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The Effect of House Dust Allergy on the Effectiveness of Allergenic Foods Elimination

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ABSTRACT
Food allergy is a primary cause of early manifestations of atopic disease. House dust mites are the main aeroallergens that underlie allergic manifestations. Both of them play a role in the pathogenesis of atopic diseases and cause an impact on the family's economy and health costs. This study was a consecutive sampling retrospective cohort with house dust allergy as an independent variable; food allergy with and without dust allergy with allergenic food elimination, sign & symptom score, medication score, combination sign & medication score, visit fee outpatient care, inpatient costs, and total medical expenses as the dependent variable. Data were collected using secondary data from medical records or patient reports via mobile phone messaging applications every month. We averaged data at 3, 6, 9, and 12 months after the patients were diagnosed with food allergies and undergoing a food elimination diet. The data were analyzed using the Kruskal-Wallis test with a significance level of <0.05. We can conclude that house dust allergy influences allergenic food elimination diet effectiveness (p=0.001).

Keywords: food allergy; house dust mite; symptom score; treatment score; cost score

INTRODUCTION
Food allergy is the primary cause of early atopic disease manifestations that are mainly caused by house dust mites and food (Perry, 2013, Walczak, Grzelak, et al., 2014, Tanukusumah, 2016, Calderón, 2015, Siregar, 2016). Around 5,9% of patients in Europe and 10,6% of children in Jakarta reported having food allergies (Tanukusumah, 2016, Judarwanto, 2016). A study by the University of Indonesia showed that children (<12 years old) with pollution and dust allergies had quadrupled in the last 20 years, from 2% in 1980 and reaching 8% in 2000 (Quamila, 2017).

Aeroallergen (inhalant allergen) is the primary in-house allergen in the tropic area. This mainly contains Dermatophagoides pteronyssinus and Dermatophagoides farinae (Siregar, 2016). Oral mite anaphylaxis (OMA) may occur in tropical and subtropical Asia with high temperature and humidity (Hossny, 2019). A study showed that around 84% of children with allergic eczema are sensitive to house dust mites (Klossek, 2012).

A national survey in the United States puts the overall cost of food allergies around $24.8 billion per year and direct costs reached US$11.5 billion (Gupta, 2013, Cox, 2015). The best treatment for these people is an elimination diet but the effectiveness is affected by exposure to allergens (Ebisawa, 2017). Studies showed that clinical symptoms of AD may improve after the avoidance of house dust mites but needs more evaluation (Escarrer, 2002, Siregar, 2016). Therefore, the purpose of this study was to determine the effect of house dust allergy on reducing allergy symptoms in children undergoing the elimination of allergenic foods according to the type of food allergy they suffer.

METHODS
Study design and population
This study is an observational analytic study with a retrospective cohort design followed by a prospective cohort in children with food allergies without house dust allergy and with house dust allergy. We conducted this study in Surabaya by taking secondary data from the allergy outpatient clinic – pediatric immunology and the practice of pediatric allergy consultant pediatrician in Surabaya. This study used data of food allergy children with or without house dust allergies who undergo allergenic food elimination. It was in the medical record at Dr. Soetomo Hospital Surabaya and the practice of allergy consultant pediatrician in Surabaya. They must fulfill the selection criteria (inclusion and exclusion) to participate. The diagnosis of food allergy is made based on a typical history of allergic symptoms and a positive skin prick test result for house dust mite allergens (Bousquet et al., 2008).

Data collection
We collected data from December 2020 until March 2021. The data source used secondary data from the medical records of the pediatric allergy-immunology outpatient clinic at RSUD dr. Soetomo and his pediatric allergy consultant practice in Surabaya from January 1, 2019, to March 30, 2021. We followed up all participants every three months. We took data on symptoms, treatment, combination score, and treatment. The patient's symptoms were scored as 0 if there were no symptoms, one if mild symptoms, two if moderate symptoms, and three if severe symptoms. The patient's treatments were scored as zero if they had no treatment, scored as one if they used topical/oral antihistamine, two if they used inhalant corticosteroid (regardless of antihistamine use), and three if used oral corticosteroid (regardless of inhalant corticosteroid or antihistamine use). Meanwhile, the combination score data is the sum of the symptom scores and treatment scores.

