

# Association between asthma and attention-deficit hyperactivity disorders in children: Potential risk factors

[Abdulbari Bener](#)<sup>1</sup>, [Mohammad S. Ehlayel](#)<sup>2</sup>, [Hale Zeynep Bener](#)<sup>3</sup>

<sup>1</sup> Department of Medical Statistics and Epidemiology, Section of Pediatric Allergy and Immunology, Hamad Medical Corporation; Department of Public Health, Weill Cornell Medical College, Qatar; Department Evidence for Population Health Unit, School of Epidemiology and Health Sciences, The University of Manchester, Manchester, UK,

<sup>2</sup> Department of Pediatrics, Section of Pediatric Allergy and Immunology, Hamad Medical Corporation; Department of Pediatrics, Weill Cornell Medical College, Qatar,

<sup>3</sup> Department of Medical Statistics and Epidemiology, Section of Pediatric Allergy and Immunology, Hamad Medical Corporation; Department of Public Health, Weill Cornell Medical College, Qatar,

## Correspondence Address:

Abdulbari Bener

Department of Public Health, Weill Cornell Medical College, P.O. Box 3050, Doha, Qatar

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## Abstract

**Background:** Childhood asthma is common in children. It might be associated with behavioral abnormalities of inattention, irritability, or hyperactivity. These abnormalities form the major components of attention deficit hyperactivity disorder (ADHD). Allergic diseases and ADHD are common pediatric conditions associated with learning difficulties and sleep disturbances. There are conflicting research data regarding the association between ADHD and atopic disorders. **Aim:** The objective of this study was to examine the potential risk factors, especially investigate vitamin D deficiency a strong contributing factor in asthmatic children with ADHD. **Design:** This was a case-control study. **Settings:** Hamad General Hospital, Rumeilah Hospital, School Health and Primary Health Care Clinics, Qatar. **Subjects and Methods:** A total of 520 asthmatic children with ADHD and 520 controls aged 5-16 years old controls were enrolled in this study and matched with age and ethnicity. The study was conducted between June 2011 and September 2013. Data based questionnaire, clinical manifestations, family history, body mass index (BMI), and clinical biochemistry variables including serum 25(OH) vitamin D, calcium, phosphorus, magnesium was obtained. Univariate and multivariate statistical analyses were performed. **Results:** Severe vitamin D deficiency was significantly higher among asthmatic children with ADHD compared with the healthy controls (18.1% vs. 10.4%;  $P < 0.001$ ). Furthermore, the proportion of overweight (24.1% vs. 18.1%) and obesity (8.2% vs. 5.4%) was significantly higher among asthmatic children with ADHD than healthy controls ( $P < 0.001$ ). Mean values of vitamin D ( $17.25 \pm 10.53$  vs.  $23.91 \pm 9.82$ ;  $P < 0.001$ ), serum iron ( $81.46 \pm 13.61$  vs.  $87.23 \pm 12.46$ ;  $P < 0.001$ ), hemoglobin ( $11.68 \pm 2.11$  vs.  $12.87 \pm 2.15$ ;  $P < 0.001$ ), magnesium ( $0.77 \pm 0.12$  vs.  $0.83 \pm 0.13$ ;  $P = 0.013$ ), potassium ( $4.22 \pm 0.53$  vs.  $4.58 \pm 0.55$ ;  $P < 0.001$ ), phosphorous ( $1.53 \pm 0.12$  vs.  $1.66 \pm 0.14$ ;  $P < 0.001$ ) were significantly lower among asthmatic children with ADHD than in controls. There was a significant

correlation between vitamin D deficiency and with age ( $r = -0.224$ ,  $P = 0.001$ ); calcium ( $r = 0.256$ ,  $P = 0.001$ ); phosphorous ( $r = 0.316$ ,  $P = 0.001$ ); magnesium ( $r = 0.288$ ,  $P = 0.001$ ); and BMI ( $r = 0.452$ ,  $P = 0.001$ ) in asthmatic with ADHD children. Vitamin D deficiency (odds ratio [OR] = 3.27;  $P < 0.001$ ), serum iron deficiency (OR = 2.81;  $P = 0.008$ ), physical inactivity (OR = 2.67;  $P = 0.005$ ), ferritin (OR = 2.53;  $P < 0.001$ ) and serum calcium level (OR = 2.04;  $P < 0.001$ ) were significant leading predictors in asthmatic children with ADHD. **Conclusion:** The present study revealed that vitamin D was a significant contributing factor in asthmatic children with ADHD followed by serum iron deficiency and physical inactivity compared with healthy controls.

