Association of allergic symptoms and allergens with diabetes mellitus: a cross-sectional study based on NHANES 2005–2006

Gan Lu
Wuhan University Renmin Hospital Department of Otorhinolaryngology
Yu-Qin Deng
Wuhan University Renmin Hospital Department of Otorhinolaryngology
Yang Xi
Wuhan University Renmin Hospital Department of Otorhinolaryngology
Shi-Ming Chen
Wuhan University Renmin Hospital Department of Otorhinolaryngology
Yong-Gang Kong
Wuhan University Renmin Hospital Department of Otorhinolaryngology
Yu Xu
Wuhan University Renmin Hospital Department of Otorhinolaryngology
Fen Li
Institute of Otolaryngology-Head and Neck Surgery, Renmin Hospital of Wuhan University
Ze-Zhang Tao (taozezhang2022@126.com)
Renmin Hospital of Wuhan University: Wuhan University Renmin Hospital https://orcid.org/0000-0002-5404-4186

Research

Keywords: Allergic symptoms, allergens, diabetes mellitus (DM), National Health and Nutrition Examination Survey (NHANES)

Posted Date: July 6th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1786803/v1

Abstract

Background

Epidemiological evidence for the association of allergies with diabetes mellitus (DM) is limited.

Objective

To Investigate the association of allergic symptoms and allergens with DM by analyzing National Health and Nutrition Examination Survey (NHANES) data.

Methods

Data from 1687 subjects were screened from the 2005–2006 NHANES (*n* = 10348) data, and logistic regression models were built and stratified analysis was performed to describe the association of allergic symptoms and allergens with DM and the constraints in which they were associated.

Results

After adjusting for confounding factors, the stratified analysis found that the risk of allergic symptoms in DM patients increased by 1.847-fold, 1.646-fold, 3.859-fold, 2.862-fold, and 1.476-fold among the middle-aged, males, people with total household size of 3 or 4, and high blood pressure (HBP) patients, but decreased by 0.024-fold and 0.285-fold in people living alone or with normal weight. In females or when the total number of people in the household was 4, the risk of allergen sensitization in DM patients increased by 2.028-fold and 4.674-fold. Compared with people without DM, people with DM had a 1.585-fold increased risk of developing a D. Pteronyssinus allergy and a 0.372-fold lower risk of developing an oak allergy.

Conclusions

DM is a risk factor for allergic symptoms and allergen sensitization under certain conditions and increases the risk of D. Pteronyssinus allergy and reduces the risk of oak allergy.

1. Introduction

Allergic rhinitis (AR) is one of the most common chronic inflammatory allergic diseases and has a high risk of comorbidity with asthma and atopic dermatitis (AD) [1, 2], and allergic symptoms have a serious impact on people's daily lives [3]. AR has the following types of allergens, which are inhalation allergens, such as dust mites, pollen, mold and so on [4], and ingestion of allergens, such as foods represented by

eggs, milk, nuts and so on [5–8], and drugs such as β-lactam antibiotics represented by penicillin [9] and sulfonamides [10]. The total average cost of treating AR per patient per year is as high as EUR 2326.70, including direct costs of EUR 553.80 and indirect costs of EUR 1772.90 [11]. The average annual cost of care for a child with food allergy alone in the United States is as high as $4184 per person [12], while direct medical costs for childhood or adult asthma are estimated to be approximately five times the cost per child with food allergy [13]. The treatment process of allergic diseases not only produces huge medical consumption, but also brings huge economic losses to the society [11–16]. The occurrence of AR is related to genetic susceptibility, environmental factors and personal constitution, and its main pathogenesis is currently considered to be type 2 T helper cell [Th2]-mediated inflammation [17].

Diabetes mellitus (DM) is a metabolic disease with symptoms affecting multiple organs throughout the body, characterized by a chronic hyperglycemic state associated with inflammation and oxidative stress, resulting in micro- and macro-vascular damage in multiple organs [18], related to T helper 1 [Th1]-mediated inflammation [19]. The development of DM involves multiple pathogenic pathways, including autoimmune destruction of pancreatic β-cells, insulin deficiency, and abnormal insulin resistance [20]. Typical symptoms of hyperglycemia include polydipsia, polyuria, weight loss, and sometimes blurred vision and polyphagia. Diabetic ketoacidosis or diabetic nonketotic hyperosmolar syndrome caused by poor glycemic control can seriously endanger the patient's life [21]. As of 2021, more than 1.2 million children and adolescents (0–19 years old) and 537 million adults (20–79 years old) have DM worldwide, and the number is expected to increase to 643 million by 2030 [22]. DM is recognized as the ninth leading cause of death in the world [23], causing 6.7 million deaths, seriously affecting people's health and safety, resulting in at least $966 billion in health expenditures, accounting for 9% of total adult spending [22].

Epidemiological studies have found an association between allergic diseases and DM [24–33], but whether the conclusion is positive or negative remains highly controversial. For example, it has been reported that children with type 1 diabetes mellitus (T1DM) have an increased risk of AR [32], while AR and type 2 diabetes mellitus (T2DM) are inversely correlated in adults aged 30 years and older [34]. Molecular mechanism studies have found that cytokines secreted by Th2 cells may signal to increase Th1 cell levels and upregulate proteins involved in the development of DM [17]. These findings suggest a correlation between AR and DM. Therefore, we provide evidence for the relationship between AR and DM by exploring the relationship between allergic symptoms and allergens with DM by using the data from NHANES.

2. Materials And Methods

2.1. Subjects

Data was extracted from National Health and Nutrition Examination Survey (NHANES). NHANES is a cross-sectional probability survey based on the U.S. population aged 0 to 85 to collect information on the health and nutrition of the U.S. family population [35]. The survey is divided into two parts: family interview and health examination. NHANES is a free public dataset approved by the Research Ethics

Review Board (ERB). The document approving the NHANES 2005–2006 data review was Protocol #2005-06 [36].

Selected from 10,348 subjects from NHANES 2005–2006, after screening for allergy, DM, and medical conditions questionnaires and excluding data for no demographic variables, BMI, serum cotinine, alcohol use, physical activity and high blood pressure (HBP), a total of 1687 subjecs were obtained as the final study population. Figure 1 shows the screening process for study subjects.

