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Asthma phenotypes and associated comorbidities in a large cohort of adolescents in Israel

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ABSTRACT

Objectives: Asthma is a multifactorial, heterogeneous, complex and common chronic respiratory disease driven by diverse mechanisms. Although asthma presents various clinical forms with different levels of severity, it is unclear whether asthma severities are a consequence of disease management or varied etiologies. We sought to investigate this question.

Methods: This article presents a cross-sectional study of 113,671 Israeli adolescents. Univariate and multivariable logistic regression models were performed to analyze the independent associations between mild asthma and moderate-to-severe asthma phenotypes and coexistent medical conditions within each gender separately. Hierarchical clustering of the odds ratios of the diverse statistically significant medical conditions associated with asthma severity-gender groups was also performed. We focused on the allergic and neurological-cognitive-mental disorders.

Results: Among males, two associations were common to both asthma groups (atopic dermatitis and allergic rhinitis), five unique to mild asthma (urticaria/angioedema, Hymenoptera/bee allergies, allergic conjunctivitis, epilepsy and migraine) and two unique to moderate-to-severe asthma (learning disabilities and ADD/ADHD (Attention-deficit disorder/Attention-deficit/hyperactivity disorder)). Among females, two associations were common to both clinical asthma groups (allergic rhinitis and urticaria/angioedema), and five unique to moderate-to-severe asthma (atopic dermatitis, learning disabilities, ADD/ADHD, anxiety/mood disorders and migraine). Allergic rhinitis was the only condition to be associated with all four groups. Learning disabilities and ADD/ADHD were only associated with moderate-to-severe asthma (but not with mild asthma), in both males and females. Hierarchical clustering analysis uncovered two prominent clusters, separating mild from moderate-to-severe asthma.

Conclusions: The differences between mild and moderate-to-severe asthma enhance asthma phenotype characterization, with respect to comorbidities, and indicate varied etiologies.

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Asthma phenotypes; comorbidities; adolescents; asthma severity; hierarchical clustering

Introduction

Asthma is a multifaceted, complex and common chronic respiratory disease that affects over 330 million people worldwide. Its prevalence, clinical impact upon quality of life and healthcare expenditure, alongside mortality and morbidity statistics, provide a complete and relevant indication of its significance and global burden (1–3). Its pathophysiology includes abnormalities of the immune regulation of allergic, inflammatory and neuroendocrine responses (4,5). It is characterized by intermittent bronchial hyper-responsiveness and reversible airway obstruction, yet presents with multiple clinical forms and levels of severity. In light of this clinical and pathophysiological

heterogeneity, there have been numerous attempts to define asthma phenotypes (6–18). Although early attempts were merely one-dimensional emphasizing a simple classification criterion such as the duality of atopic versus non-atopic asthma, later attempts were based on either disease symptom severity or asthma pathogenesis, and more recent analyses have clustered patients by multiple features (19–21). Each phenotype is defined using some or all of the following respiratory symptoms and/or other clinical, trigger-related, healthcare utilization and treatment, demographic and pathological parameters: interactions between genetic and environmental factors, clinical severity, age of onset, atopy, physiological indicators and

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inflammatory cells involved in the pathophysiologic pathway, spirometry, airway hyperresponsiveness, exhaled nitric oxide (NO) concentration, requirement for medication and type of treatment, persistence of wheezing (treatment responsiveness), triggers and trigger-related phenotypes, healthcare utilization and comorbidities. Recently, elucidation of asthma phenotypes has been further refined on the basis of pathophysiologic mechanisms (endotypes) and associated biomarkers (19,22,23). Of note, transitions between asthma phenotypes were common, mainly in early childhood but less in late childhood (18). Classification of asthma phenotypes is important for understanding these mechanistically distinct groups and identifying relevant and distinctive cellular or molecular biomarkers and then, hopefully, predicting prognosis, clinical response, outcome and ultimately, achieving personalized targeted therapy.

