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Risk factors for developing *Mycobacterium kansasii* lung disease

A case-control study in Korea

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Abstract

Previous studies have suggested that development of Mycobacterium kansasii lung disease (MKLD) was associated with COPD, pneumoconiosis, aging, male, immunosuppression, alcohol, malignancy, and certain occupations such as mining and sandblasting. However, previous studies were outdated and used non-comparative statistical methods. We aimed to determine the current risk factors for developing MKLD in Korea by using appropriate statistical techniques.

Eighty-six MKLD patients were identified through a search of the Ulsan University Hospital database between January 2010 and December 2014. These cases were matched with 172 controls who had normal respiratory systems in a health examination during the same period (matching variables, age and sex; case: control ratio of 1:2). Clinical and demographic characteristics were gathered by reviewing the medical record and telephone survey. Multivariate logistic regression analyses were performed to evaluate risk factors for developing MKLD.

Multivariate analysis showed that occupation in heavy industries (adjusted odds ratio (aOR) 6.41, 95% confidence interval (CI) 2.19−18.74, $P = .001$) and low body mass index (BMI) (aOR [per kg/m^2] 0.73, 95% CI 0.63−0.85, $P < .001$) were independent risk factors for development of MKLD. Educational attainment more than high school was associated with a lower risk of MKLD development (aOR 0.22, 95% CI 0.08−0.63, $P = .005$).

Employees in heavy industry and low BMI are independent risk factors for development of MKLD in Korea.

Abbreviations: AFB = acid fast bacilli; aOR = adjusted odds ratio; BMI = body mass index; CI = confidence intervals; COPD = chronic obstructive lung disease; CT = computed tomography; CVA = cerebrovascular accident; HIV = human immunodeficiency virus; ISCO = international standard classification of occupations; MKLD = *Mycobacterium kansasii* lung disease; NTM = nontuberculous mycobacterium; OR = odds ratio; SD = standard deviation; USD = United States dollar.

Keywords: body mass index, heavy industry, *Mycobacterium kansasii* lung disease, occupation, risk factor

1. Introduction

Nontuberculous mycobacteria (NTM) related diseases are increasing worldwide. NTM are ubiquitous in the environment; soil, water, and water pipes.[1,2] The majority of these organisms are considered to be opportunistic pathogens; however, some species can cause diseases even in immunocompetent hosts. NTM species that cause pulmonary disease vary between countries and regions. In the United States and Japan, *M. avium* complex and *M. kansasii* are the common causative organisms.[1,3,4] In Korea, the *M. avium* complex and *M. abscessus* have been reported as the major pathogens of NTM lung disease.[5,6] *M. kansasii* was reported as a rare organism in Korea.[5,7,8] However, Ulsan (an industrialized city located in the southeast of Korea) showed a high proportion of MKLD, as reported in the previous publication.[9]

Editor: Takeshi Saraya.

The study was approved by the Ulsan University Hospital Institutional Review Board (IRB).

This work received grants from Ulsan University Hospital (Biomedical Research Center Promotion Fund, UUH-2014-2) and Environmental Health Center funded by the Ministry of Environment, Republic of Korea.

The authors have no conflicts of interest to disclose.

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Medicine (2019) 98:5(e14281)

Received: 26 May 2018 / Received in final form: 14 September 2018 / Accepted: 2 January 2019

http://dx.doi.org/10.1097/MD.0000000000014281

Previous studies have suggested that development of MKLD is associated with certain occupations, such as mining (pneumoconiosis) and sandblasting.[10–13] However, these occupational risk factors were not able to explain the high prevalence of MKLD seen in Ulsan. As Ulsan is the industrialized city, there are various occupations including office workers and employees in heavy industry. Therefore, we attempted to identify the epidemiologic risk factors for developing MKLD in Korea.

