

ORIGINAL ARTICLE

Asthma and insulin resistance in children

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ABSTRACT

Background and objective: Increased BMI is a risk factor for asthma in children and may be related to adipokines. Adipokines affect insulin-stimulated glucose uptake *in vitro* but, to date there is little evidence for such a role *in vivo*. We explored relationships between obesity and allergic asthma in children.

Methods: Twenty-one allergic asthmatics (AA) and 10 non-allergic healthy controls, aged 6–17.9 years were studied. AA group included children with a positive mannitol challenge test, >25 ppb of exhaled nitric oxide and a positive skin prick test. BMI z-scores were calculated. Blood levels of insulin, glucose, leptin, resistin, tumour necrosis factor- α , IL-4, IL-5 and IL-6 were measured. Insulin resistance (IR) was estimated using the homeostasis model assessment (HOMA).

Results: There was no significant difference in BMI z-scores between AA and healthy controls (mean: 0.01 vs -0.10). However, significant differences were found in the blood levels of IL-6 ($P = 0.05$), IL-4 ($P = 0.04$), IL-5 ($P = 0.01$) and leptin ($P = 0.02$). IR was only found in the AA group (42.85%). Homeostasis model assessment insulin resistance (HOMA-IR) was significantly related to IL-6 ($r = 0.44$, $P = 0.05$) and tumour necrosis factor- α ($r = -0.45$, $P = 0.05$).

Conclusions: IR was observed in AA. Our findings are suggestive of a complex interaction between the inflammatory state and adiposity, allergy and asthma.

Key words: adipokine, asthma, body mass index, insulin resistance, obesity.

INTRODUCTION

The increase in overweight/obesity and asthma is an emerging public health concern. Obese individuals

SUMMARY AT A GLANCE

Although it has been shown that obesity and asthma are related, little is known about the linking mechanism. This study explores the underlying mechanism in this relationship by investigating insulin resistance (IR), a clinical sequel to obesity, and the blood levels of adiposity-related cytokines and chemokines (adipokines) in Australian children with persistence allergic asthma.

have an increased risk for the development of insulin resistance and diabetes.^{1–4} Recently, a large body of epidemiologic data have linked obesity with the development of asthma⁵ and obesity is a risk factor for asthma.^{6,7} Nevertheless, little is known about the biological mechanisms that relate obesity and insulin resistance to asthma.

Fat tissue is no longer considered simply a storage tissue for energy. Fat may induce systemic low-grade inflammation in obese and overweight individuals by recruiting macrophages and production and secretion of a wide range of inflammatory molecules known as adipokines that include leptin, resistin, plasminogen activator inhibitor-1 (PAI-1), tumour necrosis factor- α (TNF- α) and IL-6.^{8–10} Adipokines have local effects on the physiology of adipose tissue,¹¹ but may also have systemic effects on other organs.^{12,13} These findings have lead to excessive fat tissue accumulation being implicated as a risk factor for the development of insulin resistance, cardiovascular diseases^{14,15} and diabetes.^{15–17}

It is well known that increased BMI is associated with insulin resistance.^{2,3,18–20} Recently, an epidemiological, population-based study on the relationship of insulin resistance and asthma found that insulin resistance was associated with increased risk of aeroallergen sensitization and allergic asthma in adults.²¹ A recent 5-year prospective study in adults has reported that patients with insulin resistant are more prone to the development of wheezing and asthma-like symptoms than their non-insulin resistance counterpart and that the effect of insulin

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resistance is stronger than that (and independent) of obesity itself.²² Furthermore, adults with asthma were shown to have significantly higher Homeostasis model assessment insulin resistance HOMA-IR index, impaired fasting glucose and impaired glucose tolerance.²³

To date, no studies have reported the relationship between inflammatory adipokines, insulin resistance and adults or children with asthma. The aim of this study was to investigate the relationship between products of adiposity (adipokines) and insulin resistance in children with allergic asthma.