Data analysis

The research data will be analyzed using statistical tests using the SPSS device. The baseline characteristics of the research subjects will be presented descriptively in the form of tables listed in the appendix. We used paired T-test comparison analysis if the data distribution was normal or Wilcoxon statistical test if the distribution of the data obtained was abnormal.

Ethical clearance

Health Research Ethics committee of the Regional General Hospital Dr. Soetomo Surabaya approved the implementation of this research with a letter of exemption number Ref. No: 0347/LOE/301.4.2/II/2021.

Confidentiality of research subjects is well maintained by not mentioning their names, but writing by initials.

RESULTS

This study analyzed 146 subjects with complete data and meet the inclusion and exclusion criteria. Subjects were divided into two groups. The first group consisted of food allergy patients with house dust allergy and the second group consisted of food allergy patients without house dust allergy. Both of them had undergone allergenic food elimination. Both groups did not have a significant difference in demographic data (Table 1).

TABLE 1: Characteristic of subjects

Characteristics	Food and dust home allergy (n=98)	Food allergy without dust home allergy (n=48)	*P-value*
Age (years), mean (SD)	6,33 (3,42)	5,9 (3,21)	
Age category (years) n(%)			
1 - <5 (toddler)	34 (34,8%)	20 (41,7%)	0.255
5 – <11 (children)	50 (50,9%)	24 (50,1%)	
11 – 18 (teenager)	14 (14,3%)	4 (8,4%)	
Gender, n (%)			
Male	67 (68,4%)	29 (60,4%)	0.238
Female	31 (31,6%)	19 (39,6%)	
Nutrition status, mean (SD)			
Weight (Kg)	23,3 (9,3)	23,6 (8,41)	0.150
High (cm)	116,4 (21,7)	117,3 (19,2)	0.222
Location, n			
Surabaya	68	37	0.214
Outside Surabaya	30	11	

The majority of patients in the first group had severe symptoms at three months. The number of patients with severe symptoms increased at six months, had no significant change at nine months, and decreased at 12 months. However, the symptom scores change in this group was insignificant over time (p=0.480). At 3 months, the majority of patients in this group had a treatment score of 3. The number of patients with a treatment score of 3 increased at 6 months but decreased at 9 and 12 months (Table 2).

This group experienced a significant change in treatment scores over time (p=0.000).

The majority of patients in the second group had mild symptoms (symptoms score 1). In this group, symptom scores decreased at 9 and 12 months (p = 0.000). The majority of patients in the second group were taking oral/topical antihistamine therapy at 6 months. The treatment scores in this group continued to decline significantly at 9 and 12 months (p = 0.000) (Table 2).

TABLE 2: Score progression between group

	Food and dust home allergy					Food allergy without dust home allergy				
	3 months	6 months	9 months	12 months	p-value	3 months	6 months	9 months	12 months	p-value
Symptoms score										
0	0	0	0	0	0,480	0	0	25	30	0,000
1	0	0	0	10		26	30	17	15	
2	43	28	28	38		16	18	6	3	
3	55	70	70	50		6	0	0	0	
Treatment score										
0	0	0	0	0	0,000	0	0	26	35	0,000
1	0	0	0	13		35	38	16	10	
2	40	30	33	37		13	10	6	3	
3	58	68	65	48		0	0	0	0	

Comparative analysis between groups showed that the first and second groups did not have a significant difference in symptom scores at 3 months (p=0.096) but had significant differences in symptom scores at 6, 9, and 12 months (p<0,05). Although the two groups had no difference in symptom scores, both groups had a significant difference in treatment scores at month 3 (p=0.000). That still occurred until the 12th month (p=0.000) (Table 3).

