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Short title: Allergies, antibiotics use, and multiple sclerosis

TRANSPARENCY

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Authors' contributions

Study concept and design: J.R and C.V.A.; manuscript drafting and revision: J.R., M.K., K.L.C., R.M.V., and C.V.A.; statistical analysis: H.N., and J.R.; data acquisition: H.N., and K.L.C.

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ABSTRACT

Background: The associations between allergies, antibiotics use, and multiple sclerosis (MS) remain controversial and their mediating or moderating effects have not yet been examined. We aimed to assess the direct and indirect influences of allergies and antibiotics use on MS development, and their interactions.

Methods: A 1:3 matched case-control study was performed using the National Ambulatory Medical Care Survey database from 2006 to 2013 in the USA. Multiple sclerosis was identified based on the ICD-9 code (340.0) in any position. Cases were matched to their controls based on survey year, age, gender, race, payer type, region, and tobacco use. Allergy diseases and antibiotics prescriptions were extracted by ICD-9 code and drug classification code, respectively. Both generalized structural equation model and MacArthur approach were used to examine their intrinsic relationships.

Results: The weighted prevalence of MS was 133.7 per 100,000 visits. A total of 829 MS patients and 2,441 controls were matched. Both respiratory tract allergies (OR=0.29, 95%CI: 0.18, 0.49) and other allergies (OR=0.38, 95%CI: 0.19, 0.77) were associated with a reduction of the risk of MS. Patients with respiratory tract allergies were more likely to use penicillin (OR=8.73, 95%CI: 4.12, 18.53) and other antibiotics (OR=3.77, 95%CI: 2.72, 5.21), and those with other allergies had a higher likelihood of penicillin use (OR=4.15, 95%CI: 1.27, 13.54); however, the link between antibiotics use and MS was not confirmed although penicillin use might mediate the relationship between allergies and MS.

Conclusions: The findings supported allergy as a protective factor for MS development. We also suggest antibiotics use might be not a suitable indicator of bacterial infection to investigate the cause of MS.

Key words: multiple sclerosis; allergies; anti-bacterial agents; case-control studies; risk

INTRODUCTION

It is estimated that about 2.5 million people worldwide have MS, and 200 new cases are diagnosed each week in the United States.[1] The etiology of MS remains unclear, and its risk factors are controversial. Scientists believe that the combination of several different factors may be involved in triggering MS, including immunologic, environmental, infectious, and genetic factors. Aside from vitamin D deficiency[2-4] and smoking[5-9] that have been known risk factors, researchers have heatedly disputed the influence of *Chlamydophila pneumoniae*[10,11], antibiotics use[12-16] and allergies[17-20] on MS recently.

A 2006 study from the United Kingdom found that use of antibiotics active against *C. pneumoniae* might not decrease the risk of MS, but penicillin use could do so.[15] However, a 2011 study in the Danish cohort reported that penicillin use and use of other antibiotics similarly increased the risk of MS.[14] Previous studies also had inconsistent results on the association between allergy and the risk of MS.[19-22] These contradictory findings lead more to ongoing disputes. Obviously, more evidence is needed to unveil the direct and indirect influence of these factors in MS, which have not been paid enough attention in previous studies.

In the present study, we examined the intrinsic relationships among antibiotics use, allergies, and MS using both structural equation model and MacArthur approach[23] in the data of National Ambulatory Medical Care Survey in the United States (NAMCS). We hypothesize that MS might be trigged by a complex chain of risk factors, which may be also affected by a few mediators and moderators.

METERIALS AND METHODS

Study design and population

This is a matched case-control study nested in an annually cross-sectional survey. The data was extracted from the NAMCS database during the period of 2006 to 2013 (the latest available data) in the United States. The NAMCS is the nation's foremost study of ambulatory care provided at physicians' offices and has been conducted since 1973. It focuses on visits made to non-federally employed office-based physicians who are primarily engaged in direct patient care. Beginning in 2006, the survey also includes an annual sample of visits to community health centers (CHCs).[24]

In this cross-sectional data, we were not able to identify the temporal sequence of antibiotics use, allergies, and MS. But, we may presume the individuals in this population could have a similar prevalence of allergies in the past several years before the survey. We assume allergy is a chronic problem, and patients usually have it for a long time (even the rest of life) once it begins.[25] Similarly, individuals could have an approximate chance of antibiotic use in the past several years prior to the survey, because bacterial infections are strongly related to personal hygiene and behavior.[26]

Selection of cases and controls

Multiple sclerosis cases were identified based on the diagnosis code (*International Classification of Diseases*, Ninth Revision, ICD-9 code 340.0) in any position during the period of 2006-2013 in the NAMCS database. The rest of patients were considered as potential controls. Each MS case was randomly matched to 3 controls based on survey year, age (difference ≤3 years), gender, race, payer type, region, and tobacco use. Race consisted of White American, Black American and others. Payer type included private insurance, Medicare, Medicaid, and others. Region indicated Northeast, Midwest, South, and West. Tobacco use was defined as current use, not current use, and missing.

