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Toxocara species exposure, symptoms of asthma, and fractional exhaled nitric oxide in the US population



Asthma is a major cause of morbidity in the United States.¹ Toxocariasis is caused by exposure to the eggs of the nematodes *Toxocara canis* and *Toxocara cati*.^{2,3} Clinic-based studies have reported the association of *Toxocara* species with asthma. A study using data from the Third National Health and Nutrition Examination Survey (NHANES III) of 1988 to 1994 examined the association between *Toxocara* species infection and lung function in the United States.⁴ Infection was negatively associated with forced expiratory volume in 1 second. This study used data from a more recent NHANES to test the hypothesis that seropositivity for *Toxocara* species is associated with asthma prevalence, symptoms, and fractional exhaled nitric oxide (FeNO), a marker of airway inflammation.

The National Center for Health Statistics research ethics review board approved all protocols of the NHANES. All participants or their agents provided written informed consent. Study outcomes were self-reported diagnosed asthma, wheezing, and FeNO measured in adults and children at least 6 years of age in 2011 to 2012 in the United States.^{5,6} FeNO was measured using the Aerocrine NIOX MINO (Aerocrine AB, Solna, Sweden), a portable, handheld NO analyzer. Exposure to *Toxocara* species was measured by a Lumindex (Austin, Texas) assay using recombinant *T canis* C-type lectin-1 antigen that detects immunoglobulin G antibodies against *Toxocara* species; sera, if any, that remained in frozen storage after other testing were used. Confounding variables included demographics and serum cotinine, a metabolite of nicotine to assess exposure to tobacco smoke.

This analysis compared the means of logarithmically transformed values with 95% confidence intervals (CIs); exponentiated means of log-transformed values yielded geometric mean values. Multivariable linear regression modeling assessed *Toxocara* species exposure as a predictor of logarithmically transformed FeNO and assessed effect modification by age. Models controlled for age, sex, race and Hispanic ethnicity, immigrant status, ratio of family income to federal poverty limit, body mass index, serum cotinine (nanograms per liter), and asthma diagnosis. Data analyses using STATA 11 (StataCorp, College Station, Texas) accounted for the complex survey design, differential probability of sample selection, nonresponse, and sample non-coverage.

The total sample that was interviewed in the 2011 to 2012 NHANES was composed of 9,756 individuals. The first excluded group was composed of 1,595 individuals younger than 6 years. Of the remaining group of 8,161 individuals older than 6 years, 78 were not examined and were excluded from analysis. Of the remaining 8,083 examined individuals, 1,174 without stored serum

or missing *Toxocara* species data were excluded. Of the remaining 6,909 with valid *Toxocara* antibody data, 1,052 individuals without valid FeNO readings, body mass index, or serum cotinine were excluded. This left 5,857 subjects for analysis. The prevalence of the positive *Toxocara* species antibody was higher in those older than 40 years. Prevalence of seropositivity for *Toxocara* species was 4.91% at 6 to 19 years of age and 6.85% at 70 years and older. Male subjects had a higher prevalence of *Toxocara* species antibody than female subjects. The “other Hispanic” group had the highest positive *Toxocara* species antibody prevalence among racial and ethnic groups. Non-Hispanic whites had a prevalence of *Toxocara* species exposure that was lower than the prevalence in non-Hispanic African Americans and Mexican Americans. Immigrants had a higher prevalence of positive *Toxocara* species antibodies than nonimmigrants. Similarly, those with a ratio of family income to federal poverty limit for family size below the median (1.72) had a higher prevalence of exposure. Wheezing and asthma history did not differ by *Toxocara* species exposure. The mean of the natural log (ln) of FeNO was higher in exposed subjects (2.60, 2.50–2.70) than in unexposed subjects (2.55, 2.49–2.61; $P < .05$). The geometric mean of the FeNO in exposed individuals was 13.46 ppb (95% CI 12.18–14.88) compared with 12.81 ppb (12.06–13.60) in unexposed individuals.

Table 1 presents 4 linear regression models examining the association between *Toxocara* species exposure and FeNO and simultaneously controlling for potential confounders. When entered as an indicator variable (0 = negative, 1 = positive), *Toxocara* species exposure was not associated with ln FeNO in any of the models. As expected, age and female sex were associated with ln FeNO. Asthma history was positively and serum cotinine was negatively associated with ln FeNO. Adding poverty ratio to the model had no effect (not shown). In logistic regression models not shown, seropositivity was not associated with current asthma history ($P = .40$) or with history of wheezing in the past year ($P = .08$) after adjusting for confounders.