2. Materials and methods

2.1. Study subjects

2.1.1. Patients with MKLD. Based on the results of the acid-fast bacilli culture test, performed between January 2010 and December 2014 at Ulsan University Hospital (a 940-bed referral hospital in Ulsan), 86 patients with MKLD were identified through the medical record review. The diagnosis of MKLD was established according to the 2007 American Thoracic Society / Infectious Diseases Society of America guidelines.[14]

2.1.2. Normal controls and matching. The patients with MKLD were matched to 172 controls. Control individuals were selected from the health-screening program at Ulsan University Hospital Health Checkup Center, who demonstrated normal chest computed tomography (CT) results at a health examination that was performed from January 2010 to December 2014. A total of 922 control candidates were considered, and random case−control matching (the ratio was 1:2) was performed based on age and sex. This study was approved by the Institutional Review Board and Ethics Committee of Ulsan University Hospital.

2.2. Data collection

The epidemiological and clinical characteristics were obtained from medical records and health checkup data. The epidemiological/occupational and clinical data were default survey items of the health-screening program. Compared to the control group, the MKLD group had limitations in the epidemiological data. To overcome these limitations, we conducted telephone surveys. Questionnaire consisted of 12 questions focusing on sociodemographic characteristics, including smoking status, alcohol, education, marital status, employment, income, sources of drinking water, and etc.

For the classification of workers based on the occupation, we used the 6th revision of the Korean Standard Classification of Occupations, which was based on the recent classification in ISCO-08.[15] The classification ranged from higher skilled white-collar, lower skilled white-collar, pink-collar, green-collar, skilled blue-collar, and unskilled blue-collar workers. Skilled white-collar workers included legislators, senior officials, managers, and professionals. Lower-skilled white-collar workers included technicians and associated professionals. Pink-collar workers included clerks, and sales and customer service workers. Green-collar workers included those working in agriculture, the related sales, and forestry. Skilled blue-collar workers included craftsmen, plant and machine operators, and assemblers. Unskilled blue-collar workers included elementary workers. We obtained an individual history of occupations: the longest and current occupation. Ulsan has the world's largest shipyard and automobile plant. Thus, many workers are employees in heavy industry. Also, we divided occupations into 2 major categories: employees in heavy industry or not.

Smoking status was categorized as "never", "former", or "current". Those who smoked fewer than 100 cigarettes in their lifetime were characterized as "never smoker".[16] The sources of drinking water divided into tap water or not. Household-type was classified into 2 categories: house and apartment. Educational attainment was stratified into 3 groups: less than high school, high school or equivalent, or more than high school. We divided monthly family income groups by 3400 USD/month. For employees in the cities of Korea, approximately 3400 USD/month indicated the 5th income decile.[17]

This study was reviewed and approved by the institutional review boards of Ulsan university hospital. All subjects were informed about the aims of the study, and the informed consent was obtained by verbal explanations.

2.3. Statistical analysis

Results are shown as mean ± SD. Statistical analyses were performed using SPSS software 21.0 (SPSS Inc., Chicago, IL). Independent *t* tests and chi-square tests/Fisher exact tests were used to compare means and frequencies, respectively. Case−control matching was done by using the R statistical package (version 3.2.1, 2015). Univariate and multivariate logistic regression analyses were used to determine the risk factors for developing MKLD. Variables showing a significant correlation in univariate analyses were included in multivariate adjustment. The results of the multivariate adjustment were presented by their adjusted odds ratios and 95% confidence intervals. In addition, subgroup analyses were performed to determine the effect of the occupation (heavy industry vs non-heavy industry) on developing MKLD. All study subjects (cases and controls) were divided into heavy industry group and non-heavy industry group according to their occupations. To each subgroup, adjustments were endeavored to the same variables in the previously performed multivariate analysis except needed to differentiate subgroups variable (heavy industry or not), but variables of "drinking tap water" in non-heavy industry group and "history of malignancy" in heavy industry group were not suitable for analysis. A P value of less than .05 was considered to be significant.

