

## Short communication

## Marijuana use is associated with hypersensitivity to multiple allergens in US adults

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## ABSTRACT

**Background:** The recent legalization of marijuana use for both medical and recreational purposes in several states of the United States is expected to further increase the already high prevalence of marijuana use. Although allergic reactions are uncommon, the potential of marijuana use and cultivation to cause allergy should be considered. We aimed to investigate whether marijuana use is associated with the prevalence of sensitization to specific allergens.

**Methods:** A total of 2671 adults (aged 20–59 years) who participated in the 2005–2006 National Health and Nutrition Examination Survey were included. Participants completed a questionnaire on marijuana use and underwent sensitization tests to 19 specific allergens. Those who reported marijuana use for at least 1 day in the past 30 days were considered marijuana users.

**Results:** No difference was found in the history of allergy between marijuana users and non-users. Compared with marijuana non-users as a reference group, the adjusted odds ratio (AOR) of sensitization to a specific allergen among marijuana users was significantly greater for antibodies against the following: *Alternaria alternata* (AOR = 1.67; 95% confidence interval (CI), 1.04 – 2.70), *D. farinae* (AOR = 1.68; 95% CI, 1.27 – 2.22), *D. pteronyssin* (AOR = 1.65; 95% CI, 1.32–2.06), ragweed (AOR = 1.84; 95% CI, 1.30–2.59), rye grass (AOR = 1.49; 95% CI, 1.12 – 1.97), Bermuda grass (AOR = 1.55; 95% CI, 1.03 – 2.33), oak (AOR = 1.76; 95% CI, 1.14 – 2.70), birch (AOR = 2.09; 95% CI, 1.23 – 3.55), peanut (AOR = 1.91; 95% CI, 1.25 – 2.92), and cat dander (AOR = 1.51; 95% CI = 1.13 – 2.03).

**Conclusions:** We provide preliminary findings to suggest that marijuana use is associated with sensitization to specific allergens, including molds, dust mites, plants, and cat dander.

## 1. Introduction

Cannabis, also known as marijuana, is the most frequently used illicit drug worldwide. The overall global prevalence of marijuana use is considered to be stable, whereas it is relatively high in the United States (United Nations Office on Drugs and Crime, 2015) with an estimated 22.2 million people aged  $\geq 12$  years reported to use marijuana in 2014 (Center for Behavioral Health and Statistics Quality, 2015; United Nations Office on Drugs and Crime, 2015). Recent changes in the legal status of marijuana for both medical and recreational purposes in many states would, therefore, lead to an inevitable increase in the prevalence of marijuana use.

Although medical marijuana has been reported to confer therapeutic benefits against glaucoma and multiple sclerosis (Watson et al., 2000), there is growing evidence that general marijuana use may be harmful to overall health. Marijuana use has been associated with an

increased risk of addiction, psychological health problems, problematic behavior, and respiratory illnesses (Fergusson et al., 2006; Macleod et al., 2004; Tan et al., 2009). Moreover, exposure to marijuana smoke has been implicated in the occurrence of nasal congestion, sneezing, and anaphylaxis (Ocampo and Rans, 2015).

Allergy to marijuana has also garnered much attention recently because both personal and occupational exposure to marijuana has been associated with hypersensitivity reactions and sensitization to plant-derived foods (de Larramendi et al., 2008; Nayak et al., 2013; Perez-Bustamante et al., 2007; Prasad et al., 2009; Stokes et al., 2000). Although allergic reactions are uncommon, the potential of marijuana use and cultivation to cause allergy should be considered.

In this study, we aimed to investigate whether marijuana use was associated with sensitization to specific allergens based on data from the National Health and Nutrition Examination Survey (NHANES). Specifically, we assessed sensitization to 19 specific allergens including

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molds, mites, plants, pets, arthropods, rodents, and foods among adults based on whether or not they used marijuana in the past 30 days.

## 2. Methods

### 2.1. Data and study population

This study used the data of the 2005–2006 NHANES, which is a representative cross-sectional survey of the civilian non-institutionalized population in the United States. The study protocols and all testing procedures for the NHANES were approved by the Institutional Review Board of the National Center for Health Statistics. Both oral and written consent were obtained from all participants.

