RESEARCH ARTICLE

CORRELATION BETWEEN ALLERGY HISTORY IN FAMILY AND ALLERGY MANIFESTATION IN SCHOOL-AGE CHILDREN

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ABSTRACT

Background: Asthma, eczema and allergic rhinitis are influenced by both genetic factors and environment factors. Based on family history of allergy, allergic trace cards can identify the level of allergic risk in children. The relationship between family history of allergy and manifestation of allergic disease as a single allergy disease and allergic multimorbidity still needs to be explored. The objective of this study was to identify the associations between family history of allergic disease and manifestation of allergic disease in school-age children.

Methods: We conducted a cross-sectional study on school-age children 6-13 years old at eight elementary schools in Yogyakarta. Family history of allergy was defined as reported asthma, eczema and allergic rhinitis in a parent or sibling and classified the level of allergic risk based on allergic trace cards. Subjects were questioned by a standardized ISAAC questionnaire. The relationship between the two variables was analyzed by the Chi-squared analysis to assess the prevalence ratio (PR).

Results: A total of 272 children with an average age of 8.4 years, allergic manifestations occurred more as multimorbidity (53%) with the highest incidence of rhinitis allergy (RA)+asthma (9%) compared with one allergic disease (47%) with the highest incidence of RA (11%). There was a significant relationship between family history of allergy and all manifestations of allergic disease with an increased risk of developing allergies by 3.3 (PR 3.3; 95% CI 2.3-4.8) and 2.8 times (PR 2.8; IK95% 1.8-4.3) in the moderate and high-risk score group. Asthma, RA and allergy atopic dermatitis (AD) have a risk for coexistence with 2 other diseases of 2.5 (PR 2.5 IK95%; 1.9-3), 2.25 (PR 2.25 IK95%; 1.7 -3) and 1.9 times (PR 2.5 IK95%; 1.45-2.4).

Conclusion: Family history of allergic disease is a risk factors for the development of allergic manifestation both a single allergic disease and multimordibity.

Keywords: Allergy, Family history, Multimorbidity, Children.

INTRODUCTION

Allergy is a multifactorial disease which affected either by a genetic or external factor. Some genes were mentioned that they have relations with allergy such as systemic atopy expressions gene, barrier function control gene in target-specific organ and adaptive immune respond receptor recognition gene.[1] In the last two decades, number of allergic diseases in children is increasing both in the world and Indonesia. A metanalysis study on 31 studies from 102 countries in the world concludes that atopic dermatitis (AD) prevalence was 7.88%, 12.66% for allergic rhinitis (AR) and 12% for asthma. The prevalence distribution pattern in Asian countries shows a similar pattern as well, AD prevalence was 7.5%, 8.5% for asthma and 13.5% for AR. The study was also mentioned coexistence or multimorbidity prevalence in all three diseases in the world was 1.17%.[2]

Even though allergy is considered as a disease entity itself, coexistence from allergy disease, or called multimorbidity, was increasing even more. Multimorbidity in allergy was a coexistence of two or more allergy disease which is AD, asthma and AR, in one individual at some period.[1] A lot of studies were done to see the correlations between genetic factors in a family with allergy manifestations in children, it shows that positive allergy family history increases allergy risk in children significantly. The study then was applied to an early detection card that was published by the Coordinated work team of allergy-

immunology Indonesian Paediatric Association in 2009 to score allergy risk factors in a child.[3]

Some studies were done to see the correlation between early detection card and atopic dermatitis in which high score children had 10 to 22 times higher risk than low score children.[4] But there are no allergy prevalence studies specifically done in Indonesia yet and no studies analyzing other manifestations of the allergic disease that appear in children in populations with an increased allergy risk in an atopy family history. Based on that, this research aims to find a correlation between allergy history in a family obtained by allergy early detection score with allergy manifestation in school-age children.

METHODS

This study was a cross-sectional study based on previous research data that was done before. The previous research was a study of prevalence and comorbidity of allergic disease that was done in 2014 for elementary school students in Yogyakarta. The inclusion criteria of this study were children 6 to 13 years old and included as a research subject in the "Prevalence and comorbidity of allergic disease in Children" study that was done in 2014. Exclusion criteria were incomplete data of the previous study such as family allergy history, skin prick test (SPT) result and International Study of Asthma and Allergies in Childhood (ISAAC) score.