**Keywords:** Asthma, attention deficit hyperactivity disorder, case-control, epidemiology, risk factors, vitamin D deficiency

## Introduction

There is emerging interest in determining the factors that might be contributing in the global rise of asthma and attention deficit hyperactivity disorder (ADHD). It is well-known that the prevalence of ADHD has been reported to trends increase in many places and may affect all aspects of a child's life. <sup>[1],[2]</sup> During the past 4 decades, the prevalence of allergic diseases, including childhood asthma, has been rising, in many developing as well as well-developed countries. <sup>[3]</sup> Being a common and chronic disease, allergic diseases have a large negative impact on the affected children, their families and societies, increasing the direct and indirect costs. They negatively affect the quality-of-life of children including leading to disruptive behaviors abnormalities and reduced cognitive performance at school. <sup>[1],[2],[3],[4],[5]</sup> ADHD, one of the most prevalent neuropsychiatric disorders worldwide in developed and developing countries, affects between 5% and 15% <sup>[4],[5],[6],[7],[8]</sup> of school-aged children. This disorder, with onset before age 7 years, is characterized by developmentally poor attention, hyperactivity and impulsivity and impaired functioning in two or more settings. <sup>[7]</sup> The pathophysiology of ADHD is complex and not well-understood, without any specific etiology, but seems multi-factorial. <sup>[7],[8],[9],[10]</sup> In this aspect, it is similar to other neuropsychiatric disorders resulting from complex combination of genetic, environmental and biological factors. Prospective studies also indicate that children affected by ADHD are at a high risk of developing comorbid disorders as well as impaired social maladjustment. <sup>[5],[6],[7],[8],[9]</sup> The potential difference in the prevalence of ADHD in western and nonwestern countries is related to biological, cultural, and familial factors. <sup>[11],[12]</sup> Furthermore, the variation in prevalence rates is related to the difference in the diagnostic criteria. <sup>[7]</sup>

In 2004, the Global Initiative of Asthma estimated that more than 300 million people worldwide were affected with asthma. <sup>[13]</sup> In the 1980s and 1990s, many countries reported significant increases in asthma prevalence, with more recent studies suggesting that asthma prevalence may have reached a plateau or may even be decreasing. <sup>[14]</sup> Asthma affects 7-15% of children <sup>[15],[16],[17]</sup> as a leading cause of childhood chronic medical illness. Children with asthma have been reported to have greater difficulty in school performance compared with their peers. <sup>[15]</sup> Their often-described hyperactive and impulsive behaviors have been thought to be secondary to this chronic illness or to its treatments. The causes of asthma and why asthma seems to have increased is still not well-understood. Conversely, in North America, both Canada and the United States and Australia reported an increase in the prevalence of asthma. <sup>[18],[19],[20]</sup> Inconsistencies in findings may be attributed to differences in study designs and data collected from different sources using varying definitions and time points. <sup>[17],[21]</sup>

Biederman *et al.* [12] and Hammerness *et al.* [22] assessed the association between asthma and ADHD among boys and girls. [12],[22],[23],[24],[25] Their findings that there was no meaningful difference in risk of asthma between ADHD, and control could be related to the sample size of these studies. Relatives of ADHD probands with and without asthma were at significantly greater risk for ADHD than relatives of normal controls. Both allergic rhinitis and ADHD are common pediatric conditions associated with learning difficulties and sleep disturbances. There are conflicting research data regarding the association between ADHD and atopic disorders. [24] Therefore, understanding of trends of disease prevalence and estimates of asthma and ADHD disease burden can inform health policy makers regarding future resource allocation in order to optimize health outcomes. The objective of this study was to examine the potential risk factors, especially vitamin D deficiency in asthmatic children with ADHD.

## Subjects and methods



This is a case-control study which was conducted over a period from June 2011 to September 2013. To secure a representative sample of the study population, the sampling plan was stratified with proportional allocation. Stratification allowed both urban and semi-urban areas to be proportionally represented. The list of names of government schools was obtained from the Office of Director of General Education, Supreme Council of Education. Government schools were segregated according to the sexes.

The study was approved by the Institutional Review Board at the Hamad Medical Corporation. All human studies have been approved by the Research Ethics Committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. All the persons who agreed to participate in this study gave their informed consent prior to their inclusion in the study approved this study. All parents provided verbal informed consent, and children/parents signed an assessment form.

## Data collection

This current study studied 520 asthmatic children with ADHD [4],[8],[11] aged 5-16 years as cases and matched with age and ethnicity of 520 control subjects. The ADHD and ISAAC [16],[17] questionnaire were administered by a trained interviewer and nurses. The questionnaire addressed (a) general and respiratory health, family history, and environmental characteristics; (b) spirometry; (c) methacholine challenge testing; (d) allergy skin testing; and (e) blood sample collection for measurement of peripheral blood eosinophils, serum total IgE, and serum IgE levels to *Blatella germanica* and *Dermatophagoides pteronyssinus*.