This difference in treatment scores also resulted in significant differences in treatment costs between groups at 3, 6, 9, and 12 months (p<0.05) (Table 4).

TABLE 3: Score comparison between group

	Symptom score					Treatment score				
	0	**1**	**2**	**3**	**p-value**	**0**	**1**	**2**	**3**	**p-value**
3 months										
With dust home allergy	0	0	43	55	0,096	0	0	40	58	0,000
Without dust home allergy	0	26	16	6		0	35	13	0	
6 months										
With dust home allergy	0	0	28	70	0,000	0	0	30	68	0,000
Without dust home allergy	0	30	18	0		0	38	10	0	
9 months										
With dust home allergy	0	0	28	70	0,017	0	0	33	65	0,023
Without dust home allergy	25	17	6	0		26	16	6	0	
12 months										
With dust home allergy	0	10	38	50	0,000	0	13	37	48	0,000
Without dust home allergy	30	15	3	0		35	10	3	0	

TABLE 4: Treatment cost between groups

Months	Food and dust home allergy Mean (SD)	Food allergy without dust home allergy Mean (SD)	p-value
3	357.448,9 (190.074,92)	171.875 (65.967,63)	0.000
6	363.869,2 (197.493,9)	163.758 (61.749,3)	0.024
9	363.869,2 (197.493,9)	162.692 (60.096,9)	0.000
12	324.765,3 (184.177,9)	154.687,5 (59.370,9)	0.000

DISCUSSION

The results of sensitization tests to one or more common allergens in 2016 among schoolchildren approached 40%-50% worldwide. (Judarwanto, 2016). Epidemiological studies show a global increase in the prevalence of food allergies worldwide (De Martinis, 2020). Around 5,9% of patients in Europe and 10,6% or 7,8 million children in Jakarta reported having food allergies (Tanukusumah, 2016, Judarwanto, 2016). A study in the University of Indonesia showed that children under 12 years old with pollution and dust allergies has quadrupled in the last 20 years (2% in 1980 to 8% in 2000) (Quamila, 2017).

D. pteronisynus patch test results were positive in 34% of AD patients aged 2-10 years. At the age of < 2 years, sensitization to food allergens is more frequent, while aeroallergens and food are at the age of 2-10 years, while at the age of > 10 years, aeroallergens are more common (Escarrer, 2002). A Study of children aged 5-14 years in Germany reported a significant relationship between the severity of eczema scores with specific IgE concentrations of house dust mites and cat dander debris. (Gur Cetinkaya & Sahiner, 2019).

Follow-up of the symptom score showed that the majority of patients in the first group had severe symptoms. Around 56% patients in this group had symptom score 3 (n=55) (p=0.480).

House dust mites are the primary aeroallergens that induce allergic manifestations (Calderón, 2015). Food sensitization and aeroallergens (dust mites, animal dander) are substantial in atopic pathogenesis. It also causes problems for parents and doctors (Siregar, 2016). Food allergy has always been considered the most common trigger factor for anaphylaxis in children. It can co-occur with other atopic diseases such as atopic dermatitis (AD), allergic rhinitis, asthma, and exacerbate allergic symptoms (Popescu, 2015, Utsch et al., 2017). , Hossny, 2019).

Allergens are divided into inhalant, ingested, injectant, and contact allergens. Aeroallergen (inhalant allergen) is the primary in-house allergen in the tropic area such as Indonesia. This aeroallergen mainly contains Dermatophagoides pteronyssinus and Dermatophagoides farinae (Siregar, 2016). Both are often found on home furnishings such as mattresses, sofas, and carpets (Yang and Zhu, 2017).