3. Results

The mean age was 56.4 ± 12.9 years in the MKLD group and 54.2 ± 10.4 years in the control group. The male−female ratios were 6.2:1 (74 males, 12 females) in the MKLD group and 8.6:1 (154 males, 18 females) in the control group, respectively. The MKLD group showed a significantly lower BMI (20.7 ± 3.1 m^2/kg vs 24.8 ± 2.8 m^2/kg, $P < .001$). There were differences between the groups in terms of smoking status (current smoker, 52.3% in MKLD vs 24.1% in control, $P < .001$) and alcohol consumption (bottle/week, 1.8 ± 2.5 in MKLD vs 0.8 ± 1.8 in control, $P = .001$). Other findings that were more common in the patients of the MKLD group were a higher rate of drinking tap water (95.9% vs 86.6%, $P = .029$), family income below 3400 USD/month (78.4% vs 36.5%, $P < .001$), and low educational attainment (more than high school, 12.8% in MKLD vs 54.5% in control, $P < .001$). The MKLD group had more comorbid conditions; malignancies was more common in the MKLD group (16.3% vs 3.5%, $P < .001$); pulmonary diseases were only observed in the MKLD group (COPD in 4 [4.7%], asthma in 3 [3.5%], bronchiectasis in 6 [7.0%], and history of tuberculosis in 23 [26.7%]). There were no differences in the

Table 1

Demographic characteristics and comorbidity.

Characteristics	MKLD (n = 86)	Control (n = 172)	*P* value
Age	56.4 ± 12.9	54.2 ± 10.4	.150
Sex	74/12	154/18	.410
Height (cm)	168.4 ± 8.4	168.3 ± 7.0	.932
BMI (kg/m^2)	20.7 ± 3.1	24.8 ± 2.8	<.001
Smoking			<.001
Never a smoker	22 (25.6)	55 (32.4)	
Former smoker	19 (22.1)	74 (43.5)	
Current smoker	45 (52.3)	41 (24.1)	
Alcohol consumption (bottle/week)	1.8 ± 2.5	0.8 ± 1.8	.001
Educational attainment			<.001
Less than high school	41 (47.7)	32 (19.2)	
High school or less	34 (39.5)	44 (26.3)	
More than high school	11 (12.8)	91 (54.5)	
Drinking tap water	71 (95.9)	142 (86.6)	.029
Marital status (married)	76 (92.7)	162 (94.7)	.517
Employees in heavy industry	45 (52.3)	22 (12.8)	<.001
Family income (below $3,400/month)	58 (78.4)	61 (36.5)	<.001
Household type			.681
House	25 (29.1)	54 (31.6)	
Apartment	61 (70.9)	117 (68.4)	
Comorbidities			
Diabetes mellitus	9 (10.5)	27 (15.7)	.253
Hypertension	18 (20.9)	26 (15.1)	.242
CVA	4 (4.7)	13 (7.6)	.375
Previous TB	23 (26.7)	0 (0)	<.001
COPD	4 (4.7)	0 (0)	.004
Bronchiectasis	6 (7.0)	0 (0)	<.001
Asthma	3 (3.5)	0 (0)	.014
Liver disease	6 (7.0)	7 (4.1)	.314
Malignancy	14 (16.3)	6 (3.5)	<.001
HIV	1 (1.2)	0 (0.0)	.156

Data were presented by mean ± SD or n (%).

BMI = body mass index, COPD = chronic obstructive pulmonary disease, CVA = cerebrovascular accident, HIV = human immunodeficiency virus, MKLD = *Mycobacterium kansasii* lung disease, TB = tuberculosis.

prevalence of diabetes, hypertension, cerebrovascular accident, HIV, and liver disease (Table 1).

In terms of occupations, the MKLD group had smaller numbers of higher skilled white-collar workers (1.2% vs 24.5%) and lower-skilled white-collar workers (17.4% vs 30.4%). The control group had more pink-collar and green-collar workers than the MKLD group (10.8% vs 2.4%; 6.5% vs 2.4%). Skilled and unskilled blue-collar workers were much more common in the MKLD group (14.0% vs 3.0%; 47.7% vs 0.6%). In addition, the MKLD group was more likely to be associated with employees in heavy industry (52.3% vs 12.8%, $P < .001$) (Table 2).