METHODS

Study population

Children with asthma, aged 6.0–17.9 years were identified from outpatient clinics and emergency room database records at the Royal Children's Hospital, Brisbane. Children with asthma identified clinically in medical records with no asthma exacerbation in the previous 4 weeks were invited to take part. Inclusion criteria for the asthma group were: having diagnosed asthma, FeNo levels of ≥ 25 (ppb), not being on oral corticosteroids for a period of at least 4 weeks before the testing day, ability to withhold medication prior to the test day (the withhold duration was individualized according to each participant's medication and Pharmaxis protocol (Aridol, Pharmaxis Ltd. Sydney, Australia)); and having at least one positive skin prick. Healthy controls (HC), aged 6.0–17.9 years and matched for gender, age and BMI with the children with asthma, were recruited by convenient sampling from the same health service district. Healthy participants were recruited from previous or current studies being undertaken at the Children's Nutrition Research Centre and Department of Respiratory Medicine, at the Royal Children's Hospital, Brisbane. Inclusion criteria for the HC group were having no history of asthma or any other significant medical disease and being negative for skin prick tests. The study was approved by the Human Research Ethics Committees of the University of Queensland and the Royal Children's Hospital. Informed consent was obtained from all participants and/or guardians.

Assessment of body composition

Participants' height and weight were measured using a stadiometer (SECA model 220, SECA GmbH & Co. Kg, Hamburg, Germany) and digital scales (Wedderburn, HD 316, Wedderburn, Brisbane, Australia), respectively. BMI (kg/m^2) was calculated. BMI z-scores were calculated using child-specific BMI data, which were adjusted for both age and gender, using the LMS method.²⁴

Assessment of asthma

Children in the (allergic asthmatics (AA)) group had moderate-to-severe persistent asthma according to

the Global Initiative for Asthma guidelines.²⁵ Levels of exhaled nitric oxide (FeNo) were measured using a handheld device (Niox Mino, MDD 93/42/EEC, Aerocrine AB, Stockholm, Sweden). All AA had FeNo levels ≥ 25 (ppb) suggestive of current airway inflammation.

Mannitol challenge testing was performed to assess airway responsiveness and induce sputum using a Pharmaxis protocol. Patients with $\text{FEV}_1 \geq 70\%$ predicted underwent challenge testing. Response to bronchodilator was assessed according to the guidelines of American Thoracic Society.²⁶

Assessment of allergy

Allergic status was assessed by skin prick testing (Hollister-Stier Laboratories LLC, Spokane, WA, USA) for grass pollens (Bermuda grass and mix of seven grass pollens), one weed pollen (English Plantain), one mould (*Alternaria tenuis*) and four animal inhalants (standardized cat hair, standardized dog hair, cockroach mix), and standardized mite (*Dermatophagoides pteronyssinus*). As previously mentioned, participants were considered to be atopic if they were positive to at least one skin prick test.

Assessment of insulin resistance and levels of adipokines

Morning fasting blood samples were obtained. The plasma levels of glucose, serum levels of insulin and adipokines (leptin, resistin, $\text{TNF-}\alpha$, IL-4, IL-5 and IL-6) were measured using a high-sensitivity cytokine Milliplex kit (Millipore, Billerica, MA, USA). Leptin, resistin and PAI-1 were measured using a multiplexed sandwich ELISA assay for the Luminex 100 platform (Luminex Corporation, Austin, TX, USA). Leptin, resistin (R&D Systems Inc., Gympie, NSW, Australia) and PAI-1 (Innovative Research, Novi, MI, USA) antibodies were coupled to carboxylated xMAP Beads (Luminex, Austin, TX, USA) kindly pretreated at Bio-Layer Pty Ltd (Brisbane, Australia) with Mix & Go reagent, washed in deionized water twice, incubated in $50 \mu\text{g}/\text{mL}$ of capture antibody in $50 \text{ mmol}/\text{L}$ acetate-buffered saline, pH 5.0, for 60 min and washed twice in 0.15 M NaCl. Standards curves were constructed using recombinant proteins (R&D Systems). The assays were read on a Luminex 100 platform.

The degree of insulin resistance was estimated by the homeostasis model (HOMA-IR). HOMA-IR index was calculated by multiplying fasting plasma glucose (mmol/L) by fasting serum insulin ($\mu\text{U}/\text{L}$) and dividing this by 22.5. The HOMA-IR index has been shown to be a valid method for insulin resistance estimation in children and adolescents.^{27,28} Insulin resistance was defined as a HOMA-IR index of ≥ 1.77 .²⁹ Children with diabetes were excluded.

