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Heavy Metals and Eczema

Association of Environmental Exposure to Heavy Metals and Eczema in US population: Analysis of Blood Cadmium, Lead, and Mercury in U.S. NHANES 2005-2006

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ABSTRACT

Objectives: We aim to explore the association between blood heavy metal concentrations of cadmium, lead, and mercury with ever-report of eczema in the US population.

Methods: We used NHANES cross-sectional data from 2005-2006. Eczema was measured among 4509 adults and 3898 non-adults. The association between eczema and tertiles of concentrations of cadmium, lead, mercury was estimated using multivariate logistic regression models adjusted for different confounding variables. The estimation was also stratified by gender.

Results: The prevalence of ever-report of eczema was 7.63% in adults and 13.42% in non-adults. None of the heavy metals was significantly associated with increased ORs of eczema after potential confounding variables were adjusted in the models. Our results remained null after stratifying for gender.

Conclusions: Blood cadmium, lead, and mercury were not associated with reports of eczema in general US population.

Key words

Eczema, immune system, allergen, cadmium, lead, mercury, NHANES, environmental epidemiology.

1. Introduction

Eczema is a common chronic inflammatory skin disease with a prevalence up to 10% in adults and 20% in children^{1,2}. Most cases of eczema begin in childhood or adolescence; and the symptoms can persist into adulthood³. Incidence of eczema tends to be higher in developed countries versus developing countries⁴⁻⁶; and the prevalence of eczema has increased over the last few decades worldwide⁷.

Eczema is caused by immune response to skin antigens. Two major pathophysiological attributes are lesions of the epidermal structure, and cutaneous inflammation due to improper immune responses⁸. Complex interactions among genes, immunological factors, skin barrier defects, infections, neuroendocrine factors, and environmental factors are involved in the pathogenesis of eczema⁹. As there is currently no cure for eczema¹⁰, it is suspected that a combination of genetic, immunological, neurological, and environmental factors are involved in its mechanism¹¹.

Heavy metals may contribute to eczema by affecting immune system's inflammatory response, through modulation of immunology cells numbers, cytokines, and immunoglobulin E (IgE) antibodies, which may lead to atopic diseases^{12,13}. There is some evidence of a positive association between eczema or atopic dermatitis and blood concentrations of lead, mercury and cadmium¹⁴⁻²⁰. However, there have been studies reporting the lack of an association between eczema and heavy metal levels²¹⁻²⁴.

Due to these conflicting findings, we therefore wanted to explore whether blood heavy metals are associated with eczema in US population. We studied the cross-sectional relation between eczema and

blood concentrations of three heavy metals (lead, mercury and cadmium), among participants in the National Health and Nutrition Examination Survey (NHANES), a population of randomly selected non-institutionalized residents across the United States.

2. Methods

2.1 Study Population

National Health and Nutrition Examination Survey (NHANES) was a series of cross-sectional health and nutrition surveys conducted by the National Center for Health Statistics. The NHANES study protocol is described in detail elsewhere²⁵. The survey includes interviews and physical examinations on a variety of health topics. The sample is selected to represent the US population of all ages, with over-sampling persons 60 and older, African Americans and Hispanics. All participants completed household surveys conducted by trained study staff, which includes questions about demographic and health information. Medical examinations, blood sample collection and other in-person testing are conducted at their mobile examination centers. Informed consent was obtained from all NHANES participants.

For the current study we used publicly available NHANES data from the 2005-2006 surveys, in which eczema information was acquired through the question “Has a doctor or other health professional ever told [you/SP] that [you have/SP s/he has] eczema?”. Targets were both males and females aged 1 year to 150 years. Blood heavy metal concentrations were collected from participants aged 1 year and older who do not meet any of the exclusion criteria, including hemophiliacs, participants who received chemotherapy within last 4 weeks, the presence of the following conditions on both arms: rashes, gauze dressings, casts, edema, paralysis, tubes, open sores or wounds, withered arms or limbs missing, damages, sclerosed or occluded veins, allergies to cleansing reagents, burned or scarred tissue, shunt or

IV²⁶. Altogether our sample for analysis consisted of 8407 people. According to WHO, an adult is a person older than 19 years of age²⁷. Also in NHANES, many survey questions only target on people 20 and above. Therefore, we divided our study population into ≥ 20 years as adults (n=4509) and 1-19 years as non-adults (n= 3898).

2.2 Blood heavy metals assessment

We acquired whole blood metal concentrations data from NHANES database. The methods for blood collection, sample transportation and storage, and sample analysis for Pb, Cd, and total Hg, have been described in the laboratory procedure manual²⁸. The NHANES quality assurance and quality control (QA/QC) protocols meet the 1988 Clinical Laboratory Improvement Act mandates²⁹. Where the result was below the detection limit, the value for that sample was assigned as the detection limit divided by the square root of two.

2.3 Covariates

Demographic variables included age, gender, ethnicity (Mexican American, other Hispanic, non-Hispanic White, non-Hispanic Black, and other), education (less than 9th grade, 9th-11th grade, high school graduate, some college or associate degree, college graduate and above), and family poverty income ratio (PIR). We divided people aged 20 years and older into tertiles, and under 20 years into 1-9 and 10-19 according to WHO's definition of adolescents³⁰. Income was categorized using the PIR eligibility cut points for the United States Department of Agriculture (USDA) food assistance programs into: low (0.000-1.850), middle (1.851-3.500), and high (3.501+) incomes³¹. To avoid identifiability issue, NHANES indicates age as 85 years for all individuals > 85 years of age (1.61% of our study population).

Lifestyle variables were smoking (never, past, current), alcohol use (never, past, current light, current heavy), sleep (less than 6 hours, 6-7 hours, 7+ hours), and BMI (underweight, normal weight, overweight, obesity). Participants who smoked less than 100 cigarettes in life were classified as never smokers. Participants who smoked at least 100 cigarettes in life were classified as current smokers if they reported currently smoking “some days” or “every day” and former smokers if they reported “not at all” currently. Participants who had less than 12 alcoholic drinks in lifetime were classified as never drinker. Participants who had at least 12 alcoholic drinks in lifetime but did not drink any alcohol over past 12 months were classified as past drinkers. For participants who had drunk alcohol over past 12 month, those who consumed more than one drink per day on average were classified as heavy drinkers, and those who consumed one drink or less on average were classified as light drinkers. BMI was classified into four groups, underweight ($BMI < 18.5$), normal weight ($18.5 \leq BMI < 25$), overweight ($25 \leq BMI < 30$), and obesity ($BMI \geq 30$).