Chest CT was available for 252 participants (93% in MKLD vs 100% in control). Cavities were observed in 45 of 86 MKLD patients (52.3%), nodules were observed in 71 patients (82.6%), and bronchiectasis was observed in 31 patients (36.0%). The location of the radiological findings was in the upper lobe in 69.8% of all cases. In the MKLD group, the reported symptoms were cough (45.3%) and hemoptysis (12.8%). Dyspnea and weight loss were reported in 9.3% and 7.0%, respectively. 8.1% had febrile sense or night sweats (Table 3).

On univariate analysis, MKLD group showed a lower BMI (odds ratio (OR) [per m^2/kg] 0.62, 95% CI 0.55–0.70, $P < .001$), current smoking status (OR 2.74, 95% CI 1.43–5.26, $P = .002$), more alcohol consumption (OR [per bottles/week] 1.25, 95% CI 1.08–1.45, $P = .002$), low household income (OR [< 3400 USD/month] 6.30, 95% CI 3.33–11.91, $P < .001$), and higher education attainment (OR [above high school] 0.09, 95% CI 0.04–0.21, $P < .001$). Subjects with MKLD were more likely to be engaged in heavy industry (OR 6.59, 95% CI 3.55–12.23, $P < .001$). The MKLD group also had more history of any malignancy (OR 5.38, 95% CI 1.99–14.56, $P = .001$), and drank more tap water (OR 3.67, 95% CI 1.06–12.66, $P = .040$) (Table 4).

On multivariate analysis, factors associated with development of MKLD included employees in heavy industry (aOR (adjusted odds ratio) 6.41, 95% CI 2.19–18.74, $P = .001$) and low BMI (aOR [per kg/m^2] 0.73, 95% CI 0.63–0.85, $P < .001$). The level of education was inversely related to the development of MKLD (aOR [above high school] 0.22, 95% CI 0.08–0.63, $P = .005$). In contrast, smoking status, alcohol consumption, income, drinking tap water, and malignancy were not related to the MKLD (Table 4).

In the subgroup analyses, low BMI was independently associated with MKLD development in both non-heavy and heavy industry workers (non-heavy industry workers: aOR [per kg/m^2] 0.729, 95% CI 0.602–0.881, $P = .001$; heavy industry workers: aOR [per kg/m^2] 0.642, 95% CI 0.447–0.922,

Table 2

Occupational differences between groups.

	MKLD (n = 86)	Control (n = 172)	*P*
Occupations according to the Korean			<.001
Standard classification			
Higher skilled white-collar workers	1 (1.2)	41 (24.5)	
Lower skilled white-collar workers	15 (17.4)	51 (30.4)	
Pink-collar workers	2 (2.4)	18 (10.8)	
Green-collar workers	2 (2.4)	11 (6.5)	
Skilled blue-collar workers	12 (14.0)	5 (3.0)	
Unskilled blue-collar workers	41 (47.7)	1 (0.6)	
Housewives	8 (9.3)	14 (8.3)	
Others	1 (1.2)	12 (7.1)	
No stable job	4 (4.7)	15 (8.9)	
Employees in heavy industry	45 (52.3)	22 (12.8)	<.001

Data were presented by n (%).

MKLD = Mycobacterium kansasii lung disease.

Table 3

Clinical and radiologic characteristics of the MKLD group.

Characteristics		MKLD, n (%)
Location	Upper lobe	60 (69.8)
	Middle lobe	6 (7.0)
	Lower lobe	12 (14.0)
Radiologic findings	Nodule	71 (82.6)
	Cavity	45 (52.3)
	Bronchiectasis	31 (36.0)
	Lymphadenopathy	7 (8.1)
Symptoms	Cough	39 (45.3)
	Sputum	37 (43.0)
	Hemoptysis	11 (12.8)
	Dyspnea	8 (9.3)
	Weight loss	6 (7.0)
	Febrile sense	5 (5.8)
	Sweating	2 (2.3)

MKLD = Mycobacterium kansasii lung disease.

