ORIGINAL ARTICLE

Association of Vitamin D Levels and Other Risk Factors with Asthma Exacerbations in Children

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ABSTRACT

Background: The risk factors for asthma exacerbations are well understood. However, the effect of vitamin D levels on number of asthma exacerbations per year is not clearly studied. The objective of the study was to find out the association of serum vitamin D levels and asthma risk factors on asthma exacerbations.

Methods: In this study, ninety-nine subjects from 5 to 15 years of age were recruited at an episode of acute exacerbation. It was a cross sectional study and carried out from 2012 to 2015. Pulmonary function test was done by spirometry. Asthma exacerbation was labeled when forced expiratory volume/ forced vital capacity (FEV1/FVC) ratio was less than 80% (American Thoracic Society). Global Initiative for Asthma (GINA) guidelines were used to classify asthma into mild, moderate and severe persistent asthma. Serum vitamin D levels were measured by chemiluminescence method. Pearson Chi-square test was applied and p value (p<0.05) was considered as statistically significant.

Results: Children who had exposure to animal dander had significantly lower asthma exacerbations per year (p-value <0.046). There was no significant association between vitamin D levels and number of exacerbations per years (p-value <0.099). Asthma was prevalent in girls of low socioeconomic status (SES) compared to males. However, there was no significant association between smoke, exercise, home environment, food allergies, weather, pollen and dust with asthma exacerbations.

Conclusion: Low levels of vitamin D were not associated with increased number of asthma exacerbations per year. However, children exposed to animal dander had lesser number of exacerbations per year (p-value <0.046).

Keywords: Asthma; Vitamin D; Children; Exacerbations, Risk factors.

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INTRODUCTION

Asthma was classically defined by Global Initiative for Asthma (GINA) in 2016 as a heterogenic disease with characteristic chronic airway inflammation and a history of specific respiratory tract symptoms such as wheeze, shortness of breath, chest tightness, and cough along with a variable expiratory airflow limitation[1]. According to the Centers for Disease Control and Prevention (CDC), asthma is more prevalent in children compared to adults[2]. In the young age group, it has been found that the prevalence has risen continuously over the previous decades by more than double since the 1980s[3], reaching epidemic proportions. With the rise of urbanization in the developing countries, these numbers are likely to raise further[4]. This disease is thus a major public health issue leading to multiple admissions, high numbers of missed days at schools and work, causing early permanent disability and early death and monetary or emotional toll on society. The economic impact has been estimated

to vary from $1900-$3100 per patient per year[5]. In Pakistan, the burden of disease for bronchial asthma is estimated to be 5% of the total population with severely affected people in the 13 to 14 years age group[6].

Vitamin D deficiency (VDD) is another condition, now being recognized as a disease, and the increasing prevalence of which is now being labeled as a pandemic[7]. In Europe, the numbers of VDD adults has reached 40.4 percent[8,9]. Whereas, studies of the Pakistani population show that VDD in 53.5%, while vitamin D insufficiency (VDI) exists in 31.2% of people[10]. Regarding children, age 3 to 13 years, in the Pakistani population, prevalence of VDD according to two studies is 63.4% and 70% respectively[11,12].

The role of vitamin D in asthma exacerbations remains unclear. It has been suggested that normal vitamin D levels lead to proper pulmonary maturation in fetal life and down-regulation of atopy[13]. It has also been found via prospective follow up and vitamin D level monitoring in early childhood that deficiency of this vitamin is linked to an elevated risk for persistent asthma and its exacerbations[14,15]. However, there are contradictory researches that show no benefits associated with normal vitamin D levels or its supplementation on asthma exacerbations but instead they show that vitamin D supplementation might cause harm[16-19]. The objective of the study was to find the association of serum vitamin D levels and asthma risk factors on asthma exacerbations.

METHODS

A total of 99 asthmatic children between the ages of 5-15 years were part of the study. Informed consent was obtained; procedure, instruments and their role, and the purpose of the study were explained. The study was approved by Ethics Committee of Ziauddin University (reference number. 0260312ZABIOC). It was a cross sectional study and was carried out over three years from 2012 to 2015. Convenience sampling was done. A detailed history was recorded and proforma was filled. Anthropometric measurements were also recorded along with a comprehensive physical examination. The subject was asked to perform the test once before the actual recording to ensure it is performed satisfactorily. A FEV1/FEC ratio of <80% was used to confirm the diagnosis of acute asthma exacerbation. Blood (6ml) was drawn into a tube and after centrifugation, 500µl of serum was sent to the Ziauddin Laboratory for vitamin D level testing, while the remaining was stored at -80^{0}C. The serum vitamin D levels were measured by chemiluminescence using Abbott's ARCHITECT clinical chemistry analyzer. The level of vitamin D ≤20 ng/mL (50 nmol/L) was labeled as vitamin D deficiency, between 20-29 ng/mL(50 to 74 nmol/L) was labeled as vitamin D insufficiency whereas, vitamin D and levels of vitamin D ≥ 30 ng/ml to 100 ng/ml (75 nmol/L to 250 nmol/L) was labeled as normal.