As asthma is such a common diagnosis, other conditions frequently occur concurrently. A recent, large cross-sectional analysis (24) revealed that 36 of 39 assessed comorbidities were more common in adults with asthma, where 62.6% (compared with 46.2% of non-asthmatic adults) had at least one coexisting condition and 16.3% (compared with 8.7%) had four or more coexisting conditions. Asthma comorbidity places a significant burden on individuals and the healthcare system with higher rates of hospitalization, emergency department visits and ambulatory care claims among individuals with asthma compared with those without asthma (25–27). Increasing attention has been paid in recent years to comorbidities (28–34), including allergic diseases (such as allergic rhinitis, food allergies, hymenoptera sting allergy, atopic dermatitis and atopic skin conditions), migraine (35), attention-deficit/hyperactivity disorder (ADHD) and psychogenic disorders (depressive or mood disorders and anxiety). These were shown to be more prevalent among asthmatic subjects and some may be related to a more severe form of asthma, refractoriness to treatment, impaired health-related quality of life and increasing demand on resources. In addition, smoking-related comorbidities, metabolic syndrome, gastroesophageal reflux disease (GERD) and obstructive sleep apnea were shown to be associated with asthma and to influence its clinical manifestation and treatment response. The associations of specific asthma phenotypes with specific comorbidities and their impact on asthma control and management were investigated (33,36–38), as such comorbidities may be coincidental findings or they may contribute directly to asthma severity (39) and to difficult-to-

treat phenotype (33). Recently, a diagnostic and management algorithm for assessing comorbid conditions in patients with severe asthma was outlined (33).

A notable sex disparity has been observed in asthma prevalence, incidence, severity, hospitalization rate and duration, being more common and severe in boys during early childhood, equalizing during adolescence and having female predominance in adulthood (40–42). The role of sex hormones, genetic predisposition and comorbidities in airway inflammation, smooth muscle contraction, mucus production and airway mechanics has been demonstrated (43,44). Identifying sex-specific risk factors for asthma (45) may have potential diagnostic, therapeutic and prognostic implications.

Previously, we employed a comparative approach to characterize mild asthma and moderate-to-severe asthma with reference to subjects without asthma among Israeli adolescent males and females separately, while examining secular trends and relationships with sociodemographic variables and anthropometric indices (46). Differences between asthma severity phenotypes among males and females suggested that different mechanisms might be involved in the pathogenesis of mild compared with moderate-to-severe asthma, and between males and females (46). Here, we take a further step, defining heterogeneity of asthma among males and females based on coexistent medical conditions. This approach may shed light on the origin and development of diverse asthma phenotypes and hopefully have an impact on management.

Objectives

The objective of this study was to examine similarities and differences between mild asthma and moderate-to-severe asthma within genders regarding associations with coexistent medical conditions. We also explore the intricate and hierarchical relationships between asthma severity, gender and medical signatures.

Hypothesis

If the progression of asthma in childhood from mild to moderate-to-severe symptoms depends on proper management and treatment, one would expect similar associations with coexisting medical conditions. However, if these two groups' coexisting medical conditions are not similar, we may be dealing with separate sub-populations with differing susceptibilities to developing mild or moderate-to-severe asthma.

The study hypothesis is that the asthma severity phenotypes within each gender are characterized by unique medical signatures of allergic and neurological-cognitive-mental comorbidities. Hierarchical clustering might uncover relationships between these factors.

Methods

Data source

Military service is compulsory in Israel though various minorities and religious women are exempt. Mandatory pre-induction medical examination of all recruits takes place at regional recruitment centers where they undergo a comprehensive medical interview and physical examination by board certified physicians who then refer for further investigation as necessary. At the end of the medical process, a medical profile and appropriate Functional Classifications Codes (FCCs) describing the medical status and severity as well as an occupational ranking, are assigned to each recruit. Medical data and all FCCs are routinely stored in the main Israel Defense Force (IDF) database (47) which was the source of the data analyzed in this study. The medical processes and data are routinely assessed and evaluated for control and assurance (47–50). More detailed information on the medical process and database, as well as characteristics of the population, can be seen elsewhere (51).

The study population

The study population included all northern district recruits examined at one recruitment center between the years 1987–2010 inclusive. To ensure a uniform medical baseline, we focused on conscripts who completed the medical profiling process at the age of 16–19. No selection criteria (neither inclusive nor exclusive) were applied. Only the northern recruitment center was chosen as the medical examinations at this center were performed by a small group of highly trained medical personnel with subsequent documented high quality of its medical processes (48). The study was approved by the IDF Institutional Review Board, approval number 1199–2012 and was conducted in compliance with the Helsinki Agreement.

