Environment or Host?

A Case–Control Study of Risk Factors for *Mycobacterium avium* Complex Lung Disease

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Rationale: *Mycobacterium avium* complex lung disease is an increasingly common and chronically debilitating problem. Several host traits have been suggested or confirmed as risk factors. Potential environmental and behavioral risk factors have also been proposed. Few have been evaluated in comparative studies.

Objectives: To determine if aerosol-generating activities in the home and garden, features of the home water supply, or several pulmonary and immune-compromising conditions are associated with *Mycobacterium avium* complex lung disease.

Methods: Cases were recruited from academic medical centers and by informal referrals from nonuniversity practices in Washington and Oregon. Control subjects were recruited by random-digit dialing and matched to cases by age, sex, and partial telephone number. Associations were measured as odds ratios (OR) estimated using conditional logistic regression.

Measurements and Main Results: Known and potential risk factors were measured by in-home interview. Fifty-two matched pairs were studied. Six of 12 examined host traits were associated with disease, including history of chronic obstructive pulmonary disease (OR, 10; 95% confidence interval [CI], 1.2–80), pneumonia hospitalization

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Mycobacterium avium complex can be isolated from a variety of environmental niches in the residential environment, including aerosolized soil and water. It occasionally causes lung disease in HIV-negative adults without cystic fibrosis. It is unknown the extent to which behaviors that generate aerosols in the residential environment are risk factors for disease acquisition, or if risk is primarily determined by host susceptibility.

What This Study Adds to the Field

This study used a comparative, population-based design to examine aerosol-generating behaviors in the home and garden and several pulmonary and nonpulmonary conditions as potential risk factors for *Mycobacterium avium* complex lung disease in an HIV-negative, general adult population.

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(OR, 3.4; 95% CI, 1.1–11), and steroid use (OR, 8; 95% CI, 1.6–41). In contrast, 11 of the 14 aerosol-generating activities and all five features of home water supply studied bore little or no association with disease.

Conclusions: Aerosol-generating activities seem not to be risk factors for *Mycobacterium avium* complex lung disease in HIV-negative adults, but prior lung disease and immune-suppressing drugs seem to be associated with susceptibility.

Keywords: nontuberculous mycobacteria; matched case–control studies; gardening; aerosols; disease susceptibility

Members of the *Mycobacterium avium* complex (MAC) can cause infectious lung disease, even in adults who have no apparent immune defects. Three population-based studies of the frequency of nontuberculous mycobacterial (NTM) diseases have found evidence for increasing prevalence of MAC lung disease over the last two decades (1–3), although one such study only found evidence for increased respiratory colonization with MAC, which corresponded temporally to the introduction of new laboratory methods (4). Comparative epidemiologic studies have identified several host traits as risk factors for infectious MAC lung disease, including advanced age (5), thoracic skeletal abnormalities (6, 7), gastroesophageal reflux disease (GERD) (8), certain HLA types (9, 10), and cystic fibrosis transmembrane receptor mutations (11). Additional host factors are strongly suspected based on case-only studies or on studies of other NTM lung diseases (1, 7, 12, 13). For example, the

frequency of prior chronic obstructive pulmonary disease (COPD) and steroid use appear high in NTM pulmonary disease cases series, but these factors have not been evaluated in comparative studies.

MAC and other NTM have been identified in numerous environmental niches (14–20), including aerosols generated from colonized water (21) and soil (22). Given that aerosolized respiratory droplets play a role in tuberculosis transmission and exposure to occupational aerosols is associated with hypersensitivity responses to MAC (19, 23), it is reasonable to hypothesize that aerosolization of environmental materials colonized with MAC could cause lung disease.

Several investigators have begun to explore this hypothesis. At least three case-only studies used genotypic techniques to compare MAC isolated from lung disease patients and MAC isolated from those patients' residential environments, and these found matching or similar strains in some instances (22, 24, 25). Furthermore, many patients with NTM lung disease in one of these studies (some infected with MAC) reported that they often gardened or potted plants (22). It is not known, however, whether these patients did so more often than their nondiseased peers. Maekawa and colleagues (26) measured gardening, farming, showering, and other potentially aerosol-generating activities in cases and control subjects, and found soil activities were associated with MAC lung disease, but water activities were not. Cases and control subjects were drawn from a clinic-based bronchiectasis population, and it is unclear whether the same risk factors are relevant for a general adult population.

