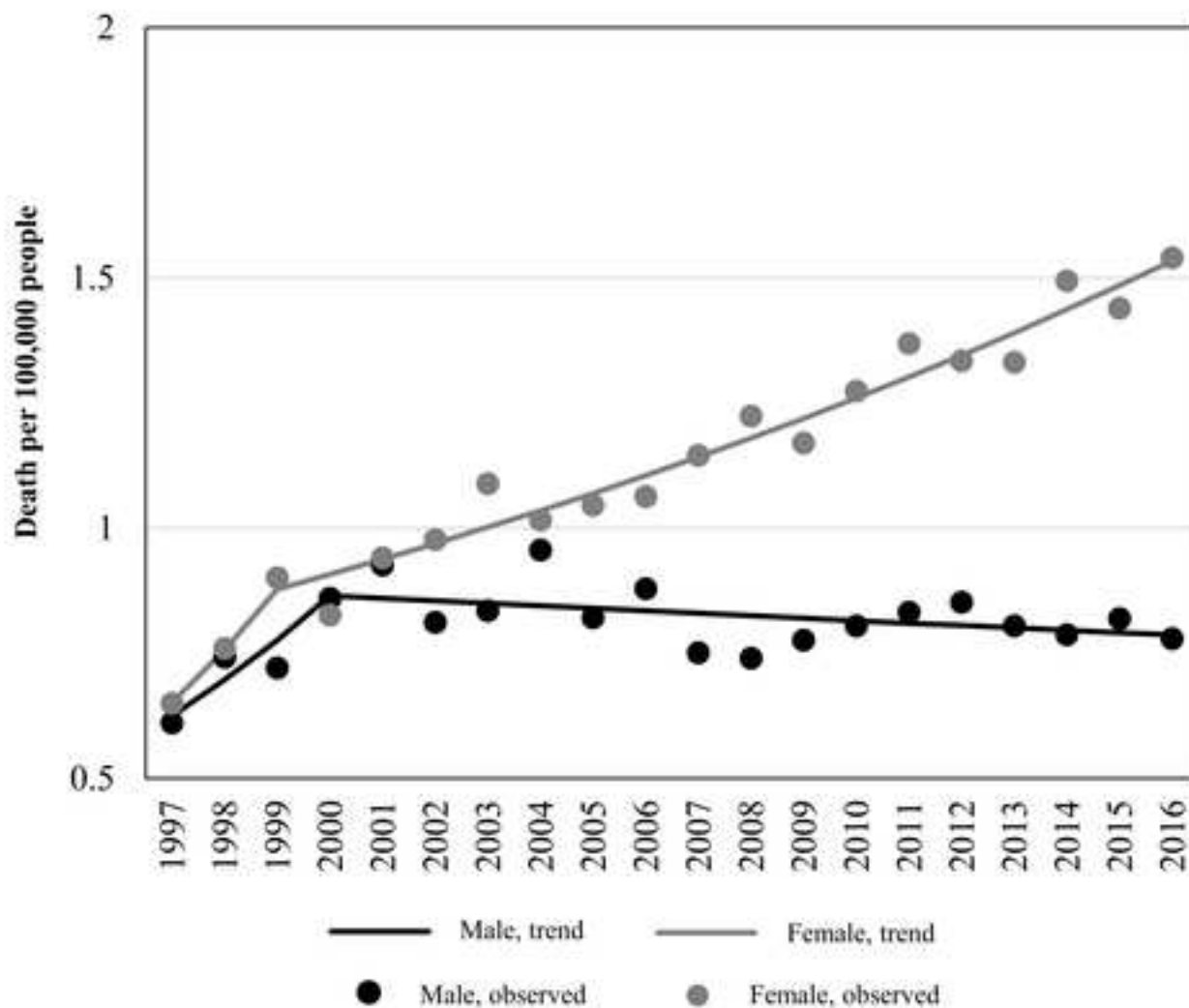