2.2. Allergic symptoms

Allergy questionnaires and medical condition questionnaires were integrated and selected to obtain allergy symptom data. Screening the questions on the Allergy Questionnaire for "Doctors diagnosed hay fever, allergy, eczema or dymptoms in the past 12 months" (AGQ010, AGQ030, AGQ040, AGQ060, AGQ100, AGQ140, AGQ180) [37] and the questions on the Medical Conditions Questionnaire for "Doctor diagnosed asthma and asthma attacks in the past 12 months" (MCQ010, MCQ040) [38]. Allergy symptoms were considered to be present if the subject answered yes to some question [39], and no allergy symptoms were considered to be present if the subject answered no to all questions.

2.3. Allergen sensitization

The lower limit of detection (LLOD) for the detection of specific immunoglobulin E (sIgE) antibodies against 19 allergens, D. Farinae, D. Pteronyssinus, cat, dog, cockroach, Alternaria, peanut, egg, milk, ragweed, rye grass, Bermuda grass, oak, birch, shrimp, aspergillus, thistle, mouse and rat, was the same at 0.35 kU/L, and there was no data exceeding the upper limit of detection [40]. Allergen sensitization was considered to be present if a subject's test values were higher than the LLOD (sIgE ≥ 0.35 kU/L), and no specific sensitization was considered to be present if all subjects' test values were lower than the LLOD (sIgE < 0.35 kU/L) [41].

2.4. Allergen allergy

A subject was considered to have allergen allergy if the subject had allergic symptoms and allergen sensitization, otherwise it was not considered to have allergen allergy.

2.5. DM

All subjects aged ≥ 12 years underwent morning FPG testing to assess DM after a 9-hour fast [42]. For the complete sample, testing for A1c was also performed [43].

Screening and integration of the questions on the Diabetes Questionnaire for "Doctors diagnosed Diabetes and taking diabetes medications" (DIQ010, DIQ070) [44]. For the missing questions in 103 prediabetics (DIQ010 = 3), estimates were refined based on the use of oral antidiabetic drugs, Acarbose, Cholopropamide, Glimepiride, Glipizide, Glucagon, Glyburide, Metformin, Miglitol, Nateglinide, Pioglitazone, Repagilinide, Rosiglitazone, Tolazamide, Troglitazone, Glipizide and Metformin, Glyburide and Metformin, Metformin and Rosiglitazone, reported in the prescription drug section of the household questionnaire [44]. The missing response code for DID070 was “1” (with DM) if the prediabetics reported

any oral antidiabetic drug for all medications used in the month prior to the interview, and if the prediabetics did not report the use of any such oral hypoglycemic agents, the code was “2” (without DM) [44].

DM was considered to be present if FPG ≥ 126mg/dL, or A1c ≥ 6.5% [20], or the subject answered yes to DM in the diabetes questionnaire interview, and no DM was considered to be present if all the above three conditions are negative.

2.6. Confounding factors

Some known confounding factors affecting the development of allergic disease and DM, such as age [45], sex, race or ethnicity, country of birth, total number of households [41], family poverty income ratio (PIR) [41], education level of household reference [46], body mass index (BMI) [47], cotinine [48], alcohol consumption [49], physical activity [49] and HBP [50] were sorted out.

Age was divided into three confounding factors: young people (< 44 years old), middle-aged people (45–59 years old), and elderly people (> 60 years old), according to the age classification criteria of the World Health Organization (WHO) [45]. Sex was divided into two confounding factors: males and females. Race or ethnicity was divided into five confounding factors: Mexican American, other Hispanic, non-Hispanic White, non-Hispanic Black, and other race. Country of birth was divided into three confounding factors: U.S., Mexico and elsewhere. Total number of households was divided into five confounding factors: 1, 2, 3, 4, ≥ 5 [41]. PIR is a measure of family economic well-beings and is the ratio of income to household poverty. When PIR < 1.85, the family is eligible for federal food assistance [51]. PIR was divided into two confounding factors: <1.85 and ≥ 1.85. The household reference person is the first household member aged ≥ 18 listed on the Screener Household Member Roster to own or lease the dwelling in which the household member lives [52]. Use information about the reference person to describe the household situation in which the survey subjects lived. Reference person education level which is the highest grade or level of school that the household reference person has received was divided into three confounding factors: <12th Grade, 12th Grade/GED, and > 12th Grade [46]. BMI is a statistical index that estimates body fat in males and females of any age group, obtained by dividing a person's weight in kilograms by the square of their height in meters [47]. BMI was divided into underweight (< 18.5 kg/m^2), normal weight (18.5–24.9 kg/m²), overweight (25-29.9 kg/m²) and obese (≥ 30 kg/m²), according to the BMI classification of WHO and the National Institutes of Health [47]. Cotinine, which was used to describe the subjects’ smoking status, was divided into three confounding factors: < 0.015 ng/mL, < 10 ng/mL, ≥ 10 ng/mL [48]. Alcohol consumption screened the alcohol use questionnaire was divided into two confounding factors: yes (drinking) and no (non-drinking) [53]. Physical activity screened the physical activity questionnaire was divided into two confounding factors: yes (moderate activity) and no (no moderate activity) [54]. HBP screened by the blood pressure & cholesterol questionnaire was divided into two confounding factors: yes (HBP) and no (no HBP) [55].

2.7. Statistical analysis

Independent logistic regression models were established, with allergic symptoms, allergen sensitization and allergy as the three outcome variables, DM as the independent variable, after adjusting for the above confounding factors. To illustrate the complex sample survey design of NHANES 2005–2006, the design variables [56, 57] were applied to all data analyses in this study.

In order to observe whether allergy symptoms and allergen sensitization are related to DM under specific conditions, stratified analysis was performed on the basis of the above independent models. Each time a confounding factor was selected as a layer variable, a logistic regression model was established under the condition that all the remaining confounding factors were adjusted, and the dependent and independent variables remained unchanged, and correlation analysis was performed.

Logistic regression analysis with complex sampling was performed using SPSS (version 23.0.0, IBM, USA). Forest plots were drawn using Rstudio (version 1.3.1073.0). The Wald test was used to check whether the constraints in the regression hold. Results were considered statistically significant when the probability (P) < 0.05.