## Selection of asthmatic children with attention deficit hyperactivity disorder

A random sample of asthmatic children who were diagnosed with ADHD were recruited from pediatric clinics of the Hamad General Hospital and School Health Clinics in Primary Health Care (PHC) Centers. Pediatric immunologist diagnosed asthma in children and it was recorded in medical records of children. The following variables were collected from the ISAAC questionnaire: Lifetime wheeze (if wheezing had ever occurred), wheeze in the past 12 months, number of wheezing attacks in the past 12 months, sleep disturbances due to wheeze, speech-limiting wheeze, physician-diagnosed asthma (if asthma had ever been diagnosed by physician), exercise-induced wheeze, and night coughing in the past 12 months. Allergic rhinitis is an allergic inflammation of

the nasal airways. It occurs when an allergen, such as pollen, dust or animal dander (particles of shed skin and hair) is inhaled by an individual with a sensitized immune system. Furthermore, the diagnosis of ADHD in asthmatic children was based on physician-diagnosis and confirmed it from medical records. The Conners' teacher scale was used to screen ADHD symptoms among asthmatic children. [\[4\].](#)[\[8\].](#)[\[11\]](#) Teacher rating scales [\[4\].](#)[\[8\].](#)[\[11\]](#) are also an important part of the evaluation and diagnosis. Teacher rating scales provide necessary information about the child in the school setting. We used SNAP questionnaire and Conner's filled by both parents and teachers in addition to the clinical history and school performance. A random sample of 716 asthmatic children with ADHD was approached and 520 gave consent and participated in study with a response rate (72.6%). The study excluded the subjects with following characteristics, calcium supplements or vitamin D intake during the last 6 month before the study; history of epilepsy or anti-epileptic drugs since they affect vitamin D; and any history of sun block use and the pubertal age since we know that behavioral problems and 25(OH) D2 are affected by puberty and use of sun block.

### **Selection of controls**

Control subjects aged 5-16 years old were identified from PHC centers if not ever been diagnosed as asthma and ADHD. This group involved a random sample of 748 healthy subjects who visited the PHC Clinics for any reason other than acute. 520 matched age and gender subjects included due to the either refusal of the mother or difficulty in drawing blood from very uncooperative subjects; with a response rate (69.5%). The healthy subjects were selected in a way matching to the age, gender and ethnicity of cases to give a good representative sample of the studied population.

The questionnaire and criteria for vitamin D deficiency in the young population were defined and developed by the primary investigator (AB). A translated Arabic version of the questionnaire was back translated by a bilingual consultant (ME). The questionnaire was performed by author (AB) in the previous published studies. Content validity, face validity, and reliability of the questionnaire were tested using 50 students. These tests demonstrated a high level of validity and reliability (Cranach's Alpha = 0.86).

### **Laboratory investigation**

#### *Blood collection and serum measurements of vitamin D*

Trained phlebotomist collected venous blood sample, and serum separated and stored at  $-70^{\circ}\text{C}$  until analysis. Serum 25-hydroxyvitamin D (25OHD), a vitamin D metabolite, was measured using a commercially available kit (DiaSorin Corporate Headquarter, Saluggia, Italy). The treated samples were then assayed using competitive binding radioimmunoassay technique. Subjects were classified into four categories: (1) Severe vitamin D deficiency, 25(OH) D  $< 10$  ng/ml; (2) moderate deficiency, 25(OH) D 10-19 ng/ml; (3) mild deficiency, 25(OH) D 20-29 ng/ml; and (4) normal/optimal level is between 30 and 80 ng/ml. [\[12\].](#)[\[17\].](#)[\[18\].](#)[\[19\].](#)[\[24\].](#)[\[25\]](#) Other biochemical parameters measured from the serum included vitamin D, calcium, phosphorus, magnesium, urea, parathyroid hormone, bilirubin, albumin, cholesterol, and triglycerides on the basis of previous recommendations. Serum levels of these biochemical parameters were determined according to standard laboratory procedures.

The participants were interviewed by health professionals and nurses concerning their socio-demographic information such as age, gender, place of residence (urban and semi-urban), and monthly income. Height and weight were measured using standardized methods and all the participants wore light clothes and no shoes for this part of the examination. Body mass index (BMI) was calculated as the weight in kg (with 1 kg subtracted to allow for clothing) divided by

height in m<sup>2</sup>. BMI <85<sup>th</sup> percentile was considered normal weight, 85<sup>th</sup>-95<sup>th</sup> percentile as overweight and >95<sup>th</sup> percentile as obese.