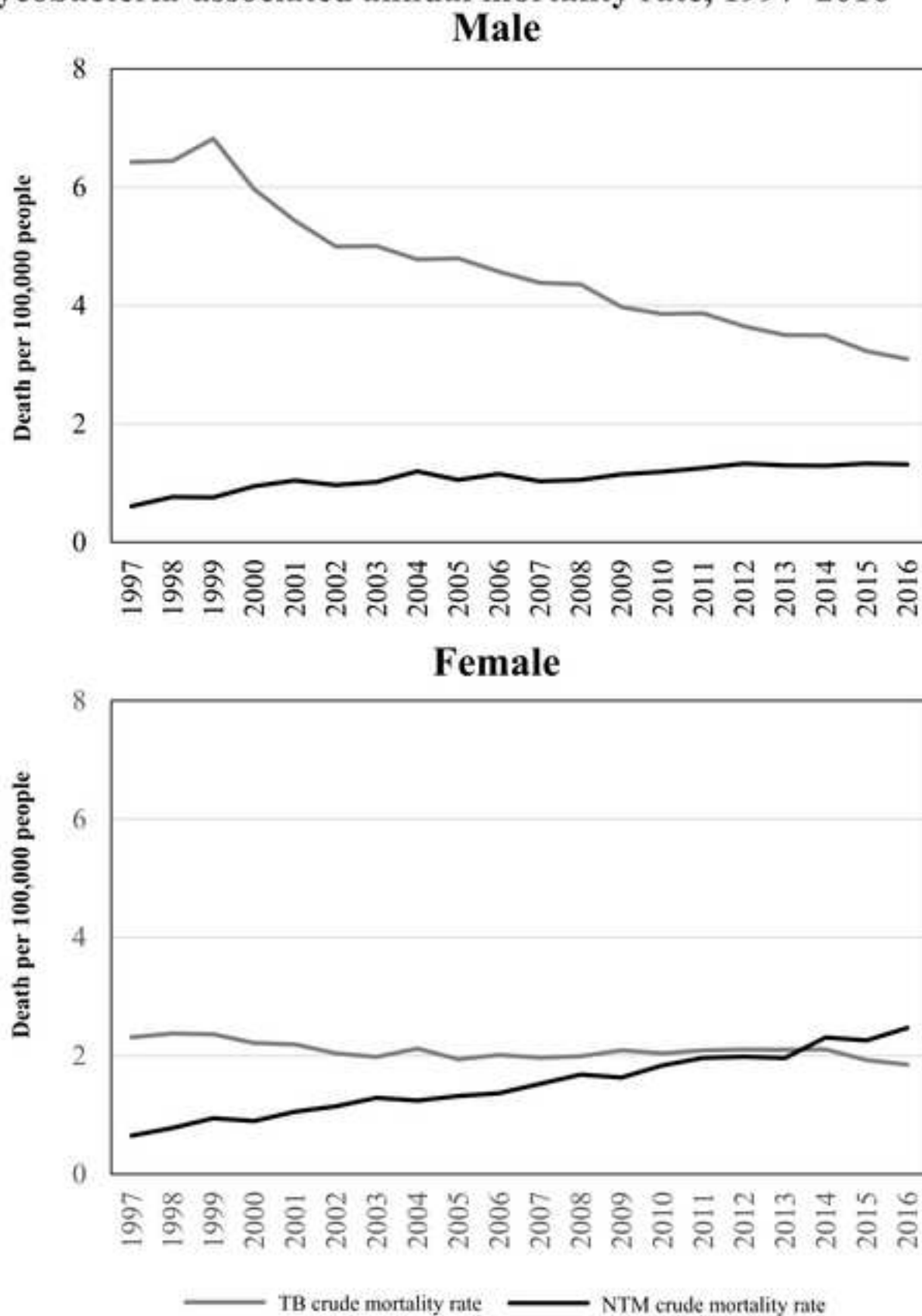
Figure 5