3. Results

3.1. Basic characteristics of study population and crude association of each variable with DM

The baseline characteristics of the 1687 participants screened in NHANES 2005–2006 and the relationship between each confounding factor and DM are shown in Table 1. A total of 237 of the subjects had DM and 1450 did not. As shown in table 1, the prevalence of DM was significantly different among subjects in different age groups (P<0.001), family economic status (P = 0.001), education level of household reference persons (P = 0.001), BMI value (P < 0.001), smoking (P = 0.026), drinking (P = 0.001), physical activity (P = 0.034) and blood pressure status (P < 0.001).

Table 1 Description of study population characteristics and crude association of each variable with DM.

Characteristic	DM (Referent = No)		
	Yes (N = 237)	No (N = 1450)	*P-value**
Age			**<0.001**
20–44y	32 (18.7%)	738 (49.4%)	
45–59y	59 (30.0%)	331 (31.1%)	
60–85y	146 (51.3%)	381 (19.5%)	
Sex			0.410
Males	119 (46.3%)	709 (50.2%)	
Females	118 (53.7%)	741 (49.8%)	
Race or ethnicity			0.128
Mexican American	52 (9.3%)	268 (7.2%)	
Other Hispanic	5 (3.8%)	46 (3.0%)	
Non-Hispanic White	106 (68.2%)	782 (74.5%)	
Non-Hispanic Black	70 (15.3%)	287 (9.8%)	
Other race	4 (3.5%)	67 (5.6%)	
Country of birth			0.608
U.S.	190 (85.4%)	1166 (87.2%)	
Mexico	30 (5.5%)	171 (4.6%)	
Elsewhere	17 (9.1%)	113 (8.2%)	
Number[a]			0.116
1	45 (14.8%)	196 (13.5%)	

The frequency in brackets is the proportion of the characteristic population in the U.S. after adjusting for the sampling weight.

* *P-value* Wald test is used to test the logistic regression coefficient.

[a] *Number* Total number of people in the Household.

[b] *PIR* Ratio of income to household poverty line.

[c] *BMI* Body mass index.

[d] *HBP* High blood pressure.

Characteristic	DM (Referent = No)		
	Yes (N = 237)	No (N = 1450)	*P-value**
2	96 (42.3%)	445 (32.3%)	
3	37 (17.9%)	288 (20.9%)	
4	24 (13.0%)	232 (17.2%)	
≥ 5	35 (12.0%)	289 (16.1%)	
PIR[b]			**0.001**
< 1.85	120 (37.5%)	517 (24.2%)	
≥ 1.85	117 (62.5%)	933 (75.8%)	
Education Level			**0.001**
< 12th Grade	79 (25.7%)	338 (15.6%)	
12th Grade/GED	73 (34.3%)	352 (25.5%)	
> 12th Grade	85 (40.0%)	760 (58.9%)	
BMI[c]			**<0.001**
< 18.5 kg/m^2	1 (0.3%)	27 (2.0%)	
< 25 kg/m^2	30 (11.1%)	448 (33.0%)	
< 30 kg/m^2	62 (25.2%)	492 (32.3%)	
≥ 30 kg/m^2	144 (63.4%)	483 (32.8%)	
Cotinine			**0.026**
< 0.015 ng/mL	50 (22.4%)	246 (14.5%)	
0.015-10 ng/mL	135 (52.5%)	831 (56.2%)	

The frequency in brackets is the proportion of the characteristic population in the U.S. after adjusting for the sampling weight.

* *P-value* Wald test is used to test the logistic regression coefficient.

[a] *Number* Total number of people in the Household.

[b] *PIR* Ratio of income to household poverty line.

[c] *BMI* Body mass index.

[d] *HBP* High blood pressure.

Characteristic	DM (Referent = No)		
	Yes (N = 237)	No (N = 1450)	*P-value**
≥ 10 ng/mL	52 (25.1%)	373 (29.2%)	
Alcohol consumption			**0.001**
Yes	128 (58.7%)	1021 (76.4%)	
No	109 (41.3%)	429 (23.6%)	
Physical activity			**0.034**
Yes	115 (51.6%)	809 (60.9%)	
No	122 (48.4%)	641 (39.1%)	
HBP[d]			**<0.001**
Yes	156 (66.0%)	405 (26.9%)	
No	81 (34.0%)	1045 (73.1%)	
The frequency in brackets is the proportion of the characteristic population in the U.S. after adjusting for the sampling weight.			
* *P-value* Wald test is used to test the logistic regression coefficient.			
[a] *Number* Total number of people in the Household.			
[b] *PIR* Ratio of income to household poverty line.			
[c] *BMI* Body mass index.			
[d] *HBP* High blood pressure.			

3.2. Allergic symptoms, allergen sensitization and DM

The associations of allergic symptoms and allergen sensitization with DM were calculated before and after adjustment for the confounding factors. As shown in table 2, DM increased the incidence of allergic symptoms and allergen sensitization although the correlation was not significant.

Table 2 Association of DM with allergic symptoms and allergen sensitization.

	Model 1[a]		Model 2[b]	
	OR[c] (95%CI) [d]	*P-value**	OR[c] (95%CI) [d]	*P-value**
DM and allergic symptoms	1.158 (0.919–1.459)	0.176	1.171 (0.887–1.546)	0.225
DM and allergen sensitization	1.197 (0.801–1.789)	0.341	1.322 (0.879–1.989)	0.144
[a] Model 1 is unadjusted for the 12 confounding factors.				
[b] Model 2 is adjusted for the 12 confounding factors.				
[c] *OR* Odds ratio.				
[d] *CI* Confidence interval.				
* *P-value* Wald test is used to test the logistic regression coefficient.				