This population-based US study of *Toxocara* species exposure and airway inflammation as measured by FeNO failed to detect an association and there was no association with asthma diagnosis or wheezing history after controlling for confounders. This is contrary to findings in previous case-control or cross-sectional studies of *Toxocara* species exposure and symptomatic asthma, mostly in middle-income countries. Li et al⁷ conducted a systematic review and meta-analysis of 10 studies with a combined sample of 1,530 participants (723 cases). The meta-analysis supported a positive association between *Toxocara* species exposure and asthma. Infection was negatively associated with forced expiratory volume in 1 second in NHANES III.⁴

Table 1
Multiple Linear Regression Models Showing the Adjusted Coefficients for Previous *Toxocara* Exposure and Natural Log of Fractional Exhaled Nitric Oxide (ppb) in Persons at Least 6 Years Old: United States, 2011–2012

Risk factors	Model 1	95% CI	Model 2	95% CI	Model 3	95% CI	Model 4	95% CI
<i>Toxocara</i> infection (vs noninfected)	0.210	−0.063 to 0.103	0.020	−0.081 to 0.122	0.006	−0.100 to 0.112	0.001	−0.105 to 0.107
Age (y)	0.004	0.003 to 0.005	0.005	0.003 to 0.007	0.005	0.003 to 0.007	0.005	0.004 to 0.007
Female (vs male)	−0.150	−0.206 to −0.095	−0.190	−0.253 to −0.128	−0.191	−0.254 to −0.127	−0.198	−0.260 to 0.137
BMI (kg/m ²)			0.002	−0.003 to 0.006	0.002	−0.003 to 0.006	0.001	−0.004 to 0.006
Cotinine			−0.002	−0.002 to 0.001	−0.002	−0.002 to −0.001	−0.002	−0.002 to 0.001
Immigrant (yes vs no)					−0.060	−0.139 to 0.018	−0.069	−0.148 to 0.011
African American (vs non-African American)					0.042	−0.010 to 0.094	0.040	−0.012 to 0.092
Mexican American (vs white)					−0.033	−0.132 to 0.066	−0.019	−0.116 to 0.078
Asthma							0.290	0.221 to 0.358

Abbreviations: BMI, body mass index; CI, confidence interval.

The current findings of no association of *Toxocara* species seropositivity with asthma history, symptoms, or FeNO could be due to at least 1 of the following reasons. First, the lower prevalence (<7%) of exposure currently seen in the United States and other high-income countries compared with low- and middle-income countries might make detecting the association more difficult. Second, a likely lower intensity of exposure in the United States and other high-income countries compared with low- and middle-income countries might attenuate the association. Third, selection bias toward an association might be more likely in previous clinic-based studies compared with population-based studies such as the NHANES. Future research should use a prospective cohort study design to determine whether seropositivity is associated with future asthma incidence, pulmonary function, or FeNO.

In conclusion, seropositivity for *Toxocara* species was not associated with prevalent asthma history or symptoms or with FeNO in the US population at least 6 years of age.

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Spectrum and prevalence of reactions to marijuana in a Colorado allergy practice



Since the legalization of medical marijuana (MJ) and recreational MJ in certain states, an increasing number of patients with allergy are presenting from MJ exposure. Most have substantial exposure from industrial cultivation or are heavy consumers, indicating that cannabis is a mild allergen.

A voluntary questionnaire addressing our patients' exposures to MJ, active or passive, and types of reactions was administered.

One hundred thirty-four questionnaires were handed out to patients, 132 answered, and 2 declined. Questionnaires were distributed from January to March 2016. Thirty-nine percent of patients were men, 49% were women, and 12% were undisclosed. Four percent of patients were 16 to 25 years old, 10% were 26 to 35, 34% were 36 to 45, 24% were 46 to 55, 27% were 56 to 65, 18% were 66 to 84, and 15% were not specified. Twenty-eight patients experienced symptoms (21%). Of 70 patients who had never used MJ (11%), 8 had symptoms from passive exposure (11%). Of 37 patients who had used MJ in the past (28%), 12 had experienced

symptoms (32%). Of 17 patients who actively used MJ (13%), 8 experienced symptoms (47%). Of those who used MJ, 28 used a cigarette or pipe (52%), 14 used an oral form (26%), and 11 used a vaporizer (20%). Twelve patients exhibited asthma, shortness of breath, or cough (43%), 6 exhibited skin rash or hives (21%), and the remaining 10 (>14% each) reported itchy or red eyes, headache, dry mouth, nausea, and unspecified. Of 9 patients who had used topical cannabidiol (7%), only 1 developed reactions (11%). Three patients worked in MJ production or distribution but showed no significant difference in reactivity (Table 1).

With increasing legalization of MJ for medicinal and recreational purposes, there has been an increase of patients seen with sensitivities and adverse reactions. Several recent reviews have nicely addressed the background and allergic potential of *Cannabis sativa*, the unconventional “weed” allergen,¹ and addressed the cross-reactivity of the implicated lipid transfer proteins, which could be responsible for primary sensitization and might induce further cross-allergies with plant foods (“cannabis-fruit/vegetable syndrome”).² This goes far beyond early reports of MJ smoking and