

Co-Morbidities and Cognitive Status in a Cohort of Teenagers With Asthma

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Summary. Background: There is limited data regarding co-morbidities and cognitive status of asthma during childhood and adolescence. The aim of the current study was to explore the presence of co-morbidities and cognitive status in a large cohort of teenagers with asthma. Methods: The medical records of 314,897 consecutive 17-year-old males, undergoing comprehensive medical and cognitive evaluation prior to recruitment for military service, were reviewed. The prevalence of co-morbidities and a cognitive assessment in subjects with asthma were compared to those without asthma. Both a univariate and multivariate logistic regression analysis were performed. Results: Active asthma was documented in 21,728 (6.9%) subjects: 3.3% were diagnosed with mild intermittent asthma, and 3.6% with persistent asthma. A significant positive correlation between a higher cognitive score and prevalence of asthma was found ($P < 0.001$), with a 55% increased prevalence of asthma in the subjects with the highest cognitive score compared to those with the lowest score. The following co-morbidities were significantly more prevalent in asthmatics compared to non-asthmatics: chronic rhinitis (35% vs. 5%), atopic dermatitis (2% vs. 0.4%), urticaria (1% vs. 0.3%), anaphylaxis (0.4% vs. 0.1%), chronic sinusitis (0.4% vs. 0.1%), overweight with body mass index (BMI) above 25 kg/m² (20% vs. 17%) and underweight with BMI less than 17 kg/m² (3.2% vs. 2.8%), irritable bowel syndrome (IBS) (1% vs. 0.5%), and thyroid disorders (0.4% vs. 0.2%). Chronic rhinitis and sinusitis, atopic dermatitis, IBS, and thyroid disorders were all significantly more prevalent in persistent compared to intermittent asthma ($P < 0.001$). Conclusions: In adolescence, a higher cognitive status was associated with a higher rate of asthma. Chronic rhinitis was the most prevalent co-morbidity and was found in one third of adolescent asthmatics. Other allergic diseases, chronic sinusitis, over and underweight, IBS, and thyroid disorders were also more prevalent in asthmatics. **Pediatr Pulmonol.** © 2016 Wiley Periodicals, Inc.

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INTRODUCTION

There is very limited data about the cognitive status in asthmatic children and adolescents. Also, little is known about the prevalence and the impact of co-morbid medical conditions on the severity and control of asthma in children and adolescents.¹ In adult patients and elderly patients with asthma, there is evidence of cognitive impairment.^{2,3} They also frequently suffer from additional medical conditions including gastro-esophageal reflux disease, obstructive sleep apnea, obesity, psychological disturbances, and sinusitis.⁴ These co-morbidities may influence the clinical expression and severity of asthma.¹ The identification of co-morbidities is now considered an integral part of the management of asthma, particularly in more severe forms of the disease. Co-morbidities of asthma during childhood include rhinitis, overweight, depressive disorders, and more.¹

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The main goal of the current study was to assess the prevalence of co-morbid conditions and to assess cognitive status in teenagers with asthma.

PATIENTS AND METHODS

We reviewed the medical records of 314,897 consecutive 17-year-old male potential conscripts to the armed forces (Israel Defense Force [IDF]). Data regarding the diagnosis and the severity of asthma and other chronic conditions were collected. Available data included: medical evaluation form completed by the family physician, a medical history taken directly from each conscript, and a full physical examination. Based on the above information, an examining physician assigned a particular medical diagnosis to each conscript. All diagnoses were coded and stored in a computerized database.

Asthma Diagnosis

Asthma diagnosis was made based on the following data: a letter submitted by the family physician, clinical interview, use of asthma medications, and physical examination. Baseline spirometry was performed by all conscripts suspected of, or having a history of asthma. As part of the evaluation, exercise with or without methacholine challenge tests were performed (according to the American Thoracic Society Guidelines⁵) when the diagnosis was not certain. At the end of the evaluation, conscripts who had active asthma during the last 3 years were categorized into two groups: (1) mild intermittent asthma: infrequent mild asthma symptoms, requiring only intermittent β_2 agonist therapy with normal spirometry ($FEV_1 > 79\%$) and a normal exercise test and (2) persistent asthma: frequent or severe asthma symptoms (documented by the family physician) treated with at least one controller medication (inhaled corticosteroids or leukotriene receptor antagonists); or active asthma with a baseline $FEV_1 < 80\%$ predicted; or a positive exercise test. The criteria for asthma severity classification are similar but not identical to the Global initiative for asthma (GINA) current classification,⁶ and did not change during the period of the study. The main difference between the classification used by the IDF and the GINA classification is that conscripts with active asthma could be defined as having persistent asthma on the basis of a positive exercise test. It was in order to prevent conscripts with exercise induced bronchospasm from serving in combat units.