These observations are consistent with at least two models of disease acquisition. The first is that some individuals, regardless of their immune status, receive an unusual dose of exposure to MAC in the environment, and thereby become sick (what we refer to as the “unusual dose” model). This unusual dose could be caused by more frequently engaging in activities that aerosolize water or soil that is colonized with MAC. The second model is that some individuals, despite receiving a typical dose of environmental MAC exposure, become sick because of known or occult immune defects (what we refer to as the “susceptible persons” model). The best etiologic model probably lies between these two extremes, with the nature and degree of both exposure and susceptibility contributing to risk, but the relative contributions of each are unclear. The present report describes the first population-based case–control study conducted to determine if activities that generate soil or water aerosols are risk factors for infectious MAC lung disease in a general adult population, as predicted by the “unusual dose” model. The study compares this with the “susceptible persons” model, by evaluating host traits that were previously known or suspected to be risk factors for MAC lung disease.

Statistics describing some of the cases in this study (27) and some results (28) have been previously reported in the form of conference abstracts.

METHODS

This was a matched case–control study. Eligible cases met 2007 American Thoracic Society diagnostic criteria (12) and visited a provider for MAC lung disease at least once since September 1, 2007. Eligible cases and control subjects were greater than or equal to 18 years old, resided in Washington or Oregon, did not live in an institution, did not have a known diagnosis of cystic fibrosis or HIV, were able to provide informed consent and communicate in English, and had a landline or cellular telephone.

Cases were recruited by a passive strategy, assisted by the Washington and Oregon Thoracic Societies and the Infectious Diseases Societies of Washington and of Oregon; and an active strategy, at the Oregon Health and Science University, Harborview Medical Center, and University

of Washington Medical Center. In the passive strategy, providers received study information by mail and shared it with apparently eligible patients. If interested, the patients returned a postcard to the investigators. In the active strategy, all potentially eligible cases were identified by systematic review of electronic medical records and sent an invitation; those who did not respond were later called (search terms are included in the METHODS section of the online supplement).

Control subjects were recruited by random-digit dialing. Telephone numbers were created by adding three random digits to the first seven digits of a case's telephone number, and dialed up to 12 times over 2 weeks. If a person was reached, the household was partially screened to identify a person living in Washington or Oregon of the same sex and age-group as the case (age groups are listed in the METHODS section of the online supplement). For efficiency, multiple numbers were dialed for each case simultaneously, which resulted in more than one control subject for some cases. When a potentially eligible individual was identified, name and address were gathered by telephone, and the individual was mailed a letter with study information before being called for complete screening and enrollment.

Potential subjects identified by the previously mentioned strategies were screened and enrolled by telephone, and then received a home visit. The visiting investigator interviewed the subject regarding activities that might lead to inhalation of aerosolized water or soil, features of the home water supply, and known or suspected host susceptibility traits. The investigator also collected environmental samples for a related microbiologic study.

The interview focused on the calendar year preceding the index year (the year of diagnosis of the case) and the calendar year 5 years before index year. For example, for a case diagnosed in 2008 and his or her matched control subject, many interview questions focused on 2007 and 2003. Before the interview, the investigator asked the subject to identify salient events in their life during the 2 years of focus, and encouraged them to refer to the calendar to help them remember or infer answers to the interview questions (instructions for this activity are found in the METHODS section of the online supplement). Because many cases said a long time elapsed between symptom onset and final MAC lung disease diagnosis, we chose to analyze answers to questions regarding the year 5 before index for items that were measured for both years.

A seven-item Likert scale was used for all questions related to aerosol-generating activities and over-the-counter GERD medication. The frequencies were then grouped by the investigators depending on the distribution of answers for that activity in all subjects combined (the Likert scale is found in the METHODS section of the online supplement).