3.3. Allergic symptoms, allergen sensitization and DM, by each confounding factor

Table 3 shows the stratified analysis of allergy symptoms and allergen sensitization with DM. As shown in table 3, middle-aged adults with DM had a higher incidence of allergic symptoms (OR, 1.847; 95% CI, 1.121–3.042). Males with DM had a higher incidence of allergy symptoms (OR, 1.646; 95%CI, 1.049–2.583). When the total number of people in the household was 3 and 4, the incidence of allergy symptoms in DM patients became higher (OR, 3.859; 95%CI, 1.066–13.968 and OR, 2.862; 95%CI, 1.001–8.658, respectively). Patients with DM and HBP had a higher incidence of allergic symptoms (OR, 1.476; 95%CI, 1.026–2.123). And when the total number of people in the household was one, or people of normal weight, the incidence of allergy symptoms was reduced when people had DM (OR, 0.487; 95%CI, 0.247–0.960 and OR, 0.285; 95%CI, 0.096–0.847, respectively).

As shown in table 3, females with DM had a higher incidence of allergen sensitization (OR, 2.028; 95%CI, 1.193–3.447). When the total number of people in the household was 4, the incidence of allergen sensitization in DM patients became higher (OR, 4.674; 95%CI, 1.992–11.363).

Table 3 Association of DM with allergic symptoms and allergen sensitization, by each confounding factor.

Characteristic	DM with allergic symptoms (Referent = No)		DM with specific sensitization (Referent = No)	
	OR[a] (95%CI) [b]	*P-value**	OR[a] (95%CI) [b]	*P-value**
Age				
20–44y	1.457 (0.641–3.311)	0.329	1.957 (0.651–5.882)	0.194
45–59y	1.847 (1.121–3.042)	**0.009**	1.088 (0.422–2.807)	0.850
60–85y	0.924 (0.550–1.553)	0.745	1.377 (0.748–2.537)	0.264
Sex				
Males	1.646 (1.049–2.583)	**0.018**	0.748 (0.334–1.677)	0.443
Females	0.843 (0.474–1.499)	0.527	2.028 (1.193–3.447)	**0.004**
Race or ethnicity				
Mexican American	0.887 (0.465–1.694)	0.693	0.565 (0.132–2.413)	0.402
Other Hispanic	0.935 (0.014–63.804)	0.973	1.321 (0.033–52.117)	0.872
Non-Hispanic White	1.189 (0.831–1.703)	0.303	1.407 (0.836–2.367)	0.162
Non-Hispanic Black	1.497 (0.821–2.727)	0.152	1.105 (0.539–2.265)	0.766
Other race	0.430 (0.025–7.442)	0.528	3.321 (0.252–43.821)	0.321
Country of birth				
U.S.	1.123 (0.836–1.509)	0.402	1.382 (0.838–2.280)	0.169
Mexico	1.268 (0.401–4.010)	0.661	0.633 (0.053–7.547)	0.694
Elsewhere	2.201 (0.392–12.347)	0.330	1.597 (0.174–14.633)	0.652
Number[c]				
1	0.487 (0.247–0.960)	**0.024**	1.255 (0.630–2.501)	0.482
2	0.938 (0.495–1.777)	0.831	0.877 (0.448–1.717)	0.677
3	3.859 (1.066–13.968)	**0.025**	1.601 (0.444–5.772)	0.434
4	2.862 (1.001–8.658)	**0.043**	4.674 (1.992–11.363)	< **0.001**
≥ 5	0.810 (0.298–2.201)	0.653	1.249 (0.428–3.650)	0.658
PIR[d]				

Characteristic	DM with allergic symptoms (Referent = No)		DM with specific sensitization (Referent = No)	
	OR[a] (95%CI) [b]	*P-value**	OR[a] (95%CI) [b]	*P-value**
< 1.85	1.093 (0.616–1.939)	0.740	1.548 (0.955–2.509)	0.054
≥ 1.85	1.267 (0.841–1.910)	0.218	1.323 (0.737–2.376)	0.308
Education Level				
< 12th Grade	1.146 (0.377–3.479)	0.794	1.178 (0.533–2.608)	0.659
12th Grade/GED	0.995 (0.366–2.707)	0.992	1.013 (0.567–1.812)	0.961
> 12th Grade	1.302 (0.690–2.456)	0.376	1.573 (0.884–2.798)	0.094
BMI[e]				
< 18.5 kg/m^2	5.222E + 53 (0.000-. [g])	0.978	2.105E-46 (0.000-. [g])	0.835
< 25 kg/m^2	0.285 (0.096–0.847)	**0.014**	1.301 (0.464–3.645)	0.586
< 30 kg/m^2	2.086 (0.820–5.306)	0.093	0.765 (0.292–2.005)	0.554
≥ 30 kg/m^2	1.145 (0.808–1.623)	0.406	1.594 (0.889–2.857)	0.089
Cotinine				
< 0.015 ng/mL	2.002 (0.539–7.440)	0.260	1.965 (0.869–4.446)	0.078
0.015-10 ng/mL	0.997 (0.601–1.590)	0.920	1.013 (0.710–1.447)	0.937
≥ 10 ng/mL	1.574 (0.619–4.001)	0.300	1.843 (0.552–6.152)	0.279
Alcohol consumption				
Yes	1.221 (0.866–1.723)	0.215	1.160 (0.649–2.071)	0.586
No	1.078 (0.548–2.120)	0.814	1.333 (0.619–2.872)	0.424
Physical activity				
Yes	1.089 (0.820–1.447)	0.521	1.237 (0.739–2.071)	0.379
No	1.260 (0.706–2.249)	0.394	1.381 (0.886–2.152)	0.121
HBP[f]				
Yes	1.476 (1.026–2.123)	**0.022**	1.433 (0.948–2.167)	0.063
No	0.852 (0.503–1.443)	0.517	1.247 (0.457–3.405)	0.639

Characteristic	DM with allergic symptoms (Referent = No)		DM with specific sensitization (Referent = No)	
	OR[a] (95%CI) [b]	*P-value**	OR[a] (95%CI) [b]	*P-value**
* *P-value* Wald test is used to test the logistic regression coefficient.				
[a] *OR* Odds ratio.				
[b] *CI* Confidence interval.				
[c] *Number* Total number of people in the Household.				
[d] *PIR* Ratio of income to household poverty line.				
[e] *BMI* Body mass index.				
[f] - Set to missing value due to floating-point overflow when computing this value.				
[g] *HBP* High blood pressure				

3.4. Allergen allergy and DM

Figure 2 shows the relationship between specific allergies caused by 19 allergens and DM. As shown in figure 2, subjects with DM had a 1.585-fold higher risk of developing a D. Pteronyssinus allergy than those without DM ($P = 0.042$). Participants with DM had a 0.372-fold higher risk of developing an oak allergy than those without DM ($P = 0.041$).