Cognitive Status

Every conscript had a battery of cognitive tests as part of routine evaluation before being assigned to a military unit. These tests yield a total score that is a highly validated measure of general intelligence and is

equivalent to a normally distributed intelligence quotient (IQ).⁷ They have both a written and verbal component and are administered by a trained technician. The cognitive assessment is composed of four subtests: (1) arithmetic, assessing reasoning, concentration, and concept manipulation; (2) similarities, assessing verbal abstraction and categorization; (3) a modified version of Raven's Progressive Matrices,⁸ which is a multiple choice measure of nonverbal abstract reasoning and problem solving abilities; and (4) a modified, Otis type, verbal intelligence test of mental ability, adapted from the U.S. Army Alpha Instructions Test,⁹ which measures the ability to understand and carry out verbal instructions. Each of these four results were amalgamated and rounded-up to give one of nine possible scores (10 = lowest, 90 = highest).

Other Co-Morbidities

All conscripts were also evaluated for the presence or absence of other chronic conditions with specific attention given to the following diagnoses: hypertension (systolic blood pressure > 140 , or diastolic blood pressure > 90), over and under-weight ($BMI > 25$ or $< 17 \text{ kg/m}^2$), atopic dermatitis, anaphylaxis (one or more events in the past), recurrent urticaria, recurrent or persistent rhinitis during the previous 3 years, chronic sinusitis (more than five events of suspected bacterial sinusitis treated with antibiotics during last 3 years with evidence of chronic sinusitis on CT scan), irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), peptic ulcer disease, thyroid disorders (hyper or hypo thyroidism), diabetes mellitus (type I), rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and familial Mediterranean fever (FMF).

The research protocol was reviewed in its entirety and approved by the Human Use Committee of the IDF medical corps.

Statistical Analysis

Prevalence of disease was calculated among those with asthma (total, intermittent, and persistent) and those without asthma. The association between asthma and other diseases was evaluated using univariate and multivariate logistic regression analyses. Odds ratios (OR) and 95% confidence intervals (95%CI) were calculated. For the multivariate analysis, all the independent variables were entered into the model in the first block using the forward LR method. Inclusion criterion for entering into the model was a score statistic of $P = 0.05$ and the exclusion criterion was a Wald statistic of $P = 0.05$. Asthma was entered in the second block. A P -value < 0.05 was considered statistical significant. Statistical analyses were performed using SPSS version 17.0.

RESULTS

Active asthma was found in 6.9% ($n=21,728$) of subjects: 3.3% with mild intermittent and 3.6% with persistent asthma.

Cognitive Score

The population frequency of asthma is shown for each centile of the cognitive score in Figure 1. There is a positive correlation between asthma prevalence and the cognitive score. The prevalence of asthma for the highest percentile of the cognitive score was 55% higher than in the lowest centile (8.4% vs. 5.4% $P < 0.001$). This was found to be consistent when reported in each year separately (Fig. 2). For the latter analysis we first grouped the subjects into three groups: lower cognitive score (10, 20, and 30) middle score (40, 50, and 60), and upper score (70, 80, and 90).

Co-Morbidities

Prevalence and odds ratio (OR) of each co-morbidity in asthmatics (all, intermittent, and persistent asthma) compared to no asthmatics are presented in Table 1.

Chronic rhinitis prevalence was significantly higher in asthmatics compared to non-asthmatics (35.5% vs. 5.3%, $OR = 9.87$, $P < 0.001$). Prevalence was higher in subjects with persistent compared to intermittent asthma (37% vs. 33%, $P < 0.0001$).