Some clinical comorbidities have been associated with eczema including hypertension, diabetes, heart condition, asthma, hay fever, and depression³²⁻³⁸. Participants who reported “Yes” to both questions “Ever told you had high blood pressure (HBP)” and “Now taking prescribed medicine for HBP” were classified as having hypertension; otherwise they were classified as not having hypertension.

Participants reporting having diabetes “Yes” or “Borderline” were classified as having diabetes, and “No” as not having diabetes. Participants who reported “Yes” to at least one of the following questions: “ever told you had congestive heart failure”, “ever told you had coronary heart disease”, “ever told you had angina/angina pectoris”, “ever told you had heart attack”, were classified as having heart condition; otherwise they were classified as not having heart condition. Depression measurement was done by answering questions of the Patient Health Questionnaire (PHQ), a validated self-reported assessment based on the nine DSM-IV symptoms for depression^{37,39}. PHQ scores were classified as none (score 0-4), mild (score 5-9), moderate (score 10-14), and severe (score 15-27). In our study, score 0-9 were seen as

not having depression, and score more than 9 were seen as having depression. These variables were considered separately because they could also be mediators of effects of heavy metal exposure on atopic dermatitis. Participants were classified as not having a certain condition if their answer was “don’t know” to questions about history of the condition. In addition, we adjusted for serum C-reactive protein, homocysteine, and IgE as biomarkers of inflammation. C-reactive protein (CRP) and IgE have been associated with eczema^{15,40}, but also could be mediators of the effects of heavy metals.

2.4 Statistical analysis

We used SAS, version 9.4 (SAS Institute Inc., Cary, NC, USA) for all analysis. We used NHANES cluster design variables (SDMVSTRA, SDMVPSU) and full sample 2-year medical examination weight WTMEC2YR for 2005-2006. In NHANES, a sample weight is assigned to each sample person. Sample weights can be considered as measures of the number of persons represented by the particular sample person. When a sample is weighted in NHANES it is considered to be representative of the US civilian noninstitutionalized population⁴¹. We used PROC SURVEYFREQ and PROC SURVEYMEANS to estimate the weighted prevalence of eczema and blood heavy metal concentrations. We used PROC SURVEYLOGISTIC to perform separate crude and adjusted logistic regressions for adults and non-adults with eczema as the dependent variable. Blood heavy metal concentrations were divided into tertiles based on its distribution in both adults and non-adults. Crude and adjusted odds ratio (OR) and 95% confidence intervals (CI) were estimated. The OR represented the odds of having eczema vs. not having eczema for each tertile increase of heavy metal concentration. Analysis were stratified by gender because there was evidence supporting that the prevalence of eczema was different between male and female⁴², and there were gender differences in the disposition and toxicity of metals⁴³. We also used

PROC SURVEYREG testing for trend by modeling a continuous blood heavy metal variable coded as the median value of each tertile.

In NHANES, many variables are only available in adults aged >20, therefore we built different models for adults and non-adults separately. For adults, our first model (model 1) was adjusted for all the demographic variables (age, gender, ethnicity, education, and income). The second model (model 2) included demographic variables and lifestyle variables (smoking, alcohol drinking, sleep, and BMI). In addition, we conducted a model that also included medical comorbidities (hypertension, diabetes, heart condition, asthma, hay fever, and depression) and inflammatory biomarkers (C-reactive protein, homocysteine, and IgE) (model 3). For adolescents, we built two models, which are the model adjusting for demographic variables (age, gender, ethnicity, and income) (model 1), and the model adjusting for demographic variables, medical comorbidities (asthma and hay fever) and serum biomarkers (C-reactive protein and IgE) (model 2). A two-sided p-value <0.05 was taken to indicate statistical significance for all estimates.

3. Results

The relation between mean heavy metal concentration and participants' characteristics is shown separately for adults and non-adults in Table 1 and Table 2, respectively. The mean concentrations in adults were 0.55 ug/L for cadmium, 1.75 ug/dL for lead, and 1.69 ug/L for mercury. The mean concentrations in non-adults were 0.22 ug/L for cadmium, 1.24 ug/dL for lead, and 0.68 ug/L for mercury. In general, blood heavy metal concentration tended to be higher in male, older people and people with a heart condition. As expected, blood lead concentration was higher in lower SES groups, however, the relationship with mercury was the opposite. Blood lead and cadmium concentrations tended to be higher in smokers, and people with depression. Respectively, blood lead concentration was

higher in people with hypertension; blood cadmium concentration was higher in people with higher levels of homocysteine and IgE.

The relation between eczema and participants' characteristics is shown for adults and non-adults in Table 3 and Table 4, respectively. The weighted prevalence of eczema in adults was 7.63% (9.06% in female and 6.07% in male). The weighted prevalence of eczema in non-adults was 13.42% (12.31% in female and 14.47% in male). In adults, reports of eczema tended to be lower in male (OR: 0.649; 95%CI: 0.519-0.811; $p=0.0009$), Mexican American (OR: 0.183; 95%CI: 0.116-0.290, $p<0.0001$), and other Hispanic (OR: 0.457; 95%CI: 0.215-0.972; $p=0.0429$), but higher in people with higher education (OR: 2.502, 2.619, 3.012, 3.288; 95%CI: 1.015-6.170, 1.306-5.251, 1.454-6.240, 1.383-7.813; $p=0.0468$, 0.0099, 0.0056, 0.0103), family income (OR: 1.466; 95%CI: 1.015-2.116, $p=0.0422$), asthma (OR: 2.037; 95%CI: 1.429-2.906; $p=0.0007$), hay fever (OR: 2.407; 95%CI: 1.642-3.526; $p=0.0002$), and depression (OR: 2.469; 95%CI: 1.705-3.575; $p=0.0001$). In non-adults, reports of eczema tended to be lower in 10-19 (OR=0.565, 95%CI: 0.430-0.744; $p=0.0005$), but higher in people with higher family income (OR: 1.398, 1.812; 95%CI: 1.029-1.900, 1.294-2.533; $p=0.0342$, 0.0019), asthma (OR: 2.191; 95%CI: 1.672-2.870; $p<0.0001$), and hay fever (OR: 2.199; 95%CI: 1.111-4.353; $p=0.0265$).