Fig. 5 Comparison of crude tuberculosis and nontuberculous mycobacteria-associated annual mortality rate, 1997–2016

Supplementary Table 1. Crude nontuberculous mycobacteria-associated annual mortality rate (per 100,000 population) by age and sex, 1997–2016.

Age (years)	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
≥40																				
Overall	0.63	0.77	0.86	0.92	1.05	1.06	1.16	1.22	1.20	1.27	1.29	1.39	1.41	1.53	1.63	1.68	1.65	1.83	1.82	1.93
Male	0.61	0.76	0.76	0.95	1.04	0.97	1.02	1.20	1.06	1.16	1.03	1.05	1.15	1.19	1.26	1.33	1.30	1.29	1.33	1.31
Female	0.65	0.78	0.95	0.90	1.06	1.15	1.29	1.24	1.32	1.37	1.53	1.68	1.63	1.84	1.97	1.99	1.96	2.31	2.26	2.47
40–59																				
Overall	0.08	0.08	0.10	0.09	0.09	0.08	0.09	0.12	0.13	0.11	0.09	0.07	0.10	0.08	0.10	0.09	0.10	0.09	0.09	0.09
Male	0.08	0.07	0.11	0.12	0.14	0.07	0.09	0.15	0.13	0.15	0.10	0.07	0.08	0.08	0.07	0.10	0.07	0.10	0.09	0.10
Female	0.08	0.08	0.09	0.06	0.04	0.08	0.09	0.09	0.14	0.07	0.07	0.08	0.12	0.07	0.13	0.08	0.14	0.08	0.09	0.08
60–79																				
Overall	0.91	1.13	1.25	1.16	1.39	1.32	1.44	1.47	1.35	1.52	1.44	1.50	1.35	1.47	1.63	1.47	1.62	1.69	1.68	1.71
Male	1.02	1.25	1.18	1.30	1.48	1.40	1.40	1.57	1.41	1.48	1.25	1.35	1.21	1.27	1.43	1.27	1.45	1.25	1.48	1.28
Female	0.83	1.02	1.30	1.04	1.32	1.26	1.48	1.38	1.30	1.55	1.61	1.62	1.47	1.65	1.80	1.66	1.77	2.09	1.86	2.09
≥80																				
Overall	3.80	4.52	4.81	5.87	6.04	6.22	6.48	6.48	6.37	6.22	6.53	6.90	7.12	7.71	7.59	8.32	7.34	8.41	8.24	8.71
Male	4.41	5.72	5.56	7.82	7.77	7.09	7.38	8.25	6.76	7.19	6.53	6.05	7.42	7.46	7.12	8.33	7.04	7.51	6.79	7.19
Female	3.50	3.94	4.46	4.94	5.22	5.81	6.06	5.66	6.19	5.75	6.53	7.32	6.96	7.83	7.83	8.32	7.50	8.88	9.02	9.53

Major Article

Trends in the nontuberculous mycobacterial disease mortality rate in Japan: A nationwide observational study, 1997-2016

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Key points

This study assessed the national trends in mortality due to nontuberculous mycobacterial (NTM) disease in Japan from 1997 to 2016. The crude and age-adjusted NTM mortality rates increased during this period, particularly among females aged ≥80 years.

Key words: nontuberculous mycobacteria; trend analysis

Running title:

Trends in NTM mortality in Japan

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Abstract

Background: The incidence of nontuberculous mycobacterial (NTM) infections has been increasing worldwide, becoming a significant healthcare burden especially among elderly people. This study aimed to evaluate the trends in NTM-associated mortality in Japan.

Methods: This study used vital statistics data and data on all NTM-associated deaths (N=18,814) among individuals aged ≥40 years in Japan from 1997 to 2016. We calculated the crude and age-adjusted mortality rates by age and sex and used joinpoint regression to analyze trends and estimate the average annual percentage change (AAPC). We compared crude NTM- and tuberculosis (TB)-associated mortality rates by sex.