4. Discussion

According to the existing reports, it can be found that the relationship between allergic diseases and DM is very controversial. But there seems to be consensus that DM exacerbates asthma [58] and AD [24]. The findings of this study of an increased risk of allergic symptoms in DM people in middle age, or in males, or with HBP were similar to those of a cross-sectional cohort study in the Danish metropolitan area that among middle-aged people aged 50–64, males or those with HBP or DM had a higher mortality rate (hazard ratio [HR], 1.83; 95%CI, 1.14–2.38, and HR, 2.42; 95%CI, 0.96–6.11, and HR, 2.47; 95%CI, 1.54–3.95, respectively) [59]. U.S. adults with AD had a higher prevalence of HBP and DM (OR, 1.46; 95%CI, 1.18–1.80 and OR, 1.52; 95%CI, 1.16–1.99, respectively), and increased with the severity of AD increased, the incidence of HBP and DM increased [24]. HBP was associated with a 1.43-fold increased risk of developing asthma, and DM was another factor that increased with asthma (adjusted odds ratio [aOR], 1.75; 95%CI, 1.06 to 3.02), and females were more likely to develop asthma than males (aOR, 1.73; 95%CI, 1.02–2.84) [60]. Similar results were found in this study in the relationship between allergen sensitization

and DM, with the prevalence of DM in females increasing the incidence of allergen sensitization. Compared with non-DM subjects, subjects with T2DM had an increased risk of asthma in both males and females (OR, 1.70; 95%CI, 1.07–2.70; $P = 0.026$ and OR, 1.88; 95%CI; 1.24–2.85; $P = 0.003$, respectively), and BMI was a very significant predictor of asthma independent of diabetic status in females, but not in males[61]. Any increase in BMI at a normal weight level was not associated with an increased risk of being diagnosed with DM complications [62], and at normal weight levels, DM was found to reduce the incidence of allergy symptoms in this study. What's interesting was differential effects of total number of people in the household on the incidence of allergic symptoms and allergen sensitization in DM patients were found.

Dust mite allergy, a very common allergic disease in the world, also known as house dust allergy, is a sensitization and allergic reaction to dust mite feces. Dermatophagoides pteronyssinus was first identified as the causative allergen of house dust allergy in 1967 [63]. House dust mites are found all over the world and are present in approximately 84% of American households [63]. We found that having DM increases the risk of developing a D. Pteronyssinus allergy. Among Korean adults, subjects susceptible to house dust mites had an increased risk of DM (OR 1.63, 95% CI, 1.03–2.59) [64]. In mouse experiments, non-obese diabetic (NOD) mice developed more severe allergic asthmatic airway inflammation and airway hyperresponsiveness than pre-Th2 BALB/c mice after house dust mite sensitization and challenge [65]. This seems to suggest that house dust mite allergy is associated with DM which may be related to IL-4 and IL-17 involving Th2 and Th17 immune responses [65].

Oak is common in the United States, and its pollen is an important allergen in North America, with approximately 30% of allergy-sensitive people in the U.S. allergic to oak [66]. This study found that having DM can reduce the risk of oak allergy, and similar results were found for other pollen allergens, although no significance was observed.

The strength of this study is that it integrates different allergic symptoms and allergens to explore the relationship with DM and find some situations when there is a correlation. NHANES is a free public data set in the U.S., of which the data is easy to obtain. Due to the complexity of the sampling, the conclusions of the analysis can be generalized to the entire U.S. The disadvantage is that this is a cross-sectional analysis and the exact causal relationship cannot be determined because of the disease and factors coexist. NHANES 2005–2006 does not provide clear diagnostic data or other potential confounding factors which may not affect the results. Due to data screening reasons, we did not discuss the association of allergic symptoms and allergens with DM in children and adolescents, and the 95% confidence interval for OR included 1 when it was statistically significant when analyzing the association of allergen allergy and DM.

The relationship between allergy caused by different allergens and DM can be explored by replacing the database and expanding the sample size. The association mechanism between allergic diseases and DM is not only related to the Th1/Th2 paradigm [17], but may also involve multiple pathways. Therefore, based on the NHANES data, it is possible to further analyze whether there is a correlation between the

detection indicators of allergic diseases such as IgE and the detection indicators of DM such as FPG and A1c.

Conclusion

DM is a risk factor for allergic diseases in middle-aged people, in males, in people with a total household size of 3-4, and in HBP patients, for allergen sensitization in females or in people with a total household size of 4, for D. Pteronyssinus allergy, but is a protective factor for allergic disease in people with a total household size of 1 or with normal weight and for oak allergy.

Declarations

Ethics approval and consent to participate: There are no permissions required to access and use the data from NHANES database. NHANES is a free public dataset approved by the Research Ethics Review Board (ERB) with protocol number or description Protocol #2005-06 at NHANES - NCHS Research Ethics Review Board Approval (cdc.gov).

Consent for publication: Not applicable.

Availability of data and materials: The allergies and diabetes mellitus data that support the findings of this study are available in the National Health and Nutrition Examination Survey (NHANES), NHANES Questionnaires, Datasets, and Related Documentation (cdc.gov).

Competing interests: The authors declare that they have no competing interests.

Funding: This work was supported by the National Natural Science Foundation of China under Grant number 81970860 81870705.

Acknowledgments: The authors thank the National Natural Science Foundation of China and all the authors contributed to this work for support and the subjects and staff of the 2005-2006 NHANES for their valuable contributions.

References

1. Khan, D.A., Allergic rhinitis and asthma: epidemiology and common pathophysiology. Allergy Asthma Proc, 2014. 35(5): p. 357-61.
2. Langan, S.M., A.D. Irvine and S. Weidinger, Atopic dermatitis. Lancet, 2020. 396(10247): p. 345-360.
3. Backman, H., et al., Increased prevalence of allergic asthma from 1996 to 2006 and further to 2016-results from three population surveys. Clin Exp Allergy, 2017. 47(11): p. 1426-1435.
4. D'Amato, G., et al., Meteorological conditions, climate change, new emerging factors, and asthma and related allergic disorders. A statement of the World Allergy Organization. World Allergy Organ J, 2015. 8(1): p. 25.