Characteristics in Table 1 are as of the time of interview. In Table 2, body mass index (BMI) is as of the year 5 before index, height is tallest lifetime, and smoking is based on lifelong history. Over-the-counter GERD medication is any use the year 5 before index, and acid-suppressor use is regular use for a month or more any time in the 5 years preceding index year (January 1, 2003 to December 31, 2007 in the example above). For all other diagnoses and medications in Table 2, subjects were asked whether and when they experienced them, and the investigators chose temporal cut-offs for establishing groups. Specifically, subjects were classified as treated with steroids or immunomodulatory drugs if they used them for a month or more at least 1 year before index, and as diagnosed with COPD, asthma, or diabetes only if diagnosis occurred at least 1 year before index. They were classified as having a history of pneumonia hospitalization only if it took place at least 2 years before index. All results shown in Tables 3, 4, and 5 are for activities ascertained for the year 5 before index.

Associations between disease and potential risk factors were measured with odds ratios (ORs) obtained using conditional logistic regression, adjusting for age, an incompletely matched matching variable (sex and area code were perfectly matched). All host traits were then considered as potential confounders, except when those host traits were thought to lie along the causal pathway between the potential risk factor and disease acquisition. If any potential confounder had a large OR for association with disease, a model was developed for each factor of interest using the matching variables and that potential confounder (arbitrary cutoffs for “large” associations were set at >1.7 or <0.6). Any potential confounder that appreciably altered the OR estimate for the factor of interest was then included in a multivariate model.

TABLE 1. DEMOGRAPHIC CHARACTERISTICS OF *MYCOBACTERIUM AVIUM* COMPLEX CASES AND CONTROL SUBJECTS

Trait	Cases Count (%) (N = 70)	Control Subjects Count (%) (N = 61)	Odds Ratio (52 Matched Groups, 52 Cases, 61 Control Subjects)*	95% Confidence Interval
Sex				
Female	58 (82.9)	50 (82)	†	
Geography (area code)				
Seattle-Tacoma area (206,425,253)	33 (47.1)	32 (52.5)	†	
Other Western Washington (360)	12 (17.1)	8 (13.1)		
Central or Eastern Washington (509)	4 (5.7)	5 (8.2)		
Portland-Salem area (503)	16 (22.9)	11 (18)		
Other Oregon (541)	5 (7.1)	5 (8.2)		
Age				
44–70 yr	37 (52.9)	38 (62.3)	†	
44–51 yr	1	0		
51–60 yr	15	12		
61–70 yr	21	26		
Over 70 yr	33 (47.1)	23 (37.7)		
71–80 yr	22	20		
81–90 yr	10	3		
>90 yr	1	0		
Race or ethnicity†				
White, non-Hispanic	65 (92.9)	56 (91.8)	Referent	—
Nonwhite or Hispanic	5 (7.1)	4 (6.6)	1.5	0.34–6.3
Asian or Pacific Islander, non-Hispanic	3	0		
Black, non-Hispanic	0	1		
Native American, non-Hispanic	1	0		
Hispanic	1	1		
Other	0	2		
Education‡				
Less than an associates degree	27 (38.6)	20 (32.8)	Referent	—
Did not complete high school	2	0		
High school or equivalent	10	7		
Some college	15	13		
Associates degree or higher	42 (60)	40 (65.6)	1.3	0.54–3.2
Associates or equivalent	9	8		
Bachelors	14	15		
Masters	10	11		
Professional	6	2		
Doctorate	3	4		

* Odds ratios were calculated using conditional logistic regression with age >70 in the model. Sex and area code were perfectly matched, and adjustment for other potential confounding variables did not appreciably change results. One or more matched control subjects were recruited and retained for 52 of the 70 cases enrolled in the study. Only matched groups of one case and one or more control subject are included in conditional logistic regression.

† Odds ratios were not calculated for sex, area code, and age >70, because these variables were used to match cases to control subjects.

‡ Race and ethnicity and education were analyzed as binary variables because of small expected cell sizes for finer groupings, but counts of subgroups are provided in italics for descriptive purposes, only.

Adjustment for multiple potential confounders did not considerably alter OR estimates, so results discussed next are presented only adjusted for matching variables.