Results: The overall crude annual mortality rate increased from 0.63/100,000/year in 1997 to 1.93/100,000/year in 2016 and was the highest among individuals aged 80–84 years. The AAPC of the crude mortality rates among males of all ages and females aged 40–59 years were stable but increased among females aged 60–79 years (3.5%, 95% confidence interval [CI]: 2.8–4.3%) and ≥80 years (4.3%, 95% CI: 3.7–4.9%). Among males, the age-adjusted mortality rates did not show a significant trend, while among females, the rates increased over the study period (AAPC: 4.6%, 95% CI: 2.7–6.6%). In females, the crude NTM-associated mortality rate exceeded the TB mortality rate in 2014, 2015, and 2016.

Conclusions: NTM mortality increased in Japan between 1997 and 2016, especially among the elderly female population. Given the increasing NTM-associated mortality and susceptible aging population, public health authorities in Japan should pay greater attention to NTM infections.

Introduction

Nontuberculous mycobacteria (NTM) are mycobacteria other than *Mycobacterium tuberculosis* and special auxotrophs such as *Mycobacterium leprae,* and currently include more than 180 species [1]. NTM are ubiquitous environmental bacteria, that are present in soil and water sources [2]; among them, *Mycobacterium avium* complex (MAC), which includes *M. avium*, *M. intracellulare*, and *M. chimaera*, is the most common cause of NTM diseases worldwide, including Japan [3, 4]. Pathogenic NTM can infect humans as a result of ingestion, inhalation, and dermal contact from the environment, causing a wide variety of diseases [5]. Although NTM can invade lymph nodes, joints, skin, and soft tissues, they most frequently cause pulmonary lesions [5]. NTM pulmonary disease (NTM-PD) has two main presentations. The first presentation is a fibrocavitary disease, that occurs in patients with pre-existing pulmonary diseases, including chronic obstructive pulmonary disease or bronchiectasis. The second manifestation is a nodular bronchiectasis of the lingula and middle lobe, that tends to affect middle-aged and elderly women [6, 7].

The incidence of NTM infection has been increasing worldwide in recent years. During the past decade, the annual NTM disease incidence rates (per 100,000) in developed countries were as follows: 0.72–0.74 in France [8], 0.9–2.9 in the United Kingdom [9], 2.7–5.6 in the United States [10, 11], and 2.2–3.2 in Australia [12]. The increasing NTM disease incidence is placing a significant burden on healthcare systems [13, 14]. In Japan, which has a rapidly aging population, the reported incidence rates are higher than those of other developed countries. For instance, the annual incidence of NTM-PD in Nagasaki Prefecture was >10.0 per 100,000 population in 2008–2009 [15]. A large, laboratory-based study that used data from 4,710 Japanese institutions, revealed that the incidence rate of NTM-PD was 24.0 per 100,000 population in 2012–2013 [3]. Additionally, a national cross-sectional study based on health insurance claims data revealed an incidence rate of NTM-PD of 29.0 per 100,000

population in Japan in 2011, which was among the highest worldwide [16]. Another study, that included 551 medical facilities certified by the Japanese Respiratory Society, revealed an NTM-PD incidence rate of 14.7 per 100,000 population in Japan in 2014; this was a 2.6-fold increase since 2007 [17].

Elderly people are more susceptible to NTM disease, and advanced age is an important risk factor [10, 18]. Since Japan has one of the most rapidly aging populations in the world, it is possible that the mortality rate owing to NTM disease has been increasing. Although evaluating longitudinal national trends in NTM-associated mortality rates is essential for effective health policy administration, there have been no previous reports on the long-term trends in NTM-associated mortality rates in Japan. This study, therefore, aimed to examine current trends in NTM-associated mortality.