The relation between eczema and blood heavy metal concentration is shown for adults and non-adults in Table 5 and Table 6, respectively. In adults, no evident relationship was observed between blood lead, mercury, and cadmium concentrations and the risk of eczema in all multivariate models (Table 5).

Results were unchanged when stratified by gender (Table 7). In non-adults, blood cadmium concentration was significantly associated with eczema, with an OR of 0.549 (95%CI: 0.338-0.893, $p=0.0190$) for the highest tertile compared to the lowest tertile in the crude model. But the association was no longer significant in the saturated model when adjusted for demographic variables, medical comorbidities and inflammatory biomarkers (Table 6). After stratified by gender, results remained the

same (Table 8). In addition, we found that blood mercury concentrations were non-significantly inversely associated with eczema in both adults and non-adults, and blood cadmium concentrations in the third tertile were non-significantly inversely associated with eczema in non-adults.

4. Discussion

In this cross-sectional study, we found that blood biomarkers of heavy metals (cadmium, lead, mercury) were not associated with an increased odd ratio for having eczema in both adults and non-adults in the US population. Our results contribute to the burgeoning body of evidence of the relationship of heavy metals and eczema. Previously, a multicenter cross-sectional study of school children aged 5-14 years in East Germany did not reveal statistically significant associations between atopic eczema and body burden of heavy metals²⁴. A Japanese cohort study of 582 mother-child pairs found that neither maternal nor children's hair mercury levels were related with eczema in children aged 29-39 months²¹. A case control study also found there was no difference in four heavy metal levels (Manganese, Arsenic, Mercury, Zinc) between eczema and non-eczema groups in a Chinese population²². The Avon Longitudinal Study of Parents and Children has shown that umbilical cord concentrations of mercury and lead were not associated with the risk of eczema at 18-30 months²³. These findings are in agreement with our results.

There are also findings of associations, in contrast to what we found. For example, a case-control study in Egypt found the serum lead levels of patients with eczema were significantly higher than control group¹⁴. A German case-control study of children found a positive relation between body burdens of mercury and acute but not chronic atopic eczema¹⁵. A Korean cross-sectional study found a positive association between blood mercury concentration and lifetime prevalence of atopic dermatitis (a type of eczema) in an adult population²⁰. These evidences are different from our current results. The

variance may be attributable in part to differences in population attributes; definition and assessment of disease, and study designs.

Our study documented a 7.63% weighted prevalence of eczema in adults aged >20 and a 13.42% weighted prevalence in non-adults aged <20, which was in accordance with the previous literature. A international cross-sectional survey found a 8.5% prevalence of ever eczema in the US population aged 13-14 years ⁵. In a population-based survey in US, empirically defined eczema was found in 10.7%, and empirically defined AD was found in 6% ⁴⁴. A cross-sectional study found the one year prevalence of eczema was 10.2% in US adults ¹. Another cross-sectional study found a 12.98% prevalence of eczema in US children under 18 years ⁴⁵.

We found, as expected, blood lead concentration was higher in lower SES groups. This may due to occupational exposure, exposure to paint chips and dust in older houses, and/or lead water pipes. People with lower SES may be more likely to live in older homes and tend to do manual work, which had higher risk of heavy metal exposure. Studies had shown that metal workers had increased blood lead ⁴⁶, and construction work was associated with increased blood lead levels ⁴⁷. In contrast, the relationship with mercury was the opposite, which was in accordance with previous findings that higher SES individuals had higher burdens of serum mercury, but lower lead and cadmium, using NHANES 2001-2010 ⁴⁸. A possible explanation was the higher consumption of fish and shellfish in higher SES group.

We found in non-adults that younger individuals had a higher risk of eczema ($p=0.0005$). We also found in adults that female had a higher risk of eczema ($p=0.0009$). Our findings were in line with previous findings that in US children, eczema was associated with age but not gender, while in US adults, the results were the opposite ^{4,49}. We also found that eczema was positively related with socioeconomic status (SES), represented by education and family income variables in our study. This suggests a possibility of “the hygiene hypothesis”, which posits that the absence of early childhood exposure to

infectious agents increases the risk of allergic diseases⁵⁰. However, it has been questionable with this concept regarding eczema or AD^{51,52}.

One of our confirmatory finding is that eczema was positively associated with depression in adults. Previous studies found that US children and adults with atopic dermatitis had significantly higher prevalence of having depression compared with those without AD^{37,53}. A cross-sectional study in Australia found that atopic disorders (asthma, hay fever and eczema) were associated with a 59% increased likelihood of depression⁵⁴. A Danish cohort study found that people with atopic dermatitis reported depression more often than non-AD subjects, and had an increased prevalence of depressive symptoms⁵⁵. These findings were partially in agreement with our current results. Other comorbidities, including hypertension, diabetes, and heart condition, were non-significantly inversely associated with eczema (OR: 0.842, 0.820, 0.976). A meta-analysis suggested that patients with type 1 diabetes have a decreased risk of AD³⁴, and a Canadian cross-sectional study also found that AD was inversely associated with subsequent hypertension, diabetes, MI, and stroke⁵⁶. However, a US study found that people with AD or eczema had higher odds of hypertension, diabetes mellitus and congestive heart failure with an OR of 1.19, 1.13 and 1.10⁵⁷, which was in contrast with our results.

Heavy metals are toxic, pervasive in the environment, and can accumulate in human body over a lifetime. They can adversely affect the immune system, causing inadequate or excessive production of inflammatory cytokines. Exposure to lead and cadmium can modify immune response so that it may increase the incidence of allergic disease^{58,59}. However, our study results did not find an association between heavy metal and eczema. The mechanisms were in need of further exploration. Furthermore, the inverse association found in our study reveals a possible protective function of heavy metal to eczema. This is partially in line with a previous study which found that higher levels of cadmium, copper, and potassium in PM2.5 were inversely associated with eczema⁶⁰. In that study, the inverse associations

may be because of the co-occurrence of protective climate factors in areas with higher pollution level.

However, in our study, the possible mechanisms are still unknown.