5. Schoemaker, A.A., et al., Incidence and natural history of challenge-proven cow's milk allergy in European children--EuroPrevall birth cohort. Allergy, 2015. 70(8): p. 963-72.
6. Xepapadaki, P., et al., Incidence and natural history of hen's egg allergy in the first 2 years of life-the EuroPrevall birth cohort study. Allergy, 2016. 71(3): p. 350-7.
7. Osborne, N.J., et al., Prevalence of challenge-proven IgE-mediated food allergy using population-based sampling and predetermined challenge criteria in infants. J Allergy Clin Immunol, 2011. 127(3): p. 668-76.e1-2.
8. Peters, R.L., et al., The prevalence of food allergy and other allergic diseases in early childhood in a population-based study: HealthNuts age 4-year follow-up. J Allergy Clin Immunol, 2017. 140(1): p. 145-153.e8.
9. Gonzalez-Estrada, A. and C. Radojicic, Penicillin allergy: A practical guide for clinicians. Cleve Clin J Med, 2015. 82(5): p. 295-300.
10. Jandus, P. and T. Harr, [Sulfonamide allergy and cross-reactivity]. Rev Med Suisse, 2013. 9(382): p. 798-802.
11. Colas, C., et al., Estimate of the total costs of allergic rhinitis in specialized care based on real-world data: the FERIN Study. Allergy, 2017. 72(6): p. 959-966.
12. Gupta, R., et al., The economic impact of childhood food allergy in the United States. JAMA Pediatr, 2013. 167(11): p. 1026-31.
13. Barnett, S.B. and T.A. Nurmagambetov, Costs of asthma in the United States: 2002-2007. J Allergy Clin Immunol, 2011. 127(1): p. 145-52.
14. Meltzer, E.O., Allergic Rhinitis: Burden of Illness, Quality of Life, Comorbidities, and Control. Immunol Allergy Clin North Am, 2016. 36(2): p. 235-48.
15. The Global Asthma Report 2018. 2022.
16. Avena-Woods, C., Overview of atopic dermatitis. Am J Manag Care, 2017. 23(8 Suppl): p. S115-S123.
17. Juneja, L. and H.S. Parmar, Ovalbumin induced allergic rhinitis and development of prediabetes to rats: possible role of Th2 cytokines. Inflamm Allergy Drug Targets, 2013. 12(3): p. 199-205.
18. Fujita, T., et al., Complement-mediated chronic inflammation is associated with diabetic microvascular complication. Diabetes Metab Res Rev, 2013. 29(3): p. 220-6.
19. Mukherjee, M. and P. Nair, Autoimmune Responses in Severe Asthma. Allergy Asthma Immunol Res, 2018. 10(5): p. 428-447.
20. Draznin, B., et al., 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2022. Diabetes Care, 2022. 45(Supplement_1): p. S17-S38.
21. Diagnosis and classification of diabetes mellitus. Diabetes Care, 2013. 36 Suppl 1: p. S67-74.
22. Facts & figures. 2022.
23. Zheng, Y., S.H. Ley and F.B. Hu, Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. Nat Rev Endocrinol, 2018. 14(2): p. 88-98.

24. Silverberg, J.I., et al., Association of atopic dermatitis with allergic, autoimmune, and cardiovascular comorbidities in US adults. Ann Allergy Asthma Immunol, 2018. 121(5): p. 604-612.e3.
25. Smew, A.I., et al., Familial Coaggregation of Asthma and Type 1 Diabetes in Children. JAMA Netw Open, 2020. 3(3): p. e200834.
26. Metsala, J., et al., The association between asthma and type 1 diabetes: a paediatric case-cohort study in Finland, years 1981-2009. Int J Epidemiol, 2018. 47(2): p. 409-416.
27. George, C., A.M. Ducatman and B.N. Conway, Increased risk of respiratory diseases in adults with Type 1 and Type 2 diabetes. Diabetes Res Clin Pract, 2018. 142: p. 46-55.
28. Shapiro, M., et al., Asthma in Youth and Early-onset Type 2 Diabetes: A Nationwide Study of 1.72 Million Israeli Adolescents. J Clin Endocrinol Metab, 2021. 106(12): p. e5043-e5053.
29. Baek, J.Y., et al., Association between diabetes and asthma: Evidence from a nationwide Korean study. Ann Allergy Asthma Immunol, 2018. 121(6): p. 699-703.
30. Mueller, N.T., et al., Asthma and the risk of type 2 diabetes in the Singapore Chinese Health Study. Diabetes Res Clin Pract, 2013. 99(2): p. 192-9.
31. Villa-Nova, H., et al., Prevalence of allergic diseases and/or allergic sensitisation in children and adolescents with type 1 diabetes mellitus. Allergol Immunopathol (Madr), 2015. 43(2): p. 157-61.
32. Kowalczyk, A. and M. Szalecki, [Allergic diseases in children with type 1 diabetes]. Pediatr Endocrinol Diabetes Metab, 2013. 19(3): p. 100-5.
33. Silverberg, J.I. and P. Greenland, Eczema and cardiovascular risk factors in 2 US adult population studies. J Allergy Clin Immunol, 2015. 135(3): p. 721-8.e6.
34. Lee, T.K., Y.J. Jeon and S.J. Jung, Bi-directional association between allergic rhinitis and diabetes mellitus from the national representative data of South Korea. Sci Rep, 2021. 11(1): p. 4344.
35. Fain, J.A., NHANES. Diabetes Educ, 2017. 43(2): p. 151.
36. NHANES - NCHS Research Ethics Review Board Approval. 2022.
37. NHANES 2005-2006: Allergy Data Documentation, Codebook, and Frequencies. 2022.
38. MCQ_D. 2022.
39. Yu, R., et al., Excess Free Fructose Beverages and Allergy in Children and Adolescents: Results From NHANES 2005-2006. Ann Fam Med, 2018. 16(5): p. 408-418.
40. NHANES 2005-2006: Allergen Specific IgE(s) & Total IgE - Serum Data Documentation, Codebook, and Frequencies. 2022.
41. Tsuang, A., et al., Endotoxin, food allergen sensitization, and food allergy: A complementary epidemiologic and experimental study. Allergy, 2020. 75(3): p. 625-635.
42. NHANES 2005-2006: Plasma Fasting Glucose & Insulin Data Documentation, Codebook, and Frequencies. 2022.
43. NHANES 2005-2006: Glycohemoglobin Data Documentation, Codebook, and Frequencies. 2022.
44. NHANES 2005-2006: Diabetes Data Documentation, Codebook, and Frequencies. 2022.