We excluded children having moderate and severe asthma. In moderate asthma child has daily symptoms with 3-4 times awakening per month and uses short acting beta-2 agonists daily. In severe asthma, symptoms are throughout the day with nighttime awakening more than once per week. Children having major cardiovascular, hepatic, renal or respiratory diseases were also excluded. Besides some children who were unable, to perform spirometry were excluded too. The analysis was done on SPSS version 20. Frequencies were estimated for quantitative data. The mean and standard deviation was determined on quantitative data. The Pearson Chi-square test was applied and $p<0.05$ was considered statistically significant.

RESULTS

The mean age of the research participants was 8.31±2.62. In addition, parents' education level (Table 1) noted that (n=49) 49.50% of the mothers were uneducated. 14.14% (n=14) mothers had done their graduation followed by middle 13.13% (n=13), Matric 10.10% (n=10), Primary (n=8) 8.08%, Intermediate 3.03% (n=3), Masters 2.02% (n=2). In father's education it was seen that 47.48% (n=47) of the fathers were uneducated. 17.17% (n=17) of the father had completed Middle followed by Graduates 13.13% (n=13), Primary 9.09% (n=9), Matric 7.07% (n=7), Masters 4.04% (n=4), Intermediate 2.02% (n=2).

Table 1: Frequency of parental education level of asthmatic children.

Parents of asthmatic children n(%)	Education						
	Masters	Graduate	Intermediate	Matric	Middle	Primary	Not Educated
Mother 99(100)	2 (2.02%)	14 (14.14%)	3 (3.03%)	10 (10%)	13 (13%)	8 (8.08%)	49 (49.40%)
Father 99(100)	4 (4.04 %)	13 (13.13 %)	2 (2.02 %)	7 (7.1%)	17 (17. 2%)	9 (9.09 %)	47 (47.48 %)

The socioeconomic status (Figure 1A) revealed 58.60% (n=59) of the subjects belong to poor or low socioeconomic status followed by middle 27.30% (n=27) and high socioeconomic status 14.10% (n=14). Furthermore, among 99 subjects (Figure 1B) 60.60% (n=60) were males and 39.40% (n=39) females with the ratio (M: F = 1: 0.65).