Asthma diagnosis and categorization

Asthma diagnosis was established by medical history including primary care records, physical examination, spirometry results together with subsequent

pulmonologist's evaluation and conclusion. The definition of *active asthma* included wheezing, chronic cough, dyspnea on effort, asthma attacks upon exposure to allergens during the last 3 years and use of medication. This was subdivided into *mild asthma* (normal rest and exercise spirometry including lack of confirmed reversible airflow obstruction or bronchial hyper-reactivity and medication only as needed) and *moderate-to-severe asthma* (evidence of airway hyper-reactivity on spirometry including confirmed reversible airflow obstruction or bronchial hyper-reactivity and medication on a daily basis). These correspond to the GINA (Global Initiative for Asthma) classifications (1,52) of “intermittent and mild” and “moderate and severe” persistent asthma groupings (http://www.medicalcriteria.com/criteria/pul_asthma.htm), which were the most recent and acceptable criteria at the time of data collection. These classification definitions remained stable over the entire study period, as well as the standards and methods for asthma diagnosis enabling comparison between years and sub-populations.

Definitions of anthropometric indices and comorbidities

In addition to anthropometric and medical data, the computerized database contained further personal, educational and socio-demographic information about each recruit as recorded by the Ministry of Internal Affairs. This was validated and updated by interviews and questionnaires. Socio-demographic variables were included in the analysis. Many findings have been previously reported (46) and we now report novel findings regarding the additional coexistent medical conditions. Definitions of these key variables, which were used in the univariate analysis (and if statistically significant also in the multivariable logistic regression analysis), are provided in detail in [Appendix A](#).

Statistical method

Characteristics were described by proportions and means $\pm$ SD.

As this study aims to investigate the independent associations between comorbidities and the outcome in the two asthma groups (mild or moderate-to-severe) for each gender separately, a three-step process was applied:

First, a distinct univariate analysis was conducted for each of the four combinations of clinical asthma group and gender (mild asthma among males, moderate-to-severe asthma among males, mild asthma among

females, moderate-to-severe asthma among females), with the two reference groups comprising subjects of the corresponding gender without asthma (males without asthma and females without asthma). Univariate analyses used Chi-square or Fisher's exact test to compare categorical variables between groups and unpaired Student's T-test for continuous variables.

Subsequently, a distinct multivariable logistic regression model was conducted for each combination of clinical asthma group and gender again using the above two reference groups. Covariates in each model included variables which were found to be significantly associated with the outcome in the univariate analysis as described in [Appendix B](#), i.e. the criterion for entrance into each of the regression models was a probability value of $P < 0.05$ in the corresponding univariate analysis, and $P > 0.10$ for removal from the model. Co-linear variables were excluded from the models, which were adjusted to control for potentially confounding effects. Associations of each of the two clinical asthma groups were compared with each other, treating each gender separately. Odds ratios (ORs) and 95% confidence intervals (95% CI) were calculated. The statistical tests were two-tailed.

A similar approach was conducted directly comparing moderate-to-severe asthma subjects to mild asthma subjects (as reference).

All analyses were carried out using the SPSS statistical package (version 22.0; IBM Corporation, Armonk, NY).

Clustering analysis

Hierarchical clustering of the ORs of the different medical conditions (only allergic as well as neurological-cognitive-mental disorders were taken into account) and asthma severity-gender groups, was performed with Partek® Genomics Suite® software, version 6.6 Copyright ©; 2014 Partek Inc., St Louis, MO, USA; with Pearson's dissimilarity and complete linkage. Of note, only statistically significant associations in the multivariable analysis were included, whereas non-significant values (variables included in the multivariable analysis) or missing values (variables not included in the multivariable analysis, due to lack of association in the univariate analysis) were conferred a value of 1, namely no significant association/difference.

Results

Study population

The initial study population comprised 158,255 subjects, of whom 59% were males. To ensure a uniform

and valid medical baseline, we focused on 116,979 records of conscripts who completed the medical profiling process between 16 and 19 years of age. Of these, 3308 records lacked height and/or weight data and were omitted. The final study population comprised 113,671 adolescents including 66,547 males and 47,124 females.

Associations with coexistent medical conditions

In order to investigate the independent associations between comorbidities and anthropometric indices and the outcome in the two asthma groups (mild or moderate-to-severe) separately within genders, analyses were conducted to compare each of the four categories (mild asthma among males, moderate-to-severe asthma among males, mild asthma among females and moderate-to-severe asthma among females) with its corresponding reference group (males without asthma and females without asthma). We conducted univariate analyses and consequent multivariable logistic regression models as described above in the Methods section. The comprehensive associations with coexistent medical conditions found by univariate analysis are shown in the [Supplementary Table S1](#) and described in [Appendix B](#). The multivariable analysis findings are shown in the [Supplementary Table S2](#). Notably, each of the multivariable logistic regression models encompasses diverse personal and socio-demographic variables, anthropometric indices and medical comorbidities which were significantly associated with the asthma severity and gender group. Yet, we focus on the well-established associations with allergic as well as neurological-cognitive-mental conditions as presented in [Figure 1](#).