Inhaled allergens are divided into indoor and outdoor aeroallergens. Both of these aeroallergens are found in many bedrooms, especially in mattresses, pillows, feather blankets, fur rugs, furry children's toys, and curtains. Others that may act as aeroallergen are Candida albicans, cockroaches also skin flakes from pets of cats, dogs, rabbits, and birds. In Singapore, Blomia tropicalis is a widely available aeroallergen in the home (Gur Cetinkaya & Sahiner, 2019). Symptoms in the respiratory tract due to food allergies classify as acute or chronic symptoms. IgE plays a role in acute symptoms. The mixture of IgE and cellular mechanisms play a role in chronic symptoms. It is not easy to identify the occurrence of food-induced allergic rhinitis, because it often appears together with other food allergy symptoms such as asthma, eczema, oral allergy syndromes, urticaria, and gastrointestinal symptoms. People with allergic rhinitis may experience a variety of signs and symptoms such as sneezing, rhinorrhea, nasal congestion, and an itchy nose. Postnasal drip and sometimes cough are other common symptoms. Some sufferers also experience itching in the eyes, throat, palate, and inner ear (deShazo & Kemp, 2020).

Then in the 6th month, the symptom score increased with severe symptoms as many as 70 patients. At 9 months, the symptom score did not change or constant. In contrast to the group of food-allergic children without house dust allergy who had also undergone food elimination at the 3rd month (n=26) and 6th month (n=30), the majority had mild symptoms or a score of 1.

TDR proteases are involved in various immune mechanisms such as destroying the epithelial barrier defense, Th2 cell proliferation, increasing IgE production, and decreasing lung clearance function (Reithofer, 2017). Theoretically, food allergies are more avoidable than inhalant allergies, because, in the modern era, it is almost impossible to avoid all inhalant allergens (Sicherer, 2018). Oral mite anaphylaxis (OMA) had occurred in tropical and subtropical Asia. Both areas had high temperatures and humidity. Mites-contaminated flour often causes OMA (Hossny, 2019).

Food allergies can co-occur with other atopic diseases include allergic rhinitis and asthma via airway inhalation. It shows that aeroallergen cause IgE sensitization in the respiratory tract and food component induce cross-reactivity. In adults, about 80% of cases of food allergy are preceded by sensitization to aeroallergens. In children, around 25% of cases of food allergy also experience this cross-reaction. Dust mites are the primary in-house allergens. The component of the allergen that most often causes cross-reactivity is tropomyosin (Popescu, 2015). Tropomyosin is an allergen that can be found everywhere, including in shellfish, dust mites (Der p 10), and cockroaches. And there is often cross-reactivity between these allergens because of the homologous amino acid structure even in different species. Shrimp-IgE sensitization can occur due to cross-reaction with other invertebrates-allergen, especially tropomyosin (Farioli, 2017). Patients with shrimp allergy had a high level of IgE against der p 1 and der p 10. The concomitant presence of asthma induced by house dust mites and IgE anti der p1 and der p2 increases the risk of shrimp allergy (Hossny, 2019). Apart from going through the digestive tract, seafood protein can also enter the body through the inhalation of aerosols containing allergens (Rahman, 2012). Wong et al. conducted a study in Asia. They concluded that tropomyosin from mites was the primary sensitizer for shellfish allergy. The incidence is quite high in Asia because Asia has high humidity (Shroba, 2019).

In the Allergic March, eczema due to food allergies preceded the onset of asthma in later life. It shows that children with allergic eczema and positive skin tests with Dermatophagoides pterenosynnus would develop severe asthma compared to children without eczema. (Escarrer, 2002, Cosickic, 2017). Around 84% of children with allergic eczema are sensitive to house dust mite, evidenced by the results of a skin patch test with house dust mite extract on skin with eczema (Klossek, 2012).