Other allergic disorders—atopic dermatitis, urticaria, and anaphylaxis—prevalence were significantly higher in asthmatics compared to non-asthmatics (2.1% vs. 0.4%, 1.0% vs. 0.3%, and 0.4% vs. 0.1%, respectively) with OR of 3.01, 1.50, and 2.52, respectively (P -values < 0.001 for all). The prevalence of atopic dermatitis, urticaria, and anaphylaxis in subjects with persistent asthma tended to be higher than in those with intermittent asthma (2.6%, 1%, and 0.4% vs. 1.6%, 0.9%, and 0.3%, respectively) but this only reached statistical significance for atopic dermatitis ($P < 0.01$).

Chronic sinusitis was significantly more prevalent in asthmatics compared to non-asthmatics (0.4% vs. 0.1%,

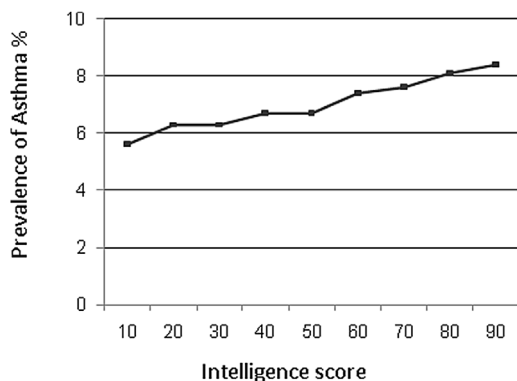


Fig. 1. Intelligence score and prevalence of asthma in 17-year-old boys (prevalence of asthma in the total cohort was 6.9%).

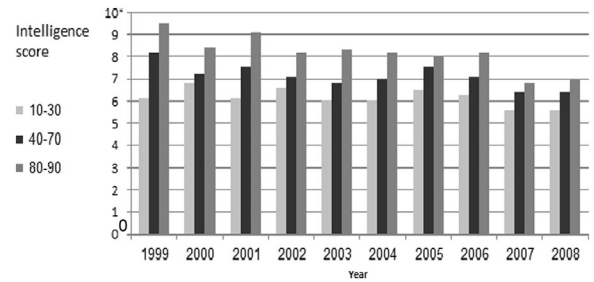


Fig. 2. Prevalence of asthma, at each intelligence score level, broken down per year.

$OR = 4.42$, $P < 0.001$) and in those with persistent asthma compared to those with intermittent asthma (0.5% vs. 0.3% ($P < 0.001$)).

Body mass index (BMI): a “U” shape relationship was found between BMI and asthma (Fig. 3). Prevalence of overweight was significantly higher in asthmatics than in non-asthmatics (19.9% vs. 16.8%, $OR = 1.25$, $P < 0.001$). The prevalence of overweight in subjects with persistent asthma was slightly higher than in those with intermittent asthma (20.1% vs. 19.6%) but the difference was not statistically significant. Prevalence of underweight (BMI < 17 kg/m²) was significantly higher in asthmatics than in non-asthmatics (3.2% vs. 2.8%, $P < 0.001$). There was an increased risk of low BMI for those with persistent asthma compared to non-asthmatics ($OR = 1.27$, $CI = 1.14$ – 1.41) but not for those with intermittent asthma ($OR = 1.06$, $CI = 0.93$ – 1.19).

Gastrointestinal diseases: prevalence of IBS was significantly higher in asthmatics compared to non-asthmatics (1.0% vs. 0.5%, $OR = 1.20$, $P < 0.001$). This remained significant in the persistent asthma group (1.2% compared to 0.5% in non-asthmatics, $P < 0.001$, $OR = 1.52$, $CI = 1.26$ – 1.83), but not in the mild asthma group (0.8%, $P = 0.40$). Prevalence of IBD and peptic ulcer disease was not significantly different in asthmatics compared to non-asthmatics.

Endocrine disorders: prevalence of thyroid disorders (hypo- or hyper-thyroidism) were significantly higher in asthmatics (0.4%) than in non-asthmatics (0.2%, $OR = 1.52$, $CI = 1.19$ – 1.93). The increased prevalence of thyroid disorders was only seen in the persistent asthma group (0.5%, vs. 0.2% in non-asthmatics, $P < 0.001$, $OR = 1.52$, $CI = 1.30$ – 2.35).

