Prevalence of isocyanate contact dermatitis and cross-reactivity with atopy

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Summary:
Introduction Isocyanates are reactive organic compounds primarily used in polyurethane synthesis, a growing industry. They are found in products like foams, coatings, and adhesives. Occupational exposure to isocyanates can lead to allergic reactions, including allergic contact dermatitis. This study investigates the prevalence of isocyanate contact allergy and its potential cross-reactivity with atopic conditions.
Methods This study used a dataset of 376 patients referred to the Amsterdam Medical Center from January 2020 to December 2024, suspected of occupational contact allergy to isocyanates. Data were collected through patch testing and patient history. Statistical analysis assessed the prevalence of contact dermatitis and potential cross-reactivity with atopic conditions using R.
Results Over four years, 376 patients were patch tested for isocyanates, with 55 excluded due to missing data, leaving 321 patients for analysis. The most common symptom location were the hands. Of the 215 patients with allergic contact dermatitis to isocyanates, 58.14% had at least one atopic condition. Statistical analysis showed no significant association (p-values: 0.1648 to 0.624). In the reassessed cohort of 313 patients, 56.55% had at least one atopic condition, and 70.62% of these were positive for allergic contact dermatitis, with also no significant risk correlation found.
Discussion This study found a higher prevalence of atopy among patients with allergic contact dermatitis to isocyanates, but no significant association between atopy and allergic contact dermatitis risk. Similarly, it did not appear to be a risk factor for atopy, suggesting that individual risk factors, rather than atopy itself, contribute to sensitization for isocyanates.

List of used abbreviations

ACD – Allergic Contact Dermatitis
OR – Odds ratio
CI – Confidence interval

Introduction

Isocyanates are a group of reactive organic compounds characterized by the presence of one or more isocyanate groups (-N=C=O). (1) The primary use of isocyanates is in the synthesis of polyurethanes, which are polymers formed through a reaction between diisocyanates and polyols. These polyols are typically polyesters, polyethers or blends of both. This process involves a chemical reaction, either condensation or adduction, that allows the creation of durable and versatile materials used in various industries. (2) Commonly used diisocyanates include methylene diphenyl diisocyanate, toluene diisocyanate, and hexamethylene diisocyanate, with polyisocyanates often derived from these diisocyanates and containing multiple isocyanate groups. (3)
Polyurethanes are considered one of the most prevalently applied classes of polymeric materials worldwide. (4) They are used in a variety of industrial and consumer applications, including foams, coatings, adhesives, and elastomers. (5) In addition, isocyanates are a key component in spray-on polyurethane products, which are widely used in commercial and industrial settings to protect materials such as cement, wood, fiberglass, steel, and aluminium. These isocyanate-based protective coatings are commonly applied to surfaces like trailers, boats, foundations, and decks. (6)

Occupational exposure to isocyanates is a concern in several industries such as painting, auto body repair, polyurethane foam manufacturing, and foam processing for mattresses and furniture. Workers are particularly at risk during the manufacturing and handling of polyurethane products. (2)
Isocyanates are known to irritate the mucous membranes of the eyes, respiratory system, and gastrointestinal tract. Chronic exposure can lead to sensitization, where individuals develop allergic reactions. Both respiratory and dermal exposure to isocyanates can cause hypersensitivity, leading to conditions like allergic asthma, extrinsic allergic alveolitis, and allergic contact dermatitis (ACD). (6)
Although ACD caused by isocyanates is less frequently reported (7), multiple cases of ACD to isocyanates have been documented in various settings including the manufacturing of heat exchangers, lacquer production, bulletproof glass fabrication, as well as among workers in bakeries and auto body shops. (8–11)

Atopy refers to a genetic predisposition to develop allergic diseases such as allergic rhinitis, allergic asthma, and atopic eczema. These conditions are characterized by an exaggerated immune response to environmental allergens, which leads to inflammation and tissue damage. Allergic rhinitis and asthma are often driven by the activation of T-helper 2 cells, resulting in the release of cytokines like interleukine-4, interleukine-5, and interleukine-13, which contribute to IgE production and the recruitment of eosinophils and mast cells. (12) Atopic eczema, commonly seen in early childhood, is a chronic inflammatory skin disorder linked to genetic mutations affecting the skin barrier, such as those in the filaggrin gene, which can lead to increased susceptibility to allergens. (13) Due to this increased susceptibility to allergens, the development of ACD for specific compounds is theoretically logical and is also observed in several studies. (14,15) This leads to the hypothesis that atopic patients are also at a higher risk of developing ACD to isocyanates.

