# Folic acid Deficiency and Bronchial Asthma Exacerbations in Children

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## ABSTRACT

**Background**: Little is known about folate and asthma exacerbations. We examined whether folate deficiency is associated with asthma exacerbations in Children. **Aim of the work:** was to assess association of folate deficiency with increased asthma exacerbations in children. **Subjects and methods:** The study carried out on fifty children known to have a history of bronchial asthma aged from 6–15 years. All subjects were subjected to thorough medical history, full clinical examination, laboratory investigations including pulmonary function tests (spirometry) and serum folic acid levels. **Results**: this study showed Percentage of asthma in males more than in females. Viral infection, exercise, exposure to cold and fumes are the commonest precipitating factors. Analysis of Forced Expiratory Volume in the first second (FEV1) showed that 30% of cases had a level above 80% (mild impairment), 54% had a level between 60 and 80% (moderate) and 16% had a level below 60% (severe). Serum level of folic acid was lowest in the severe group (1.2±0.1), followed by the moderate (2.4±0.3) then the mild group (3.4±0.4), with a significant difference when all the groups were compared with each other ($p < 0.001$).There were significant, positive strong correlations between folic acid level and each of FEV1% and FEV1/FVC%. Serum folic acid level contributed significantly to the degree of asthma severity, when adjusted for the other variables and indicated that increase in asthma severity with associated with each decrease in folic acid level. **Conclusions**: It could be concluded that folate deficiency is associated with increased degree of severe asthma exacerbations in children.

**Keywords**: Asthma; children; folate.

## INTRODUCTION

Asthma is a chronic inflammatory disease common in the airways characterized by the obstruction of the airway variable, and excessive excretion of airway inflammation and excessive inflammation in the airway [(1)].

The prevalence of asthma and allergic conditions is increasing worldwide and has coincided with the rapid and ongoing increase in the percentage of the population residing in urban areas, The higher prevalence of asthma and allergic conditions in urban areas compared to the rural areas suggests that urban-related environmental factors may contribute to the pathogenesis of these conditions [(2)]. In susceptible individuals, airway inflammation may cause recurrent or persistent bronchospasm which causes symptoms, such as wheezing, shortness of breath, chest tightness, and cough, particularly at night [(3)].

Changes in dietary habits or supplementation of nutrients may partly explain the current burden of asthma in industrialized countries [(4)].

Folate, a cofactor in the transfer of one-carbon moieties, aids in the formation of S-adenosylmethionine, a key molecule in DNA methylation. Because DNA methylation can affect gene expression, there has been considerable interest in the role of folate in the pathogenesis of asthma [(5)].

Even though multiple studies have examined the relationship between prenatal use of folate and new-onset asthma, very few studies have examined whether folate status is associated with disease morbidity or disease severity in subjects with established asthma [(6)].

High dietary intake of vegetables (a source of folate) is associated with 11% reduced risk of wheeze in children, Moreover, folate deficiency or a low folate level has been associated with increased risks of wheeze in children [(7)].

Brehm et al hypothesized that Folate deficiency is significantly associated with severe asthma exacerbations in children with asthma [(8)].

The aim of the current study was to assess association of folate deficiency with increased asthma exacerbations in children.

## PATIENTS AND METHODS

This case study included a total of fifty children aged 6–15 years known to have a history of bronchial asthma diagnosed according to Global Initiative for Asthma (2018-GINA) [(1)], attending at outpatient clinic of Al-Azhar University and Kotor General Hospitals. **Approval of the ethical committee and a written informed consent from all the subjects were obtained.** This study was conducted between April 2018 to March 2019.

The studied children were sub-classified according to severity in three group (mild, moderate and severe). **Exclusion criteria:** Children who had to be free of respiratory illnesses for 4 or more weeks. Avoid (when possible) the use of inhaled short- and long-acting bronchodilators for at least 12 hours before testing, respectively.

**All children included in the study were subjected to the following:** ***Full history taking:*** **Personal data:** name, age, sex and residence. **Present history:** Age of onset of the disease. Symptoms including wheezes, shortness of breath, cough and sputum production. Atopic manifestations other than asthma (urticaria,



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rhinitis, conjunctivitis). Precipitating factors including respiratory tract infections, passive smoking, food, exercise or others.