The NHANES only provided drug use statistics for participants aged 20–59 years; therefore, the original population included 3409 participants (aged 20–59 years) in the study. Of these, we included 2743 participants who completed a questionnaire on marijuana use and underwent a complete panel of allergen-specific immunoglobulin E (IgE) tests. Another 72 individuals were excluded because information for at least one of the variables of interest was unavailable, leaving a total of 2671 adults for inclusion in the final analyses.

### 2.2. Measures

A person was considered as a current marijuana user if they had a positive response to the question: “During the past 30 days, for how many days did you use marijuana?” Participants who reported marijuana use for at least one day in that period were defined as marijuana users.

For the allergen-specific IgE tests, serum levels of specific IgE were analyzed in peripheral blood sample of participants using the Pharmacia Diagnostics Immuno-CAP 1000 System (Pharmacia Diagnostics, Kalamazoo, MI). Specific allergens included 15 aeroallergens [*Alternaria alternata*, *Aspergillus fumigatus*, Bermuda grass (*Cynodon dactylon*), birch (*Betula verrucosa*), cat dander, cockroach (*Blattella germanica*), dog dander, dust mite (*Dermatophagoides farinae* and *D. pteronyssinus*), mouse urine proteins, oak (*Quercus alba*), ragweed (*Ambrosia elatior*), rat urine proteins, Russian thistle (*Salsola kali*), and rye grass (*Lolium perenne*)] and four food allergens [egg white, cow's milk, peanut (*Arachis hypogaea*), and shrimp (*Pandalus borealis*)]. The specific allergen of interest, which was covalently coupled to the ImmunoCAP, reacted with the specific IgE in the serum sample of the participant. After washing the non-specific IgE, an enzyme-labeled antibody was added to form a complex, which was incubated. Unbound anti-IgE was then washed, and the remaining bound complex was then incubated with a developing agent. Higher response values indicated the presence of more allergen-specific IgE in the samples. Sensitization by specific IgE was defined as a level of  $\geq 0.35$  kU/L (Min and Min, 2015).

The following confounding variables were obtained: age (20–29, 30–39, 40–49, or 50–59 years), race/ethnicity (non-Hispanic white, non-Hispanic black, Mexican-American or other), sex (male or female), and family income ( $< \$20,000$  or  $\geq \$20,000$ ). Participants were categorized as current smokers, former smokers, or never smokers based on the history of smoking and as ‘yes’ or ‘no’ response to whether they currently consumed alcohol. Body mass index (BMI) was calculated by dividing weight by the square of height and was classified as  $< 30$  kg/m<sup>2</sup> or  $\geq 30$  kg/m<sup>2</sup>. A history of allergic disease was defined as a positive response to the following question – “Has a doctor or other health professional ever told you that you have allergies?” Hypertension was defined as a systolic blood pressure of  $\geq 140$  mm Hg and diastolic blood pressure of  $\geq 90$  mm Hg, the use of antihypertensive drugs or previous physician-diagnosed hypertension. Diabetes was defined as a fasting plasma glucose level of  $\geq 6.99$  mmol/L, a non-fasting plasma glucose level of  $\geq 11.1$  mmol/L, current insulin use or a prior physician diagnosis of diabetes. The presence of thyroid and liver diseases were based on diagnosis by a physician or health professional. Blood lead and

cadmium levels were included as biomarkers of exposure to heavy metals.

### 2.3. Analysis

The prevalence of sensitization to specific allergen between marijuana users and non-users was compared with chi square test. Logistic regression analyses were conducted using the SURVEYLOGISTIC procedures to assess the association between allergen sensitization and marijuana use. The model provided odds ratios (ORs) and corresponding 95% confidence intervals (95% CIs) for sensitization to each allergen, compared with marijuana non-user as the reference group. Statistical models were adjusted for all confounding variables.