Among males, the multivariable logistic regression models conducted for each group revealed seven positive associations with mild asthma ([Figure 1A](#)) and four with moderate-to-severe asthma ([Figure 1B](#)) – only two were common to both groups (atopic dermatitis and allergic rhinitis), five unique to mild asthma (urticaria/angioedema, Hymenoptera/bee allergies, allergic conjunctivitis, epilepsy and migraine) and two unique to moderate-to-severe asthma (learning disabilities and ADD/ADHD).

Among females, the multivariable logistic regression models conducted for each group revealed only two positive associations with mild asthma ([Figure 1C](#)) and seven with moderate-to-severe asthma ([Figure 1D](#)) – two were common to both clinical asthma groups (allergic rhinitis and urticaria/angioedema), and five unique to moderate-to-severe asthma

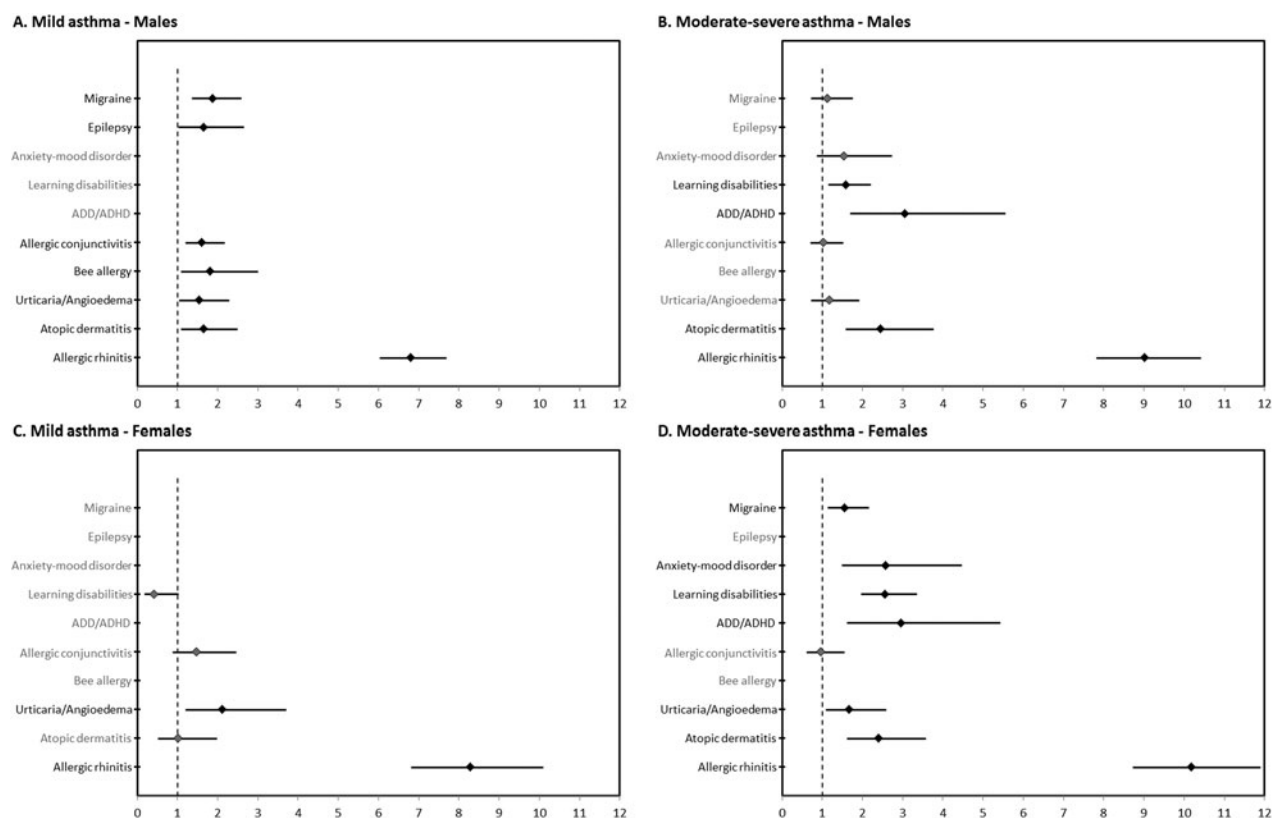


Figure 1. Correlates (ORs and 95% CIs) of mild asthma (A, in males; B, in females) and moderate-to-severe asthma (C, in males; D, in females) with comorbidities in the multivariable logistic regression analysis. Significant associations are marked by black text and rhombus, whereas non-significant associations are marked by gray text and rhombus. Medical conditions are grouped to allergic conditions and neurological-cognitive-mental conditions, and sorted by OR within the moderate-to-severe asthma phenotype. Of note, only these variables which were significant in the univariate analysis and included in the multivariable regression analysis are shown.