Statistical analysis

Summary data are presented as mean $\pm$ SD. Categorical variables were analysed using contingency

Table 1 Demographic characteristics of AA and HC groups

Variable	Total (n = 31)	HC (n = 10)	AA (n = 21)	P-value
Age (years) (mean $\pm$ SD)	11.7 ($\pm$ 3.2)	11.8 ($\pm$ 3.3)	11.6 ($\pm$ 3.1)	NS [†]
Height (cm)	147.8 ($\pm$ 16.2)	147.3 ($\pm$ 16.1)	148.4 ($\pm$ 16.4)	NS [†]
Weight (kg)	41.8 ($\pm$ 15.6)	40.8 ($\pm$ 16.0)	42.8 ($\pm$ 15.3)	NS [†]
BMI (kg/m ²)	18.2 ($\pm$ 3.8)	18.0 ($\pm$ 3.4)	18.5 ($\pm$ 4.2)	NS [†]
BMI z-score	-0.02 ($\pm$ 1.04)	-0.19 ($\pm$ 0.95)	0.15 ($\pm$ 1.14)	NS [†]
Baseline FEV ₁ /FVC (%)	80.31 ($\pm$ 13.42)	85.6 ($\pm$ 5.5)	75.0 ($\pm$ 16.81)	0.02 [†]
FeNo levels (ppb)	23.0 ($\pm$ 25)	6.4 ($\pm$ 2.4)	30.1 ($\pm$ 27.0)	0.01 [†]
Mannitol positive response (n)	21	0	21	0.01 [†]
Receiving regular ICS (n) [§]	20	0	20	—

[†] Unpaired *t*-test.[‡] Mann-Whitney *U*-test.[§] Receiving regular ICS was stopped for participation in the study according to Pharmaxis sputum induction protocol. AA, allergic asthma; HC, non-allergic healthy control; ICS, inhaled corticosteroids; NS, not significant.

chi-square tests. Statistical comparisons for the means were performed by *t*-tests appropriately corrected for non-equal variance where needed. Mann-Whitney *U*-tests were performed if a Gaussian distribution was absent. Distributions of continuous variables were examined for skewness and kurtosis. Variables included in the analysis were age, gender, BMI, BMI *z*-scores, cytokines and adipokines, and HOMA-IR. Age, BMI *z*-scores, adipokines and HOMA-IR were treated as continuous variables. All possible models with a maximum of three-level interactions were tested. A *P*-value <0.05 was considered statistically significant. All analyses were performed using SPSS (version 16.0; SPSS Inc, Chicago, IL, USA).

RESULTS

Thirty-one participants, 21 AA and 10 non-allergic HC, aged 6.0–17.9 years were included in this study. Summary demographic characteristics and biochemical and cytokine measurements are shown in Table 1, Figure 1, Table S1 (online supplement), and Table 2. There was no significant difference in demographic characteristics. However, blood levels of IL-4 (*P* = 0.04), IL-5 (*P* = 0.01), IL-6 (*P* = 0.05) and leptin (*P* = 0.02) had significantly different variances comparing the AA group with the HC; therefore, an unpaired *t*-test with Welch's correction was performed (Table 2). Significant differences were found in the blood levels of IL-4 (*P* = 0.04), IL-5 (*P* = 0.01) and IL-6 (*P* = 0.05) between the two groups. HOMA-IR index was normally distributed in both groups. However, each had significantly different variances (*P* = 0.01). After correcting for the observed homoscedasticity, a significant difference in HOMA-IR index (*P* = 0.01) between the AA and HC groups was observed (Fig. 2). Insulin resistance (HOMA-IR $\geq$ 1.77) was found in 42.9% of the AA group, whereas no subjects in the HC group had insulin resistance (*P* = 0.05). Significant correlations were found between BMI *z* and leptin both in AA (*r* = 0.67, *P* = 0.01) and HC (*r* = 0.77, *P* = 0.01) (Table 3). There was no significant correlation between HOMA-IR and

Table 2 Comparison of biochemical and adipokine parameters in AA and HC groups

Variable	HC (n = 10)	AA (n = 21)	P-value
IL-6 (pg/mL) (mean $\pm$ SD)	11.6 ($\pm$ 14.6)	31.0 ($\pm$ 37.0)	0.05 [†]
IL-5 (pg/mL)	0.6 ($\pm$ 0.4)	1.4 ($\pm$ 1.1)	0.01 [†]
IL-4 (pg/mL)	56.2 ($\pm$ 70.6)	126.7 ($\pm$ 132.5)	0.04 [†]
TNF- α (pg/mL)	6.1 ($\pm$ 3.1)	5.7 ($\pm$ 2.5)	NS [†]
Leptin (ng/mL)	7.1 ($\pm$ 6.0)	9.7 ($\pm$ 12.4)	NS [†]
Resistin (ng/mL)	6.8 ($\pm$ 1.5)	6.5 ($\pm$ 2.3)	NS [†]
PAI-1 (ng/mL)	5.5 ($\pm$ 2.8)	5.8 ($\pm$ 2.9)	NS [†]
Insulin (mIU/L)	4.1 ($\pm$ 1.6)	5.1 ($\pm$ 3.9)	NS [†]
Glucose (mmol/L)	4.9 ($\pm$ 0.3)	4.8 ($\pm$ 0.5)	NS [†]
HOMA-IR index	0.7 ($\pm$ 0.3)	1.7 ($\pm$ 1.4)	0.01 [†]
IR (HOMA-IR index $\geq$ 1.77)	0.0%	42.8%	0.05 [§]