The aim of this article is to determine the prevalence of ACD to isocyanates within the patient population of the department of dermatology/allergology in the Amsterdam Medical Center and to investigate potential cross-reactivity with atopic patients.

Methods

This study utilized a dataset obtained from the Amsterdam Medical Center, encompassing a total of 376 patients collected from January 2020 until December 2024. All individuals were referred to this hospital with a suspicion of an occupational ACD to isocyanates.
Given the referral criteria, it is assumed that all patients included in the dataset had documented occupational exposure to isocyanates.

The data collection process involved retrieving clinical records of these patients. Data for this analysis were gathered through patch testing conducted on the patients. Patch tests (16) were applied to the back of the patient using a standardized series of seven isocyanates mixed with a vaseline base (17). The full list of isocyanates included in the test series is provided in Appendix 1.
Testing and reactions assessment followed standard protocols (16), were the occlusion time of the patches consisted of 48 hours. Reading of test reaction was performed on day 2, day 3 and in most cases day 7 to confirm allergic responses. Reactions were classified as positive if they involved redness, itching, and/or swelling of the skin, thereby indicating dermatitis. (16)
Prior to the patch testing, information was collected regarding the location of the patient's symptoms. If the location of the symptoms prior to the patch testing matched the site of dermatitis observed after the patch testing, a diagnosis of ACD was established. However, if the location of dermatitis from the patch testing did not align with the site of the symptoms reported beforehand, this was not classified as ACD caused by isocyanates.

In addition to patch testing, information regarding the presence of atopy was collected per patient. Atopy was defined as a history of allergic asthma, atopic eczema and/or allergic rhinitis. This anamnestically obtained information was verified through medical records or clinician documentation of a general practitioner, pulmonologist, or otorhinolaryngologist to ensure accuracy.
The dataset was anonymized before analysis to ensure confidentiality. Statistical evaluations focused on the prevalence of confirmed ACD in this cohort and potential cross reactivity with atopy. In this article, a p-value of <0.05 is regarded as significant. Data management and analysis were performed with the R software package, version 4.4.0.

Results

In a period of 4 years, a total of 376 patients were patch tested for isocyanates. Patients were excluded if all values in the columns were recorded as "not specified," indicating that no data were available. Additionally, patients were excluded if data were not available in the column regarding the presence or absence of ACD. A total of 55 patients were eventually excluded, remaining a total of 321 patients that were analysed.

The most common location of the symptoms, prior to patch testing, was the hand (N=122), followed by the foot (N=81), the arm (N=55), the leg (N=47) and the head (N=42). Other described sites of symptoms included the trunk (N=21), the neck (N=19) and the face (N=18). Less reported locations were the soles (N=10), the ear (N=8), the palms (N=8), the back (N=3) and the chest (N=1). 12 patients presented generalized symptoms and from 55 patients the location of the symptoms was not specified. All locations were categorized into subgroups and are presented in Figure 1.

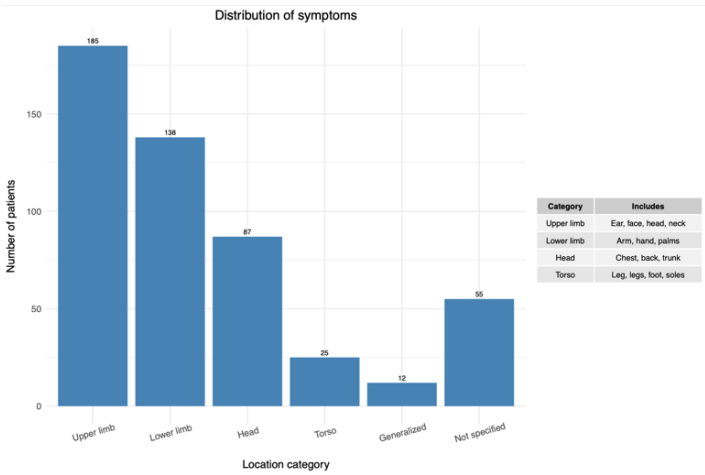

Figure 1: distribution of the symptoms prior to patch testing

Atopy prevalence among patients with and without ACD for isocyanates

Out of the 321 patients, 215 (66.98%) patients were tested positive for an ACD for isocyanates, their ages ranged from 8 to 84 years (mean 48, median 50). An overview of the distribution of this cohort, is presented in Figure 2.