## 3. Results

### 3.1. Characteristics by marijuana use status

Of the 2671 study participants, 316 (11.8%) were current marijuana users. Compared with marijuana non-users, marijuana users were more likely to be young, non-Hispanic black, male, and current smokers, and current drinkers. They were found to have an average family income of  $< \$20,000$ , BMI of  $< 30$  kg/m<sup>2</sup>, high blood lead (1.85  $\mu$ g/dL vs. 1.52  $\mu$ g/dL; p-value = 0.0003) and cadmium (0.89  $\mu$ g/L vs. 0.47  $\mu$ g/L; p-value  $< 0.0001$ ) levels, and have neither diabetes nor thyroid disease. We found no differences regarding the history of allergy, hypertension, or liver disease between marijuana users and non-users. In addition, compared with participants not sensitized to allergens, those sensitized to at least one allergen were more likely to be young, non-Hispanic black, male, and non-smokers, and were also more likely to have a history of allergies and high blood lead (1.62  $\mu$ g/dL vs. 1.52  $\mu$ g/dL; p-value = 0.0093) and cadmium (0.47  $\mu$ g/L vs. 0.56  $\mu$ g/L; p-value = 0.0077) levels. There were no differences between the two groups in any other variable (Table 1).

### 3.2. Proportion and likelihood for sensitization to allergens by marijuana use status

The proportion of marijuana users with sensitization to allergens not related to cannabis varied from 3.0% for rodents and egg to 32.2% for *D. pteronyssinus* and was significantly higher than that of marijuana non-users, except for Bermuda grass, white oak, Russian thistle, cockroach, egg, and milk. Compared with marijuana non-users as the reference group, the AOR of sensitization to allergens among marijuana users was significantly greater for antibodies against *Alternaria alternata* (AOR = 1.67; 95% CI, 1.04 – 2.70), *D. farinae* (AOR = 1.68; 95% CI, 1.27 – 2.22), *D. pteronyssinus* (AOR = 1.65; 95% CI, 1.32 – 2.06), ragweed (AOR = 1.84; 95% CI, 1.30 – 2.59), rye grass (AOR = 1.49; 95% CI, 1.12 – 1.97), Bermuda grass (AOR = 1.55; 95% CI, 1.03 – 2.33), oak (AOR = 1.76; 95% CI, 1.14 – 2.70), birch (AOR = 2.09; 95% CI, 1.23 – 3.55), peanut (AOR = 1.91; 95% CI, 1.25 – 2.92), and cat dander (AOR = 1.51; 95% CI = 1.13 – 2.03). The results suggested that marijuana exposure via usage or cultivation may be associated with an increased risk of sensitization to allergens unrelated to cannabis (Fig. 1).

## 4. Discussion

In this study, we aimed to investigate whether marijuana use was associated with sensitization to specific allergens in adults from a representative sample of the US population. After adjusting for covariates, marijuana users were more likely than non-user to be sensitized to molds (*Alternaria alternata*) dust mite (*D. farinae* and *D. pteronyssinus*), plants (ragweed, rye grass, Bermuda grass, oak, birch, and peanut), and cat dander than non-users. These results therefore indicate that marijuana exposure via use or cultivation may be associated with an

**Table 1**

General characteristics of the study subjects according to the use of marijuana and sensitization to at least one allergen.