Materials and methods

Data source

Death certificates in Japan are comprehensively collected and saved as computerized files after being completed by medical doctors. The data files including patient's basic information are publicly available after anonymization. We examined the Japanese Vital Statistics data from 1997 to 2016, collected by the Japanese Ministry of Health, Labour and Welfare, which uses the *International Classification of Diseases, 10th revision* (ICD-10) to code the underlying causes of death [19]. NTM-associated mortality was defined using the ICD-10 codes A31 (A31.0, A31.1, A31.8, and A31.9), namely, "infection due to other mycobacteria," based on previous studies [20, 21]. Data on NTM-associated mortality analyzed in the present study were those recorded as the underlying cause of death in the death certificate, as performed in the previous study [21]. Data of patients aged ≥40 years were stratified by age and sex to calculate crude and age-adjusted mortality rates per 100,000 population. The age

was categorized as follows: 40–59 years, 60–79 years, and ≥80 years. All patients aged <40 years were excluded from the analysis owing to the small number of deaths in this age category. For comparison, we also examined tuberculosis (TB)-associated deaths among patients aged ≥40 years during the same period as the underlying cause of death (ICD–10 codes A15–A19).

Statistical analyses and data processing

To estimate the trends in crude and age-adjusted mortality rates, a joinpoint regression model was applied using the Joinpoint Regression Program, version 4.7.0.0, February 2019 (Statistical Research and Applications Branch, National Cancer Institute, USA). The annual percentage changes (APCs) between trend-change points were determined with 95% confidence intervals (CI). We used the direct age-standardization method to calculate age-adjusted rates of NTM-associated mortality using the Japanese population in 1997 as the standard population, expressed per 100,000 population, with 5-year age groups. To compare differences in mortality trends among population subgroups, we estimated the average annual percentage change (AAPC) for the entire period. A p-value <0.05 was defined as the level at which the slope was statistically significantly different from zero.

Ethics approval

This study used data published by the Japanese Ministry of Health, Labour and Welfare and the Statistics Bureau of the Ministry of Internal Affairs and Communications. Ethics approval was obtained by the institutional review board of Okayama University Hospital (No. 1910-009). The requirement for informed consent was waived, as the study was a retrospective analysis of routinely collected data.

Results

Number of NTM-associated deaths

In total, 18,791 NTM-associated deaths occurred over the 20-year study period. The annual number of deaths by sex is shown in **Fig. 1**. During the study period, the total number of deaths per year increased from 402 in 1997 to 1,487 in 2016. Although the number of NTM-associated deaths among males and females was similar in 1997 (183 and 219, respectively), the number of deaths among females were approximately double that of males in 2016 (478 and 1,009, respectively). The numbers of NTM-associated deaths by 5-year age groups are shown in **Fig. 2**. The number of NTM-associated deaths increased from 45 years of age, reaching its peak in both sexes in the 80–84-year age group.

Trends in the crude NTM mortality rates by age and sex

Fig. 3 summarizes the crude mortality rates of NTM-associated deaths among patients aged ≥40 years, by 20-year age groups and sex. The detailed results for each age group are provided in **Supplementary Table 1**. The overall crude annual mortality rate per 100,000 population increased from 0.63 in 1997 to 1.93 in 2016. The crude mortality rates were higher in both sexes of the older age groups. The results of the joinpoint regression analysis of the crude mortality rates by 20-year age groups are shown in **Table 1**. In males, AAPCs for the entire period of the crude mortality rates remained stable in all three age groups. Among females, although AAPCs in the 40–59-year age group were stable, those in the 60–79-year age group and ≥80-year age group showed continuous increases.

Trends in the age-adjusted NTM mortality rates by age and sex

The overall trends in age-adjusted NTM mortality rates by sex are shown in **Fig. 4**, and the

results of the joinpoint regression analysis by sex are shown in **Table 2.** The overall age-adjusted NTM mortality rates increased significantly over the study period.

Comparison of trends in the crude TB-associated and NTM-associated mortality rates

Fig. 5 shows the comparison of trends in the crude annual mortality rate of TB-associated deaths and NTM-associated deaths per 100,000 population, in all age groups combined. While the crude TB mortality rate decreased from 4.25/100,000 in 1997 to 2.44/100,000 in 2016, the crude NTM mortality rate increased from 0.63/100,000 in 1997 to 1.93/100,000 in 2016. While the crude TB mortality rate decreased in males, it remained higher than the NTM mortality rate. Conversely, in females, the crude NTM mortality exceeded the TB mortality rate during 2014–2016 and continued to increase.