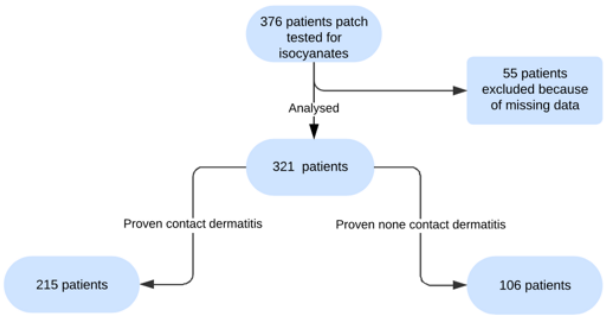

Figure 2: overview of the cohort and prevalence of ACD for isocyanates

Those tested positive, were analysed for the prevalence of atopy. A total of 125 (58.14%) patients were identified as having at least one atopic condition (allergic rhinitis, allergic asthma, allergic dermatitis) in the group that is positive for ACD (N=215) and 52 (49.1%) patients in the group that did not have ACD (N=106). In Figure 3, the presence of the atopic conditions is shown with the absence or presence of ACD.

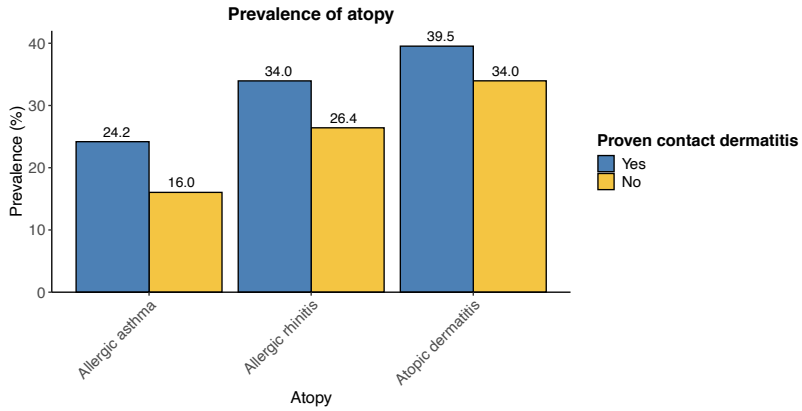

Figure 3: presence of the different atopic conditions and the absence or presence of ACD.

A Fisher's Exact Test was performed to assess whether atopy is a risk factor for ACD to isocyanates, chosen due to small group sizes. Comparing patients with at least one atopic condition versus no atopy yielded a p-value of 0.1648, odd's ratio (OR) 1.427516 (95% confidence interval (95% CI): 0.8450278–2.4102190). For patients with all three atopic conditions versus no atopy, the p-value was 0.624, OR 0.6689911 (95% CI: 0.1843169–2.0007465). Comparing all three atopic conditions to no atopy, the p-value was 0.2307, OR 2.129982 (95% CI: 0.6971629–7.8624485).

ACD prevalence among patients with and without atopy

Subsequently, the entire cohort was reassessed. Patients were in this reassessment also excluded if all values in the columns of the atopic conditions were recorded as "not specified," indicating that no data were available. A total of 63 patients were eventually excluded, remaining a total of 313 patients that were analysed, see Figure 4 for an overview. The occurrence of ACD was then evaluated within these groups.

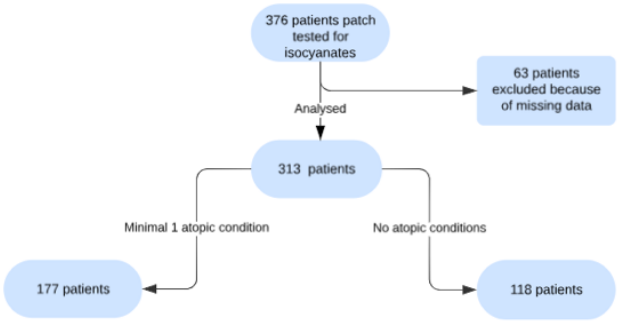

Figure 4 : overview of the cohort and prevalence of atopic conditions

Among the 313 patients that were analyzed, 177 (56.55%) were found to have at least one atopic condition, the distribution is shown in Figure 5. Since information about the presence of the atopic conditions was not available for every patient, the amount of 177 patients reflects the presence of at least one atopic condition, whereas the VENN-diagram includes an additional limitation (the absence of the other atopic conditions). As a result, the numbers in the VENN-diagram differ from those described in this article. Of these 177 patients, 125 also were positive patch tested for isocyanates (70.62%). 23 patients suffered from all three atopic conditions, 18 of these patients were also positive for ACD for isocyanates (78.26%). From the 118 patients with no atopic conditions, 74 were positive for ACD (62.71%).