Outcome analysis of statistics in this study was using SPSS ver.22 programme. The statistic test was analyzed by SPSS chi-square test to find the significance and the correlation was described by Prevalence Ratio (PR) between early detection risk score with allergy manifestations. The Outcome would be analyzed by bivariate analysis to see the significance and correlation between outcome and dependent variable described by Odd Ratio (OR). If the result showed p<0.25, the variable would be analyzed by Mantel-Haenzel multivariate analysis to find the correlation between those two variables. The previous study had an ethical clearance from the ethical committee in Faculty of Medicine, Public Health and Nursing Universitas Gadjah Mada with license number KE/FK/1015/EC. This study's ethical clearance number was KE/FK/1136/EC/2019.

RESULTS

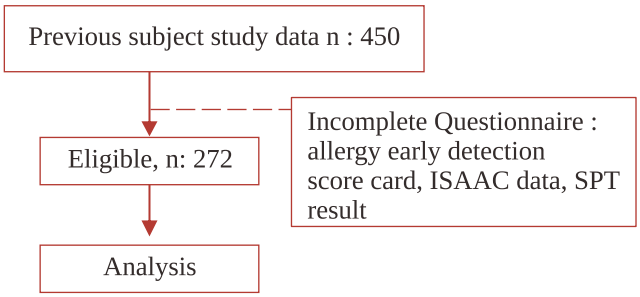

Figure 1. Study Subject's Inclusion and Exclusion

272 children who met the inclusion and exclusion criteria. The total study sample that was analyzed is described in Figure 1. Four hundred and fifty subjects meet the study inclusion criteria. A total of 179 children didn't meet subject eligibility criteria result in 272 subjects that meet the criteria was analyzed. The study design to collect the samples for analysis is shown in Figure 2.