Table 4

Logistic regression model analysis of demographic characteristics associated with MKLD.

Variable	OR	95% CI	*P*	aOR	Adjusted 95% CI	*P*
BMI (per kg/m^2)	0.62	0.55–0.70	<.001	0.73	0.63–0.85	<.001
Current smoker	2.74	1.43–5.26	.002	1.02	0.33–3.14	.976
Alcohol (per bottles/week)	1.25	1.08–1.45	.002	1.22	0.98–1.53	.078
Familial income <3400USD/month	6.30	3.33–11.91	<.001	2.01	0.78–5.20	.151
Educational attainment (more than high school)	0.09	0.04–0.21	<.001	0.22	0.08–0.63	.005
Employees in heavy industry	6.59	3.55–12.23	<.001	6.41	2.19–18.74	.001
Drinking tap water	3.67	1.06–12.66	.040	2.67	0.50–14.35	.253
Malignancy	5.38	1.99–14.56	.001	2.88	0.36–23.26	.320

MKLD = Mycobacterium kansasii lung disease, USD = United States dollar.

P = .016). The level of education showed different results in subgroup analyses: in non-heavy industry workers, education status was inversely related to the development of MKLD (aOR [above high school] 0.061, 95% CI 0.012–0.298, P = *.001), however, in heavy industry workers, there was no independent relation between education status and MKLD (aOR [above high school] 3.613, 95% CI 0.286–45.711,* P = *.321) (Fig. 1).*

4. Discussion

Unlike other regions in Korea, Ulsan has had a high proportion of *M. kansasii* isolations and a high prevalence rate of MKLD according to a recent study.[9] The reason for this predilection is unclear; therefore, we attempted to identify epidemiological (including occupational) risk factors for development of MKLD in Korea. Based on multivariate analysis, a lower BMI and employees in heavy industry were identified as independent risk factors for MKLD. Educational attainment above high school was associated with a lower risk of development of MKLD.

In this study, the MKLD group was more likely to have jobs in heavy industry. It has previously been noted that MKLD was more prevalent in urban areas and among those with dusty occupations, such as coal mining, steelmaking, and glass manufacturing.[10,12,18–20] In British Columbia, *M. kansasii* isolates were reported from the area of smelting industry.[19] During 1968 to 1979, in Czechoslovakia, *M. kansasii* was isolated from a total of 297 individuals residing in the Karviná, where almost 56% of individuals were heavy industry workers and were occupationally exposed to high dust concentrations.[10] In Japan, the south coast area along the Pacific Ocean, which is the principal industrial area, the incidence of disease due to *M. kansasii* was 0.03 to 0.11 per 100,000 people per year, until 1977; it further increased after 1978, reaching 0.33 per 100,000 in 1981.[20]

In the animal study reported in 1967, guinea-pigs were infected with *M. kansasii* via an intravenous route under the dusty conditions of coal and quartz.[21] This experiment demonstrated that dust increased the pulmonary infection. Furthermore, as dust deposits in the lungs increased, the extent of lung lesions increased with a linear relationship. In our study, 51% of the MKLD group was employed in heavy industry and 47% of this group was unskilled blue-collar workers. The majority of cases might be involved in elevated dust concentrations due to the grinding of metals, welding, and etc. These findings imply that the high rate of MKLD in Ulsan might be attributable to the dusty conditions associated with heavy industrial occupations.

Our finding that the MKLD group had lower BMI supports prior reports stating that slender individuals are more susceptible to NTM lung disease.[22–25] Besides low BMI, previous reports have also identified a number of risk factors for MKLD, such as smoking, COPD, corticosteroids, or other immunosuppressive agents. Another study found that the probability of NTM isolation of patients with bronchiectasis was significantly higher in the females with low BMI.[26] Although NTM infection is able to reduce body weight, Kim and colleagues showed that self-reported BMI before NTM diagnosis were significantly lower than control subjects.[25]