Statistical significance between two continuous variables was determined using a Student's *t*-test and Mann-Whitney test was used for nonparametric data. Chi-square and Fisher Exact test were performed to test for differences in proportions of categorical variables between two or more groups. Multivariate logistic regression analysis using the forward inclusion and backward deletion method was used to assess the relationship between dependent and independent variables and to adjust for potential confounders and orders the importance of risk factors (determinant) for the ADHD and asthma.  $P < 0.05$  was considered to be statistically significant.

## Results



[\[Table 1\]](#) compares socio-demographic characteristics among the asthmatic children with ADHD and healthy children. There were statistically significant differences between asthmatic children with ADHD and healthy children with respect to ethnicity, educational level of father ( $P = 0.003$ ), occupation of father ( $P < 0.001$ ), educational level of mother ( $P < 0.001$ ), type of house ( $P = 0.007$ ), consanguineous marriages of parent ( $P = 0.003$ ), and number of people living at home ( $P < 0.002$ ).

| Variables                     | n (%) (n=520)       |                 | P value |
|-------------------------------|---------------------|-----------------|---------|
|                               | Asthmatic with ADHD | Healthy control |         |
| Age group (years)             |                     |                 |         |
| ≤5                            | 114 (21.9)          | 130 (25.0)      | 0.193   |
| 6-10                          | 200 (38.5)          | 173 (33.3)      |         |
| 11-15                         | 206 (39.6)          | 217 (41.7)      |         |
| Sex                           |                     |                 |         |
| Male                          | 293 (56.3)          | 270 (51.9)      | 0.171   |
| Female                        | 227 (43.7)          | 250 (48.1)      |         |
| Ethnicity                     |                     |                 |         |
| Qatari                        | 364 (70)            | 405 (77.9)      | 0.002   |
| Non-Qatari                    | 156 (30)            | 115 (22.1)      |         |
| Education of father           |                     |                 |         |
| Illiterate                    | 34 (6.5)            | 45 (8.7)        | 0.003   |
| Primary                       | 45 (8.7)            | 78 (15.0)       |         |
| Intermediate                  | 80 (15.4)           | 85 (16.5)       |         |
| Secondary                     | 186 (35.8)          | 177 (34.0)      |         |
| University                    | 175 (33.7)          | 134 (25.8)      |         |
| Education of mother           |                     |                 |         |
| Illiterate                    | 22 (4.2)            | 52 (10.0)       | <0.001  |
| Primary                       | 71 (13.7)           | 71 (13.7)       |         |
| Intermediate                  | 132 (25.4)          | 160 (30.8)      |         |
| Secondary                     | 153 (29.4)          | 127 (24.4)      |         |
| University                    | 142 (27.3)          | 110 (21.2)      |         |
| Occupation of father          |                     |                 |         |
| Sedentary/professional        | 213 (41.0)          | 138 (26.5)      | <0.001  |
| Clerk                         | 65 (12.7)           | 77 (14.8)       |         |
| Business man                  | 121 (23.3)          | 161 (31.0)      |         |
| Government officer            | 120 (23.1)          | 144 (27.7)      |         |
| Occupation of mother          |                     |                 |         |
| Sedentary/professional        | 149 (28.6)          | 115 (22.1)      | <0.001  |
| Clerk                         | 52 (10.0)           | 54 (10.4)       |         |
| Business                      | 55 (10.8)           | 119 (22.8)      |         |
| House wife                    | 263 (50.6)          | 232 (44.6)      |         |
| Type of house                 |                     |                 |         |
| Flat                          | 65 (12.5)           | 40 (7.7)        | 0.007   |
| Villa                         | 455 (87.5)          | 480 (92.3)      |         |
| Household income (US\$/month) |                     |                 |         |
| <\$3000                       | 150 (28.8)          | 124 (23.8)      | 0.077   |
| \$3000-5000                   | 170 (32.7)          | 201 (38.7)      |         |
| >\$6000                       | 200 (38.5)          | 195 (37.5)      |         |
| No. of people living at home  |                     |                 |         |
| ≤5                            | 130 (25.0)          | 165 (31.7)      | 0.002   |
| 6-10                          | 291 (56.0)          | 293 (56.3)      |         |
| >10                           | 99 (19.0)           | 62 (11.9)       |         |
| Consanguineous parents        |                     |                 |         |
| None                          | 304 (58.5)          | 352 (67.7)      | 0.003   |
| First degree relatives        | 162 (31.2)          | 137 (26.3)      |         |
| Second degree relatives       | 54 (10.4)           | 31 (6.0)        |         |

ADHD - Attention deficit hyperactivity disorder

Table 1: Socio - demographic characteristics of asthmatic children with ADHD and healthy controls

[\[Table 2\]](#) shows the family characteristics and school performance in asthmatic children with ADHD and healthy controls. All variables showed statistically significant differences between the two groups except type of family ( $P = 0.131$ ) and parents living together ( $P = 0.086$ ).