Asthma, allergic rhinitis, and atopic dermatitis have an abnormal basis of IgE response hypersensitivity and tissue-specific inflammation characterized by local infiltration of memory T lymphocytes, eosinophils, and monocytes/macrophages. T lymphocyte infiltration will be seen with the expression of IL-4, IL-5, and IL-13 in the tissues experiencing acute inflammation. These cytokines play a major role in allergic responses. House dust mite particles may induce anaphylaxis through contaminated food (Yu, 2014). Among the 95 patients with shrimp allergy, 90.5% had a positive skin test for house dust mites (Rosenfield, 2017). The presence of asthma induced by house dust mites and positive IgE anti Der p 1,2 and 10 simultaneously increases the risk of shrimp allergy (Farioli, 2017).

Another study states that 84% of children with atopic dermatitis are sensitive to house dust mites as evidenced by the results of skin patch tests with house dust mite extract on skin with eczema (Klossek, 2012). Inhaled allergens (house dust mites and animal dander) are significantly associated with the severity of atopic dermatitis (Celakovska, 2017).

The last evaluation at 12 months revealed a decrease in symptoms. Although most patients still had severe symptoms scores (50 patients), patients with moderate symptoms increased by 38 persons. In this group, the majority of patients received house dust immunotherapy and education about house dust avoidance and continued to undergo an allergenic food elimination diet. Meanwhile, in the group of food allergy children without house dust allergy who had undergone an allergenic food elimination diet at the 9th and 12th months, 26 patients had no symptoms.

Determination of allergy trigger factors and their avoidance is one of the important factors in the success of allergy treatment. The role of various precipitating factors such as airborne allergens or food allergens has been proven in various studies (Zakiudin, 2002).

A definite diagnosis of food allergy can only be confirmed by the Double-Blind Placebo Control Food Challenge (DBPCFC) or by eliminating food provocations. The best treatment for people with food allergies is to avoid the food causing it (elimination diet). The emergence of allergy symptoms is not only influenced by the cause of the allergy (allergen) but is also influenced by the trigger of the allergy (Judarwanto, 2011, Ebisawa, 2017). Specific therapy for food hypersensitivity is certain to avoid the cause (elimination diet) (Judarwanto, 2011).

A study conducted by Hankin et al. in 2013 found that there was a significant decrease in the average frequency of outpatient, inpatient, and treatment in allergic rhinitis children who received immunotherapy and those who did not. Averages and total cost of overall treatment (immunotherapy and other therapy) in allergic rhinitis children for 18 months decreased significantly.

Food allergy patients with dust allergy had higher medical costs when compared to the food allergy group without house dust allergy who had undergone allergenic food elimination.

Food allergies in children have an impact on the family's economy and health costs. Direct costs incurred to treat the disease (doctor, hospital fees, laboratory test, and pharmacological therapy) and transportation. Indirect costs include non-health costs related to illness, such as the cost of not attending school and work and decreased productivity due to illness. Other indirect costs include the time spent by both the patient and the person caring for the patient during illness (Blaiss, 2010).

A national survey of parents of children with food allergies in the United States puts the overall cost of food allergies at an estimated $24.8 billion per year (95% CI, $20.6 - $29.4) (Gupta, 2013). A survey in the United States (USA) estimated that the direct costs of allergic colds due to dust mites reached US$11.5 billion, of which 59% came from prescription treatments (Cox, 2015.) Treatment costs contributed the most (46%) to the total direct costs (Ngamphaiboon et al., 2012).

Allergic rhinitis accounts for 2.5% of all doctor visits, 2 million lost school days, 6 million lost workdays, and 28 million restricted workdays per year (deShazo & Kemp, 2020).

Asthma incidence and prevalence are increasing in some countries. The average cost per patient per year of all asthmatic patients (intermittent, mild, moderate, and severe asthma) in Europe is $USD 1,900 and $USD 3,100 in the USA(Nunes, 2017). The cost of treating atopic dermatitis reaches $ 576-$ 1,097 per year (Bhanegaonkar, 2014).

The Kruskal-Wallis test SPSS software showed that the asymp sig is 0.000 and <0.05, so the hypothesis of this study can be accepted. It means that house dust allergy influences the effectiveness of allergenic food elimination, treatment, and costs.