Our study has several strengths. It is based on data from the US CDC National Health and Nutrition Examination Survey (NHANES) from 2005-2006, which is a nationwide population-based sample representative of non-institutionalized Americans. Our study has a relatively large sample size and a large age range. We include three metals: lead, mercury, and cadmium in our study, and built several models adjusted for a wide range of demographic variables, lifestyle variables, medical comorbidities, and inflammatory biomarkers. Our outcome is measured with relatively high accuracy, since the criterion for reported eczema is the diagnosis of doctors or health professionals. However, there are several limitations to our study. First, NHANES has a cross-sectional design, namely the exposure and outcome are assessed at the same time, which does neither permit to give an indication of the sequence of events nor to draw causation. Second, heavy metal exposure was assessed in a single “spot” sample, which may not necessarily capture the long-term or average exposure that is more relevant to eczema, especially given that the half-life in blood is roughly 1 month, 2-3 month, and 3-4 month for lead, mercury, and cadmium respectively⁶¹⁻⁶³. Third, since the information of eczema was obtained by self-report questionnaire, there is a potential for reporting bias, including recall bias or differences in access to physicians. These could bias our study, but it is likely that it is biased towards the null. Finally, the outcome measurement is not comprehensive. Eczema is divided into two subtypes: atopic and non-atopic, whose differences lie in the level of IgE in serum, response to allergens in skin prick tests, and detection of specific IgE antibodies^{64,65}. These two types are not differentiated in NHANES. Finally, there is no information about the persistence and severity of eczema in NHANES dataset. Previous studies found that while the blood concentrations of lead were not different between subjects with and without eczema, it had significant correlations with disease severity^{18,19}. Our current study found no association between blood heavy metal concentration and eczema prevalence, but there may be a possibility that

the persistence and severity are different. Future studies can explore the relationship with longitudinal study design and measurement of a wider spectrum of outcomes.

5. Conclusions

Blood concentrations of cadmium, lead, and mercury were not associated with eczema in US population, suggesting environmental exposure to these heavy metals may not be a risk factor for eczema. Given the insistency in the current literature on heavy metal associations with eczema, future studies are warranted to ascertain whether heavy metals exposure causes eczema.

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Table 1 Blood heavy metal biomarker concentrations by demographic, lifestyle, medical comorbidities, and inflammatory biomarker in adults (age 20 or above)

Characteristics	Participants [n (%)]	Lead (ug/dL)	Mercury, total (ug/L)	Cadmium (ug/L)
Overall	4509(100)	1.75 ± 0.04	1.69 ± 0.07	0.55 ± 0.02
Age(y),tertile				
20-36	1508(33.44)	1.24 ± 0.05	1.38 ± 0.10	0.48 ± 0.02
37-58	1529(33.91)	1.75 ± 0.05	1.86 ± 0.08	0.57 ± 0.03
59-85	1472(32.65)	2.41 ± 0.08	1.77 ± 0.12	0.60 ± 0.03
Gender				
Female	2351(52.14)	1.46 ± 0.03	1.62 ± 0.07	0.56 ± 0.02
Male	2158(47.86)	2.08 ± 0.07	1.75 ± 0.09	0.53 ± 0.03
Ethnicity				
Mexican American	913(20.25)	1.91 ± 0.10	1.05 ± 0.09	0.37 ± 0.02
Other Hispanic	137(3.04)	1.62 ± 0.17	1.57 ± 0.10	0.36 ± 0.03
White (non-Hispanic)	2279(50.54)	1.72 ± 0.06	1.71 ± 0.08	0.57 ± 0.02
Black (non-Hispanic)	1004(22.27)	1.90 ± 0.08	1.54 ± 0.14	0.55 ± 0.03
Other	176(3.90)	1.71 ± 0.14	2.74 ± 0.36	0.67 ± 0.05
Education				
Less than 9th grade	556(12.33)	2.41 ± 0.12	1.41 ± 0.14	0.52 ± 0.03
9th - 11th grade	694(15.39)	2.15 ± 0.07	1.23 ± 0.11	0.76 ± 0.04
High school graduate	1066(23.64)	1.84 ± 0.06	1.38 ± 0.07	0.64 ± 0.03
Some college or associate's degree	1288(28.57)	1.52 ± 0.05	1.58 ± 0.09	0.54 ± 0.03
College graduate and above	900(19.96)	1.50 ± 0.05	2.36 ± 0.14	0.38 ± 0.02
N/A	5(0.11)	2.66 ± N/A	0.98 ± N/A	1.17 ± N/A
Family Poverty Income Ratio (PIR)				
0-1.85	1882(41.74)	1.98 ± 0.05	1.34 ± 0.07	0.63 ± 0.03
1.86-3.50	1165(25.84)	1.82 ± 0.07	1.45 ± 0.11	0.61 ± 0.03
>3.50	1462(32.42)	1.56 ± 0.04	2.08 ± 0.09	0.45 ± 0.02
Smoking				
Never smoker	2372(52.61)	1.53 ± 0.04	1.76 ± 0.08	0.30 ± 0.01
Past smoker	1144(25.37)	1.90 ± 0.06	1.87 ± 0.10	0.40 ± 0.01
Current smoker	990(21.96)	2.08 ± 0.08	1.33 ± 0.11	1.23 ± 0.05
N/A	3(0.07)	0.98 ± N/A	1.12 ± N/A	0.42 ± N/A
Alcohol Use				
Never drinker	588(13.04)	1.62 ± 0.08	1.25 ± 0.12	0.41 ± 0.01
Past drinker	892(19.78)	1.87 ± 0.06	1.28 ± 0.06	0.64 ± 0.05
Current drinker light	920(20.40)	1.65 ± 0.06	1.96 ± 0.13	0.46 ± 0.03
Current drinker heavy	1785(39.59)	1.79 ± 0.06	1.78 ± 0.09	0.59 ± 0.02
N/A	324(7.19)	1.83 ± 0.10	1.81 ± 0.17	0.53 ± 0.03
Sleep				
Less than 6 hours	681(15.10)	1.84 ± 0.06	1.42 ± 0.08	0.66 ± 0.04
6-7 hours	2214(49.10)	1.74 ± 0.04	1.72 ± 0.08	0.53 ± 0.02
7+ hours	1604(35.57)	1.75 ± 0.06	1.74 ± 0.09	0.52 ± 0.02
N/A	10(0.22)	1.87 ± 0.27	0.78 ± 0.19	0.65 ± 0.11
BMI				
Underweight	145(3.22)	2.05 ± 0.12	1.79 ± 0.28	0.67 ± 0.06