[†] Mann-Whitney *U*-test.[‡] Unpaired *t*-test.[§] Chi-square test.

AA, allergic asthma; HC, non-allergic healthy control; HOMA-IR, homeostasis model assessment insulin resistance; IR, insulin resistance; NS, not significant; PAI-1, plasminogen activator inhibitor-1; TNF- α , tumour necrosis factor- α .

any of the measurements in the HC group; only in AA group, HOMA-IR was related to (i) BMI *z* (*r* = 0.57, *P* = 0.01); (ii) raw BMI (*r* = 0.74, *P* = 0.01); (iii) percentage of body fat mass (%FM) (*r* = 0.57, *P* = 0.01); (iv) leptin (*r* = 0.55, *P* = 0.01); (v) resistin (*r* = -0.47, *P* = 0.03); and (vi) IL-4 (*r* = 0.40, *P* = 0.04) (Table 4). After adjustment for BMI *z*-scores, the correlations between HOMA-IR and leptin and resistin became non-significant, but a significant positive correlation emerged between HOMA-IR and IL-6 (*r* = 0.44, *P* = 0.05), and a significant negative correlation with TNF- α (*r* = -0.45, *P* = 0.05). The correlation for IL-4 (*r* = 0.49, *P* = 0.03) remained significant. Raw BMI values were found to be significantly correlated only to leptin both in AA (*r* = 0.68, *P* = 0.01) and HC (*r* = 0.75, *P* = 0.01) (Table 3).

DISCUSSION

In this study, we confirmed the findings of other studies showing that BMI z-scores and raw BMI are

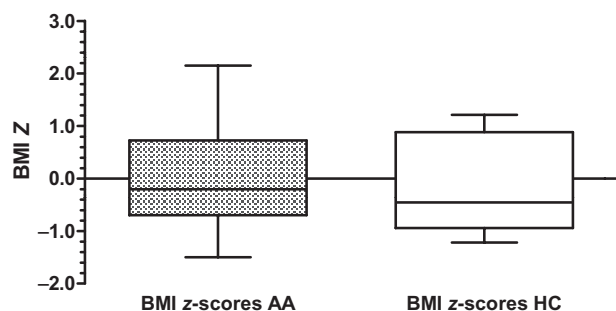


Figure 1 BMI z-scores in allergic asthma (AA) and healthy control (HC) groups.

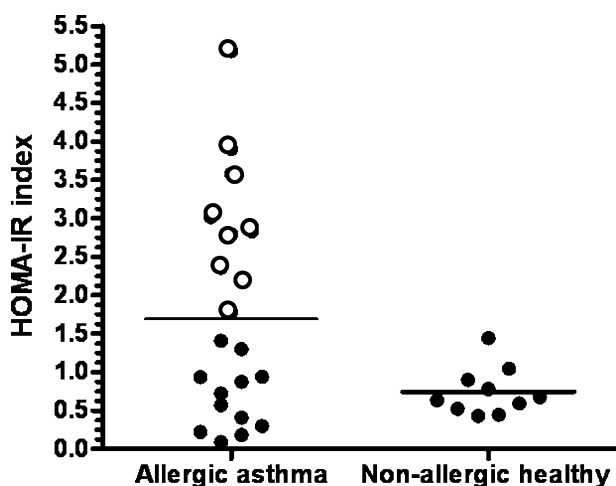


Figure 2 Variance in HOMA-IR in allergic asthma and healthy control groups. (●) HOMA-IR index <1.76; (○) HOMA-IR index ≥1.77.

positively related to leptin. Although AA and HC groups did not differ in their body size characteristic, insulin resistance was observed only in the AA group where a higher variance of HOMA-IR was also found. In the AA group BMI z-scores, leptin, IL-6 and resistin were significantly related to insulin resistance; in addition, correlations between insulin resistance and IL-6 and TNF- α were found, which was independent of BMI z-scores. However, many of the correlations were weak and require cautious interpretation.