Allergy diseases

Common allergic diseases include upper respiratory diseases, asthma, bronchitis, skin allergy, eye allergy, ear allergy, and other unspecified allergies based on the common ICD-9 diagnosis codes for allergies.[27] In this study, we combined upper respiratory disease, asthma, and bronchitis into one category of respiratory tract allergies, and integrated the rest into the category of other allergies.

Use of antibiotics

The anti-infective drug classification codes in the database were used to identify antibiotics use. The code '013' indicated penicillin use including amoxicillin, ampicillin, dicloxacillin, floxacillin, penicillin, oxacillin, and so on. Other antibiotics use was defined as any of following codes: '002-012', '014-018', '240', '315' and '406'. We also utilized the medicine codes to validate the penicillin use, and we got very similar results between the two sets of codes.

Statistical analysis

Although the sample size estimation for modeling remains inconsistent[28-31], we believe that over 800 MS patients in the NAMCS data (2006-2013) should be sufficient for the present study. Annual data was read, appended, and analyzed in the SAS 9.4 (SAS Institute Inc. Cary, NC, USA). The weighted prevalence of MS was estimated. Demographics information in both MS patients and controls were reported as mean and standard deviation for continuous variables, and frequency and percentage for categorical variables. The 1:3 matching between MS patients and controls was done based on the greedy method that developed by Bergstralh EJ and Kosanke JL.[32]

A conditional logistic regression model was employed to estimate the main effects and interactions of influence factors for MS. The survey weight was considered during modeling since it was a survey data. We also examined the association between antibiotics use and allergies by logistic regressions adjusting for other confounders. Model coefficient, standard error, and p value were calculated to present each effect. A statistical significance level of 0.05 was set for relevant inferential tests. Based on the MacArthur approach[23], we further identified the mediators and moderators that might affect the causal chains of MS.

In view of the strength of structural equation model (SEM), we also fit a generalized SEM in Stata 13.1 (StataCorp LP) in order to better understand the complex chains of influence factors for MS. Generalized SEMs can fit models with continuous, binary, ordinal, count or multinomial responses to single-level or multilevel data, and include latent variables (unobserved effects) at any level.[33] The hypothesized SEM was shown in Figure 1A. Odds ratio (OR) and 95% confidence interval (95%CI) were estimated to indicate each association on the SEM.

RESULTS

The weighted prevalence of MS was 133.7 per 100,000 visits, which did not vary much over time. Among 834 MS patients, 797 patients were matched to three controls, 32 patients had partial controls (one or two), and 5 patients were excluded due to no available controls. Thus, the case-control analysis included 829 MS patients and 2,441 controls. The average age was 48.6 (±12.2) years, over three quarters were female, and the majority (89.8%) were Caucasians. Above half enrolled private insurance (Table 1).

As depicted in Table 2, respiratory tract allergies, penicillin use, and other antibiotics use were related to a reduction of the risk of MS ($p=0.039$, $p<0.001$, and $p=0.046$, respectively). Other allergies also had interaction effects on MS with non-penicillin antibiotics use ($p<0.001$). Meanwhile, respiratory tract allergies were significantly associated with use of penicillin ($p<0.001$) and other antibiotics ($p<0.001$), while other allergies were only associated with penicillin use ($p=0.011$). According to the MacArthur approach (Table 3), use of penicillin might play a role of mediating the relationship between allergies and MS, and non-penicillin antibiotics use might moderate the relationship between some allergies (non-respiratory tract) and MS.

In the SEM (Figure 1B), we found a significantly inverse association between allergies and MS, and the direct effects were OR=0.29 (95%CI: 0.18, 0.49) and OR=0.38 (95%CI: 0.19, 0.77) for respiratory tract allergies and other allergies, respectively. In other words, people without allergies could have about 3 times higher risk of MS than those with allergies. Persons with respiratory tract allergies were more likely to use penicillin (OR=8.73, 95%CI: 4.12, 18.53) and other antibiotics (OR=3.77, 95%CI: 2.72, 5.21), and those with other allergies also had a higher likelihood of penicillin use (OR=4.15, 95%CI: 1.27, 13.54). However, the association between antibiotics use and MS was not significant ($p>0.05$ for both penicillin and other antibiotics).