Discussion

This study showed that the absolute number of deaths associated with NTM infections increased in Japan between 1997 and 2016; the overall crude annual mortality rate per 100,000 population increased from 0.63 to 1.93. Notably, our study showed significant differences in NTM mortality rates and NTM mortality trends, that is, dramatic increases in the number of deaths, especially in the older female population; this persisted even after age adjustment. Considering the increase in the aging population worldwide, the high NTM-associated mortality rate in the elderly may increase the socioeconomic burden on health services.

Increased NTM-associated mortality rates can be explained by the increased incidence of NTM disease in Japan. The number of newly diagnosed cases of NTM-PD has increased, with the incidence rate of 14.7 cases per 100,000 person-years in 2014; this increased from 5.7 cases per 100,000 person-years reported in 2007 [17]. Several factors may be contributing

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to the increasing incidence of NTM disease, including increased awareness of NTM among healthcare practitioners, improved laboratory techniques for NTM identification, changes in host factors such as advanced age and various immunocompromising conditions, increased pathogenicity in the organisms, and changes in environmental factors [22, 23]. Among them, the increasing life-span among individuals of both sexes over the past 20 years is a prominent contributor in Japan, where the population aged over 65 years increased from 15.7% of the total population in 1997 to 27.3% in 2016. Considering the fact that NTM typically affects older individuals [10, 18], an increased number of the aged population must be an important contributing factor. Agricultural activities have been associated with NTM transmission [24], but we could not assess whether agricultural activities affected NTM mortality rates in this study owing to a lack of data.

In our study, the female population experienced a greater increase in mortality rates than the male population over the study period. Differences in NTM disease according to sex have varied among studies, but there are several possible explanations for the difference observed in the trend. First, a recent large population-based study in Korea reported that the overall ratio of female-to-male patients with NTM infection was 1.57, and the incidence of NTM infection in 2016 was approximately 2.5-fold higher in females than in males [25]. Additionally, it showed an age-adjusted mortality rate ratio of 2.16 among individuals with NTM disease relative to the general population [25]. Given these results, it is not surprising that in our study, females aged ≥80 years had a higher NTM mortality rate than in other sex and age groups in our study. Second, nearly 90% of pulmonary NTM in Japan is caused by MAC, and the prevalence of MAC infection occurs predominantly in the female elderly population [3]. Although the prognosis of MAC infection is considered to be relatively good, a recent systematic review by Diel *et al.* [26] reported that the 5-year all-cause mortality rate among individuals with MAC lung disease was as high as 27%. Third, *M. abscessus* complex

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comprises a group of rapidly growing, multidrug-resistant NTM, with a relatively poor prognosis compared to other NTM infections [27]. The rate of *M. abscessus* complex infections is high among elderly females [27], and is reported to have increased approximately 5-fold from 1 case in 2001 to 5 cases per 1,000,000 person-years in 2014 [17]. This increase may have contributed to the increased mortality rate in the elderly female population.

Sex hormones may play an important role in postmenopausal women as a causative factor for NTM infection [28]. It is known that low serum estradiol levels are strongly related to MAC lung disease in middle-aged or elderly women, and that compared to uninfected controls, women with MAC lung disease have lower serum dehydroepiandrosterone sulfate levels [28, 29]. Chan *et al*. [30] reported that an abnormal expression of sex hormones, adipokines, and/or TGF-beta may explain why women of low weight and older age are more susceptible to NTM lung disease. Although these studies suggested that lower levels of sex hormones, especially estrogen, may result in an increased occurrence of NTM disease in elderly women, further investigation of these hormonal effects on immune function in NTM infection is required.