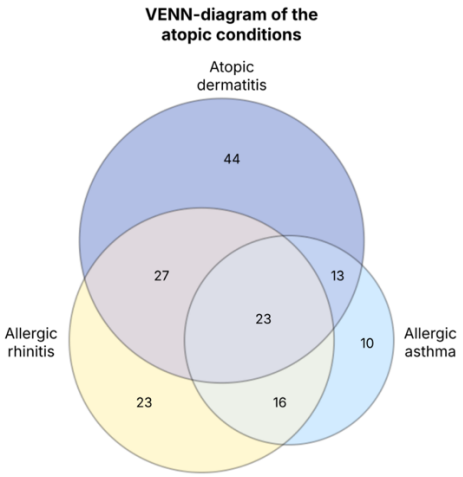

Figure 5: VENN-diagram presenting the distribution prevalence of the atopic conditions

A Fisher's Exact Test was conducted to evaluate whether ACD is a risk factor for atopy. Fisher's Exact Test was employed to ensure reliable p-values, given the relatively small sample sizes. Comparing patients with at least one atopic condition versus no atopy yielded a p-value of 0.1648, OR 1.427516 (95% CI: 0.8450278–2.4102190). For patients with at least one versus all three atopic conditions, the p-value was 0.624, OR 0.6689911 (95% CI: 0.1843169–2.0007465). Comparing patients with all three atopic conditions versus no atopy yielded a p-value of 0.2307, OR 2.129982 (95% CI: 0.6971629–7.8624485).

Further statistical analyses were conducted to evaluate individual atopic conditions, specific combinations of atopic conditions, and the absence of atopic conditions as risk factors for ACD. It is important to note that when analyzing specific atopic conditions, the others were required to be defined as 'no' in the dataset.

The analysis of all possible combinations of atopic conditions revealed no significant correlations with an ACD to isocyanates. A complete overview of these combinations, along with the corresponding p-value, OR and 95% CI, can be found in Appendix 2.
As examples, two comparisons from the analysis are highlighted. First, the association between proven ACD and having only rhinitis compared to only asthma showed an OR of 0.540 (95% CI: 0.086–3.545) with a p-value of 0.4438, indicating no statistically significant difference in the prevalence of proven ACD between these groups. Second, patients with a combined profile of rhinitis, eczema, and asthma were compared to those with no atopic conditions, yielding an OR of 2.130 (95% CI: 0.697–7.862) and a p-value of 0.2307, also showing no significant association.

Discussion

An analysis of the results reveals that the hands are the most frequently affected site of symptoms. The predominance of hand involvement in ACD due to isocyanates is logically attributed to occupational exposure patterns. Workers handling isocyanate-containing materials, such as lacquers or treated fabrics, often experience direct skin contact, particularly on the hands, leading to localized sensitization and subsequent dermatitis. (1,5,9,18)

Exposure to isocyanates

Exposure to isocyanates occurs through both aerogenic and dermal routes, presenting significant challenges for occupational health. Aerogenic exposure is particularly prevalent during the use of spray, coatings and foams and similar applications, where airborne isocyanates are inhaled and pose a risk of respiratory sensitization and can also lead to skin sensitization. (19,20) Dermal exposure, although less overt, is equally important, as isocyanates can be absorbed through direct skin contact. The risk of dermal absorption is exacerbated when the skin barrier is compromised, which can occur due to pre-existing conditions like eczema, cuts, or prolonged exposure to irritants. (21) Workers often face inadequate protective measures, with protection products frequently limited to gloves, leaving respiratory exposure unaddressed. (5,22) Animal studies have further demonstrated that aerogenic exposure to isocyanates can result in skin sensitization. These findings suggest that inhaled isocyanates may contribute to dermal sensitization, likely through systemic distribution following pulmonary absorption. (20)
Alarmingly, studies have reported that certain protective materials, including gloves, can allow isocyanates to penetrate, rendering them insufficient for complete protection. (23,24)