**Family history:** of asthma or atopy.

**Complete general examination including:**

- **General examination:** Through anthropometric measurement which include height and weight and then calculation of body mass index (BMI). Vital signs: respiratory rate and heart rate.
- **Systemic examination: Chest**: Inspection, palpation, and auscultation. **Cardiovascular system**: Examination. **Gastrointestinal tract:** Examination.
- **Investigations**
- **Laboratory investigations:** All subjects were subjected to the following: Complete blood count (CBC) by automated cell counter Sysmex K21 [9]**.** Assessment of serum folate level by Enzyme linked Immunosorbent assay (ELISA) method.
- **Pulmonary Function Test:** Pulmonary Function testing was performed using MEDISOFT-HYPERAIR compact+ flowmeter pulmonary function testing device (Medisoft, Sorinnes, Belgium).
- **Spirometric parameters include lung volumes, capacities, and flow rates as:** ***Forced Vital Capacity (FVC):*** Represent the maximal amount of air exhaled irrespective to time**.** ***Forced Expiratory Volume in the first second (FEV1):*** It is the volume of gas expired at the first second of the FVC maneuver (during expiring forcefully and rapidly after maximal inspiration)**.** ***FEV1/FVC:*** The ratio between the forced expiratory volumes in the first second to the forced vital capacity, expressed as a percentage [10]**.**

***Statistical analysis***

Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) program version 22 for Windows.

All numerical data were found to follow normal distribution (tested by Shapiro-Wilk test for normality) and were summarized as mean ± standard deviation. Comparison between the severity groups was achieved using one-way ANOVA test followed by Games-Howell post hoc test (due to violated assumption of homogeneity of variance). Correlation between severity groups and numerical variables was tested using Spearman's rank order correlation. Correlation between other numerical variables and folic acid level was tested using Pearson's correlation.

For qualitative data, they were summarized as frequencies and percentages and Fisher-Freeman-Halton Exact test was used to examine association between two variables.

Ordinal regression was carried out to assess the association between relevant variables and severity of asthma.

***Ordinal regression analysis:*** To predict the probability that an observation falls into one of categories of an ordinal dependent variable based on one or more independent variables that can be either continuous or categorical.

## RESULTS

**Table (1):** Anthropometry and the onset of bronchial asthma of the studied children (total n = 50).

| | **Min – Max** | **Mean ± SD** |
|---|---|---|
| **Age (years)** | 6.0 - 15.0 | 10.3 ± 3.0 |
| **Weight (**kg**)** | 18.0 - 40.0 | 27.5 ± 6.0 |
| **Height (cm)** | 110.0 - 160.0 | 135.1 ± 15.7 |
| **BMI (kg/m$^2$)** | 11.4 - 18.9 | 15.0 ± 1.9 |
| **Onset (years)** | 2.0 – 4.0 | 2.9 ± 0.7 |

**Table (2):** Sex distribution, exposure to smoking and precipitating factors of asthma, history of atopy and asthma severity in the studied children (total n = 50):

| | | **N** | **%** |
|---|---|---|---|
| **Sex** | Female | 15 | 30.0% |
| | Male | 35 | 70.0% |
| **Passive smoking** | No | 16 | 32.0% |
| | Yes | 34 | 68.0% |
| **Precipitating factor** | Cold | 10 | 20.0% |
| | Exercise | 11 | 22.0% |
| | Food | 1 | 2.0% |
| | Fumes | 8 | 16.0% |
| | Viral Infection | 20 | 40.0% |
| **Family history of atopy** | Positive | 27 | 54.0% |
| | Negative | 23 | 46.0% |
| **Family history of asthma** | Positive | 42 | 84.0% |
| | Negative | 8 | 16.0% |

**Table (3):** Folic acid level, FEV1% and FEV1/FVC% in the studied children (total n = 50):

| | Min – Max | Mean ± SD |
|---|---|---|
| **Serum Folic Acid (ng/ml)** | 1.1 - 4.1 | 2.4 ± 0.8 |
| **FEV1%** | 42.0 - 86.0 | 73.6 ± 12.1 |
| **FEV1/FVC%** | 58.0 - 87.0 | 76.1 ± 7.0 |