Theoretically, food allergies are more avoidable than inhalant allergies, because, in the modern era, it is almost impossible to avoid all inhalant allergens(Sicherer, 2018). Many factors play a role, both exogenous or endogenous factors or a combination of both. Genetic factors are endogenous factors. Exogenous factors such as food and aeroallergens may trigger AD, allergic rhinitis, and asthma. There is still disagreement about food as a cause of allergy reaction but allergy symptoms may improve if they avoid allergenic food. Inhaled allergens (such as house dust mites) play a role in the pathogenesis of AD, especially in children. It is based on several clinical observations, skin tests, and high specific IgE. There is an improvement in clinical symptoms of AD after the avoidance of house dust mites (Escarrer, 2002, Siregar, 2016).

The etiology and pathogenesis of this disease is a complex interaction between genetic susceptibility. This complex interaction results in skin barrier defect, innate immune system defect, and enhanced immunologic responses to allergens and microbial antigens. Genetic factors have an important role, but environmental factors also play a role. (Leung, 2012).a

Allergens classify into inhalant, ingestion, parenteral, and contact allergens. Allergens in the air (inhalants) can come from inside and outside the home. Some examples of allergic symptoms are allergic rhinitis, bronchial asthma, and atopic dermatitis (Baratawijaya, 2009). Avoidance of airborne allergens that trigger atopic dermatitis may control atopic dermatitis symptoms. By clearing the mites from the patient's environment, it can improve clinical symptoms without other treatment. If the patient returns, the disease will exacerbate within 1-2 days.

Dust mites can cause airway inflammation that is influenced by dendritic cells. They act as professional antigen-presenting cells and play an important role in the allergy sensitization phase of this airway inflammation. After desquamation of the epithelial cells and disruption of the tight junctions by the TDR, dendritic cells (DCs) can identify and process antigens. And present these antigens to major histocompatibility complex class II molecules to naive T lymphocytes in local lymph nodes. This shift causes a cascade of T helper 2 (Th2) and causes an inflammatory response by cytokine mediators (Yu, 2014). Several important components of dust mites such as Der p 1, a cysteine protease, can bind specific IgE on basophils and mast cells and can have highly potent proteolytic activity on the epithelium, resulting in a range of specific and nonspecific responses. Der p2 and its specific IgE are highly correlated with allergic hypersensitivity in patients with asthma, atopic dermatitis, and allergic rhinitis. Der p3 can induce cytokine release from human lung epithelial cells (Vogel, 2015). OAS (oral allergy syndrome) or PFAS (pollen food allergy syndrome) are symptoms of allergies to some foods in patients who have allergies to aeroallergens (pollen, dust, etc). The most common symptom is oral-pharyngeal pruritus.

Other symptoms include tightness in the throat, difficulty swallowing, nausea, dysphonia, an itchy nose, and itchy ears. In addition, there is a relationship between early allergen sensitization and cross-reactivity (Carlson, 2019). The proteolytic activity of house dust mite allergen (TDR) affects various innate immune response pathways, increasing the severity and chronicity of the allergic disease. TDR bioactivity is a potential therapeutic target and has been clinically developed as immunotherapy (Thomas, 2015). Studies have reported that indoor house dust mite levels are associated with the severity of skin lesions. The mite's bio-reactive molecules consist of proteins and endotoxins derived from the body and feces. Various extracts from house dust mites have been used for diagnostic tests, immunotherapy, and induction of atrophic dermatrophy-like lesions in mice (Zhang, 2017; Moore, Morris-Jones, and Nabarro, 2020).

CONCLUSIONS

Symptom scores, treatment scores, and medication costs decreased in children without house dust allergy, increased in those with house dust allergy who underwent food allergenic elimination at 3, 6, 9, and 12 months after treatment. So both have significant symptom scores, treatment scores and treatment costs different.

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