We found that subjects with lower educational attainment might be more vulnerable to developing MKLD. In contrast, income, smoking, and alcohol use were not independently related to the development of MKLD. In a previous 5-year population based study in the United States, indicators of lower socioeconomic status were common among MKLD: median incomes per year were $32,317 with cases and $38,048 without cases.[27] People of a lower socioeconomic status tend to exhibit unhealthy behaviors, such as cigarette smoking, drinking, lack of exercise, and low intake of vegetables. On the other hand, an increased risk for *M. kansasii* infection among those with a higher socioeconomic status has been reported previously.[28] Higher socioeconomic status is related to more social support and easier access to health care. Potential confounders, including drinking alcohol, smoking, and individual behavior of seeking health care examination could influence the consistency of the results of socioeconomic status between the studies.

In the present study, subgroup analyses were performed to determine the effect of the occupation (heavy industry vs non-heavy industry) on developing MKLD. Results showed that regardless of whether they are engaged in heavy industry or not, BMI is considered to be an independent factor associated with MKLD development. Conflicting results in subgroup analyses about the level of education and MKLD development suggest that the impact of environmental condition (employee in heavy industry) is greater than the educational impact on the development of MKLD. Further studies in other cohorts are needed in this regard.

In terms of tap water, many NTM species, including *M. kansasii* are relatively chlorine-resistant[29] and *M. kansasii* have frequently been isolated from tap water samples.[30,31] In our adjusted model, it did not contribute to the development of MKLD. Previous studies have shown that clusters of infection by environmental mycobacteria occur in areas where the water supply is contaminated.[24] In addition, a recent study from the Czech reported the presence of *M. kansasii* in water used for employee hygiene in industrial companies and collieries.[32] Some investigators supported the idea that the presence of NTM in drinking water should be of no concern.[13] Tanaka and