DISCUSSION

In this nationwide population-based case-control study in the United States, we found that allergies significantly reduced the risk of MS; use of penicillin might mediate the association between allergies and MS, whereas the direct relationship between antibiotics use and MS was not confirmed. Our findings supported recent studies in Iran and Italy, in which they found a significant inverse association between allergies and MS.[19,20] Furthermore, this is the first study that examined mediators and moderators for MS using the MacArthur approach.

It has been known that the imbalance of T-helper type 1 (Th1) and type 2 (Th2) results in the clinical expression of allergy and/or asthma.[34] An enhanced Th2 immune responses and the elaboration of cytokines could induce allergy. Although the mechanism leading to an enhanced Th2 response remains uncertain, some people think that the suppression of T-regulatory cells as well as Th1 cells may result in Th2-dominated immune responses. Interestingly, the shift from a Th1 towards a Th2 cytokine profile might benefit MS patients[35], because Th1 cells are the main effector T cells responsible for the autoimmune inflammation[36]. Based on above reasons, we may explain why allergies could reduce the risk of MS. Another population-based case-control study in Italy also concluded that atopic allergies confer protection against MS[20]. However, the findings were not confirmed by Karimi's study in Iran[22], in which no statistical significance might be due to the small sample size.

Previous studies have indicated that infections might play a role in the pathogenesis of MS, such as *C. pneumonia* and Epstein-Barr virus (EBV) infection.[37,38] Therefore, some epidemiologic investigations further examined whether use of antibiotics in treating bacterial infection could reduce the risk of MS. Alonso's study found use of antibiotics active against *C. pneumoniae* did not decrease the risk of short-term MS, but penicillin users had a lower risk of MS.[15] However, conflicting findings appeared in the other studies.[14] In our study, the findings about the relationship between antibiotics use and MS were not consistent, either. Thus, antibiotics use might not be an appropriate indicator of the causal relationship between bacterial infection and MS, as it is plausible that MS could be only related to bacterial infection in childhood[39]. Moreover, some bacterial infections (e.g. *Helicobacter pylori*) might even be a protective factor for developing MS.[40]

Other risk factors for MS include vitamin D deficiency, smoking, and genetic susceptibility. Epidemiological studies have detected significant association between latitude, deliberate sun exposure,

and vitamin D supplementation and health outcomes in MS, suggesting vitamin D plays a key role in these associations.[2] Smoking may also increase the risk of MS because the priming of immune response in the lungs may subsequently lead to MS in genetically susceptible people.[41] For MS patients in relapsing-remitting disease course, continued smoking will accelerate in time to secondary progressive MS.[42] Although we believe MS is likely to occur among people with particular gene susceptibility, the findings remain inconsistent in previous studies. Notably, a most recent study found a nuclear receptor NR1H3 (LXRA) in familial multiple sclerosis, suggesting a disruption in transcriptional regulation as one of the mechanisms underlying MS pathogenesis.[43] Changes in gene HLA-DRB1 (15 locus) have been considered as the strongest genetic risk factors for developing MS by itself alone, or the interaction with EBV infection.[44]

We have seen a few limitations in our study, nevertheless it was well-designed utilizing a nationwide population. Firstly, the evidence from cross-sectional data is not as strong as that from longitudinal data. In this cross-sectional data, we were not able to distinguish the temporal sequence of antibiotics use, allergies, and MS, but we may presume that antibiotics use (bacterial infections) and/or allergies precede MS, based on common sense and evidence in previous studies. Secondly, this study did not consider vitamin D deficiency and family history of MS due to unavailable information in the NAMCS data. However, the matching technique might minimize the potential bias. For example, to match the region might be helpful for balancing the level of sun exposure. Thirdly, MS patients in this study might include newly diagnosed cases, preexistent cases, and different types of diagnosis, in a certain extent, which increase difficulty to interpret our findings.