RESULTS

Recruitment

Thirty-two individuals responded by mail or telephone to passive recruitment attempts. Three of them could not be contacted for screening and enrollment, two were ineligible, and two were screened eligible, but declined to participate; 25 were eligible and enrolled. Seventy-six apparently eligible individuals were identified by electronic record searches at the three medical centers. Five declined screening, six could not be contacted for further screening and enrollment, eleven were ineligible, three were screened eligible, but declined to participate; 51 were eligible and enrolled. Of the 76 cases that enrolled, six later withdrew from the study (two from the passively recruited group, and four from the actively recruited group).

In recruiting control subjects by random-digit dialing, 1,877 numbers were dialed and determined to be residential or cellular; 1,126 of these were successfully screened for sex and age group, for a screening response proportion of 60%. From the

numbers screened, 165 age- and sex-matched individuals were ascertained. Twenty-five of these declined to receive the initial letter explaining the study. Sixteen were mailed letters but could not be reached for further screening, two were ineligible on further screening, 61 declined further screening or participation, and 61 participated in the study, for a participation proportion of 37.4%. These 61 control subjects were matched to 52 cases.

Thus, our study recruited and retained a total of 70 cases, but had one or more matched control for only 52 of them. Frequencies are reported for all 70 cases and 61 control subjects, but conditional logistic regression models included only 113 subjects in 52 groups.

Demographics and Other Host Traits

Cases recruited for this study were predominantly female, non-Hispanic whites, of advanced age and high education (Table 1). The control subjects were demographically similar to the cases (characteristics in Table 1 are as of the time of interview).

Several host traits were associated with disease status (Table 2): BMI (OR, 0.11; 95% confidence interval [CI], 0.03–0.49 for high vs. low BMI); thoracic skeletal abnormality (scoliosis, kyphosis, or pectus excavatum; OR, 5.4; 95% CI, 1.5–20);

TABLE 2. HOST TRAITS OF *MYCOBACTERIUM AVIUM* COMPLEX CASES AND CONTROL SUBJECTS

Trait	Cases Count (%) (N = 70)	Control Subjects Count (%) (N = 61)	Odds Ratio	95% Confidence Interval
			(52 Matched Groups, 52 Cases, 61 Control Subjects)*	
GERD treatment [†]				
None	31 (44.3)	27 (44.3)	Referent	—
OTCs only	15 (21.4)	18 (29.5)	0.72	0.22–2.3
Acid-suppressor medication, with or without OTCs	24 (34.3)	15 (24.6)	1.6	0.63–4.1
Height				
Lowest tertile for sex	30 (42.9)	18 (29.5)	Referent	—
Middle tertile for sex	15 (21.4)	28 (45.9)	0.29	0.08–1
Tallest tertile for sex	25 (35.7)	15 (24.6)	1.1	0.37–3.4
Body weight index				
Low	58 (82.9)	27 (44.3)	Referent	—
Underweight	7	1		
Normal	51	26		
High	9 (12.9)	29 (47.5)	0.11	0.03–0.49
Overweight	9	20		
Obese	0	9		
Thoracic skeletal abnormality [‡]	19 (27.1)	5 (8.2)	5.4	1.5–20
Osteoporosis or osteopenia diagnosis	33 (47.1)	22 (36.1)	2	0.85–4.5
Hospitalized for pneumonia	17 (24.3)	5 (8.2)	3.4	1.1–10.9
Smoking history				
None (<100 lifetime cigarettes)	35 (50)	37 (60.7)	Referent	—
Light (≤10 lifetime pack-years)	17 (24.3)	14 (23)	2.3	0.78–6.6
Heavy (>10 pack-years)	18 (25.7)	10 (16.4)	2.7	0.93–7.9
COPD diagnosis	13 (18.6)	1 (1.6)	10	1.2–80.4
Asthma diagnosis	11 (15.7)	12 (19.7)	0.84	0.26–2.7
Diabetes diagnosis	2 (2.9)	3 (4.9)	0.67	0.11–4
Steroid use	18 (25.7)	3 (4.9)	8	1.6–41.4
Mean duration of use, wks (SD)	227 (253)	33 (50)	—	—
Immunomodulatory drug use [§]	8 (11.4)	0	∞	—

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; GERD = gastroesophageal reflux disease; OTC = over-the-counter.