45. (PDF) Ahmad OB, Boschi-Pinto C, Lopez AD, et al. 2000. Age Standardization of Rates: A New WHO Standard. GPE Discussion Paper Series: No 31, World Health. 2022.
46. Visness, C.M., et al., Association of obesity with IgE levels and allergy symptoms in children and adolescents: results from the National Health and Nutrition Examination Survey 2005-2006. J Allergy Clin Immunol, 2009. 123(5): p. 1163-9, 1169.e1-4.
47. Weir, C.B. and A. Jan, BMI Classification Percentile And Cut Off Points. 2022.
48. Peng, Q., S.D. Harlow and S.K. Park, Urinary arsenic and insulin resistance in US adolescents. Int J Hyg Environ Health, 2015. 218(4): p. 407-13.
49. Lee, S., J.Y. Min and K.B. Min, Caffeine and Caffeine Metabolites in Relation to Insulin Resistance and Beta Cell Function in U.S. Adults. Nutrients, 2020. 12(6).
50. Xie, X., et al., Association between triclocarban and triclosan exposures and the risks of type 2 diabetes mellitus and impaired glucose tolerance in the National Health and Nutrition Examination Survey (NHANES 2013-2014). Environ Int, 2020. 136: p. 105445.
51. Thorne, P.S., et al., Endotoxin Exposure: Predictors and Prevalence of Associated Asthma Outcomes in the United States. Am J Respir Crit Care Med, 2015. 192(11): p. 1287-97.
52. DEMO_D. 2022.
53. ALQ_D. 2022.
54. NHANES 2005-2006: Physical Activity Data Documentation, Codebook, and Frequencies. 2022.
55. BPQ_D. 2022.
56. Salo, P.M., et al., Allergy-related outcomes in relation to serum IgE: results from the National Health and Nutrition Examination Survey 2005-2006. J Allergy Clin Immunol, 2011. 127(5): p. 1226-35.e7.
57. Trasande, L., et al., Urinary phthalates and increased insulin resistance in adolescents. Pediatrics, 2013. 132(3): p. e646-55.
58. Price, D., et al., Predicting frequent asthma exacerbations using blood eosinophil count and other patient data routinely available in clinical practice. J Asthma Allergy, 2016. 9: p. 1-12.
59. Tupper, O.D., Z.J. Andersen and C.S. Ulrik, Demographic, lifestyle and comorbid risk factors for all-cause mortality in a Danish cohort of middle-aged adults with incident asthma. BMJ Open, 2021. 11(10): p. e049243.
60. Lee, K.H. and H.S. Lee, Hypertension and diabetes mellitus as risk factors for asthma in Korean adults: the Sixth Korea National Health and Nutrition Examination Survey. Int Health, 2020. 12(4): p. 246-252.
61. Thomsen, S.F., et al., Risk of asthma in adult twins with type 2 diabetes and increased body mass index. Allergy, 2011. 66(4): p. 562-8.
62. Gray, N., et al., Relation between BMI and diabetes mellitus and its complications among US older adults. South Med J, 2015. 108(1): p. 29-36.
63. Biagtan, M., R. Viswanathan and R.K. Bush, Immunotherapy for house dust mite sensitivity: where are the knowledge gaps? Curr Allergy Asthma Rep, 2014. 14(12): p. 482.

64. Kim, M.K., et al., House dust mite and Cockroach specific Immunoglobulin E sensitization is associated with diabetes mellitus in the adult Korean population. Sci Rep, 2018. 8(1): p. 2614.
65. Foray, A.P., et al., IL-4 and IL-17 Are Required for House Dust Mite-Driven Airway Hyperresponsiveness in Autoimmune Diabetes-Prone Non-Obese Diabetic Mice. Front Immunol, 2020. 11: p. 595003.
66. Bernstein, D.I., et al., Allergy to oak pollen in North America. Allergy Asthma Proc, 2021. 42(1): p. 43-54.