Normal	1272(28.21)	1.76 ± 0.07	1.86 ± 0.11	0.64 ± 0.03
Overweight	1524(33.80)	1.86 ± 0.06	1.70 ± 0.09	0.52 ± 0.03
Obesity	1568(34.77)	1.62 ± 0.05	1.50 ± 0.08	0.48 ± 0.02
Hypertension				
Yes	1047(23.22)	2.11 ± 0.08	1.69 ± 0.08	0.55 ± 0.02
No	3228(71.59)	1.65 ± 0.05	1.71 ± 0.08	0.55 ± 0.02
N/A	234(5.19)	1.82 ± 0.07	1.39 ± 0.10	0.51 ± 0.03
Diabetes				
Yes	535(11.87)	1.79 ± 0.06	1.69 ± 0.13	0.48 ± 0.03
No	3974(88.13)	1.75 ± 0.05	1.69 ± 0.07	0.55 ± 0.02
Heart Condition				
Yes	393(8.72)	2.45 ± 0.08	1.77 ± 0.21	0.73 ± 0.11
No	4116(91.28)	1.70 ± 0.04	1.68 ± 0.07	0.53 ± 0.02
Asthma				
Ever	580(12.86)	1.51 ± 0.07	1.57 ± 0.13	0.57 ± 0.03
Never	3929(87.14)	1.79 ± 0.05	1.70 ± 0.07	0.54 ± 0.02
Hay fever				
Ever	467(10.36)	1.58 ± 0.06	1.77 ± 0.14	0.47 ± 0.03
Never	4042(89.64)	1.78 ± 0.05	1.67 ± 0.07	0.56 ± 0.02
Depression				
Yes	268(5.94)	1.78 ± 0.10	1.12 ± 0.07	0.71 ± 0.05
No	3891(86.29)	1.74 ± 0.05	1.71 ± 0.07	0.54 ± 0.02
N/A	350(7.76)	1.87 ± 0.08	1.80 ± 0.15	0.55 ± 0.03
C-Reactive Protein				
Tertile 1	1541(34.18)	1.72 ± 0.05	1.88 ± 0.07	0.49 ± 0.02
Tertile 2	1489(33.02)	1.90 ± 0.07	1.54 ± 0.09	0.57 ± 0.03
Tertile 3	1454(32.25)	1.64 ± 0.04	1.54 ± 0.10	0.59 ± 0.03
N/A	25(0.43)	1.57 ± 0.16	3.19 ± 1.98	0.76 ± 0.23
homocysteine				
Tertile 1	1496(33.18)	1.22 ± 0.03	1.68 ± 0.09	0.44 ± 0.02
Tertile 2	1493(33.11)	1.75 ± 0.05	1.75 ± 0.09	0.51 ± 0.02
Tertile 3	1494(33.13)	2.30 ± 0.06	1.62 ± 0.06	0.70 ± 0.04
N/A	26(0.58)	1.56 ± N/A	1.27 ± N/A	0.74 ± N/A
IgE				
Tertile 1	1497(33.20)	1.64 ± 0.07	1.71 ± 0.07	0.53 ± 0.02
Tertile 2	1494(33.13)	1.77 ± 0.04	1.63 ± 0.08	0.54 ± 0.03
Tertile 3	1493(33.11)	1.90 ± 0.06	1.68 ± 0.10	0.58 ± 0.03
N/A	25(0.55)	1.27 ± 0.12	3.36 ± 0.48	0.54 ± 0.21

Table 2 Blood heavy metal biomarker concentrations by demographic, lifestyle, medical comorbidities, and inflammatory biomarker in non-adults (age 1-19)

Characteristics	Participants [n (%)]	Lead (ug/dL)	Mercury, total (ug/L)	Cadmium (ug/L)
Overall	3898(100)	1.24±0.04	0.68±0.03	0.22±0.01
Age				
1-9	1570(40.28)	1.57±0.07	0.57±0.03	0.16±0.003
10-19	2328(59.72)	1.00±0.03	0.76±0.04	0.26±0.01
Gender				
Female	1964(50.38)	1.14±0.04	0.70±0.04	0.22±0.01

Male	1934(49.62)	1.34±0.05	0.65±0.04	0.22±0.01
Ethnicity				
Mexican American	1323(33.94)	1.31±0.07	0.58±0.04	0.19±0.01
Other Hispanic	140(3.59)	1.67±0.16	0.73±0.11	0.20±0.02
White (non-Hispanic)	1031(26.45)	1.10±0.04	0.66±0.05	0.23±0.01
Black (non-Hispanic)	1189(30.50)	1.63±0.11	0.65±0.05	0.21±0.01
Other	215(5.52)	1.22±0.13	0.98±0.15	0.24±0.02
Family Poverty Income Ratio (PIR)				
0-1.85	2235(57.34)	1.54±0.09	0.67±0.03	0.25±0.01
1.86-3.50	901(23.11)	1.09±0.04	0.63±0.06	0.21±0.01
>3.50	762(19.55)	0.99±0.04	0.73±0.06	0.19±0.01
Asthma				
Ever	599(15.37)	1.15±0.06	0.67±0.05	0.24±0.02
Never	3299(84.63)	1.26±0.04	0.68±0.03	0.21±0.01
Hay fever				
Ever	127(3.26)	0.85±0.52	0.54±0.07	0.22±0.03
Never	3771(96.74)	1.26±0.04	0.68±0.03	0.22±0.01
C-Reactive Protein				
Tertile 1	1369(35.12)	1.27±0.07	0.68±0.03	0.20±0.01
Tertile 2	1096(28.12)	1.18±0.06	0.69±0.06	0.23±0.02
Tertile 3	1214(31.09)	1.19±0.05	0.71±0.04	0.24±0.01
N/A	221(5.67)	1.72±0.11	0.47±0.05	0.16±0.01
IgE				
Tertile 1	1280(32.84)	1.20±0.05	0.65±0.04	0.21±0.01
Tertile 2	1284(32.94)	1.22±0.05	0.67±0.04	0.22±0.01
Tertile 3	1275(32.71)	1.20±0.07	0.73±0.03	0.24±0.01
N/A	59(1.51)	1.42±0.12	0.63±0.10	0.16±0.003

Table 3 Eczema by demographic, lifestyle, medical comorbidities, and inflammatory biomarker variables in adults (age 20 or above)