* Odds ratios were calculated using conditional logistic regression with age >70 in the model. Sex and area code were perfectly matched, and adjustment for other potential confounding variables did not appreciably change results. One or more matched control subjects were recruited and retained for 52 of the 70 cases enrolled in the study. Only matched groups of one case and one or more control subjects are included in conditional logistic regression.

[†] Subjects were read generic and commercial names for omeprazole, lansoprazole, esomeprazole, pantoprazole, rabeprazole, cimetidine, famotidine, ranitidine, and nizatidine.

[‡] Subjects were asked if they were ever diagnosed with any of the following: scoliosis, kyphosis, or pectus excavatum.

[§] Subjects were read both generic and commercial names for methotrexate, azathioprine, mycophenolate, rituximab, etanercept, infliximab, and adalimumab.

history of pneumonia hospitalization (OR, 3.4; 95% CI, 1.1–10.9); COPD (OR, 9.9; 95% CI, 1.2–80); use of oral prednisone for at least a month greater than or equal to 1 year before index (OR, 8; 95% CI, 1.6–41.4); and use of other immunomodulatory drugs (methotrexate, azathioprine, mycophenolate, rituximab, etanercept, infliximab, or adalimumab) for at least a month greater than or equal to 1 year before index (eight exposed cases, zero exposed control subjects). Heavy lifetime smoking seemed to be associated with disease, but the point-estimate for this association was statistically imprecise (OR, 2.7; 95% CI, 0.93–7.9). Use of medications to treat GERD, tall stature, and diagnoses of osteoporosis or osteopenia, asthma, and diabetes were not associated with disease.

The associations shown in Table 2 persisted after adjustment for potential confounding factors. Associations of smoking and osteoporosis and osteopenia with disease were strengthened by adjustment for thoracic skeletal abnormalities and BMI, respectively.

Potentially Aerosol-generating Activities and Home Water Supply

As shown in Table 3, only one of the activities hypothesized to increase exposure to water aerosols colonized with MAC (spraying plants with a spray bottle) was positively associated with disease (OR, 2.7; 95% CI, 1.1–6.7). Frequent swimming pool use (defined as “about monthly” or more) was significantly associated with lower risk of disease (OR, 0.15; 95% CI, 0.04–0.67), as was washing dishes mostly or exclusively by hand (OR, 0.23; 95% CI,

0.06–0.93). These associations persisted after adjusting for potential confounding factors (use of acid-suppressor medications, maximum adult stature, high vs. low BMI, thoracic skeletal abnormality, height loss in adulthood, osteoporosis diagnosis, COPD diagnosis, history of pneumonia hospitalization, smoking history, and use of steroids or other immunomodulatory drugs), with adjusted ORs ranging from 1.7–3.2 for spray bottles, 0.08–0.21 for swimming pools, and 0.15–0.31 for dish-washing.

None of the features of the home water supply hypothesized to increase exposure to MAC were associated with disease (Table 4). None of the activities hypothesized to increase exposure to soil aerosols colonized with MAC were associated with disease (Table 5). In analyses of soil-related activities, the four subjects who reported they sometimes wore a mask for these activities were classified based only on their frequency of engaging in the activities without wearing a mask, which was the same or greater than the frequency with a mask in all cases.

DISCUSSION

It is likely that the nature and degree of MAC exposure and host susceptibility are factors in MAC lung disease acquisition. Either factor, however, may predominate in determining disease risk in the general population. This was the first case–control study conducted to determine if activities that generate soil or water aerosols are risk factors for infectious MAC lung disease in a general adult population, as predicted by the “unusual dose” model of acquisition. Simultaneously, the study evaluated the