(atopic dermatitis, learning disabilities, ADD/ADHD, anxiety/mood disorders and migraine).

Among the allergic and neurological-cognitive-mental conditions, allergic rhinitis was the only condition to be associated with all four groups. The positive associations of allergic rhinitis with asthma had the largest OR (at least 6.8 compared with a range of ~1.5–3). Learning disabilities and ADD/ADHD were only associated with the moderate-to-severe form of asthma but not with mild asthma, in both males and females (Figure 1). Pneumothorax was only associated with moderate-to-severe asthma in males and with mild asthma in females (OR of ~6 and 19, respectively, [Supplementary Table S2](#)). No protecting effects in these two clinical asthma groups were observed.

Hierarchical clustering

Distinctive patterns of associations of medical conditions with clinical asthma phenotypes emerged within genders and between genders. In addition, within each of the four groups, diverse positive associations were observed among the allergic and neurological-

cognitive-mental conditions. To further investigate the intricate relationships between clinical asthma severity and gender (with regard to medical signature of allergic and neurological-cognitive-mental conditions) hierarchical clustering was conducted.

Two prominent clusters were obtained: one within the mild asthma categories of both genders, and the other, within the moderate-to-severe categories of both genders (Figure 2). The medical conditions were mixed rather than being segregated into allergic and neurological-cognitive-mental conditions.

The cluster of moderate-to-severe asthma was characterized by positive associations of asthma with allergic rhinitis, ADD/ADHD, learning disabilities and atopic dermatitis in both genders. Anxiety/mood disorder, urticaria/angioedema and migraine were associated with asthma only in females and there were no associations with allergic conjunctivitis, epilepsy and Hymenoptera/bee allergies.

The cluster of mild asthma was characterized by positive associations of asthma with allergic rhinitis and urticaria/angioedema. Allergic conjunctivitis, migraine, Hymenoptera/bee allergies, epilepsy,