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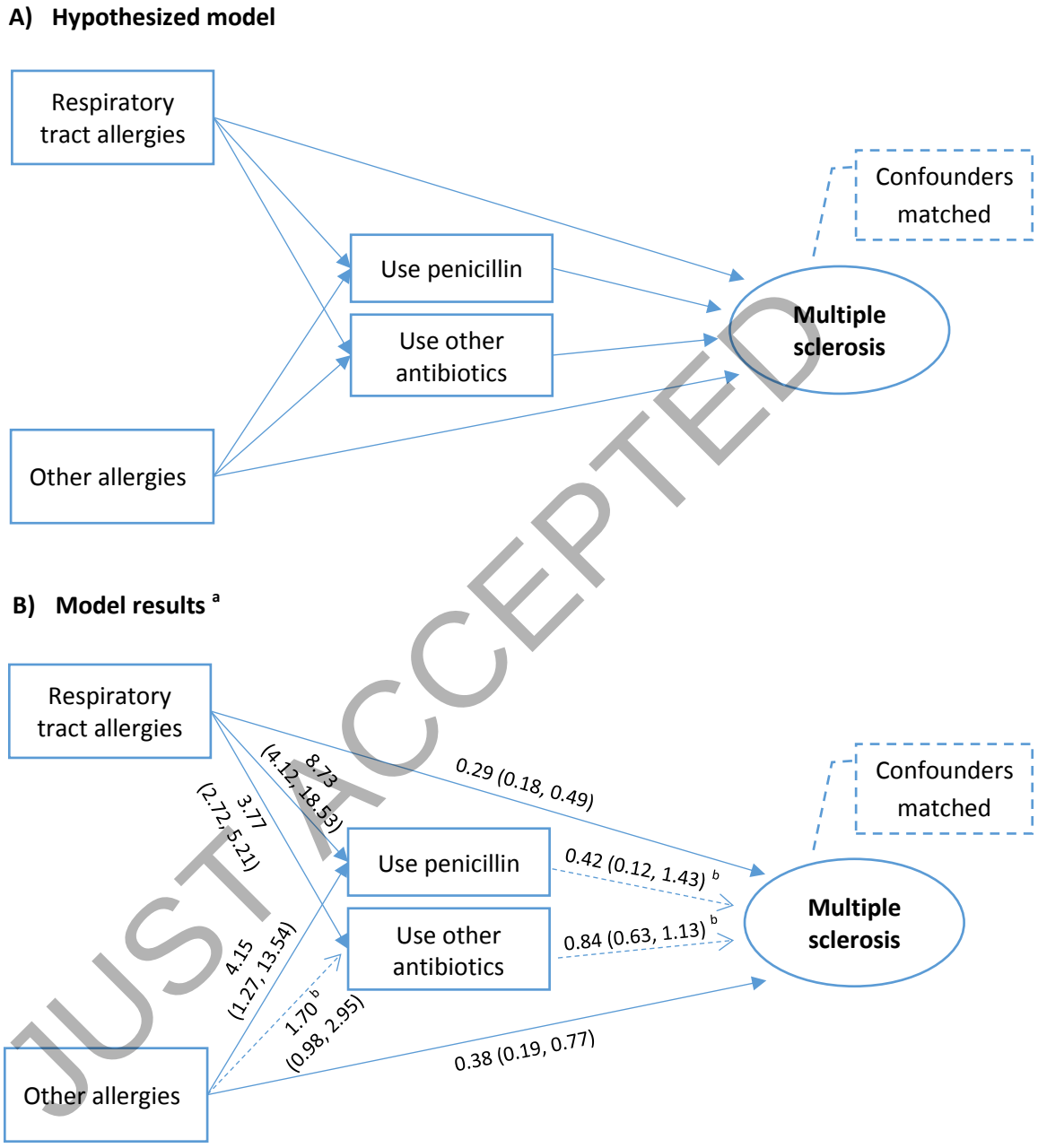
Figure 1: Simple Structural Equation Model for Multiple Sclerosis, National Ambulatory Medical Care Survey, United States, 2006-2013



[a] The value on each line stands for odds ratio and 95% confidence interval for the association.
[b] Not statistically significant association (p>0.05).