The primary routes of isocyanate exposure and the challenges in protective measures highlight the need for improved workplace practices. Despite the absence of unified European occupational exposure limits for isocyanates, recent regulatory developments are working towards establishing enforceable thresholds. Proposals by the European Commission suggest an occupational exposure limit of 6 µg/m³ and a short-term exposure limit of 12 µg/m³, accounting for both dermal and respiratory sensitization risks. (25) Protective strategies must include advanced materials capable of reliably preventing isocyanate penetration, alongside measures to protect respiratory health. Additionally, worker education on the importance of skin barrier maintenance and the risks associated with compromised personal protection materials is essential. (26,27)

Atopy among patients with and without ACD

The findings reveal a higher prevalence of atopy among patients with ACD to isocyanates (58.14%) compared to those without ACD (49.1%). However, statistical analysis showed no significant association between atopy and ACD, with wide confidence intervals suggesting variability and potential underpowering due to small subgroup sizes. These results challenge the notion that atopy serves as a direct risk factor for ACD, aligning with previous research indicating that the relationship between atopy and ACD may be more nuanced and condition-specific. (28,29)

Sensitization involves immune activation via haptens, small reactive chemicals that penetrate the skin or are inhaled, binding to endogenous proteins to form immunogenic complexes. These trigger T-cell-mediated delayed-type hypersensitivity reactions, similar to mechanisms seen in ACD. Despite theoretical links between impaired skin barriers and enhanced sensitization, data connecting atopy to increased isocyanate sensitivity remain inconclusive, similar to the findings in our cohort. (27,28,30)

ACD among patients with and without atopy

When examining the results of the prevalence of ACD in patients with and without atopy, the analysis reveals also no statistically significant associations between any single or combined atopic condition and the prevalence of ACD, as all p-values are above 0.05. For example, individuals with eczema alone show an OR of 1.457 compared to those with no atopic conditions, suggesting a slightly elevated risk; however, this result is not significant (p-value = 0.5865, 95% CI: 0.428–5.490). Similarly, asthma combined with eczema has the highest OR of 3.245, but this association also fails to reach significance (p-value = 0.1381, 95% CI: 0.662–31.476). A systematic review and meta-analysis supports these findings, concluding that there is no clear evidence linking atopic dermatitis with an increased risk of contact sensitization. (29)

The OR for other comparisons, such as asthma alone versus rhinitis alone (OR: 0.540, p-value= 0.4438) or rhinitis combined with eczema versus no atopic conditions (OR: 1.187, p-value = 0.8258), indicate minimal or no effects with high variability. These findings suggest that, while there may be trends toward increased susceptibility to ACD in certain atopic groups, these patterns are not robust or consistent enough to draw definitive conclusions. The lack of significant associations may stem from relatively small sample sizes in some subgroups, as indicated by the wide confidence intervals, or from other confounding factors not accounted for in the analysis, such as occupational exposure, environmental triggers, or genetic variations. These findings prove that multiple factors affect the association between atopic dermatitis and contact sensitization, emphasizing the complexity of this relationship. (31)

Interpretation of the results

The aim of this study was to investigate the prevalence of ACD to isocyanates within a cohort of patients referred with a suspicion of ACD due to occupational exposure to isocyanates. Additionally, the study explored potential cross-reactivity with atopic conditions (allergic rhinitis, atopic dermatitis, and allergic asthma), to determine whether individuals with a history of atopy might have a higher risk of developing ACD due to isocyanates exposure. These results could provide recommendations for additional medical screening for atopic conditions for workers in high-risk occupations and routine testing for individuals with a confirmed ACD to isocyanates for underlying atopic conditions.

The results of the study did not reveal a significant association between atopy and the development of ACD to isocyanates. This finding challenges the hypothesis that atopic conditions predispose individuals to ACD for isocyanates. Similarly, the study found no evidence suggesting that ACD to isocyanates increases the risk of developing atopic conditions. The findings indicate that any potential risk may be more individual in nature, rather than being attributable to atopy itself.
Given these findings, the study does not support the need for routine pre-employment screening for atopy in workers exposed to isocyanates. Similarly, employees with a confirmed ACD to isocyanates do not appear to require additional testing for atopic conditions based on the current data. Considering that the development of ACD to isocyanates appears to be an individual risk, it is essential to emphasize the use of appropriate personal protective equipment in high-risk environments. Proper protective measures should always be a priority to mitigate the risk of skin sensitization and allergic reactions.