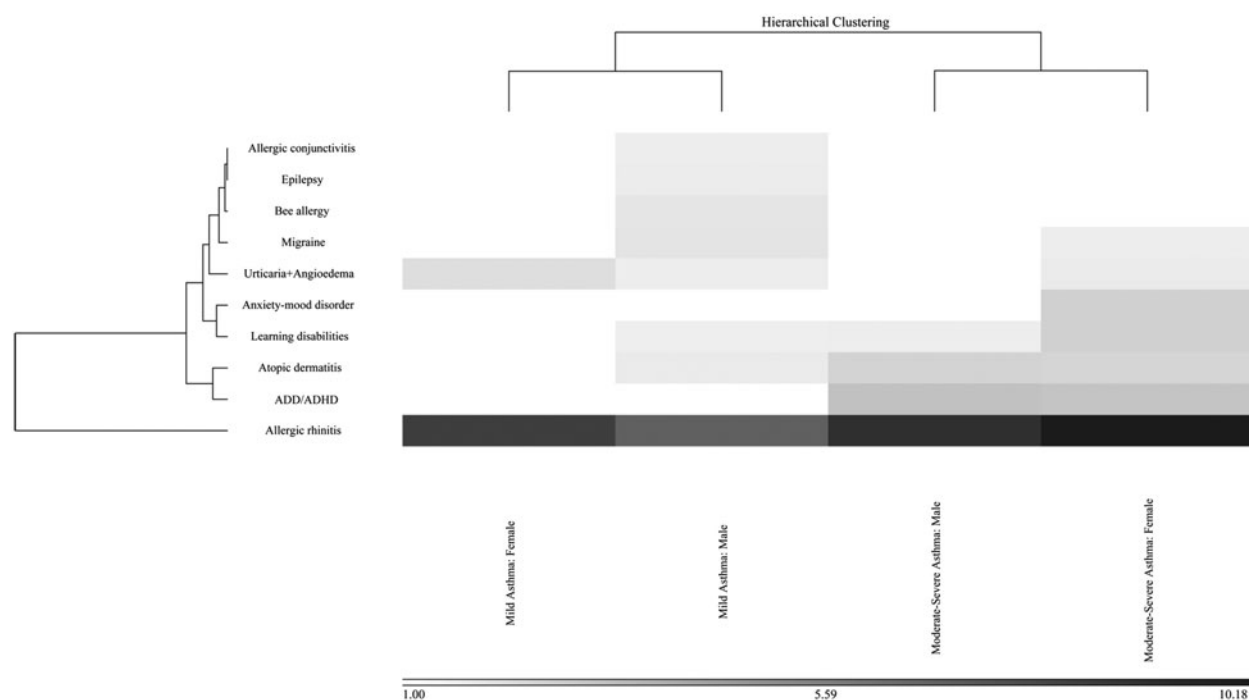


Figure 2. Hierarchical clustering of odds ratios of the allergic and neurological-cognitive-mental conditions and gender–asthma severity groups. Statistically significant increased risks are denoted by blue shades, whereas white demarcates nonsignificant ORs.

learning disabilities and atopic dermatitis were associated with asthma only in males and there were no associations with anxiety/mood disorder and ADD/ADHD.

In females the neurological-cognitive-mental conditions were mainly associated with moderate-to-severe asthma, and in males the allergic conditions were mainly associated with mild asthma (Figures 1 and 2).

Direct comparison of asthma phenotypes' associated comorbidities

To further assess differences between comorbidities associated with asthma severity groups, moderate-to-severe asthma subjects ($n=2,077$) were directly compared with mild asthma subjects ($n=2,504$). A similar approach was applied, in which variables significantly associated with increased/decreased risk of developing moderate-to-severe asthma were entered into a multi-variable logistic regression model. This direct analysis further supports the association of the allergic comorbidities (allergic rhinitis, atopic dermatitis, allergic conjunctivitis, and borderline significance of urticaria and angioedema) and neurological-cognitive-mental comorbidities (learning disorders, migraine, ADD/ADHD and anxiety-depression) with increased risk of developing moderate-to-severe asthma (Figure 3). In addition, female gender, above normal body mass index (BMI) and hypertension are all associated with

increased risk of developing moderate-to-severe asthma, whereas family related variables (eldest child and bigger family size) display a protective effect.

Discussion

The disparities between mild and moderate-to-severe asthma, among both males and females, with regard to associations with comorbidities (mainly allergic and neurological-cognitive-mental conditions) may suggest varied etiologies. The findings of this study are consistent with our previous analysis based on secular trends of asthma prevalence as well as association with socio-demographic and anthropometric risk factors (46). This study further strengthens the growing body of evidence supporting this notion.

This study's major strengths include a large population size (113,671 adolescents), long period of data collection (24 years), a uniform screening process for all subjects based on thorough anamnesis and standardized high-quality medical examinations, and stable diagnostic criteria for asthma and the other medical conditions, throughout the study period. A high-quality asthma diagnosis was made by experts in pulmonology based on physical examination and pulmonary function tests and supported by inquiry about medical history and documentation. Other objective evidence including exhaled NO and methacholine bronchial challenge, was collected in some subjects and we