Table 1: Characteristics of Persons With Multiple Sclerosis and Matched Controls in The National Ambulatory Medical Care Survey, United States, 2006-2013

Characteristics	Label	Total subjects n=3,270 (%)	Cases n=829 (%)	Controls n=2441 (%) [a]
Survey year	2006	312 (9.5)	81 (9.8)	231 (9.5)
	2007	357 (10.9)	91 (11.0)	266 (10.9)
	2008	468 (14.3)	119 (14.4)	349 (14.3)
	2009	394 (12.0)	99 (11.9)	295 (12.1)
	2010	390 (11.9)	99 (11.9)	291 (11.9)
	2011	407 (12.4)	104 (12.5)	303 (12.4)
	2012	590 (18.0)	148 (17.9)	442 (18.1)
	2013	352 (10.8)	88 (10.6)	264 (10.8)
Age	Under 18 years	4 (0.1)	1 (0.1)	3 (0.1)
	18-34 years	438 (13.4)	111 (13.4)	327 (13.4)
	35-49 years	1234 (37.7)	316 (38.1)	918 (37.6)
	50-64 years	1279 (39.1)	321 (38.7)	958 (39.2)
	65 years and over	315 (9.6)	80 (9.7)	235 (9.6)
Gender	Female	2474 (75.7)	625 (75.4)	1849 (75.7)
	Male	796 (24.3)	204 (24.6)	592 (24.3)
Race	White	2935 (89.8)	739 (89.1)	2196 (90.0)
	Black	294 (9.0)	79 (9.5)	215 (8.8)
	Other	41 (1.3)	11 (1.3)	30 (1.2)
Payer type	Private insurance	1846 (56.5)	462 (55.7)	1384 (56.7)
	Medicare	804 (24.6)	208 (25.1)	596 (24.4)
	Medicaid or CHIP [b]	283 (8.7)	72 (8.7)	211 (8.6)
	Other	337 (10.3)	87 (10.5)	250 (10.2)
Tobacco use	Not current	1738 (53.1)	440 (53.1)	1298 (53.2)
	Current	375 (11.5)	97 (11.7)	278 (11.4)
	Missing	1157 (35.4)	292 (35.2)	865 (35.4)

CHIP, Children's Health Insurance Program.

[a] Each case was matched 3 controls based on survey year, age (difference≤3 years), gender, race, payer type, region and tobacco use. Five cases were excluded due to no matched controls, and 32 cases only had partial controls.

Table 2: Relationship Among Antibiotics Use, Allergies and Multiple sclerosis, National Ambulatory Medical Care Survey, United States, 2006-2013

Model [a]	Variable	Label	Estimated coefficient	Standard error	P value
Model1: Risk of multiple sclerosis by antibiotics use and allergies	X1a	Respiratory track allergies	-1.58	0.76	**0.039**
	X1b	Other allergies	-0.17	0.16	0.281
	X2a	Penicillin use	-1.49	0.34	**<0.001**
	X2b	Other antibiotics use	-0.80	0.40	**0.046**
	X1a*X2a	Interaction between respiratory track allergies and penicillin use	1.48	1.42	0.295
	X1a*X2b	Interaction between respiratory track allergies and other antibiotic use	0.72	0.58	0.219
	X1b*X2a	Interaction between other allergies and penicillin use	2.76	1.56	0.076
	X1b*X2b	Interaction between other allergies and other antibiotic use	-12.55	0.50	**<0.001**
Model 2: Association between penicillin use (X2a) and allergies	X1a	Respiratory track allergies	2.17	0.39	**<0.001**
	X1b	Other allergies	1.42	0.56	**0.011**
Model 3: Association between other antibiotics use (X2b) and allergies	X1a	Respiratory track allergies	1.33	0.17	**<0.001**
	X1b	Other allergies	0.53	0.30	0.075

[a] Model 1 was a conditional logistic regression with a strata of matching variable; Model 2 and Model 3 were logistic regressions adjusting for survey year, age, gender, race, payer type, and tobacco use.

Table 3: Identification of Mediators and Moderators According to MacArthur Approach [a]

Variable	Label	Eligibility criteria		Analytic criteria		MacArthur approach conclusions
		X1 precedes X2	Association between X1 and X2	Interaction between X1 and X2	Main effect of X2	
X1a vs. X2a	Respiratory track allergies vs. Penicillin use	YES	YES	NO	YES	Penicillin use ***mediates*** respiratory tract allergies
X1a vs. X2b	Respiratory track allergies vs. Other antibiotics use	YES	YES	NO	NO	Neither
X1b vs. X2a	Other allergies vs. Penicillin use	YES	YES	NO	YES	Penicillin use ***mediates*** other allergies
X1b vs. X2b	Other allergies vs. Other antibiotics use	YES	NO	YES	NO	Other allergies ***moderate*** other antibiotics use

[a] Based on the criteria published by Kraemer, HC (2008) and the analytic results in the Table 2.