|                          | Marijuana use     |         | Sensitization to allergen |         |
|--------------------------|-------------------|---------|---------------------------|---------|
|                          | % of current user | p-value | % of sensitized subjects  | p-value |
| Age, year                |                   |         |                           |         |
| 20–29                    | 17.6              | < .0001 | 53.9                      | < .0001 |
| 30–39                    | 10.7              |         | 51.6                      |         |
| 40–49                    | 9.1               |         | 47.8                      |         |
| 50–59                    | 8.2               |         | 40.6                      |         |
| Ethnicity                |                   |         |                           |         |
| White                    | 13.4              | < .0001 | 44.4                      | < .0001 |
| Black                    | 15.3              |         | 60.4                      |         |
| Hispanic                 | 6.1               |         | 48.1                      |         |
| Others                   | 10.4              |         | 52.2                      |         |
| Sex                      |                   |         |                           |         |
| Male                     | 17.6              | < .0001 | 55.1                      | < .0001 |
| Female                   | 6.9               |         | 44.0                      |         |
| Family income, \$        |                   |         |                           |         |
| < 20,000                 | 17.7              | < .0001 | 50.4                      | 0.4915  |
| ≥ 20,000                 | 10.3              |         | 48.8                      |         |
| Cigarette smoking        |                   |         |                           |         |
| Current smoker           | 27.4              | < .0001 | 45.3                      | 0.0037  |
| Former smoker            | 10.2              |         | 46.0                      |         |
| Never smoker             | 5.1               |         | 52.1                      |         |
| Alcohol drinking         |                   |         |                           |         |
| Currently drinker        | 15.1              | < .0001 | 49.7                      | 0.4079  |
| Currently non-drinker    | 3.4               |         | 47.9                      |         |
| BMI, kg/m <sup>2</sup>   |                   |         |                           |         |
| < 30                     | 13.8              | < .0001 | 48.9                      | 0.6833  |
| ≥ 30                     | 8.3               |         | 49.7                      |         |
| History of allergy       |                   |         |                           |         |
| Yes                      | 12.4              | 0.5128  | 60.1                      | < .0001 |
| No                       | 11.5              |         | 43.6                      |         |
| History of hypertension  |                   |         |                           |         |
| Yes                      | 15.3              | 0.0992  | 18.1                      | 0.3015  |
| No                       | 19.3              |         | 19.6                      |         |
| History of liver disease |                   |         |                           |         |
| Yes                      | 3.6               | 0.6870  | 3.4                       | 0.7083  |
| No                       | 3.3               |         | 3.2                       |         |
| History of diabetes      |                   |         |                           |         |
| Yes                      | 3.7               | 0.0425  | 6.7                       | 0.5333  |
| No                       | 6.7               |         | 6.1                       |         |
| History of thyroid       |                   |         |                           |         |
| Yes                      | 3.0               | 0.0048  | 5.8                       | 0.0234  |
| No                       | 7.4               |         | 8.0                       |         |

\*p-value was based on the chi-square test.

increased risk of allergen-specific sensitization in adults.

The question about whether marijuana triggers hypersensitivity reactions to allergens is not new, but has recently become a public health concern because of changes in the legislation of marijuana use and cultivation in many states. Since the first report on hypersensitivity to tetrahydrocannabinol (the psychoactive component of marijuana) after marijuana smoking (Liskow et al., 1971), studies on sensitization to marijuana exposure through inhalation, ingestion, and skin contact have been frequent. However, no study to date has completely characterized the allergenic composition of marijuana and its derivatives.

Marijuana pollen grains, like those of other pollen-bearing plants, are very buoyant and can travel considerable distances. A positive skin reaction to marijuana pollen is often detected in patients with clinical symptoms of allergy (Prasad et al., 2009; Stokes et al., 2000). Moreover, marijuana can be contaminated with fungi, bacteria, molds, and heavy metals during cultivation, which confound the issue. Of these potential allergens, fungi (especially *Aspergillus* antigens) are more commonly

isolated from marijuana users than from non-users (Kagen et al., 1983). Recent studies have demonstrated that sensitization to marijuana is associated with hypersensitivity to IgE-binding protein bands with molecular weights of 9–70 kDa, which match leaf, flower, and bud extracts (de Larramendi et al., 2008; Nayak et al., 2013; Perez-Bustamante et al., 2007). Some of these proteins are responsible for cross-reactivity with plant-derived foods, in which the same IgE molecule binds to several allergens with common structural features (Perez-Bustamante et al., 2007; de Larramendi et al., 2008; Nayak et al., 2013). de Larramendi et al. (2008) noted that there was a high prevalence of sensitization to tomato and peach among patients who were sensitive to marijuana leaf extracts, and subsequent studies have reproduced this evidence of allergic cross-reactivity between marijuana and plant food allergens (Armentia et al., 2011; Ebo et al., 2013). Although uncommon, multiple sensitizations to indoor and outdoor aeroallergens (i.e., pollens, dog and cat dander, and mites) were also observed in people with occupational exposure to marijuana (Silvers, 2016). Taken together with the results of this study, we concluded that personal or occupational exposure to marijuana was associated with allergic reactions to marijuana or other multiple allergens.