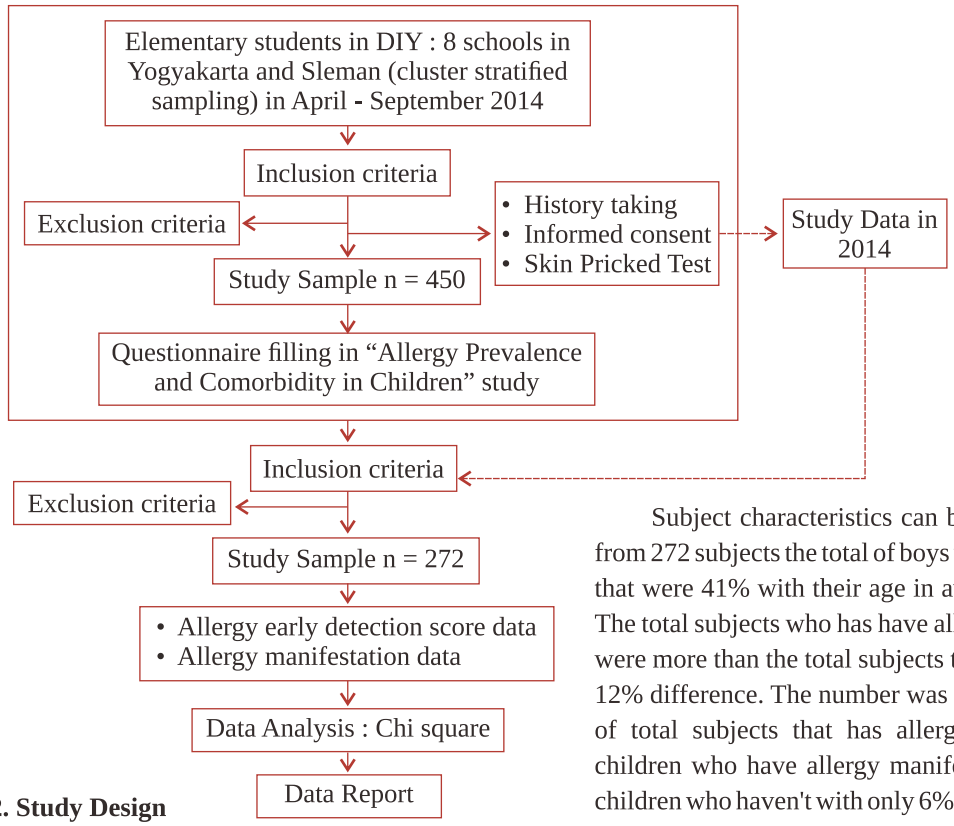

Figure 2. Study Design

Subject characteristics can be seen in Table 1, which from 272 subjects the total of boys were 56%, more than girls that were 41% with their age in average was 8.4 years old. The total subjects who has have allergy history in the family were more than the total subjects that those who hasn't with 12% difference. The number was matched with the number of total subjects that has allergy manifestations, which children who have allergy manifestations were more than children who haven't with only 6% difference.

Table 1. Study Subject Characteristics

Characteristics	Total (n)	Percentage (%)
Study Subject (n)	272	100
Gender		
Boys	162	59
Girls	110	41
Age (average) y.o.	8,4	
Allergy history in Family		
Yes	154	56
No	118	44
Allergy Manifestation		
Yes	145	53
No	127	47

Clinical manifestations pattern was showed in allergy multimorbidity with the highest percentage in every group was moderate-risk group, even in two allergy disease group such as AD+AR (50%), AD+asthma (40%), AR+asthma (49%) and all-three multimorbidity (42%) just like showed in Figure 3. As the lowest percentage consistently showed in the low-risk group in every allergy multimorbidity manifestation.

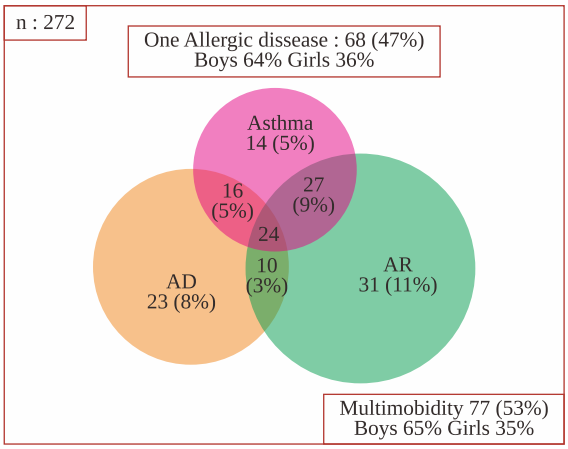

Figure 3. Allergy Clinical Manifestation Percentage

Generally, allergy manifestation has the biggest percentage in the moderate risk score group with 52% and the smallest percentage was 20% in the low-risk score group as showed in Table 2. In one allergic disease, AD and AR also has biggest percentage in the moderate risk score group. But AD was the only one that has the lowest percentage in the high-risk score group and asthma was the only group with zero number in the low-risk score group.

Table 2. Allergic Disease Percentage Based on Allergy Early Detection Card

Allergy early detection score	Allergic disease (%)	One allergic disease		
		AD	AR	Asthma
Total (n) (100%)	145	23	31	14
Low risk score (0)	30 (20%)	6 (26%)	8 (26%)	0 (0%)
Moderate risk score (1-3)	75 (52%)	14 (61%)	13 (42%)	10 (71%)
High risk score (4-6)	40 (28%)	3 (13%)	10 (32%)	4 (29%)

Table 3 shows the allergy manifestation that happened in the last 12 months in elementary school children in Yogyakarta. More children have multimorbidity with a total of 77 children (53%) compared with one allergic disease with a total of 68 children (47%). In one allergic disease, most children have allergic rhinitis (11%) and asthma (5%) was the fewest. More boys (64%) got one allergic disease than girls (36%) even though the total of boys and girls that have asthma were similar.

Allergy multimorbidity generally also happened more in boys (65%) than girls (35%). Coexistence of asthma and AR was the most multimorbidity that happened with 9% and all-three diseases multimorbidity follows with 8%. The fewest multimorbidity was AD+AR with only 10 children (3%) which also the fewest in all allergy manifestations. If we add each allergic disease with their coexistence, it showed that AD's frequency in multimorbidity was 18%, AR was 22% and the highest was Asthma's multimorbidity with 24%. Furthermore, we knew that asthma manifested more as coexistence than one allergic disease (5%).