Given the increasing use of isocyanates across various industries, it remains crucial to continue to monitor the prevalence of ACD to isocyanates and their potential cross-reactivity with atopic conditions. Future research with larger sample sizes and more comprehensive longitudinal data is needed to determine if patterns emerge over time that suggest a higher susceptibility to isocyanate-induced ACD among individuals with pre-existing atopic conditions. Further studies may also clarify whether other factors, such as occupational exposure duration, exposure routes environmental influences, play a more significant role in the development of ACD.

Strengths and limitations

A strength of this study is the use of standardized patch testing and a comprehensive patient history allowed for a robust and reliable diagnosis of ACD, reducing the potential for misclassification bias. Moreover, by including only atopic conditions confirmed by medical professionals, the study ensured a systematic and thorough analysis of the patient history, which contributed to the accuracy of the overall assessment.

Another strength is the creation of well-defined subgroups with appropriate limitations, allowing for clear separation of potential risk factors. This approach enhances the reliability of the conclusions by minimizing confounding and ensuring that the associations observed are more robust and accurately reflect the underlying relationships.

The limitations of this study include its retrospective design, which resulted in the absence of data regarding the patients' occupations and the specific substances within the tested series that elicited reactions. As a result, it is not possible to identify high-risk occupations or determine which substances in the series were most or least frequently associated with reactions. Additionally, the lack of detailed data on atopic conditions resulted in very small subgroup sizes, which made the analysis more challenging and potentially limited the robustness of the findings. This represents a significant area for future research, as collecting such data would allow for more concrete and targeted recommendations to be made. Moreover, we acknowledge that gender analysis would have been valuable. However, due to the anonymization of the data, it was not possible to include gender as a variable in our analyses. Furthermore, the monocentric nature of data collection may affect the generalizability of our results.

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Appendix

Appendix 1

The standardized series of isocyanates used for patch testing and their test concentration

1.	1,6-Hexamethylene diisocyanate	0.1%
2.	Diaminodiphenylmethane	0.5%
3.	Isophorone diamine	0.1%
4.	Isophoronediisocyanate	1 %
5.	Diphenylmethane-4,4-diisocyanate	1%
6.	Toluenediisocyanate	2 %
7.	Triglycidyl isocyanurate	0.5%

Appendix 2

		Proven contact dermatitis (N=)	Proven non-contact dermatitis (N=)	P-value	95%-CI	OR
Only rhinitis vs		17	6			
	Only asthma	6	4	0.4438	0.2821199 – 11.5798362	1.850823
	Only eczema	29	15	0.5865	0.4280376 – 5.4896523	1.457346
	No atopic conditions	74	44	0.3498	0.5764366 5.5996278	1.678803
Only eczema vs		29	15			
	Only rhinitis	17	6	0.5865	0.1821609 2.3362434	0.6861787
	Only asthma	6	4	0.7277	0.2294259 - 6.4252806	1.282673
	No atopic conditions	74	44	0.8545	0.5274742 2.5731076	1.148569
Only asthma vs		6	4			
	Only rhinitis	17	6	0.4438	0.08635701 3.54459243	0.5403003
	Only eczema	29	15	0.7277	0.1556352 4.3587063	0.779622
	No atopic conditions	74	44	1	0.1989901 4.5450156	0.8927013
Asthma + rhinitis vs		12	4			
	Only eczema	29	15	0.7544	0.377103 - 7.702070	1.540821
	No atopic conditions	74	44	0.4138	0.4982103 8.0272322	1.776632
Asthma + eczema vs		11	2			
	Only rhinitis	17	6	0.682	0.2722289 - 22.6622334	1.907643
	No atopic conditions	74	44	0.1381	0.6623455 31.4763964	3.245902
Rhinitis + eczema vs		18	9			
	Only asthma	6	4	0.7158	0.2164798 7.4089208	1.322753
	No atopic conditions	74	44	0.8258	0.4585199 3.2758422	1.18779
Rhinitis + eczema + asthma vs		18	5			
	No atopic conditions	74	44	0.2307	0.6971629 7.8624485	2.129982