**Table (4):** Severity of asthma according to FEV1% and FEV1/FVC% in the studied children (total n = 50).

| | | N | % |
|---|---|---|---|
| **FEV1%** | Mild (> 80%) | 15 | 30.0% |
| | Moderate (60 - 80%) | 27 | 54.0% |
| | Severe (< 60%) | 8 | 16.0% |
| **FEV1/FVC%** | Mild (> 80%) | 14 | 28% |
| | Moderate (75 - 80%) | 26 | 52% |
| | Severe (< 75%) | 10 | 20% |

**Table (5):** Comparison between the grades of asthma severity, age, onset of asthma and serum folic acid levels in the studied children (total n = 50).

| | Severity of asthma | | | One-way ANOVA test | |
|---|---|---|---|---|---|
| | Mild (n = 14) | Moderate (n = 26) | Severe (n = 10) | | |
| | Mean ± SD | Mean ± SD | Mean ± SD | F | p |
| **Age (years)** | 10.1 ± 3.5 | 11.0 ± 2.8 | 8.8 ± 2.1 | 2.158 | 0.127 |
| **Onset (years)** | 2.9 ± 0.9 | 2.8 ± 0.6 | 2.9 ± 0.7 | 0.139 | 0.871 |
| **Serum folic acid (ng/ml)** | 3.4 ± 0.4 | 2.4 ± 0.3 | 1.2 ± 0.1 | 25.202[a] | <0.001*<br>P1 <0.001*<br>P2 <0.001*<br>P3 <0.001* |

**Table (2):** Association between the grades of asthma severity and each of precipitating factors, history of asthma and atopy in the studied children (total n = 50).

| | | Severity of asthma | | | | | | Fisher-Freeman-Halton exact test | |
|---|---|---|---|---|---|---|---|---|---|
| | | Mild (n = 14) | | Moderate (n = 26) | | Severe (n = 10) | | | |
| | | N | % | n | % | N | % | $X^2$ | P |
| **Precipitating factor** | Cold | 3 | 21.4% | 4 | 15.4% | 3 | 30.0% | 11.968 | 0.103 |
| | Exercise | 4 | 28.6% | 7 | 26.9% | 0 | 0.0% | | |
| | Food | 1 | 7.1% | 0 | 0.0% | 0 | 0.0% | | |
| | Fumes | 0 | 0.0% | 7 | 26.9% | 1 | 10.0% | | |
| | Viral Infection | 6 | 42.9% | 8 | 30.8% | 6 | 60.0% | | |
| **Family history of atopy** | Negative | 6 | 42.9% | 14 | 53.8% | 3 | 30.0% | 1.693 | 0.419 |
| | Positive | 8 | 57.1% | 12 | 46.2% | 7 | 70.0% | | |
| **Family history of asthma** | Negative | 4 | 28.6% | 4 | 15.4% | 0 | 0.0% | 3.211 | 0.225 |
| | Positive | 10 | 71.4% | 22 | 84.6% | 10 | 100.0% | | |

## DISCUSSION

The present study has showed that folate deficiency is significantly associated with the degree of asthma in children. We have also reported that folate deficiency is significantly associated with severe asthma exacerbations.

In the present study, the age of the study group ranged from 6 to 15 years old. Their weight ranged from 18.0 to 40.0 kg. The height ranged from 110.0 to 160.0 cm. The BMI of the patients ranged from 11.4 - 18.9 kg/m2.

As regarded sex distribution in the present study, among the 50 asthmatic children, 35 were males (70%) and 15 were females (30%). It's known that childhood asthma is more common in boys than girls [11].

**Mansour *et al***. showed that the increased risk for asthma in males during childhood is probably related to greater degree of bronchial liability in males. Airway in boys are smaller in comparison to their lung sizes compared to girls [12].

Additionally, this higher prevalence in males could be because males are more exposed to environmental pollutants as they are more commonly exposed to the environment than females [13].