| Variables                           | n (%) (n=520)       |                  | P value |
|-------------------------------------|---------------------|------------------|---------|
|                                     | Asthmatic with ADHD | Control children |         |
| Exposure to sun                     |                     |                  |         |
| Yes                                 | 171 (32.9)          | 210 (40.4)       | 0.012   |
| No                                  | 349 (67.1)          | 310 (59.6)       |         |
| Physical activities                 |                     |                  |         |
| Daily vigorous activity >30 min/day | 158 (30.4)          | 236 (45.4)       | <0.001  |
| Type of family                      |                     |                  |         |
| Nuclear                             | 353 (67.9)          | 382 (73.5)       | 0.131   |
| Extended                            | 116 (22.3)          | 93 (17.9)        |         |
| More than one                       | 51 (9.8)            | 45 (8.6)         |         |
| Multiple marriages                  |                     |                  |         |
| Yes                                 | 86 (16.5)           | 41 (7.9)         | <0.001  |
| No                                  | 434 (83.5)          | 479 (92.1)       |         |
| Good relationship among parents     |                     |                  |         |
| Yes                                 | 469 (90.2)          | 486 (93.5)       | 0.035   |
| No                                  | 51 (9.8)            | 34 (6.5)         |         |
| Parents living together             |                     |                  |         |
| Yes                                 | 463 (89)            | 477 (91.7)       | 0.086   |
| No                                  | 57 (11)             | 43 (8.3)         |         |
| Performance at school               |                     |                  |         |
| Excellent                           | 148 (28.5)          | 198 (38.1)       | <0.001  |
| Very good                           | 179 (34.4)          | 174 (33.5)       |         |
| Good                                | 110 (21.2)          | 112 (21.5)       |         |
| Average                             | 83 (16.0)           | 36 (6.9)         |         |
| Obeys rule                          |                     |                  |         |
| Yes                                 | 358 (68.8)          | 409 (78.7)       | <0.001  |
| No                                  | 162 (31.2)          | 111 (21.3)       |         |
| Noisy/hyperactive                   |                     |                  |         |
| Yes                                 | 91 (17.5)           | 57 (11)          | 0.002   |
| No                                  | 429 (82.5)          | 463 (89)         |         |
| Cry for any reason                  |                     |                  |         |
| Yes                                 | 95 (18.3)           | 38 (7.3)         | <0.001  |
| No                                  | 425 (81.7)          | 482 (92.7)       |         |
| Create problems                     |                     |                  |         |
| Yes                                 | 75 (14.4)           | 44 (8.5)         | 0.002   |
| No                                  | 445 (85.6)          | 476 (91.5)       |         |
| Nervous                             |                     |                  |         |
| Yes                                 | 66 (12.7)           | 45 (8.7)         | 0.022   |
| No                                  | 454 (87.3)          | 475 (91.3)       |         |
| Any children like him/her           |                     |                  |         |
| Yes                                 | 192 (36.9)          | 186 (31.9)       | 0.050   |
| No                                  | 328 (63.1)          | 354 (68.1)       |         |

AJHD - Attention deficit hyperactivity disorder

Table 2: Family characteristics and school performance among asthmatic children with ADHD and healthy controls

[Table 3] shows baseline bio-chemistry values and BMI percentiles among asthmatic children with ADHD and healthy controls. Severe vitamin D deficiency was significantly higher among asthmatic children with ADHD compared with healthy controls (18.1% vs. 10.4%;  $P < 0.001$ ). Furthermore, the proportion of overweight (24.1% vs. 18.1%) and obesity (8.2% vs. 5.4%) was significantly higher among asthmatic children with ADHD than healthy controls ( $P < 0.001$ ). Mean values of vitamin D (17.25 ± 10.53 vs. 23.91 ± 9.82;  $P < 0.001$ ), serum iron (81.46 ± 13.61 vs. 87.23 ± 12.46;  $P < 0.001$ ), hemoglobin (11.68 ± 2.11 vs. 12.87 ± 2.15;  $P < 0.001$ ), magnesium (0.77 ± 0.12 vs. 0.83 ± 0.13;  $P = 0.013$ ), potassium (4.22 ± 0.53 vs. 4.58 ± 0.55;  $P < 0.001$ ), phosphorous (1.53 ± 0.12 vs. 1.66 ± 0.14;  $P < 0.001$ ) were significantly lower among asthmatic children with ADHD than in controls.