Figures

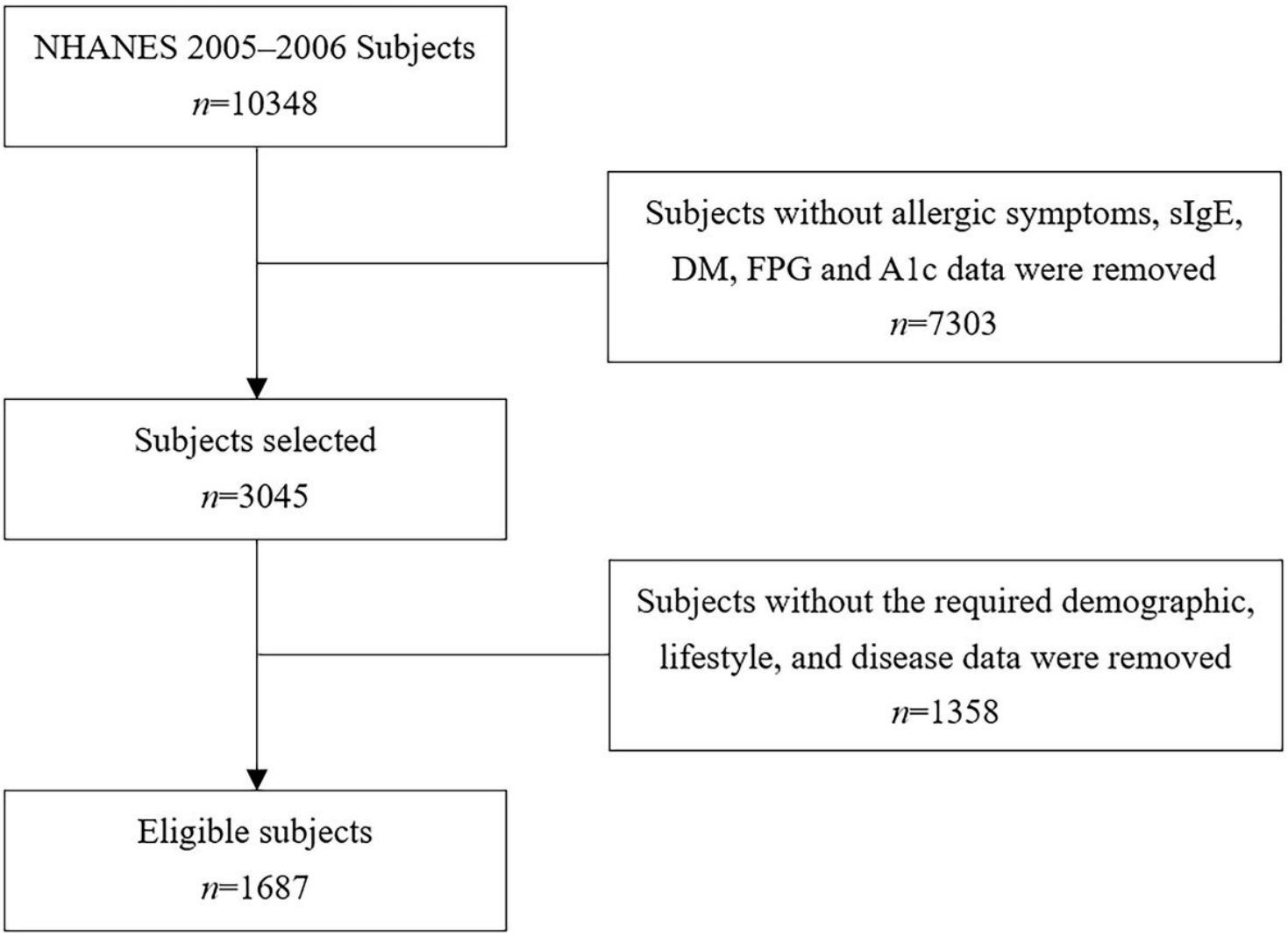

Figure 1

Study subjects flow chart

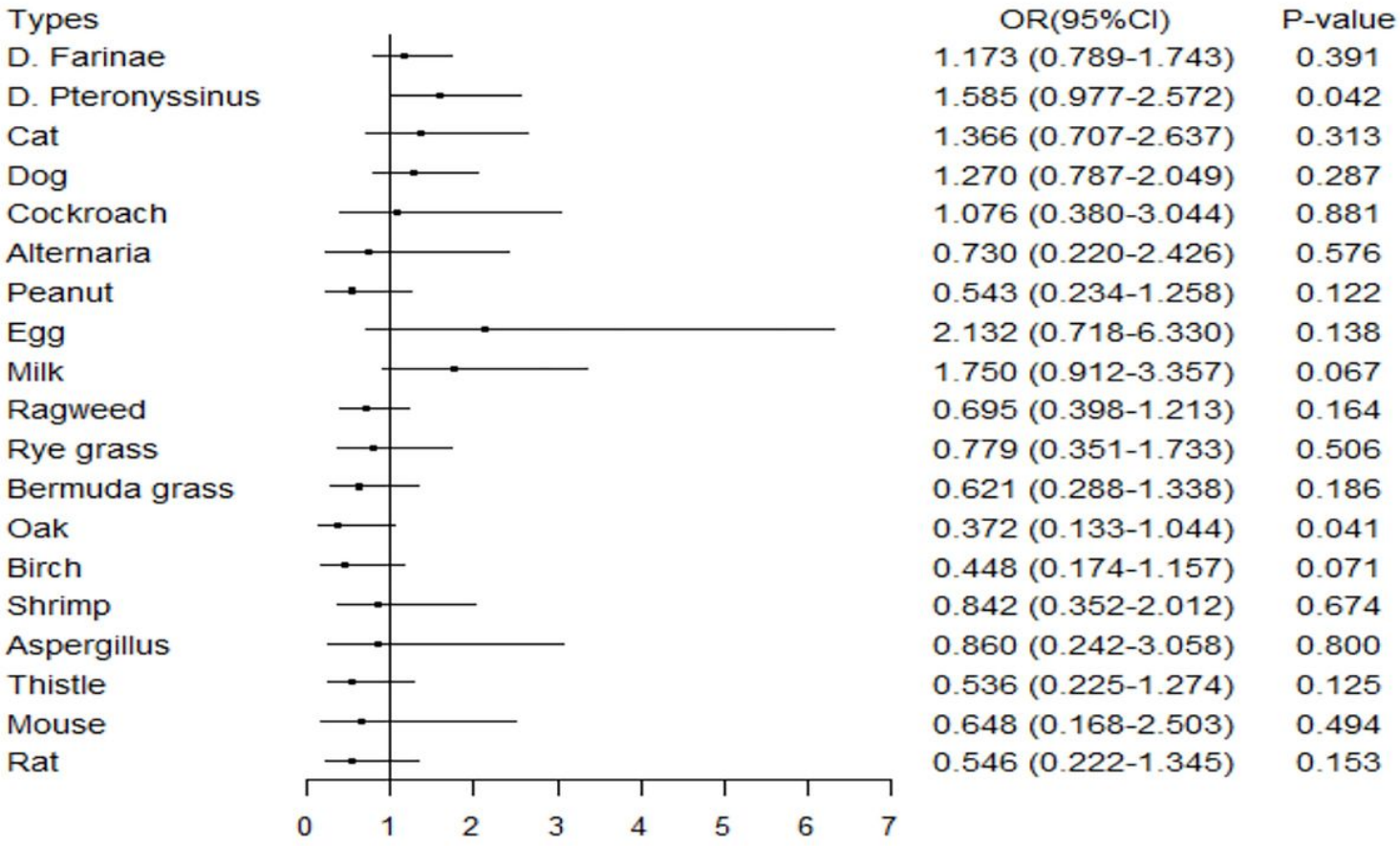

Figure 2

Association of 19 allergen allergies with DM.