Despite the current increase in NTM incidence and mortality, the appropriate regimen and length of treatment for NTM-PD have not been established [31]. The management of NTM-PD is a challenge, as it requires prolonged use of combinations of multiple drugs such as macrolides, rifampin, and ethambutol, which have significant potential for toxicity and drug-drug interactions [32]. The decision to start treatment must be made based on the potential risks and benefits of therapy in individual patients. Based on recent studies [15, 33, 34], advanced age, male gender, low body mass index (<18.5 kg/m^2), underlying respiratory diseases (especially chronic pulmonary aspergillosis), particular radiographic findings (cavitary or nodular bronchiectasis), malignancy (pulmonary or extrapulmonary), chronic

heart or liver disease, anemia, hypoalbuminemia, and an erythrocyte sedimentation rate of >50 mm/h are indicators of poor prognosis. Considering these risk factors, the quality of life, and a patient-centered approach, rather than solely expecting microbiologic eradication [35], clinicians should determine whether to initiate treatment. Considering the increasing mortality rate in the elderly population, especially in women, decisions regarding the initiation and discontinuation of NTM treatment may become more challenging and open to question in the future.

We previously conducted similar research on trends in the incidence and mortality rate of TB in Japan from 1997 to 2016 [36]; this showed a decrease in the TB mortality rate over the 20-year period. Of note, our current study revealed that in females, the crude NTM mortality rate exceeded the crude TB mortality rate in 2014, 2015, and 2016. These results suggest that NTM has become a more serious threat than TB, especially among aged women. Therefore, we believe that healthcare and political measures to combat NTM infection should be taken urgently in Japan.

A strength of the present study is that it is the first to use the national database for the purpose of trend analysis for NTM-associated mortality in Japan, using joinpoint regression analysis. However, the study has several limitations owing to the nature of the data and the methods used. First, since the underlying causes of death were analyzed from death certificates, NTM-associated death rates may have been underestimated. Second, this study obtained data by selecting the causes of death from the nosological classifications provided in ICD-10; thus, it was impossible to determine whether the recorded cause of death was accurate. For example, the diagnosis of NTM lung disease is made by at least two isolations of an identical NTM organism from sputum or a single detection of NTM in invasive examinations, such as bronchoscopy or lung biopsy [37]. Thus, the diagnosis of NTM death can be inappropriately made and recorded. Finally, owing to the absence of clinical data, we could not determine the

infectious foci of NTM, perform in-depth analyses at a species level, or determine the prognosis of NTM infections. Moreover, data on comorbidities were not available from the death certificate, and the effect of immunocompromised states associated with NTM infection may have been underestimated. Since our study did not include ICD-10 code B20.0 (HIV disease resulting in mycobacterial infection and HIV disease resulting in tuberculosis), NTM-associated deaths related to HIV infection were not included in the analysis. However, other immunosuppressive conditions, which may have predisposed patients to NTM infections, were not excluded in this study. Despite these limitations, the present study evaluated the Japanese national NTM-associated mortality trends over a 20-year period. The findings of this study are useful for future policy decision making.

In conclusion, we identified an overall increasing trend of NTM-associated mortality, especially among the elderly female population in Japan over a 20-year period. In addition to the increasing size of the elderly population, we assume that an increased awareness of the disease among clinicians and technical advancements in bacterial identification may have contributed to the observed increase in NTM-associated mortality. Given the increased mortality and a susceptible aging population, NTM infections warrant greater attention from public healthcare providers to improve understanding on clinical care and healthcare planning.

Conflicts of interest

The authors declare no conflicts of interest in association with the present study.

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1 **Figure legends**

2 Fig. 1. Nontuberculous mycobacteria-associated deaths by year and sex, 1997–2016

3 Fig. 2. Age and sex distribution of nontuberculous mycobacteria-associated deaths,

4 1997–2016

5 Fig. 3. Crude nontuberculous mycobacteria-associated annual mortality rate (per

6 100,000 population) by age and sex, 1997–2016

7 Fig. 4. Age-adjusted nontuberculous mycobacteria-associated annual mortality rate (per

8 100,000 population) by sex, 1997–2016

9 Fig. 5. Comparison of crude tuberculosis and nontuberculous mycobacteria-associated

10 annual mortality rate, 1997–2016

11

12 Supplementary Table 1. Crude nontuberculous mycobacteria-associated annual

13 mortality rate (per 100,000 population) by age and sex, 1997–2016.