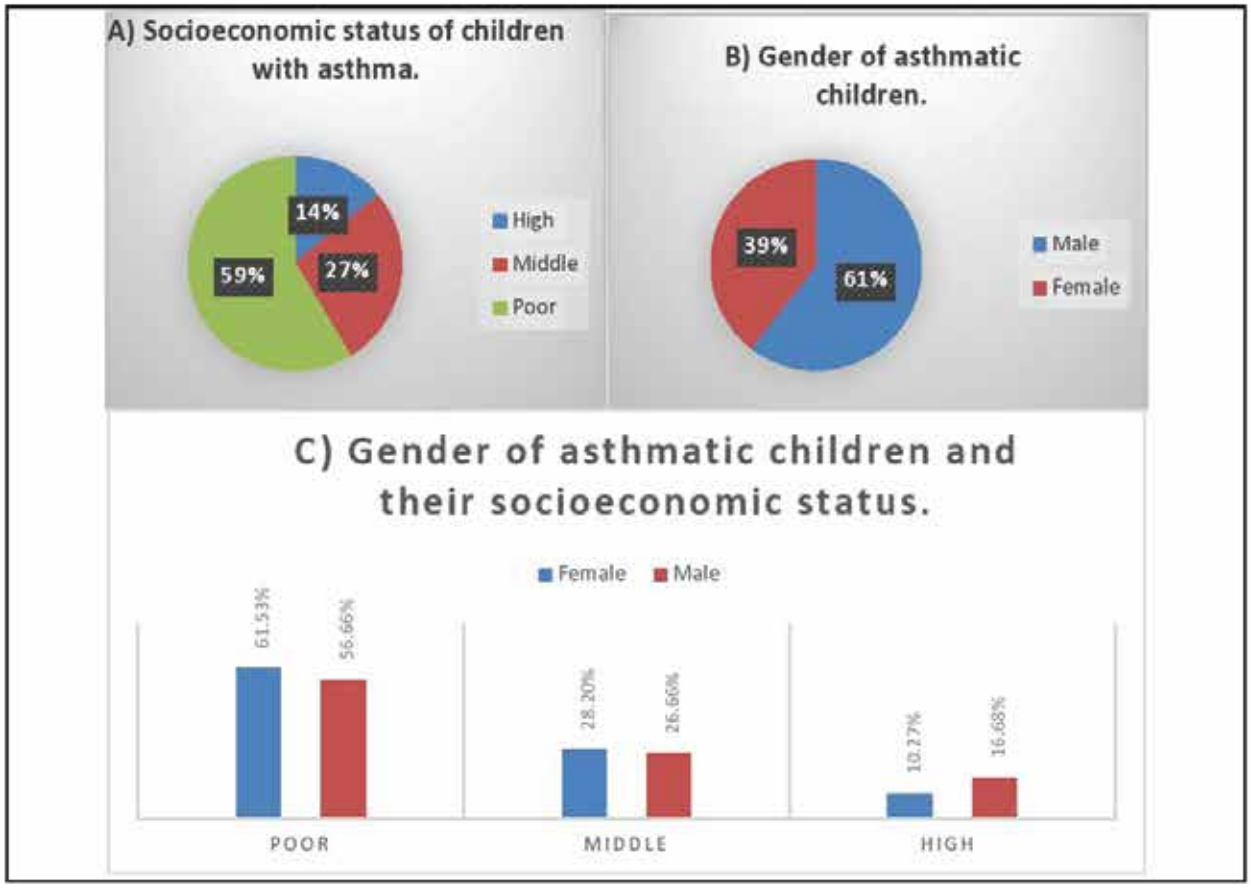

Figure 1: A) Socioeconomic status of children with asthma. B) Gender of asthmatic children. C) Gender of asthmatic children and their socioeconomic status.

Gender of asthmatic children (Figure 1C) was compared to their socioeconomic status. It was seen that majority of the females (61.53%) belonged to poor SES as compared to males (56.66%). Thus, 28.20% of females belonged to middle SES as opposed to 26.66% of males, whereas 0.27% of females and 16.68 % of males belonged to high SE status.

The study showed the association of risk factors (Table 2) of asthma with exacerbations. It was seen that 46.40% (n=26) of the children had more than six exacerbations per year when they did exercise. Similarly, 51.10% (n=24) had more than six exacerbations when they were exposed to pollens. It was seen that 43 % (n=37) children had more than six exacerbations per year when they were exposed to weather changes. 42.90% (n=24) children had more than 6 exacerbations when they were exposed to smoke. It was seen that 46.60% (n=41) had more than six exacerbations per year when associated with allergy to dust. However, this association was not significant. It was noted that 23.50% (n= 4) children allergic to animal dander had more than six exacerbations per year (*p*-value <0.046) showing significant association. Since, 52.90% (n=18) had more than six exacerbations per year when exposed to different smells. It was noted that 45.10% (n=23) who had viral infections of respiratory tract had more than six exacerbations per year.

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Table 2: Association of risk factors of asthma with exacerbations.

Risk Factor	Up to 6 exacerbations per year n(%) 54	More than 6 exacerbations per year n(%) 55	*p*-Value
Exercise	30(53.60%)	26(46.40%)	0.824
Exposure to insects	1(50.00%)	1(50.00%)	0.896
Home environm ent	5(71.40%)	2(28.60%)	0.352
Allergy to pollens	23(48.90%)	24(51.10%)	0.287
Allergy to animal dander	13(76.50%)	4(23.50%)	0.046

However, there was no significant association of vitamin D levels (Table 3) with exacerbations per year (*p*- value=0.099).

Table 3: Association of vitamin D levels with number of exacerbations per year.

Exacerbations	Vitamin D Groups			*p*-Value
	Deficient (≤20 ng/mL) n(%)	Insufficient (20–29 ng/mL) n(%)	Normal (≥ 30 ng/ml to 100 ng/ml) n(%)	
Up to 6 Exacerbations/year	42(77.80%)	8(14.80%)	4(7.40%)	0.099
6 and above Exacerbations/year	42(93.30%)	2(4.40%)	1(2.20%)	

DISSCUSSION

In our study, we found that exposure to animal dander resulted in less number of asthma exacerbations. This was supported by a review article that concluded if infants are exposed to furry animals they tend to have less allergies and asthma. According to them this protective effect could be because of exposure to diverse microbes[20]. Similar findings were reported by another study done in Sweden that followed a birth cohort of 1029 children. It was seen that the allergies were reduced with increasing number of pets like cats and dogs[21]. This could be because although very few people kept cats or dogs as pets in their houses, however, they were exposed to stray dogs and cats, which are in abundance not only in our city but as well as in our country.