Table 3. Allergic Clinical Manifestation in School-age Children

Allergic clinical manifestations	Total	Boys (n)	Girls (n)	Age (y.o.) (Average)
One allergic disease	68 (47%)	44 (64%)	24 (36%)	8.7
AD	23 (8%)	17 (74%)	6 (26%)	8.5
AR	31 (11%)	20 (64%)	11 (36%)	8.7
Asthma	14 (5%)	7 (50%)	7 (50%)	9.1

Allergic clinical manifestations	Total	Boys (n)	Girls (n)	Age (y.o.) (Average)
Multimorbidity	77 (53%)	50 (65%)	27 (35%)	8.2
AD+AR	10 (3%)	7 (70%)	3 (30%)	8.4
AD+Asthma	16 (5%)	12 (75%)	4 (25%)	8.8
AR+Asthma	27 (9%)	13 (44%)	14 (56%)	7.8
AD+AR+Asthma	24 (8%)	18 (75%)	6 (25%)	7.9

The Chi-square analysis results in Table 4 showed a significant correlation between allergic disease in general in a moderate-risk group with a PR value of 3.3 and in a high-risk group PR value was 2.8. Both are the biggest PR value in this study result. In the moderate-risk group, PR value was significantly increasing in AD, AR and asthma as one allergic disease with a similar value which is 1.2, 1.2 and 1.1. As for allergy multimorbidity, two diseases showed insignificant correlation, that was AD+asthma and all three diseases, AD+AR+ Asthma, coexistence.

On the other side, the high-risk group showed significant PR value in almost every allergic disease group except for AD as one allergic disease. PR value in the high-risk group was not so big different, around 0.1-0.2, then PR value in the moderate-risk group. But it constantly showed in almost every allergic disease group, either as one allergic disease or multimorbidity.

Table 4. Correlation Between Allergy Early Detection Score and Allergy Clinical Manifestations

Allergy Early Detection Score	Prevalence Ratio (PR) (95% CI)			
	Allergic disease	One allergic disease		
		AD	AR	Asthma
Low Risk Score (0)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)
Moderate Risk Score (1-3)	3.3 (2.3-4.8) $p < 0.001$	1.2 (0.26-3.8) $p = 0.004$	1.2 (1.01-1.3) $p = 0.014$	1.1 (1.06-1.3) $p < 0.05$*
High Risk Score (4-6)	2.8 (1.8-4.3) $p < 0.001$	1.02 (1.01-1.1) $p = 0.62$	1.3 (1.03-1.6) $p = 0.002$	1.1 (1.026-1.3) $p < 0.001$*

Allergy Early Detection Score	Prevalence Ratio (PR) (95% CI)			
	Multimorbidity			
	AD+AR	AD+Asthma	AR+Asthma	AD+AR+Asthma
Low Risk Score (0)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)
Moderate Risk Score (1-3)	1.1 (0.36-4.2) p =0.006	1.1 (1.01-1.2) $p = 0.06$	1.2 (1.07-1.4) $p = 0.001$	1.06 (1.01-1.15) $p = 0.14$
High Risk Score (4-6)	1.2 (1.01-1.3) $p = 0.01$	1.2 (0.6-6.5) $p = 0.002$	1.3 (1.05-1.5) $p = 0.002$	1.1 (1.01-1.25) $p = 0.031$

* Fisher's exact test.

Significance and correlation between outcome value, such as gender, and dependent value showed in Table 5.

Table 5. Bivariate Analysis on Gender in Allergy Disease (Prevalence Ratio)

Allergy Early Detection Score	Prevalence Ratio (PR) (95% CI)			
	Allergic disease	One Allergic disease		
		AD	AR	Asthma
Gender (Boys)	1.2 (0.9-1.6) $p = 0.05$	1 (0.9-1.1) $p < 0.07$	1 (0.9-1.1) $p = 0.4$	1 (0.9-1.1) $p = 0.5$
	Prevalence Ratio (PR) (95% CI)			
	Multimorbidity			
	AD+AR	AD Asthma	AR+Asthma	AD+AR+Asthma
Gender (Boys)	1 (0.9-1.1) $p = 0.07$	1.1(1-4.8) $p = 0.031$	1 (0.9-1.1) $p = 0.8$	1 (0.9-1.1) $p = 0.106$