Moderate-severe asthma vs. Mild asthma

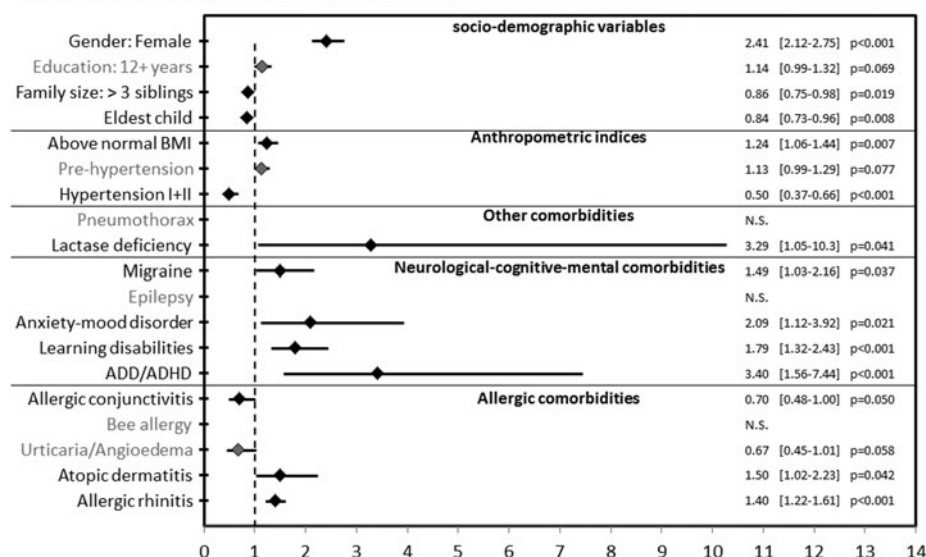


Figure 3. Correlates (ORs and 95% CIs) of moderate-to-severe asthma vs. mild asthma in the multivariable logistic regression analysis. Significant associations are marked by black text and rhombus, whereas non-significant associations are marked by gray text and rhombus. Variables are grouped to socio-demographic ones, anthropometric indices and medical conditions (allergic conditions, neurological-cognitive-mental conditions, and other conditions). N.S. stands for “Not significant” in the univariate analysis, therefore not included in the multivariable regression analysis (for variables which were shown in Figure 1).

found the great majority were consistent with the reported physician-designated diagnosis and severity (data not shown). Similar rigorous screening procedures were applied for all other comorbidities, regardless of asthma existence and conditions. Noteworthy, diagnosis of medical conditions among all study population – both asthmatic subjects and non-asthmatic ones – is based on the same medical screening process, rather than a subject-driven referral to clinic. Cross-sectional surveys and small cohorts support the relationship of asthma with diverse comorbidities including: upper airway diseases (rhinitis – usually allergic, sinusitis and rhinosinusitis), neurologic disorders (learning disorders – mainly ADHD, migraine and epilepsy) and psychological dysfunction (depression, anxiety, mood and behavioral disorders), GERD and other gastrointestinal (GI) diseases (dyspepsia), laryngeal dysfunction (mainly paradoxical vocal fold movement), pulmonary and bronchial diseases (chronic obstructive lung disease, bronchiectasis, bronchitis, bronchopneumonia, recurrent respiratory infections), atherosclerotic cardiac disease and circulatory disorders, dermatologic conditions (eczema/psoriasis), connective tissue/rheumatic diseases, metabolic disorders and hormonal imbalance, immunologic and hematologic disease, obesity, sleep apnea and chronic pain conditions (24,28–31). Assessing the prevalence of physical and mental health comorbidities in asthmatic subjects has often served to inform clinicians

about the close relationships between asthma and these diverse conditions, to help identify asthma early and appropriately control, treat and manage both asthma and the comorbidities and to improve the outcomes and quality of life. The potential for comorbidity clusters to exert combined effects on asthma outcome was recently highlighted (32). Cluster analyses of asthma-related comorbidities have identified diverse profiles and clinical asthma phenotypes in children and adults (9,53,54). Evidence about unique associations between coexisting morbidities and diverse asthma phenotypes is now emerging (36–38), yet without considering the distinction between genders. The significance of gender to asthma development and the differences in asthma-associated comorbidities between genders (and asthma severity groups) have strongly emerged in this study.

This study aimed to shed light on the coexistence of medical conditions with asthma severity phenotypes among adolescent males and females. Most of the aforementioned medical conditions were indeed associated with asthma (in the univariate analysis), yet not necessarily with both mild and moderate-to-severe asthma, and some conditions were prevalent in either males or females. After adjustment for background variables (in the multivariable logistic regression analysis), the allergic and neurological-cognitive-mental conditions were determined to be associated with asthma. Further hierarchical clustering analysis uncovered

unique associations, separating mild from moderate-to-severe asthma and supporting the notion of differential mechanisms in the development of asthma severity groups. The medical conditions were mixed rather than segregated into allergic and neurological-cognitive-mental conditions, suggesting intricate interactions between asthma and coexistent diseases.

Direct comparison between moderate-to-severe asthma to mild asthma further supported the associations of allergic comorbidities and neurological-cognitive-mental comorbidities with increased risk of developing moderate-to-severe asthma. It also brought to light associations of lactase deficiency and hypertension with development of moderate-to-severe asthma. Little is known on these associations which required further study. Altogether, this analysis strengthens the notion that the two asthma severity groups are probably etiologically distinct phenotypes of asthma.

Focusing on associations with particular comorbidities

The following will focus on associations of asthma severity and gender groups with ADHD and atopic dermatitis – and discuss the possible implications of these associations. These were both associated the moderate-to-severe asthma, and the latter with mild asthma only in males.

Asthmatic children have a higher risk of ADHD, where the magnitude of association increases with asthma severity (55). Increased rates and severity of attention-deficit symptoms have been demonstrated in asthmatic children, with distinct gender differences (56). This may be due to the burden of their medical condition and may reflect the negative impact of asthma on neurobehavioral health. Swedish twin modeling indicated that the association of childhood asthma with the subsequent development of hyperactivity-impulsivity could be partly explained by genetic influences. Nevertheless, it was suggested that ADHD and asthma are independently transmitted in families.