This study has several limitations that should be considered. The most important is that we cannot exclude the possibility that differences in sensitization to specific allergens resulted primarily from covariates other than marijuana use. Of particular concern is the disparity in race and socioeconomic stats. Researchers have highlighted that there are important differences in allergic sensitization caused by race and socioeconomic factors (i.e., income and residential location) (Lewis et al., 2001; Yang et al., 2008). In the univariate analysis (Table 1), we also found significant differences in race and family income between marijuana users and non-users, despite failing to observe difference in family income between sensitized and non-sensitized participants. Therefore, it is difficult to control for the impact of potential confounders affecting sensitization to allergens, despite adjusting for race and income in the regression model. Another important limitation is that our study used a cross-sectional design; this precludes making any causal conclusions regarding the association between marijuana use and sensitization to specific allergens. In the current study, marijuana users were defined as those who used marijuana in the past month only, and we did not obtain information on use before that time, the amount of use, the frequency of use, the duration of use, or the age at first use. Moreover, despite including many covariates, we cannot exclude the potential for bias arising from unmeasured factors. In future studies, including analysis of these other confounding factors will be needed to substantiate our findings. We specifically recommend the inclusion of confounding variables such as poor air quality in the home, exposure to harmful substances in utero, exposure to secondhand smoke during childhood, genetics, and occupational exposure to marijuana. These factors could be essential to clarifying the association observed in this study.

## 5. Conclusion

In conclusion, we found that marijuana use in adults was associated with a high prevalence of sensitization to specific allergens, including molds, dust mites, plants, and cat dander. The NHANES data were not designed for studies with our specific aim; therefore, not all variables affecting the study outcome were considered. In addition, cross-sectional and observational design meant that the observed association between marijuana use and allergic sensitization can only be considered preliminary. Therefore, the study results should be interpreted with caution.

## Conflict of interest

The authors have no conflict of interest.

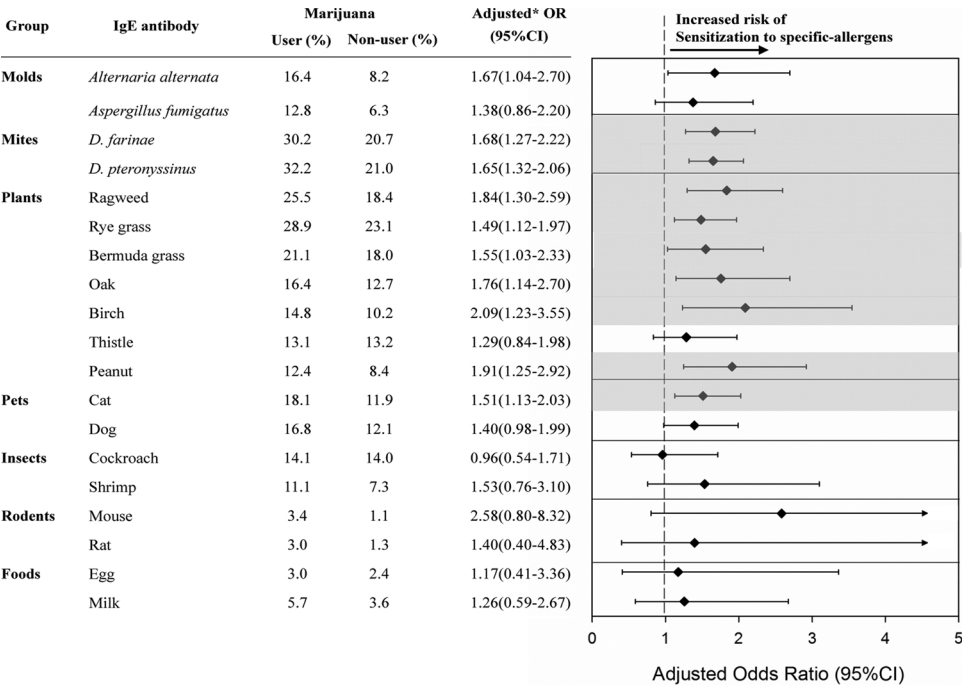


Fig. 1. Odds of sensitization to specific allergens among marijuana users. The black diamond indicates the odds ratio value, and the black line indicates it's the corresponding 95% CI. Gray-shaded panel indicates the statistical significance of the adjusted odds ratio ( $p < 0.05$ ).

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Contributors

KB was responsible for the study concept and design and was assisted by JY. JY acquired the data. KB and JY conducted the statistical analysis and interpreted the data. JY drafted the manuscript. KB critically revised the manuscript for important intellectual content. All authors reviewed and approved the manuscript.

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