This agrees with **Suresh and Zahin** [14] who stated that the mean sex of the patients was 20 (62.5%) were males and 12 (37.5%) were females. The male: female ratio was 1.6:1.

While **Hassab Allah *et al.*** [15] reported that the mean value and standard deviation of age in children with bronchial asthma was 9.65 ± 2.63 years and they were 29 males and 31 females.

In the present study, the mean age of onset of the disease in studied asthmatic children was 2.9 ± 0.7 years. It was considered as early onset asthma, but its persistence due to a lot of triggering factors; upper respiratory tract infection, passive smoking, house dust mite, food, fumes, pollens, and exercise. The duration of asthma of our studied patients ranged between 6-15 years with a mean of (10.3 ±3.0 years).

The mean age of onset of asthma group in the study done by **Osman *et al.*** [16] study was (13±9) month and the mean duration of asthma was (6±2) years and also **Shereen** [17] observed that the mean age of onset of asthma was at 14±11.6 month and the mean duration of disease was 6.34±1.8 years.

In our study, a positive history of parent smoking was observed in 68% and negative history 32%of asthmatic children.

These results agree with **Abdel Salam *et al.*** [18] who found that children exposed to the passive smoking at home or staging in the same place with a smoker are at a higher risk of asthma.

Parent smoking of above half a pack of cigarettes per day was identified as an independent risk factor for childhood asthma developing in first year of life and related to asthma severity [19].

On the contrary, **Bjerg *et al.*** [20] mentioned that although a family history of asthma is an important risk factor, it is neither necessary nor sufficient for predisposing an individual to developing asthma and that it is likely that a family history of asthma also includes environmental and social factors.

In the present study shows demonstrates the precipitating factors of asthma, history of atopy and asthma severity in the studied patients. The most commonly reported precipitating factor was viral infection (40%), followed by exercise (22%), exposure to cold (20%), fumes (16%) and the least was food (in one case, 1%).

In agreement with our study **Osman *et al.*** [16] reported that upper respiratory tract infections represented the most common precipitating factor for asthma in asthmatic patients (63.30%).

Our study was in consistence with **Loengard** [21] who studied asthmatic patients admitted to a hospital in England over the course of 1 year, he found out that most of the patients (37%) had evidence of a viral infection and that the majority of children with episodes of wheezing have viral infections.

Viral and bacterial infections are important causes of recurrent wheezing in children [22]. It precipitates acute exacerbations of asthma and was the most common reason for hospital admissions [23].

In the present study, the positive history of atopy was reported in 54% of cases. While positive history of asthma was reported in 84% of cases.

In agreement with our study **Hossny *et al.*** [24] found that 53.3% of studied asthmatic children has associated allergic diseases (atopic dermatitis, allergic rhinitis or food allergy).

This agreed with ***Stanford et al.*** [25] they reported an increase in the prevalence of asthma among first degree relatives with asthma to 20-25% compared with a general population prevalence of 4%.While **Gruchalla *et al.*** [26] found increasing the risk of asthma with positive family history of allergy or chronic rhinitis.

These results were supported by **Broms *et al.*** [27] who stated that positive family history of asthma was risk factor for asthma.

In agreement with this study, **Osman *et al.*** [16] reported that 60% of cases had family history of asthma.

**Gruchalla *et al.*** [26] also found increasing the risk of asthma with positive family history of allergy or chronic rhinitis and **Hassab Allah *et al.*** [15] reported that 48% of asthmatic children had positive family history of bronchial asthma.

In the present study, the forced expiratory volume (FEV1%) was lowered in most cases and ranged from 42 to 86%, with a mean value of (73.6 ± 12.1). The FEV1/FVC% ratio was lowered also in most patients, with a range of (58.0 - 87.0) and a mean value was (76.1 ± 7.0).

These results were similar to those reported by both [28].

Asthma severity can be classified in to three groups. Mild asthma, Moderate asthma and severe asthma [30].

In asthma, airways blockage results in reduced airflow with forced exhalation, an FEV1: FVC ratio <0.80 indicates significant airflow obstruction. Low FEV1 as a percentage of predicted norms is 1 of 6 criteria used to determine asthma severity and control in asthma management guidelines sponsored by the U.S. National Institutes of Health (NIH) and the Global Initiative for Asthma (GINA) [1].