Prevalence of type I diabetes mellitus was lower in asthmatics compared to non-asthmatics (0.1% vs. 0.3%), but this difference was not significant.

The prevalence of hypertension was similar in asthmatics and non-asthmatics (3.1% in both groups).

Chronic inflammatory or connective tissue diseases (RA, SLE, and FMF) prevalence was not different in asthmatics compared to non-asthmatics.

TABLE 1—Prevalence and Odds Ratio for Having Various Co-Morbidities in 17-Year-Old Conscripts Males With Asthma Compared to Conscripts Without Asthma

Co-morbidity	Group	Prevalence (%)	OR	95%CI	P
Recurrent/persistent rhinitis	No asthma	5.3		1	
	All asthmatics	35.5	9.87	99.32–10.01	<0.001
	Intermittent asthma	33.0	8.84	8.46–9.24	<0.001
	Persistent asthma	37.8	10.90	10.47–11.37	<0.001
Atopic dermatitis	No asthma	0.4		1	
	All asthmatics	2.1	3.01	2.66–3.42	<0.001
	Intermittent asthma	1.6	2.42	2.03–2.89	<0.001
	Persistent asthma	2.6	3.52	3.05–4.08	<0.001
Urticaria	No asthma	0.3		1	
	All asthmatics	1.0	1.50	1.28–1.78	<0.001
	Intermittent asthma	0.9	1.5	1.23–1.92	<0.001
	Persistent asthma	1.0	1.48	1.20–1.82	<0.001
Anaphylaxis	No asthma	0.1		1	
	All asthmatics	0.4	2.52	1.90–3.35	<0.001
	Intermittent asthma	0.3	2.29	1.56–3.37	<0.001
	Persistent asthma	0.4	2.73	1.94–3.84	<0.001
Severe chronic sinusitis	No asthma	0.1		1	
	All asthmatics	0.4	4.42	3.61–5.71	<0.001
	Intermittent asthma	0.3	2.93	1.99–4.33	<0.001
	Persistent asthma	0.5	5.90	4.49–7.77	<0.001
Over Weight (BMI > 25)	No asthma	16.8		1	
	All asthmatics	19.9	1.25	1.20–1.29	<0.001
	Intermittent asthma	19.6	1.22	1.16–1.29	<0.001
	Persistent asthma	20.1	1.27	1.20–1.33	<0.001
Under Weight (BMI < 17)	No asthma	2.8		1	
	All asthmatics	3.2	1.17	1.07–1.27	<0.001
	Intermittent asthma	2.9	1.06	0.93–1.19	0.38
	Persistent asthma	3.4	1.27	1.14–1.41	
Irritable Bowel Syndrome (IBS)	No asthma	0.5		1	
	All asthmatics	1.0	1.20	1.14–1.32	<0.001
	Intermittent asthma	0.8	1.10	0.88–1.38	0.4
	Persistent asthma	1.2	1.52	1.26–1.83	<0.001
Thyroid disorder (hypo or hyperthyroidism)	No asthma	0.2		1	
	All asthmatics	0.4	1.52	1.19–1.93	0.001
	Intermittent asthma	0.3	1.26	0.88–1.80	0.21
	Persistent asthma	0.5	1.75	1.30–2.35	<0.001
Peptic ulcer	No asthma	0.2		1	
	All asthmatics	0.3	1.17	0.88–1.56	0.27
	Intermittent asthma	0.3	1.13	0.75–1.67	0.56
	Persistent asthma	0.3	1.22	0.84–1.76	0.30
Inflammatory bowel disease (IBD)	No asthma	0.2		1	
	All asthmatics	0.1	0.88	0.50–1.55	0.65
Connective tissue disease (RA or FMF or SLE)	No asthma	0.2		1	
	All asthmatics	0.2	1.04	0.78–1.38	0.78
Diabetes mellitus	No asthma	0.3		1	
	All asthmatics	0.1	1.01	0.67–1.55	0.94
Hypertension	No asthma	3.1		1	
	All asthmatics	3.1	1.00	0.92–1.09	0.93

RA, rheumatoid arthritis; FMF, familial Mediterranean fever; SLE, systemic lupus erythematosus.