TABLE 3. ACTIVITIES THAT MAY GENERATE WATER AEROSOLS, AS OF 5 YEARS BEFORE INDEX

Behavior	Cases Count (%) (N = 70)	Control Subjects Count (%) (N = 61)	Odds Ratio	95% Confidence Interval
			(52 Matched Groups, 52 Cases, 61 Control Subjects)*	
Showering				
Never or as much as once per week	11 (15.7)	5 (8.2)	Referent	—
Several times a week	16 (22.9)	19 (31.2)	0.40	0.07–2.2
Daily	43 (61.4)	37 (60.7)	0.79	0.15–4.3
Tub-bathing				
Never	29 (41.4)	26 (42.6)	Referent	—
Some, as much as once per week	21 (30)	26 (42.6)	0.66	0.23–1.8
More than once per week	20 (28.6)	9 (14.8)	1.4	0.44–4.6
Jacuzzi or hot-tub use				
Never	44 (62.9)	31 (50.8)	Referent	—
At least once, but less than monthly	11 (15.7)	16 (26.2)	0.49	0.16–1.5
Once per month or more	15 (21.4)	14 (23)	0.46	0.14–1.5
Sauna use	7 (10)	15 (24.6)	0.53	0.20–1.4
Humidifier use	14 (20)	10 (16.4)	1.5	0.54–4.4
Dishwashing				
Never, rarely, or exclusively by machine	24 (34.29)	12 (19.7)	Referent	—
By hand and by machine, frequently	29 (41.4)	28 (45.9)	0.25	0.07–0.92
Exclusively or mostly by hand, frequently	17 (24.3)	21 (34.4)	0.23	0.06–0.93
Swimming pool use				
Never	36 (51.4)	20 (32.8)	Referent	—
Rarely	25 (35.7)	22 (36.1)	0.75	0.25–2.2
Once per month or more	7 (10)	18 (29.5)	0.15	0.04–0.67
Spraying plants with hose	51 (72.9)	51 (83.6)	0.67	0.22–2.1
Spraying plants with spray-bottle	25 (35.7)	11 (18)	2.7	1.1–6.7
Water plants with can, bucket, or bottle	49 (70)	46 (75.4)	0.79	0.32–2
Spending time near running sprinklers	35 (50)	29 (47.5)	1.2	0.51–2.8

* Odds ratios were calculated using conditional logistic regression with age >70 in the model. Sex and area code were perfectly matched, and adjustment for other potential confounding variables did not appreciably change results. One or more matched control subjects were recruited and retained for 52 of the 70 cases enrolled in the study. Only matched groups of one case and one or more control subjects are included in conditional logistic regression.

“susceptible persons” model by examining several host traits that were previously presumed to be risk factors for MAC lung disease.

Host Traits

Our study detected strong, positive associations between disease status and COPD, history of severe pneumonia, steroid use, and other immunomodulatory drugs. These have all been suspected as risk factors for MAC lung disease based on case-only studies (5, 12, 13), but never previously confirmed in a comparative epidemiologic study. Furthermore, the association noted for steroid use persisted after adjustment for COPD, suggesting it is not caused by confounding by indication, although specific

indications for steroids and other immunomodulators were not measured. Our study also confirmed two risk factors previously identified in epidemiologic studies: low BMI and thoracic skeletal abnormalities (6, 7). Measuring the presence of thoracic skeletal abnormality by self-report, particularly pectus excavatum, would tend to bias toward positive findings, because this previously reported risk factor would be more often diagnosed by pulmonary physicians in patients with MAC than by other kinds of providers in the source population. We believe, however, that cases and control subjects would tend to report weight and height 5 years before index with the same social biases, producing comparable estimates of BMI.

Few studies have formally evaluated smoking as a risk factor for MAC lung disease. Many studies have limited their study

TABLE 4. HOME WATER SUPPLY AS OF 5 YEARS BEFORE INDEX*

Feature	Cases Count (%) (N = 70)	Control Subjects Count (%) (N = 61)	Odds Ratio	95% Confidence Interval
			(52 Matched Groups, 52 Cases, 61 Control Subjects)†	
Home construction				
1990s or later	15 (21.4)	8 (13.1)	Referent	—
1970s or 1980s	23 (32.9)	24 (39.3)	0.41	0.10–1.6
Before 1970	32 (45.7)	27 (44.3)	0.52	0.14–1.9
Well	10 (14.3)	8 (13.1)	0.67	0.16–2.8
Air conditioning	24 (34.3)	19 (31.2)	0.68	0.25–1.9
Inline water filters	8 (11.4)	8 (13.1)	0.62	0.19–2.1
Filtered pitchers	17 (24.3)	14 (23)	2.1	0.84–5.5

* Subjects were questioned about the home they lived in during the calendar year 5 before index; if they moved over the course of the year, they were asked to give what would be the correct answer most months of that year.