The current study did not find any association of asthma exacerbation with vitamin D levels. This is supported by another similar study on 148 children age 7 to 17 years. They did not find any association of vitamin D levels with pulmonary function test [22]. However, there are studies that suggest an association of vitamin D levels with asthma exacerbation[23,24]. We found that 60.6% (n= 60) were males and 39.4% (n= 39) females. Female to male ratio was (M: F = 1: 0.65) showing male predominance. This is very similar to studies conducted in Karachi and south Punjab where asthma prevalence in boys was 56% as compared to girls 44% in the latter study[25,26]. This finding was attributed to the difference in sex hormones between males and females in a study on animal model[27].

The prevalence of asthma was more in girls belonging to low socioeconomic class than the middle and upper class (61.53% vs. 28.20% and 10.27%). This finding was also supported by cohort study in Western Australia. They found that asthma risk was increased two folds especially in girls who had lived in a low socioeconomic family[28]. The exact reason for this disparity could not be clarified by the existing knowledge and needs further probing. In our study, almost 50% of the parents were uneducated, and compulsory education level was 8.08% for mothers and 9.09% for fathers. This is comparable to a study by Bröms et al. 2013 where education level was divided into nine-year of compulsory education, two-year upper secondary education, a three to four-year upper secondary education or university or any other tertiary education. Their prevalence for

compulsory education was 5%, suggesting a little higher education level in our study as compared to them[29]. This could be because educational awareness among the people has started rising and government and NGO driven schools have made it easier for people to find the means to educate. This difference could also be because in Pakistan anyone who can write his name is considered a literate. Secondly, people used to hesitate to disclose the actual status of their education level. However, this issue needs further probing.

The association of exercise with asthma exacerbations was insignificant in our study. This is in line with another study conducted on 195 children having asthma. Although 43% of their children had, exercise-induced wheeze, but they did not find any association between exercise-induced wheeze and lung functions in multivariable models. In fact, their result showed the asthmatics that exercised regularly had less asthma symptoms like wheeze and shortness of breath, and asthma symptom score was reduced by -0.45 points/hour of exercise when Poisson regression model was applied (95% CI: -0.72 - -0.17)[30]. The children in our study did not exercised sufficiently. Majority of them were not given sufficient time to play at schools because the schools did not have proper playgrounds or the time allocated for break / physical training was very limited (< 30 min). In addition, their schedule at home, like going to tuitions, finishing homework and religious education did not allow them to play. Similar findings were seen in other more recent studies[31].

There were no significant associations of asthma exacerbations with exposure to insects like cockroaches, dust mites, etc. However, there are studies that suggest the role of allergens like insects (including but not limited to cockroaches and dust mites) in allergic diseases including asthma. One such study related the role of sensitization to Blomia and other aeroallergens to asthma and rhinitis in 1713 children in French Caribbean Island (Guadeloupe). They found a significant association between the house dust mites, pollens and cockroaches with children who had both asthma and rhinitis[32]. However, contradictory results were also reported. Raj et al. studied the relationship between prevalence of sensitization of common aeroallergens in asthmatic children in a prospective cohort study of asthmatic children between age group 5 to 18 years. The allergens included cockroaches and house dust mites. They did not find any association between allergens like cockroach and common dust mites[33]. This aspect needs to be further investigated.

The current study did not find any association between the pollens and asthma exacerbation. This was supported by other studies where tree pollen counts and the visit to emergency department due to asthma were recorded in a high-density urban center in pediatric and adult asthmatics. They did not find any association between asthma in fall season and pollen counts despite the fact the pollen counts for different plants are different for the four seasons, and their count is high in the fall season[34]. Other studies estimating the pollen counts and correlating them with allergic diseases like asthma are few in Pakistan. One such study showed association between asthma and the pollens of Conocarpus species[35]. Similar findings were reported in another study[36]. These results contrast with our study. In addition, in this study we included asthmatic children who had two or more exacerbations per year diagnosed by the pediatrician[37]. We did not correlate these levels with the actual pollen count and type, and it was determined by the question if the child had allergies to pollen season. This could be subject to recall bias as well as lack of awareness regarding allergies to pollen on behalf of both parents as well as children.

CONCLUSION

The low levels of vitamin D were not associated with increased number of asthma exacerbations per year. Children who had exposure to animal dander had a lesser number of exacerbations per year than who were not exposed. In addition, we found that majority of our female children were low socioeconomic status.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ETHICS APPROVAL

Ziauddin University Ethical Review committee reference number: 0260312ZABIOC approved the research.

PATIENT CONSENT

Patient consent was obtained before sample collection.

AUTHORS' CONTRIBUTION

This work was done by collaboration between all authors. SZA, AJ and KH were involved in the conception of the idea, study design, first draft of the manuscript, literature research, analysis of the study, sample collection, experimental process, and statistical analysis. SSN was also involved in literature search and drafting of the manuscript.

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