P-values and odds ratios are for the difference between asthmatics (total, intermittent, and persistent asthma) and non-asthmatics and were calculated using multiple regression analysis.

DISCUSSION

This large cohort study of teenage boys showed a positive association between high cognitive score and asthma. We also demonstrated the wide spectrum of asthma co-morbidities in adolescence.

The cognitive status of adults with asthma was reported in previous studies^{2,3} showing significant cognitive impairment. It was speculated that low cognition may be responsible for the lack of adequacy in using the inhalers.³

We found a single report from Scotland (1973), in children aged 10–15 years with asthma,

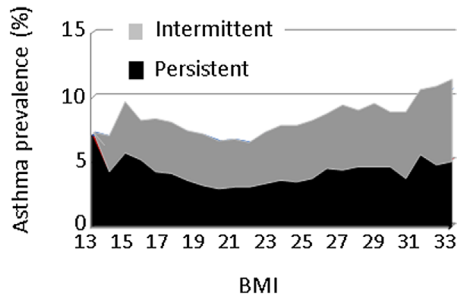


Fig. 3. Prevalence of asthma in 17-year-old males according to body mass index (intermittent asthma in gray and persistent asthma in black).

demonstrating a higher mean IQ than the general study population.¹⁰

There are several potential explanations for the difference in the cognitive level between adults and children with asthma. First, asthma has a different pathophysiology in children¹¹: the majority of children with asthma have an allergic background (“extrinsic asthma”) with a high remission rate while in adults, asthma is less often associated with allergy and atopic diseases (“intrinsic asthma”), and has a low remission rate. Similarly, adult asthma might be related to occupation, cigarette smoking, and stressful life events—all are strong risk factors for adult and less so in childhood asthma. Secondly, adult asthma tends to become more severe over the years. Consequently, the decrease in the cognitive level seen in adult asthmatics might be a result of cumulative hypoxic damage to the brain which becomes significant only after many years of disease activity.¹² Thirdly, according to the hygiene theory, asthmatic children tend to grow up in a cleaner family home,^{13–17} which is more common in families with higher cognitive and socioeconomic levels.^{14,17} Children born in such families might be more intelligent. Finally, it is possible that in families with higher cognitive level the likelihood of missing the diagnosis of asthma is low. The opposite might also be true. It was reported that children from poorer families are less likely to receive a diagnosis of asthma and treatment for asthma, reflecting different levels of access to health care.¹³

The most frequent co-morbidity found in our study population was recurrent or persistent rhinitis. It was present in about one third of those teenagers with asthma compared to only 5% in those without asthma. The association between asthma and atopic phenomena is well documented and was described as the “atopic march.”^{18,19} Atopic dermatitis starts first in infancy and is followed by food allergies, aeroallergen sensitization, rhinitis, and finally asthma, with increasing age. Chronic rhinitis and sinusitis in our cohort were more common in asthmatics than in non-asthmatics (OR of 9.87 and 4.42, respectively). The relationship between asthma and rhinitis is