† Odds ratios were calculated using conditional logistic regression with age >70 in the model. Sex and area code were perfectly matched, and adjustment for other potential confounding variables did not appreciably change results. One or more matched control subjects were recruited and retained for 52 of the 70 cases enrolled in the study. Only matched groups of one case and one or more control subjects are included in conditional logistic regression.

TABLE 5. ACTIVITIES THAT MAY GENERATE SOIL AEROSOLS, AS OF 5 YEARS BEFORE INDEX

Behavior	Cases Count (%) (N = 70)	Control Subjects Count (%) (N = 61)	Odds Ratio	95% Confidence Interval
			(52 Matched Groups, 52 Cases, 61 Control Subjects)*	
Potting plants				
Never	16 (22.9)	11 (18)	Referent	—
Rarely	36 (51.4)	35 (57.4)	0.77	0.24–2.5
Once per month or more	18 (25.7)	15 (24.6)	1.2	0.39–3.9
Gardening				
Never	25 (35.7)	18 (29.5)	Referent	—
Rarely	3 (4.3)	6 (9.8)	0.82	0.15–4.4
Once per month or more	42 (60)	37 (60.7)	0.97	0.42–2.2
Lawn maintenance				
Never	33 (47.1)	25 (41)	Referent	—
Rarely	6 (8.6)	5 (8.2)	1.8	0.44–7.8
Once per month or more	31 (44.3)	31 (50.8)	0.93	0.40–2.1

* Odds ratios were calculated using conditional logistic regression with age >70 in the model. Sex and area code were perfectly matched, and adjustment for other potential confounding variables did not appreciably change results. One or more matched control subjects were recruited and retained for 52 of the 70 cases enrolled in the study. Only matched groups of one case and one or more control subjects are included in conditional logistic regression.

population to nonsmokers. Our results suggest an association between smoking and MAC lung disease, but our estimate of the association was statistically imprecise.

Three conditions (osteoporosis and osteopenia, asthma, and diabetes) were considered because they have similarities to other skeletal, lung, and immune-compromising conditions. They were not found to be associated with disease.

Our study looked for, but did not find, an association between MAC lung disease and GERD, contrary to data from a previous study by Thomson and colleagues (8). The lack of association in our study may be caused by nondifferential misclassification of exposure. Thomson and coworkers (8) found significant differences between cases and control subjects in the frequency of clinical GERD diagnosis and in the use of prescription-type acid-suppressor medications, corresponding to ORs of 2–3. It seems that Thomson and colleagues (8) asked their subjects about GERD treatment in the 12 months preceding their interview, and it is unclear how they defined “regular” use. In contrast, we asked subjects about their GERD treatment during the year 5 before index, and included occasional or infrequent use, so long as it persisted over more than 30 days. Thus, our study may have classified individuals with less severe disease and less frequent acid-suppressor use into the acid-suppressor-exposed category. Our choice to measure an earlier time-point may have missed the appropriate window for measuring effects on MAC lung disease acquisition, or made it difficult for all subjects to recall their use accurately. However, this choice may have removed a diagnostic bias caused by prescription of acid-reducing medication to patients seeking pulmonary care.

Our study also looked for, but did not observe, an association between MAC lung disease and tall stature, contrary to the results of a study by Kim and colleagues (7). This may be caused by a nonrepresentative height distribution among our control subjects. Kim and coworkers (7) used data from the National Health and Nutrition Examination Survey to measure height in the source population, and National Health and Nutrition Examination Survey makes greater effort to overcome barriers to participation by nondiseased individuals than our study. The lack of public awareness about MAC lung disease, requirement for subjects to be available for an extended home visit, and modest financial compensation may have biased our control sample toward those with higher socioeconomic status, which has been associated with tall stature in numerous studies (29).