| Variables                                   | Reference normal value | Mean $\pm$ SD (%) (n=520) |                   | P value |
|---------------------------------------------|------------------------|---------------------------|-------------------|---------|
|                                             |                        | Asthmatic with ADHD       | Control           |         |
| Vitamin D (ng/ml)                           | 30-80 ng/ml            | 17.25 $\pm$ 10.53         | 23.91 $\pm$ 9.82  | <0.001  |
| Serum iron (ug/dL)                          | 37-158                 | 81.46 $\pm$ 13.61         | 87.23 $\pm$ 12.46 | <0.001  |
| Ferritin (ng/ml)                            | 15-150                 | 32.40 $\pm$ 7.45          | 37.12 $\pm$ 8.36  | <0.001  |
| Hemoglobin (g/dL)                           | 11.2-16.5              | 11.68 $\pm$ 2.11          | 12.87 $\pm$ 2.15  | <0.001  |
| Magnesium (mmol/L)                          | 0.65-1.05              | 0.77 $\pm$ 0.12           | 0.83 $\pm$ 0.13   | 0.013   |
| Potassium (mmol/L)                          | 3.4-4.7                | 4.22 $\pm$ 0.53           | 4.58 $\pm$ 0.55   | <0.001  |
| Calcium (mmol/L)                            | 2.10-2.5               | 2.35 $\pm$ 0.15           | 2.38 $\pm$ 0.13   | 0.136   |
| Phosphorous (mmol/L)                        | 0.4-1.3                | 1.53 $\pm$ 0.12           | 1.66 $\pm$ 0.14   | <0.001  |
| PTH, pg/ml                                  | 11-54                  | 44.88 $\pm$ 5.93          | 48.14 $\pm$ 4.96  | 0.636   |
| Log10 IgE                                   | -                      | 2.3 $\pm$ 0.75            | 1.7 $\pm$ 0.69    | <0.001  |
| BMI (kg/m <sup>2</sup> )                    |                        |                           |                   |         |
| Normal (<85 <sup>th</sup> percentile)       |                        | 352 (67.7)                | 398 (76.5)        |         |
| Overweight (85-95 <sup>th</sup> percentile) |                        | 125 (24.1)                | 94 (18.1)         | <0.001  |
| Obesity (>95 <sup>th</sup> percentile)      |                        | 43 (8.2)                  | 30 (5.4)          |         |

BMI - Body mass index, ADHD - Attention deficit hyperactivity disorder, SD - Standard deviation, PTH - Parathyroid hormone

Table 3: Clinical biochemistry and BMI values among asthmatic children with ADHD and controls

Furthermore, there was significant correlation between vitamin D deficiency and with age ( $r = -0.224$ ,  $P = 0.001$ ); calcium ( $r = 0.256$ ,  $P = 0.001$ ); phosphorous ( $r = 0.316$ ,  $P = 0.001$ ); magnesium ( $r = 0.288$ ,  $P = 0.001$ ); and BMI ( $r = 0.452$ ,  $P = 0.001$ ) in asthmatic with ADHD children.

The predictors for asthmatic children with ADHD using multivariate logistic regression analysis are shown in [Table 4]. Vitamin D deficiency (odds ratio [OR] = 3.27;  $P < 0.001$ ), serum iron deficiency (OR = 2.81;  $P = 0.008$ ), physical inactivity (OR = 2.67;  $P = 0.005$ ), ferritin (OR = 2.53;  $P < 0.001$ ) and serum calcium level (OR = 2.04;  $P < 0.001$ ), nervous behavior (OR = 1.73;  $P < 0.01$ ), were significant leading predictors in asthmatic children with ADHD.

| Independent variables       | Odds ratio | 95% confidence interval | P value |
|-----------------------------|------------|-------------------------|---------|
| Vitamin D deficiency ng/ml  | 3.27       | 1.65-5.90               | <0.001  |
| Serum iron deficiency ng/ml | 2.81       | 1.72-4.53               | 0.008   |
| Physical activity           | 2.67       | 1.68-4.26               | 0.005   |
| Ferritin ng/ml              | 2.53       | 1.81-3.45               | <0.001  |
| Serum calcium level         | 2.04       | 1.01-3.58               | <0.001  |
| Nervous behavior            | 1.73       | 1.14-2.56               | <0.010  |
| Consanguinity               | 1.49       | 1.16-1.92               | <0.003  |
| BMI in percentiles          | 1.38       | 1.15-1.54               | <0.002  |
| Child order                 | 1.26       | 1.42-3.56               | 0.019   |

ADHD - Attention deficit hyperactivity disorder, BMI - Body mass index

Table 4: Potential risk factors in asthmatic children with ADHD using multivariate logistic regression analysis

[Figure 1] compares the vitamin D level in asthmatic children with ADHD and healthy controls. Moderate (34.4% vs. 29%) and severe (18.1% vs. 10.4%) vitamin D deficiency was significantly higher in asthmatic children with ADHD compared with healthy controls ( $P < 0.001$ )