Characteristics	Eczema	Non-Eczema	Crude OR	95% CI	p-value
Overall	288	4221			
Age(y), tertile					
20-36	103	1405	1(ref)		
37-58	110	1419	1.024	0.676-1.550	0.3002
59-85	75	1397	0.780	0.509-1.196	0.2349
Gender					
Female	173	2178	1 (ref)		
Male	115	2043	0.649	0.519-0.811	0.0009
Ethnicity					
Mexican American	14	899	0.183	0.116-0.290	< 0.0001
Other Hispanic	6	131	0.457	0.215-0.972	0.0429
White (non-Hispanic)	190	2089	1 (ref)		
Black (non-Hispanic)	68	936	0.781	0.598-1.019	0.0665
Other	10	166	0.633	0.361-1.110	0.1033
Education					
Less than 9th grade	12	544	1 (ref)		

9th - 11th grade	36	658	2.502	1.015-6.170	0.0468
High school graduate	62	1004	2.619	1.306-5.251	0.0099
Some college or associate's degree	100	1188	3.012	1.454-6.240	0.0056
College graduate and above	77	823	3.288	1.383-7.813	0.0103
N/A	1	4			
Family Poverty Income Ratio (PIR)					
0-1.85	100	1782	1 (ref)		
1.86-3.50	71	1094	1.246	0.764-2.034	0.3534
>3.50	117	1345	1.466	1.015-2.116	0.0422
Smoking					
Never smoker	136	2236	1 (ref)		
Past smoker	78	1066	1.245	0.895-1.731	0.1776
Current smoker	74	916	1.153	0.850-1.563	0.3348
N/A	0	3			
Alcohol Use					
Never drinker	28	560	1 (ref)		
Past drinker	45	847	1.013	0.539-1.901	0.9668
Current drinker light	79	841	1.891	0.960-3.724	0.0634
Current drinker heavy	124	1661	1.454	0.824-2.567	0.1804
N/A	12	312			
Sleep					
Less than 6 hours	46	635	0.952	0.677-1.338	0.7607
6-7 hours	136	2078	1 (ref)		
7+ hours	106	1498	1.100	0.685-1.766	0.6734
N/A	0	10			
BMI					
Underweight	6	139	0.423	0.171-1.048	0.0614
Normal	95	1177	1 (ref)		
Overweight	79	1445	0.621	0.388-0.994	0.0476
Obesity	108	1460	0.833	0.640-1.083	0.1577
Hypertension					
Yes	61	986	0.842	0.589-1.202	0.3192
No	211	3017	1 (ref)		
N/A	16	218			
Diabetes					
Yes	28	507	0.820	0.451-1.491	0.4906
No	260	3714	1 (ref)		
Heart Condition					
Yes	24	369	0.976	0.587-1.623	0.9213
No	264	3852	1 (ref)		
Asthma					
Ever	72	578	2.037	1.429-2.906	0.0007
Never	238	4091	1 (ref)		
Hay Fever					
Ever	61	227	2.407	1.642-3.526	0.0002

Never	406	3815	1(ref)		
Depression					
Yes	37	231	2.469	1.705-3.575	0.0001
No	236	3655	1(ref)		
N/A	15	335			
C-Reactive Protein					
Tertile 1	109	1432	1 (ref)		
Tertile 2	82	1407	0.825	0.562-1.210	0.3015
Tertile 3	95	1359	1.026	0.722-1.428	0.2792
N/A	2	23			
Homocysteine					
Tertile 1	98	1398	1 (ref)		
Tertile 2	98	1395	0.955	0.611-1.493	0.8293
Tertile 3	91	1403	0.981	0.660-1.416	0.9145
N/A	1	25			
IgE					
Tertile 1	89	1408	1 (ref)		
Tertile 2	103	1391	1.136	0.815-1.583	0.4253
Tertile 3	94	1399	1.032	0.764-1.394	0.8249
N/A	2	23			

Table 4 Eczema by demographic, lifestyle, medical comorbidities, and inflammatory biomarker variables in non-adults (age 1-19)

Characteristics	Eczema	Non-Eczema	Crude OR	95% CI	p-value
Overall	445	3453			
Age					
1-9	233	1337	1 (ref)		
10-19	212	2116	0.565	0.430-0.744	0.0005
Gender					
Female	217	1747	1 (ref)		
Male	228	1706	1.206	0.888-1.638	0.2114
Ethnicity					
Mexican American	63	1260	0.302	0.215-0.424	< 0.0001
Other Hispanic	16	124	0.789	0.403-1.543	0.4626
White (non-Hispanic)	155	876	1 (ref)		
Black (non-Hispanic)	185	1004	1.127	0.838-1.517	0.4023
Other	26	189	0.789	0.361-1.721	0.5268
Family Poverty Income Ratio (PIR)					
0-1.85	207	2028	1 (ref)		
1.86-3.50	112	789	1.398	1.029-1.900	0.0342
>3.50	126	636	1.812	1.294-2.538	0.0019
Asthma					
Ever	130	469	2.191	1.672-2.870	< 0.0001
Never	315	2984	1 (ref)		
Hay Fever					
Ever	29	98	2.199	1.111-4.353	0.0265

Never	416	3355	1(ref)		
C-Reactive Protein					
Tertile 1	166	1203	1 (ref)		
Tertile 2	124	972	0.940	0.697-1.269	0.6665
Tertile 3	128	1084	1.007	0.687-1.477	0.9676
N/A	27	194			
IgE					
Tertile 1	136	1144	1(ref)		
Tertile 2	132	1152	0.934	0.656-1.329	0.6846
Tertile 3	174	1101	1.228	0.875-1.725	0.2163
N/A	3	56			

Table 5 Blood heavy metal biomarker concentrations in relation to eczema in adults (age 20 or above)