We used BMI z-scores calculated from CDC (Centres for Disease Control and Prevention) data.^{24,30} Many previous studies investigating obesity and asthma have used raw BMI scores (kg/m²), rather than BMI z-scores, as a measure of adiposity.^{21,31,32} BMI needs to be adjusted for both age and gender in studies involving children,³³ and this may be done by the calculation of a z-score. In contrast to previous reports, we have calculated age- and gender-specific z-scores for our cohort, which strengthens the result presented here and allows direct comparison between the groups. Furthermore, the importance of using BMI z-scores was highlighted by our finding that relationships between variables only emerged when BMI z-scores, rather than raw BMI values, were used.

In our cohort, the diagnosis of asthma was confirmed by objective tests including mannitol challenge test, response to bronchodilator and levels of exhaled nitric oxide according to American Thoracic Society;²⁶ in addition, the allergic status of all participants was defined by the skin prick test, with participants required to have at least one positive skin prick test to be considered allergic. This is in contrast to the majority of previous asthma studies. Although often involving large populations, these studies use simple self-reports or have based their diagnosis on clinical observations of the patient's signs and symptoms, for example, wheezing. For example, in the study by Husemoen *et al.*,²¹ asthma was ascertained by self-administered questionnaire (positive answer to 'has a physician ever told you that you have asthma?' and

Table 3 Associations of various measurements in allergic asthma and healthy non-allergic groups

		Leptin (ng/mL)	Resistin (ng/mL)	TNF- α (pg/mL)	HOMA-IR index	IL-4 (pg/mL)	IL-5 (pg/mL)	IL-6 (pg/mL)
In children with allergic asthma (<i>n</i> = 21)								
BMI (kg/m ²)	Correl.	0.68	0.23	-0.38	0.74	-0.35	0.14	-0.15
	Sig.	0.01	0.32	0.09	0.01	0.13	0.55	0.53
BMI z-score	Correl.	0.67	0.09	-0.12	0.6	-0.45	0.27	-0.31
	Sig.	0.01	0.70	0.60	0.01	0.04	0.23	0.17
In non-allergic healthy children (<i>n</i> = 10)								
BMI (kg/m ²)	Correl.	0.75	0.42	-0.02	-0.14	0.45	-0.20	0.47
	Sig.	0.01	0.23	0.96	0.70	0.19	0.57	0.17
BMI z-score	Correl.	0.77	0.42	-0.08	0.10	0.56	0.09	0.45
	Sig.	0.01	0.23	0.83	0.78	0.09	0.81	0.19

Correl., correlation coefficient; HOMA-IR, homeostasis model assessment insulin resistance; *n*, number of the subjects; Sig., two-tailed significance; TNF- α , tumour necrosis factor- α .

Table 4 Associations between adipokines and HOMA-IR index in allergic asthma and non-allergic healthy subjects

		Leptin (ng/mL)	Resistin (ng/mL)	TNF- α (pg/mL)	IL-4 (pg/mL)	IL-5 (pg/mL)	IL-6 (pg/mL)	Raw BMI (kg/m ²)	BMI z-score	%FM
In children with allergic asthma ($n = 21$)										
HOMA-IR index	Correl.	0.55	-0.47	-0.36	0.40	0.17	-0.09	0.74	0.57	0.57
	Sig.	0.01	0.03	0.11	0.04	0.45	0.71	0.01	0.01	0.01
In non-allergic healthy children ($n = 10$)										
HOMA-IR index	Correl.	0.19	0.07	-0.10	0.03	-0.16	-0.07	-0.14	0.10	0.42
	Sig.	0.60	0.85	0.78	0.93	0.66	0.85	0.70	0.78	0.23

%FM, percentage of body fat mass; Correl., correlation coefficient; HOMA-IR, homeostasis model assessment insulin resistance; n , number of the subjects; Sig., two-tailed significance; TNF- α , tumour necrosis factor- α .

allergy by 'having aeroallergen sensitisation'). We believe the objective confirmation of both asthma and allergy in our participants strengthens the value of our findings.

We observed that AA children had a greater variance in HOMA-IR. Interestingly, a natural biological variation of insulin resistance in both healthy and diabetic individuals has recently been reported.³⁴ In this study, age, BMI and ethnicity were found to be confounding factors.³⁴ To account for this, the two groups in our study were closely matched for age, BMI and ethnicity. While the reasons for this variability remain speculative, it nonetheless needs to be further investigated in studies of insulin resistance in individuals with asthma.