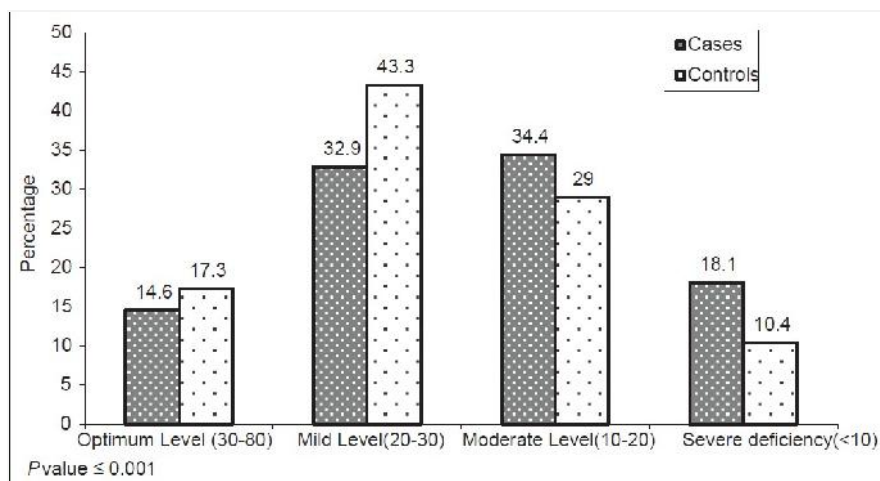


Figure 1: Comparison in vitamin D status between asthmatic children with attention deficit hyperactivity disorder and healthy controls ( $P \leq 0.001$ )

## Discussion



It is well-known that the prevalence of both ADHD and asthma has been reported to increase in many places around the world during the last decades. [\[2\],\[3\],\[7\]](#) Epidemiologic studies have yielded various rates of ADHD symptoms ranging from 3.2% to 17%, respectively. [\[7\],\[10\],\[12\]](#) The increase in asthma prevalence has been suggested in some way to be related to western lifestyle factors, as most often increased prevalence rates are reported from westernized countries, namely USA, Canada, Norway. [\[18\],\[19\],\[20\],\[21\],\[23\]](#) Further support for the western lifestyle hypothesis is noted in the emergence of the of asthma prevalence in adopting the western life. Such a transition is currently taking place in Qatar at a much higher speed and during a shorter period than in many other countries. [\[1\]](#)

Bronchial asthma remains the most common chronic disease of childhood [\[14\],\[15\],\[16\],\[17\],\[18\]](#) and is one of the leading causes of morbidity in children worldwide. [\[16\],\[17\]](#) Currently, the burden of asthma in both developed and in the developing world is significant and increasing rapidly with more than 300 million people affected worldwide. Industrialized countries furthest away from the equator such as Australia, New Zealand, and the United Kingdom are said to have the highest prevalence. [\[18\],\[19\],\[20\],\[21\]](#) The prevalence of asthma and allergies in some western countries has reached alarming proportions, affecting more than one-third of children from the general population. [\[17\],\[18\],\[19\],\[20\],\[21\],\[22\],\[23\]](#)

Both allergic diseases and ADHD are common pediatric disorders that may lead to mental and physical complications. The population-based case-control design reported in Taiwan demonstrated high correlation and the risk of ADHD with asthma and allergic diseases among a pediatric population. [\[23\]](#) In addition, most of the children with ADHD had a strong association with allergies, especially allergic rhinitis, perhaps, awareness of these comorbidities may help clinicians to provide better comprehensive management and reduce the burden of disease. The study performed in United States [\[24\]](#) showed that most children with ADHD displayed symptoms and skin prick test results consistent with allergic rhinitis. Nasal obstruction and other symptoms of allergic rhinitis could explain some of the cognitive patterns observed in ADHD, which might result from sleep disturbance known to occur with allergic rhinitis, therefore, evaluation and treatment of allergic rhinitis could benefit patients with ADHD.

In Taiwan using a nationwide population-based prospective case-control cohort study (1:4,

age/gender-matched), they hypothesized that asthma in infancy or early childhood would increase the risk of ADHD in later life. [25] Children with asthma had a higher incidence of developing ADHD (7% vs. 4.6%,  $P < 0.001$ ) than control cohort during the follow-up period. After adjusting for age at enrollment, gender, level of urbanization, and co-morbid allergic diseases (allergic rhinitis and atopic dermatitis), children with asthma had an elevated risk (HR: 1.31, 95% confidence interval: 1.07-1.59) of developing ADHD compared with control group. Their prospective study supported a temporal relationship between asthma and ADHD. Asthma in very early life increased the risk of developing ADHD during the school years. Perhaps the prompt treatment of asthma and comorbid allergic diseases might prevent the development of ADHD or decrease ADHD symptoms.