Total		Crude Model		Model 1		Model 2		Model 3		
Tertile Range	Ecze ma [n(%)]	No ecze ma [n(%)]	Effective estimate (95%CI)	p-value	Effective estimate (95%CI)	p-value	Effective estimate (95%CI)	p-value	Effective estimate (95%CI)	p-value
Lead(ug/dL)										
0.18-1.09	111	1404	1(ref)		1(ref)		1(ref)		1(ref)	
1.10-1.99	93	1399	0.936(0.602-1.456)	0.755	1.161(0.781-1.725)	0.461	1.144(0.745-1.758)	0.537	1.073(0.645-1.785)	0.786
2.00-26.4	84	1418	0.791(0.460-1.360)	0.370	1.091(0.640-1.860)	0.748	1.092(0.621-1.923)	0.759	1.025(0.534-1.970)	0.940
Trend	288	4221		0.331		0.803		0.814		0.941
				3		6		3		0
Mercury(ug/L)										
0.14-0.64	91	1439	1(ref)		1(ref)		1(ref)		1(ref)	
0.65-1.40	95	1388	0.880(0.579-1.337)	0.524	0.842(0.559-1.287)	0.439	0.851(0.563-1.287)	0.445	0.912(0.631-1.316)	0.621
1.41-33.2	102	1394	0.893(0.568-1.406)	0.603	0.805(0.518-1.252)	0.335	0.757(0.485-1.182)	0.220	0.821(0.546-1.235)	0.344
Trend	288	4221		0.678		0.373		0.240		0.353
				2		3		7		4
Cadmium(ug/L)										
0.14-0.25	85	1471	1(ref)		1(ref)		1(ref)		1(ref)	
0.26-0.48	96	1373	1.089(0.664-1.785)	0.718	1.152(0.716-1.856)	0.559	1.138(0.682-1.898)	0.621	1.153(0.638-2.084)	0.637
0.49-10.80	107	1377	1.188(0.906-1.559)	0.196	1.218(0.900-1.649)	0.202	1.231(0.741-2.044)	0.422	1.293(0.706-2.369)	0.405
Trend	288	4221		0.157		0.222		0.475		0.484
				4		3		2		3

Model 1: adjustment for demographic variables including age, gender, ethnicity, education and PIR

Model 2: Model 1 + adjustment for lifestyle variables including smoking, alcohol use, sleep and BMI

Model 3: Model 1 + Model 2+ adjustment for medical comorbidities including hypertension, diabetes, heart condition, asthma, hay fever, depression, CRP, homocysteine and IgE

Table 6 Blood heavy metal biomarker concentrations in relation to eczema in non-adults (age 1-19)

Total		Crude Model		Model 1		Model 2		
Tertile Range	Eczema[n(%)]	No eczema [n(%)]	Effective estimate (95%CI)	p-value	Effective estimate (95%CI)	p-value	Effective estimate (95%CI)	p-value
Lead(ug/dL)								

0.18-0.77	135	1175	1(ref)		1(ref)		1(ref)	
0.78-1.36	156	1144	1.091(0.691-1.720)	0.6905	0.989(0.619-1.580)	0.9618	1.006(0.641-1.578)	0.9792
1.37-55.20	154	1134	1.079(0.740-1.572)	0.6743	0.900(0.599-1.352)	0.6115	0.956(0.619-1.475)	0.8378
Trend	445	3453		0.6913		0.5822		0.9035
Mercury(ug/L)								
0.14-0.23	192	1322	1(ref)		1(ref)		1(ref)	
0.24-0.61	123	964	0.959(0.654-1.405)	0.8172	0.999(0.702-1.421)	0.9941	0.984(0.660-1.468)	0.9371
0.62-12.9	130	1167	0.803(0.517-1.248)	0.3056	0.885(0.598-1.311)	0.5436	0.884(0.583-1.341)	0.5624
Trend	445	3453		0.3083		0.5312		0.5209
Cadmium(ug/L)								
0.14	335	2415	1(ref)		1(ref)		1(ref)	
0.19-0.26	69	531	0.960(0.639-1.443)	0.8344	1.115(0.793-1.569)	0.5311	1.058(0.779-1.435)	0.7192
0.27-3.45	41	507	0.549(0.338-0.893)	0.0190	0.737(0.452-1.202)	0.2219	0.704(0.421-1.176)	0.1802
Trend	445	3453		0.0025		0.2647		0.1679

Model 1: adjustment for demographic variables including age, gender, ethnicity and PIR

Model 2: Model 1 + adjustment for medical comorbidities including asthma, hay fever, CRP and IgE

Table 7 Blood heavy metal biomarker concentrations in relation to eczema in adults, male

Total		Crude Model			Model 1		Model 2		Model 3	
Tertile Range	Eczema[n(%)]	No eczema [n(%)]	Effective estimate (95%CI)	p-value	Effective estimate (95%CI)	p-value	Effective estimate (95%CI)	p-value	Effective estimate (95%CI)	p-value
Lead(ug/dL)										
0.18-1.44	43	676	1(ref)		1(ref)		1(ref)		1(ref)	
1.45-2.42	41	679	0.929(0.526-1.638)	0.7850	0.968(0.572-1.638)	0.9037	1.002(0.542-1.854)	0.9941	0.884(0.425-1.839)	0.7414
2.43-26.4	31	688	0.753(0.434-1.305)	0.2883	0.744(0.352-1.572)	0.4380	0.725(0.333-1.578)	0.4181	0.739(0.343-1.590)	0.4385
Trend	115	2043		0.2386		0.4196		0.3831		0.4241
Mercury(ug/L)										
0.14-0.65	34	685	1(ref)		1(ref)		1(ref)		1(ref)	
0.66-1.49	38	684	0.956(0.523-1.749)	0.8772	0.844(0.481-1.479)	0.5532	0.834(0.461-1.510)	0.5494	0.714(0.381-1.338)	0.2937
1.50-28.90	43	674	0.929(0.573-1.507)	0.7507	0.722(0.424-1.229)	0.2302	0.690(0.405-1.175)	0.1720	0.576(0.328-1.011)	0.0544
Trend	115	2043		0.7606		0.2716		0.1835		0.1089
Cadmium(ug/L)										
0.14-0.24	32	717	1(ref)		1(ref)		1(ref)		1(ref)	
0.25-0.49	41	663	1.060(0.546-2.057)	0.8546	1.140(0.657-1.977)	0.6422	1.145(0.610-2.150)	0.6732	1.250(0.635-2.459)	0.5181
0.50-8.55	42	663	1.171(0.724-1.893)	0.4952	1.118(0.706-1.772)	0.6335	1.194(0.665-2.143)	0.5533	1.220(0.673-2.212)	0.5131
Trend	115	2043		0.5228		0.7287		0.6508		0.5725

Blood heavy metal biomarker concentrations in relation to eczema in adults, female