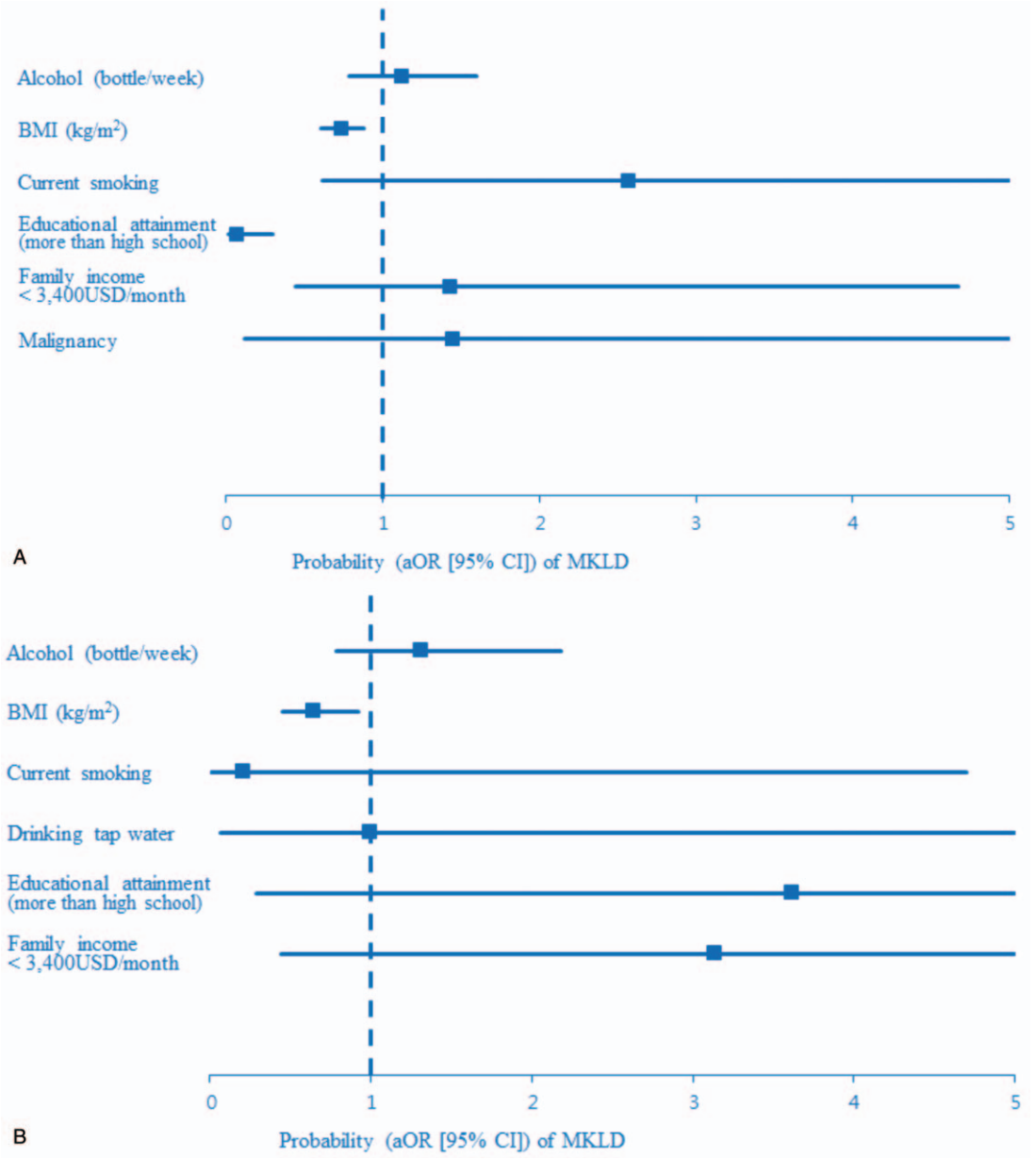

Figure 1. Subgroup Analyses for MKLD development: (A) Non-heavy industry workers, (B) Heavy industry workers. aOR = adjusted odds ratio, CI = confidence interval, MKLD = *Mycobacterium kansasii* lung disease.

colleagues found no distinct association of pulmonary NTM with specific water exposures.[33] Drinking boiled tap water, which is a common practice in Korean cultures, might explain the disparity between these analyses. Unfortunately, we did not examine the sources of drinking water at the workplaces or the processes before drinking such as boiling, filtering, and storage methods. Further studies are needed to determine whether *M. kansasii* is present in the water sources and the water distribution system at their workplaces.

In terms of demographic characteristics, we observed a predominance of the disease among men. These results were consistent with a recent study on MKLD in Korea.[34] We also found that the MKLD group had a more frequent history of pulmonary tuberculosis, COPD, asthma, and bronchiectasis than the control group. There are often predisposing lung conditions, including pneumoconiosis[35] and COPD.[18] In Great Britain, among 154 patients with MKLD, 33 had pneumoconiosis.[35] In southern California, seven of 12 patients with MKLD had preexisting pulmonary disease.[18] In our study, history of any malignancy was more prevalent in the MKLD. *M. kansasii* could be an infrequent but serious cause of pulmonary infection in patients with cancer, presumably due to the malignancy itself or chemotherapy.[36,37]

Our radiological investigations yielded similarities with previous studies. A high proportion of nodules and cavities were most frequently found in the upper lobe. It is known that *M. kansasii* infection is associated with cavity and a predilection for upper lobe disease.[38–40]

The present study has several limitations. First, this study is a retrospective study based on medical records. Although we

conducted telephone surveys to overcome this limitation, it is possible that some bias remained. Second, heavy industry workers in dusty conditions might be related to the development of MKLD. However, we did not investigate individual workplace environments or which types of dust (e.g., metallic, mineral, and chemical dust) contributed greatly to MKLD. Therefore, further study is needed to assess the workplace environment and to measure inhalable dusts. Lastly, there could have been a selection bias: the control group could afford to pay for and seek out health care; socioeconomic status may have affected the differences between 2 groups.

We found that MKLD patients have varying demographic profiles, including harmful environmental exposures in heavy industry and increased individual susceptibility characteristics (low BMI and education status). Further studies assessing more precise environmental risk factors for development of MKLD are needed.

Author contributions

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