well established in adults. It has been claimed that most patients with asthma also have rhinitis and 10–40% of patients with allergic rhinitis have co-morbid asthma.²⁰ Children with allergic rhinitis have a similar risk of asthma as those with non-allergic rhinitis.²¹ In our population, rhinitis was more common in persistent compared to intermittent asthma. The link between the severity and/or control of both diseases in children and adults has been previously demonstrated in large studies^{22–25} and patients with severe uncontrolled asthma commonly have severe nasal disease (often chronic rhinosinusitis).^{26,27} Although treatment of rhinitis could improve the control of asthma also in children,²⁸ patients with mild rhinitis might not see a physician, and most patients who seek medical care have moderate-to-severe disease.^{29–33} Rhinitis is under diagnosed and undertreated in asthmatic children. It was found that in only half of asthmatic children with symptoms of allergic rhinitis were treated as such by a physician.³⁴ Our findings support the recommendation that assessment of asthma should include a search for and treatment of rhinitis and sinusitis.^{35,36} Although there are reports of the increased risk of asthma in patients with atopic dermatitis (around 30%),¹⁸ we were unable to find reports regarding the reverse association. In the current study, we found that the OR for atopic dermatitis in asthmatics is 3.0. The higher prevalence of atopic dermatitis in conscripts with persistent compared to intermittent asthma strengthens this association, suggesting that atopy is a risk factor for asthma. Asthma is a risk factor for anaphylaxis and food allergy.^{37,38} In our study, the OR for anaphylaxis in asthmatics was 2.52. The co-existence of food allergy and asthma is an important risk factor for anaphylaxis mortality. It is critical that the asthma be well controlled to reduce the likelihood of fatal food-related anaphylaxis, especially in young adults and adolescents.³⁹ Recurrent urticaria, was diagnosed in our study in 1.0% of asthmatics compared to 0.3% of the no-asthmatics (adjusted OR = 1.50). A recent study similarly showed that asthmatics up to the age of 10 years have an increased risk of urticaria (OR of 2.33).⁴⁰ In our cohort, a “U” shape relationship was found between BMI and asthma (Fig. 3). Both BMI above 25 kg/m² and below 17 kg/m² were associated with an increased risk for asthma. This relationship has been previously reported.^{41–43} Litonjua et al. showed that men with BMI in the lowest and highest quartiles were more likely to develop airway hyper-responsiveness.^{44,45} Our study confirms these findings in young males. The mechanism for this association is not clear, and it is possible that the association exists from birth. This is suggested by a meta-analysis of 147,252 children from 31 birth cohort studies reporting that both younger gestational age at birth (lower birth weight) and higher infant weight gain were associated with childhood asthma.⁴⁶ Irritable bowel syndrome in our study was also

found more frequently among asthmatics compared to non-asthmatics (OR 1.5). Only those with persistent asthma were at an increased risk for IBS while the prevalence in those with mild asthma was similar to those without asthma. Previous studies already reported the association between asthma and IBS with an OR ranging from 1.3 to 5.0.^{47–52} An association between IBS and severity of asthma has not been previously documented. Generalized abnormality of smooth muscle and of the autonomic nervous system in both the lungs and the intestine has been suggested to explain this association.⁵³ Thyroid disorders were found significantly higher in asthmatic teenagers in our cohort, and were more common in those with persistent asthma compared to mild or no asthma. We couldn't find any previous report of this association. Hyperthyroidism has been reported to negatively impact upon asthma control, with subsequent improvement of the asthma when the euthyroid state is restored.⁵⁴

The main strengths of this study are the large number of participants, the reliable diagnosis of asthma, and also the thorough investigation for any chronic disease done as part of the routine medical evaluation. Therefore, we believe that the observations reported in this study are highly reliable. The main limitation of the study is the lack of information on asthmatic female teenagers. Although female conscripts undergo medical evaluation similar to males we felt that the data is less reliable. Females are usually not candidates for combat assignments, and therefore generally less investigations are performed to find diseases that can limit their physical activity in the army, for example, asthma. Therefore, we elected not to include them in the study. A further limitation is the lack of racial diversity in our cohort which limits the ability to generalize our observations. Additionally, information was not available regarding smoking prevalence, and prevalence of other co-morbidities such as gastroesophageal-reflux; neither were we able to perform allergy tests.

CONCLUSIONS

A significant positive correlation between a higher cognitive score and prevalence of asthma was found in our cohort of adolescents. This association was found to be inversed in adult studies and the pathophysiology is unclear. The most likely explanation in children is that those with a higher cognitive score tend to live in a cleaner environment, increasing the incidence of asthma. Rhinitis is by far the most prevalent co-morbidity found in one third of adolescent asthmatics. A strong association was found between asthma and atopic diseases such as atopic dermatitis and anaphylaxis. Also, recurrent sinusitis, high and low BMI, irritable bowel syndrome, and thyroid disorders were found more commonly in asthmatics. The co-morbidities: atopic dermatitis, rhinitis and sinusitis,

irritable bowel syndrome, and thyroid disorders—were found more commonly in those with persistent asthma compared to those with mild intermittent asthma. Clinicians treating patients with asthma should search for co-morbidities and treat them, especially in patients with persistent or difficult asthma. These co-morbidities might affect the ease of control and the severity of the asthma. We have reported for the first time an association between high cognitive level and asthma in adolescence, and this should prompt further evaluation.

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