Total	Crude Model	Model 1	Model 2	Model 3
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Tertile Range	Eczema[n(%)]	No eczema [n(%)]	Effective estimate (95%CI)	p-value	Effective estimate (95%CI)	p-value	Effective estimate (95%CI)	p-value	Effective estimate (95%CI)	p-value
Lead(ug/dL)										
0.18-0.85	69	714	1(ref)		1(ref)		1(ref)		1(ref)	
0.86-1.58	59	728	1.026(0.650-1.622)	0.9048	1.173(0.754-1.823)	0.4794	1.191(0.693-2.046)	0.5270	1.132(0.628-2.041)	0.6801
1.59-14.30	45	736	0.694(0.440-1.094)	0.1076	0.926(0.548-1.563)	0.7729	0.895(0.482-1.664)	0.7263	0.783(0.374-1.640)	0.5166
Trend	173	2178		0.0551		0.6040		0.5801		0.3531
Mercury(ug/L)										
0.14-0.62	57	738	1(ref)		1(ref)		1(ref)		1(ref)	
0.63-1.34	58	719	0.811(0.422-1.561)	0.5058	0.791(0.422-1.481)	0.4634	0.811(0.445-1.476)	0.4921	0.972(0.543-1.740)	0.9244
1.35-33.2	58	721	0.843(0.457-1.555)	0.5614	0.786(0.425-1.453)	0.4419	0.749(0.396-1.418)	0.3751	0.917(0.511-1.646)	0.7719
Trend	173	2178		0.6388		0.4937		0.3925		0.7010
Cadmium(ug/L)										
0.14-0.26	57	747	1(ref)		1(ref)		1(ref)		1(ref)	
0.27-0.48	52	732	0.907(0.538-1.527)	0.6939	1.049(0.618-1.779)	0.8604	1.039(0.585-1.843)	0.8971	0.975(0.533-1.781)	0.9331
0.49-10.80	64	699	1.063(0.710-1.592)	0.7512	1.200(0.808-1.782)	0.3664	1.213(0.602-2.447)	0.5888	1.211(0.556-2.640)	0.6296
Trend	173	2178		0.6124		0.3356		0.6061		0.6925

Model 1: adjustment for demographic variables including age, gender, ethnicity, education and PIR

Model 2: Model 1 + adjustment for lifestyle variables including smoking, alcohol use, sleep and BMI

Model 3: Model 1 + Model 2+ adjustment for medical comorbidities including hypertension, diabetes, heart condition, asthma, hay fever, depression, CRP, homocysteine and IgE

Table 8 Blood heavy metal biomarker concentrations in relation to eczema in non-adults, male

Total		Crude Model		Model 1		Model 2		
Tertile Range	Eczema[n(%)]	No eczema [n(%)]	Effective estimate (95%CI)	p-value	Effective estimate (95%CI)	p-value	Effective estimate (95%CI)	p-value
Lead(ug/dL)								
0.18-0.87	69	583	1(ref)		1(ref)		1(ref)	
0.88-1.46	77	562	0.907(0.512-1.605)	0.7199	0.927(0.492-1.745)	0.8136	0.861(0.465-1.593)	0.6337
1.47-55.20	82	561	1.008(0.657-1.547)	0.9673	1.030(0.651-1.628)	0.9010	1.084(0.639-1.839)	0.7642
Trend	228	1706		0.9097		0.7554		0.5799
Mercury(ug/L)								
0.14-0.23	108	692	1(ref)		1(ref)		1(ref)	
0.24-0.56	58	439	1.115(0.653-1.906)	0.6705	1.237(0.745-2.053)	0.4109	1.274(0.734-2.211)	0.3898
0.57-6.96	62	575	0.747(0.397-1.403)	0.3396	0.847(0.489-1.467)	0.5532	0.850(0.452-1.599)	0.6146
Trend	228	1706		0.3119		0.4860		0.5027
Cadmium(ug/L)								
0.14	175	1215	1(ref)		1(ref)		1(ref)	
0.20-0.26	33	247	1.000(0.605-1.654)	0.9996	1.184(0.712-1.967)	0.5154	1.068(0.658-1.732)	0.7903
0.27-3.45	20	244	0.651(0.331-1.280)	0.1956	0.843(0.421-1.688)	0.6302	0.842(0.426-1.664)	0.6205

Trend	228	1706	0.1590	0.7990	0.6873
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Blood heavy metal biomarker concentrations in relation to eczema in non-adults, female								
	Total		Crude Model		Model 1		Model 2	
Tertile Range	Eczema[n(%)]	No eczema [n(%)]	Effective estimate (95%CI)	p-value	Effective estimate (95%CI)	p-value	Effective estimate (95%CI)	p-value
Lead(ug/dL)								
0.18-0.69	66	603	1(ref)		1(ref)		1(ref)	
0.70-1.24	81	566	1.299(0.836-2.019)	0.2255	1.066(0.724-1.569)	0.7457	1.132(0.758-1.650)	0.5438
1.25-33.10	70	578	1.087(0.671-1.762)	0.7166	0.728(0.432-1.227)	0.2329	0.786(0.428-1.443)	0.4366
Trend	217	1747		0.8831		0.2018		0.3430
Mercury(ug/L)								
0.14-0.23	84	630	1(ref)		1(ref)		1(ref)	
0.24-0.67	65	540	0.747(0.490-1.138)	0.1606	0.692(0.466-1.027)	0.0678	0.577(0.461-0.995)	0.0468
0.68-12.90	68	577	0.954(0.590-1.543)	0.8378	0.937(0.589-1.491)	0.7843	0.930(0.572-1.513)	0.7701
Trend	217	1747		0.9939		0.9822		0.9654
Cadmium(ug/L)								
0.14	160	1200	1(ref)		1(ref)		1(ref)	
0.19-0.26	36	284	0.936(0.490-1.791)	0.8317	1.018(0.594-1.744)	0.9486	1.013(0.600-1.710)	0.9622
0.27-3.20	21	263	0.452(0.224-0.914)	0.0291	0.599(0.303-1.185)	0.1406	0.558(0.277-1.122)	0.1014
Trend	217	1747		0.0156		0.1264		0.0825

Model 1: adjustment for demographic variables including age, gender, ethnicity and PIR

Model 2: Model 1 + adjustment for medical comorbidities including asthma, hay fever, CRP and IgE