In our study, when participants were classified according to insulin resistance (HOMA-IR ≥ 1.77), nine of the AA group were found to be insulin-resistant, in contrast to none of the HC group. This finding is in agreement with a study of adults that reported an association between insulin resistance and allergic asthma.²¹ Similarly, in a retrospective study of morbidly obese children, it was shown that those with asthma had higher levels of insulin resistance compared with those without.³⁵

Leptin is highly expressed in differentiated adipocytes,³⁶ and the association between leptin and HOMA-IR is well recognized.³⁷ However, the association between resistin and BMI is not as clear. Some studies have shown a BMI-dependent association between resistin and HOMA-IR,³⁸ and others have shown a correlation but only in a subpopulation of obese individuals.³⁷

The role of IL-6 in insulin resistance is controversial. While some studies suggest a BMI-dependent association between IL-6 and HOMA-IR,³⁷ other larger studies fail to show any association.³⁷ In this study we show a significant BMI-independent correlation between IL-4, IL-6 and HOMA-IR. We also showed that children with AA had significantly higher levels of IL-4, IL-5 and IL-6, compared with non-allergic HC. *In vitro* studies have shown that IL-6 can both increase and decrease insulin sensitivity depending on the dose and time of incubation.^{39,40}

A limitation of studies was that children with allergic asthma were compared with healthy non-allergic

controls. There was no comparison that included controls without asthma but who were allergic and hence we could not determine whether the observed insulin resistance was related to asthma or allergy *per se* in this study. Moreover, it should be remembered that many of the associations noted were weak and may indeed be spurious.

In conclusion, we confirmed findings of other studies showing a relationship between BMI z-scores and leptin. We found significantly higher blood levels of IL-4, IL-5, IL-6 and HOMA-IR index in the children with allergic asthma. Children with allergic asthma had greater HOMA-IR variance and showed an insulin resistance profile. Our studies suggest that metabolic abnormalities may be linked to asthma and that further research in this field is warranted.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1 Characteristics of the laboratory variables in the allergic asthmatic and non-allergic healthy control groups.

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Table S1. Characteristics of the laboratory variables in the allergic asthmatic and non- allergic healthy control groups.

		Leptin (ng/ml)	Resistin (ng/ml)	TNF- alpha (pg/ml)	HOMA- IR index	IL-4 (pg/ml)	IL-5 (pg/ml)	IL6 (pg/ml)	IL13 (pg/ml)
Children with allergic asthma (n=21)									
Mean		9.7	6.5	5.7	1.4	126.7	1.4	31	36.5
Std. Error of Mean		2.7	0.5	0.6	0.3	28.9	0.2	8.1	8.1
Median		3.7	6.2	6.2	0.9	55.9	1.2	12.5	20.2
Std. Deviation		12.2	2.3	2.6	1.4	132.5	1.0	37.1	37.1
Variance		148.6	5.1	6.7	2.0	17567	1.0	1374	1373.4
Range		45.7	9.1	8.9	6.1	358.5	4.7	147.9	106.9
Minimum		0.2	1.9	0.9	0.1	2.0	0.2	0.4	0.6
Maximum		45.8	11	9.7	6.2	360.5	4.9	148.3	107.5
Percentiles	25	1.7	5.1	3.5	0.4	11.1	0.8	3.2	3.7
	50	3.7	6.2	6.2	0.9	55.9	1.2	12.5	20.2
	75	18.6	8.3	7.8	1.9	240	1.9	50.7	74.1
Non-allergic healthy children (n=10)									
Mean		7.1	6.7	6.1	0.9	56.2	0.7	11.6	19.5
Std. Error of Mean		1.9	0.5	1.0	0.1	22.3	0.2	4.6	7.6
Median		5.8	6.8	5.5	0.7	30.0	0.6	6.2	11.4
Std. Deviation		6.0	1.7	3.1	0.4	70.6	0.6	14.6	24.2
Variance		35.8	3	9.5	0.2	4987.6	0.4	212.2	584.2
Range		19.2	6.9	8.9	1.1	225.7	2.0	45.9	75.2
Minimum		0.4	3.0	1.7	0.4	2.0	0.1	0.2	0.5
Maximum		19.6	9.9	10.5	1.5	227.7	2.1	46.1	75.7
Percentiles	25	3.0	6.2	3.6	0.6	7.4	0.2	2.4	1.8
	50	5.8	6.8	5.5	0.7	30	0.6	6.2	11.4
	75	9.8	7.5	9.7	1.1	86.3	0.9	17.3	28.9