The present study classifies asthma severity in the studied patients according to spirometry. Analysis of FEV1% showed that 30% of cases had a level above 80% (mild impairment), 54% had a level between 60 and 80% (moderate) and 16% had a level below 60% (severe). Analysis of FEV1/FVC% ratio showed that 28% of cases had mild impairment (> 80%), 52% had moderate impairment (75- 80%) and 20% had severe impairment (<75%).

In agreement of our study, **Al Musawi *et al.*** [31] found that patient with mild asthma (30%), patient with moderate asthma (38%) and patient with severe asthma (8%).

In the present study, the percentage of patients exposed to smoking were highest in the severe group (80%), followed by the moderate (76.9%) then the mild group (42.9%), but did not reach statistical significance (p = 0.076).

This agrees with **Hasssab Allah *et al.*** [15], who reported that 56.7% of studied asthmatic children were exposed to passive smoking.

In agreement of our study, **Neogi *et al.*** [32] who reported that 523 asthmatic children from 4 to 16 years ago were exposed to secondhand smoke had more doctor visits, more frequent flares, and higher disease severity scores than children who weren't exposed.

**Abo Elkheir *et al.*** [33] found that there was highly statistical increase in asthmatic children group exposed to secondhand smoke.

The present study demonstrates that viral infection was the most common precipitating factor in the three groups, with no significant association with the severity of asthma. Also, no significant association between severity of asthma and family history of atopy or asthma.

In the present study, the mean folic acid level was lowest in the severe group (1.2 ± 0.1), followed by the moderate (2.4 ± 0.3) then the mild group (3.4 ± 0.4), with a significant difference when all the groups were compared with each other (p <0.001).There were significant (p <0.001), positive strong correlations between folic acid level and each of FEV1% (r = 0.885) and FEV1/FVC% (r=0.895) (i.e. in most cases, folic acid level tended to decrease with the decrease in FEV1% and FEV1/FVC% ratio).

In agreement of our study on pediatric **Blatter *et al.*** [5] report that folate deficiency is significantly associated with severe asthma exacerbations among Puerto Rican children with asthma.

Also, **Brehm *et al.*** [8], hypothesized that Folate deficiency is significantly associated with severe asthma exacerbations in children with asthma.

In the present study shows the results of a cumulative odds ordinal logistic regression that was run to determine the effect of body weight, leucocytic count, serum folic acid and no smoking on asthma severity in the studied patients. These four variables were chosen as they had p values <0.01 in univariate analysis that compared the variables across the categories of asthma severity.

The model was statistically significant, $\chi 2$ = 85.304, p <0.001. Only serum folic acid level contributed significantly to the degree of asthma severity, when adjusted for the other variables (odds ratio confidence interval 0.0 – 0.024, p = 0.001) and indicated that increase in asthma severity with associated with each decrease in folic acid level.

In agreement of our study ***Nicholson et al.*** [34] among children with asthma, lower serum folate concentrations were associated with higher risk of uncontrolled asthma on children.

Also, **Thuesen *et al.*** [35] Among Peruvian children with asthma, lower serum folate concentrations were also associated with worse asthma control. The findings that support an inverse association between folate concentrations and odds of asthma.

## CONCLUSION

Among the studied asthmatic children, the percentage of asthma in males more than in females. Viral infection, exercise, exposure to cold and fumes are the commonest precipitating factors.

Among the studied asthmatic children, the percentage of patients exposed to smoking were highest in the severe group, followed by the moderate group then the mild group. 16% of cases of the studied asthmatic children were severe according to spirometry.

There were significant, positive strong correlations between folic acid level and each of FEV1% and FEV1/FVC% (i.e. in most cases, folic acid level tended to decrease with the decrease in FEV1% and FEV1/FVC% ratio).

Serum folic acid level contributed significantly to the degree of asthma severity, when adjusted for the other variables. There were significant positive strong correlations between the increase in asthma severity and the decrease in folic acid level.

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