An Allergic disease that has a p-value<0.25 was allergic disease in general, AD as one allergic disease, and for multimorbidity were AD+AR, AD+Asthma and AD+AR+Asthma. And so, these five manifestations continued to multivariate analysis, the logistic regression, to see the significance of the correlation between two variables that showed in Table 6. Based on multivariate analysis, there was no significant correlation between allergy manifestation and gender (boys).

Table 6. Multivariate Analysis Result With Gender as an External Variable

Allergy Early Detection Score	Prevalence Ratio (PR) (95% CI)			
	Allergic disease	One Allergic disease		
		AD	AR	Asthma
Low Risk Score (0)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)
Moderate Risk Score (1-3)	3.3 (2.3-4.8) $p < 0.001$	1.2 (0.26-3.8) $p = 0.004$	1.2 (1.01-1.3) $p = 0.014$	1.1 (1.06-1.3) $p < 0.05$*
High Risk Score (4-6)	2.8 (1.8-4.3) $p < 0.001$	1.02 (1.01-1.1) $p = 0.62$	1.3 (1.03-1.6) $p = 0.002$	1.1 (1.026-1.3) $p < 0.001$*
Gender (Boys)	1.5 (0.9-2.8) *p = 0.1*	2.3 (0.8-6.3) *p = 0.9*		
Allergy Early Detection Score	Prevalence Ratio (PR) (95% CI) Multimorbidity			
	AD+RA	AD+Asthma	AR+Asthma	AD+AR+Asthma
Low Risk Score (0)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)
Moderate Risk Score (1-3)	1.1 (0.36-4.2) p =0.006	1.1 (1.01-1.2) $p = 0.06$	1.2 (1.07-1.4) $p = 0.001$	1.06 (1.01-1.15) $p = 0.14$
High Risk Score (4-6)	1.2 (1.01-1.3) $p = 0.01$	1.2 (0.6-6.5) $p = 0.002$	1.3 (1.05-1.5) $p = 0.002$	1.1 (1.01-1.25) $p = 0.031$
Gender (Boys)	1.9 (0.8-4.4) *p = 0.1*	2.1 (0.9-4.5) *p = 0.06*		2 (0.7-5.3) *p = 0.1*

* Fisher's exact test.

Every allergic disease has the opportunity to manifest as multimorbidity either with one or two other diseases. How big the risk value could be determined by prevalence ratio analysis in Table 7. It shows all three diseases significantly had a PR value of more than 1, with the highest PR value was Asthma that had 2.5, which means a child with Asthma has 2.5 times more risk to manifest a coexistence with other allergic diseases. As for AD PR value was 1.9 and AR was 2.25

Table 7. Multimorbidity Risk in Every Allergic Disease

	AD	AR	Asthma
Rasio Prevalensi (RP) (95% CI)	1.9 (1.4-2.4) $p < 0.01$	2.25 (1.7-3) $p < 0.01$	2.5 (1.9-3.0) $p < 0.01$

DISCUSSIONS

General characteristics on gender in this study match with ISAAC phase 3 study that allergy manifested in boys more in 6-7 years old group.[5] A study in Germany also showed boys age 3-9 years old more had allergies than girls.[6] The total number of children that have an allergy history in the family was more which is 54%. In Surabaya, 55% of children manifested allergy and 48% in Germany.[6,7] As for allergy disease prevalence, this study showed AR 11%, AD 8% and asthma 5% with more boys has an allergy and the average age was 8.5 years old in AD, 8.7 years old or AR and 9.1 years old in asthma. On ISAAC 2012 in Pacific Asia, it showed allergic prevalence was 10.5% for RA, AD 10.1% and Asthma 9.5% in children with 6-7 years old and boys were more than girls. In Surabaya, AR prevalence was 23.0%, Asthma 6.8% and AD was 1.8%.[7] On a Global scale,

for children in the 6-7 years old group, the highest prevalence was Asthma with 11.7%, AR 8.5% and AD 7.9%.[5] Other studies show AR, Asthma and AD prevalence was 12.7%, 12% and 7.9% in 0-18 years old children.[2]