Water- and Soil-related Activities

Concerns about the risk of acquiring MAC lung disease from aerosols in the residential environment have appeared in scientific and popular press (20, 30). This is the first epidemiologic study to formally evaluate whether activities that generate water and soil aerosols, or features of the home water supply, are associated with disease in a general, HIV-negative adult population. De Groote and coworkers (22) and Kim and coworkers (7) both reported the frequency of some of our activities of interest among cases in their studies, but could not draw conclusions about whether they are risk factors, because they lacked information from a control group.

In the present study, a number of aerosol-generating activities involving water or soil and water-supply characteristics bore little or no association with the presence of infectious MAC lung disease. One aerosol-generating activity, spraying plants with a spray bottle, had a modest positive association with disease, but because many comparisons were made, this may be a spurious association. We found swimming pool use and hand-washing dishes to be strongly negatively associated with disease, contrary to our hypotheses. Persons susceptible to MAC lung disease may have long-standing health issues that decrease their likelihood of participating in activities in pools or doing chores manually that can be automated.

Our findings contrast those of Maekawa and coworkers (26), who found that engaging in soil-related activities greater than two times per week was strongly associated with MAC lung disease in a bronchiectasis patient population. This difference may be caused in part by the greater statistical power afforded by their larger sample size, or by their choice to form a composite “high soil exposure group” based on frequency of engaging in any of several soil-related activities, rather than measuring associations with each soil-related activity individual. The most likely explanation for the difference, however, is the different population under study; engaging in activities that generate soil aerosols may be a risk factor for MAC lung disease in patients with bronchiectasis, but not the general adult population.

Limitations and Their Mitigation

Several limitations, some inherent to the study of MAC lung disease, must be considered in evaluating the meaning of the study’s findings. First, our relatively small sample had low study power. This limited our ability to detect subtle associations and associations specific

to subgroups that may be differentially affected by environmental factors.

Second, the etiologically relevant time period for aerosol-generating activities and MAC lung disease is unknown. If an individual's aerosol-generating activities changed in frequency over time, our interview questions might have focused on a period before or after cases became infected. Nonetheless, by focusing on activities during the year 5 before index, we believe we are likely to have ascertained typical activities before symptom onset.

Third, because of our inclusion of prevalent cases and our focus on the year 5 before index, subjects were asked about experiences in the remote past, which are difficult to remember. If this led only to decreased accuracy of recall for all subjects, this would tend to bias our study toward the null. We attempted to mitigate this problem by having subjects construct calendars of salient life events during the periods of interest, and by asking about diagnoses and medications of interest by name (providing generic and brand names for drugs); similar aids to recall have been validated previously (31, 32). If, however, cases believed their disease resulted from behaviors under study, this would tend to bias the study toward positive findings, which we did not observe for most aerosol-generating activities.

Fourth, visits to case subjects took place between January 2009 and March 2011, but visits to control subjects were delayed because of difficulties with control recruitment, so all control subjects were visited between July 2010 and August 2011. If the manner of conducting interviews drifted over time, cases and control subjects would be differentially affected, and those differential interview-based measures could lead to biased estimates of association.

Fifth, many of the aerosol-generating activities we studied are common, requiring detailed information on the frequency, intensity, or specific manner of performing the activity to detect associations with disease. We measured frequency of these activities, but could not measure all potentially relevant aspects of the activities, such as duration of gardening sessions, use of fans during showers, and so forth. The consistency of our results across many aerosol-generating activities, however, increases our confidence that null results are not merely caused by misspecifying one measurement of behavior.

Conclusions

The results of our study support the impression from case-only studies of NTM lung disease that certain preexisting lung diseases and the use of immune-suppressing medications are risk factors for MAC lung disease. It also confirms that body morphotype is associated with risk. Our results also suggest that aerosol-generating activities are not associated with acquisition of MAC lung disease in a general, HIV-negative adult population. We cannot rule out the possibility that these activities have small associations with disease that could not be detected in our relatively small study. We also cannot rule out the possibility that aerosol-generating activities are risk factors for specific, susceptible subpopulations, or only when the aerosols' source is colonized with specific, virulent strains of MAC. Overall, however, our findings favor a "susceptible persons" model of MAC lung disease acquisition, in which host traits outweigh the behavioral factors addressed in this study.

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