More recently ADHD has received wide international recognition as a chronic neurodevelopmental disorder leading to comorbid impairment. Concerns have been raised about cross-national variation in the prevalence of ADHD, under the assumption that cultural differences are likely to underlie disparities between countries. [26] However, a meta-regression analysis by Polanczyk *et al.* [27] showed that despite international variation in prevalence estimates for ADHD (around an overall mean of slightly more than 5%), most of the cross-country variation was attributable to methodological differences-such as diverging definitions of the disorder or different algorithms for combining assessment information-rather than to cultural or national-level factors.

The results extend to boys' and girls' probands previously reported findings that asthma and ADHD are independently transmitted in families. [12] These findings further support the conclusion that ADHD symptoms should not be dismissed as part of asthma symptomatology or a consequence of its treatment. [12],[21] This is in agreement with the current study.

It is well-documented in the literature [16],[28],[29] that positive allergic status, exposure and sensitization to environmental allergens and/or familial history of allergic disease are significant risk factors associated with development of asthma, which ADHD has similar pattern associated with genetics and environmental factors. In current study, ADHD were associated with the higher prevalence rate of asthma, allergic rhinitis and wheezing, which is confirmative with previous reported studies. Although there have been a number of previous studies of the link between ADHD and asthma and allergic diseases, [9],[22],[23],[24],[25],[30] this is the first study to investigate the relationship of asthma and allergic diseases to ADHD with the large sample as a case-control in the general population. Since asthma and allergic diseases are chronic in nature and affect the child extensively, it is important to evaluate the initial period of allergic diseases in this early age group in order to identify possible mechanisms to explain the relationship between allergic diseases and ADHD. [9]

Furthermore, the Pediatric Asthma Quality of Life Questionnaire by Juniper *et al.* [31] reported that children with asthma have identified as troublesome in their daily lives. The Pediatric Asthma Quality of Life Questionnaire was able to detect quality of life changes in those patients who altered their health status either as a result of treatment or natural fluctuations in their asthma and to differentiate these patients from those who remained stable. The questionnaire showed good levels of both longitudinal and cross-sectional correlations with the conventional asthma indices and with general quality-of-life. The Pediatric Asthma Quality of Life Questionnaire had good measurement properties and is valid both as an evaluative and a discriminative instrument. It captures aspects of asthma most important to the patient and adds additional information to conventional clinical outcomes. The previous reports by Juniper *et al.* [31],[32],[33] are consistent with the current study instrument adopted from ISAAC. [16]

Finally, optimizing control is the main goal in pediatric asthma management and reliable

instruments that can help physicians to evaluate asthma control in an easy way are valuable. The article by Juniper *et al.* [\[31\]](#) provides some initial insights on the use of the Asthma Control Questionnaire, an instrument that was originally developed for adult asthma, to assess asthma control in children. In fact, the process of developing and validating such a questionnaire is a delicate one. In 2010 Juniper *et al.* [\[32\]](#) published a critical editorial about the consequences of even small modifications to original questionnaires and how this could influence the validity of these instruments. Based on previous research, differences in reliability of scores between the younger and older group of patients could be expected. [\[33\]](#) Overall, our instrument and vitamin D marker can be considered similar to instruments developed by Juniper *et al.* [\[31\],\[32\],\[33\]](#) for the purposes of the asthma control and prevention.

Some limitations of the study must be considered in the interpretation of the findings very cautious. Since this is a case and control study, certain risk factors would have been reversed during the time of data collection as the condition is known. Therefore the true relationship of certain current factors could have been reduced. Asthma and ADHD is increasing in Qatar and world over due to several modifiable factors. One of the strengths of our study was the use of a large population-based database which minimized selection bias. In addition, our diagnoses were more reliable than possible diagnoses derived by proxy, e.g., questionnaires and parental reports. First, a case-control design was used, which meant that it was possible to establish a causal relationship based on the observed association between ADHD and asthma and allergic diseases'. Second, data on some important risk factors for atopic diseases such as exposure to cigarette smoking at home, early life exposure to animals and family histories of allergy were not available. Therefore, we were unable to evaluate the influence of these factors. Another limitation is the vitamin D source. It is known that vitamin is readily available either by oral intake or skin biosynthesis through UVB. The study did not include data on children kept on avoidance/restriction diet. It is known that avoidance or restriction diet is one of the modalities of therapy in some case of ADHD and for a relatively short period of time. One limitation of using health administrative databases or medical records to identify individuals with asthma is that it was based on the use of physician-diagnosed asthma only, which can be subject to misclassification bias.

## Conclusion



The present study revealed that vitamin D deficiency was higher in asthmatic children with ADHD disorders compared to healthy children. Vitamin D was a significant predictor in asthmatic children with ADHD followed by serum iron deficiency and physical inactivity. Supplementing infants with vitamin D might prove to be a safe and effective strategy for reducing the risk of ADHD in asthmatic children.

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