Either in an allergy disease or multimorbidity, the total of subjects was increasing along with the increasing score in family risk. A study in Bandung showed 17% allergy disease, with AD 5%, AR 15% and asthma 8.5%, more occurred in children with positive allergy history in the family.[8] As in Bali showed 46% baby that diagnosed with AD had an atopy history in the family.[9]

Some factors were predicted to be the reason for an increased number of allergy manifestations in elementary-age children in Yogyakarta. The Genetic and external factor was also the cause of increased allergy prevalence globally.[5] These external factors have been studied before, such as hygiene hypothesis, early age infection and air pollution.[11] Geological and climate factors, socio-economy and air pollution were others factors that increase allergy prevalence as well.[5]

In this study, allergic disease prevalence as multimorbidity in elementary-age children in Yogyakarta was 9% for AR+Asthma, AD+AR was 3% and AD+AR+Asthma got 8%. The prevalence in a study in Pacific Asia with 6-7 years old children was 21.5% for AR+Asthma, 14.7% for AD+AR and 11.5% for AD+Asthma.[5] And a study in Kuwait showed AR+Asthma was the highest with 5.1% as well as other study showed AR+Asthma was 13%.[6, 12]

There was a significant correlation between family history and the moderate and the high-risk allergy score in this study, which was 3.3 and 2.8. In allergy early detection cards, the moderate-risk group risk ratio (RR) was around 1.3-2.7 and 2.7-4 in the high-risk group. In one allergic disease, AD, AR and Asthma have a significant correlation between family history and allergic risk score. As for multimorbidity, AD+Asthma and all-three multimorbid AD+AR+Asthma didn't get a significant correlation.

In Indonesia, allergy history in the family showed an increased risk in AD manifestation in children with 22.5 times more in 0-4 months old baby.[9] While other studies showed a high score has 10.5 times more risk to manifest AD compared to low or moderate scores.[4] Both studies pointed to a high score and the number was quite different caused by children's age when they were diagnosed.[6]

Genetic factors had a big contribution to determine allergic risk. The genetic influence at an allergic disease manifestation was also the result form interactions of multiple genes simultaneously.[13] As the allergy manifestation depends on allergen sensitization, external factors were more contributed in determining people's sensitivity by another specific allergen. The underlying gene and environment interaction are a mechanism that is proven as a factor in the increasing prevalence of allergic diseases.[14] Gender was thought to be related to allergy manifestations in children. But the multivariate analysis result between them was not significant. So, gender didn't affect the correlation between family history and allergic disease manifestations in children.[15]

Every allergic disease had a risk to manifest a coexistence. The risk could be determined with a PR probability value. Asthma risk value was 9.5 times, AR was 4.7 times and 8.3 times for AD. Another study showed Asthma's coexistence risk was 5.41 times riskier, AD was 4.24 times and AR was 6.20 times.[2] Atopic march became one of the theories that underlie the increase of multimorbidity. Multimorbidity would manifest more in children with positive IgE sensitization, but a non-IgE mechanism that correlated with allergic manifestation as multimorbidity ~~is~~ has existed as well. One cohort study found that multimorbidity at age 8 with positive allergen sensitization in only 38% of multimorbidity cases overall. Thus, it is argued that the IgE-mediated immune response mechanism as the main pathophysiology of allergic disease can not be considered a major cause of multimorbidity events. However, there are also non-IgE mechanisms associated with the development of allergic disease as a multimorbidity.[16] Types of research on multimorbidity of allergic disease still need to be done because the high incidence of multimorbidity in allergic diseases is considered clinically important and they were related to the severity of the disease, causes, management and prognosis in those patients.

CONCLUSION

Allergy history in the family has a strong correlation with allergy manifestation, which was a high allergy early detection score it was 4-6, which showed an increased risk more than twice than almost every other allergic disease, compared with a low-risk score. Allergic coexistence had quite a big prevalence, which means allergy couldn't only be seen as a disease itself but also be seen comprehensively to get better management and prognosis.

Conflict of Interest

None declared.

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