Children with ADHD are more likely to have not only asthma but also atopic dermatitis as well as allergic conditions (allergic rhinitis and allergic conjunctivitis). In addition, the odds of having ADHD and asthma have been reported to significantly increase in children with atopic dermatitis. Boulet and Boulay (29) claimed that “there is epidemiological evidence of an overlap between asthma and atopic dermatitis in early life, in addition to being a risk factor for asthma, particularly in regard to some severe forms of asthma”.

The mechanism of this association remains unclear. Yet, the hippocampus might potentially be the connecting link between these conditions. Both asthma (in males) (57) and ADHD (58) are associated with structural brain differences – mainly a smaller hippocampal volume. The hippocampus has been shown to be associated with other medical conditions whose association with asthma was established previously and in this study, such as epilepsy (59) and allergic conditions (60).

Another potential connecting link is the transient receptor potential vanilloid type 1 which was shown to play a key role in both the manifestation of various symptoms of airway hypersensitivity including asthma (61), disorders associated with hyperdopaminergia such as ADHD, and atopic dermatitis. It was also shown to be involved in migraine pathophysiology.

High levels of stress are associated with all these conditions and predominantly, the more severe form of asthma (62). Not only was drug treatment for asthma, allergic rhinitis and atopic dermatitis more common among ADHD subjects, but also medication prescription for asthma and allergic rhinitis among parents was associated with ADHD treatment in their children (63). Diverse, common immune-related pathophysiological mechanisms and genes have been suggested to underlie both asthma and ADHD, some of which may also be related to atopic dermatitis. All these possible connecting links are expected to be more prominent in subjects with a more severe form of asthma.

Although a limited influence of more health seeking behavior is possible, the stringent screening active procedures to substantiate the diagnoses as well as the mechanisms that we bring as possible biological explanation of the association, and the already well-established association described in the literature all point toward a true association between asthma and ADHD. Furthermore, had the association been due to health seeking behavior, it would have the same effect in mild asthma and moderate- severe asthma groups, rather than only the later.

Concluding remarks, limitations and future directions

Whereas the symptoms of asthma severity groups are easily recognized, our understanding of the incident factors, pathogenesis, prognosis and treatment of asthma remains incomplete. Better characterization of asthma phenotypes is required, from both an etiological and clinical perspective. This cross-sectional

study contributes innovative insights into the field of asthma research by providing a comparative view of mild asthma and moderate-to-severe asthma in reference to subjects without asthma, among Israeli adolescent males and females separately, while incorporating coexisting medical conditions. This study adds to our previous report that used a similar protocol but focused on secular trends in asthma prevalence and its associations with anthropometric indices and socio-demographic variables (46).

This study illuminates differences and similarities based on stratification of gender and asthma severity. The findings suggest that perhaps different mechanisms and probably etiological bases are involved in the pathogenesis of mild compared with moderate-to-severe asthma, and between males and females. The differences might have implications not just for our view of asthma pathogenesis and progression in different sub-populations, but also for asthma (and comorbidities) diagnosis, monitoring and treatment.

The limitations of this study include being restricted to one recruitment center and to a certain age group, an under-representation of certain populations (such as minorities and religious women that are exempt from service), lack of additional background information on socio-demographic and lifestyle factors (socio-economic status (SES) and smoking habits) and genetic information. Information about age of asthma onset, which is directly related to some asthma phenotype classifications (13,14), was not available. We have no longitudinal data therefore we could not assess natural history and progression of the disease. Furthermore, the initial classification of asthma severity were based on asthma symptoms exacerbation frequency – as evident in the more recent and common GINA classifications at the time of data collection. However, advances in asthma research led to the development of evidence-based guidelines, rather than a consensus of expert opinion, and a major paradigm shift to control-based asthma management, as developed by The National Heart, Lung, and Blood Institute, The British Thoracic Society and GINA – “each using the same volume of evidence but emphasizing aspects particular to their specific patient populations and socioeconomic needs” (64). It would be interesting and valuable to apply a similar study design employing the current classification of asthma phenotypes and severity.

Future attempts to profile the “medical signature” of asthmatic adolescents should use parallel protocols among children and adults (males and females separately), as well as longitudinally follow the progression

of such profiles over time. This could provide a high-resolution and dynamic definition of asthma phenotypes (6) and promote our understanding of the disease state and identify more precise preventive strategies, leading to personalized therapeutics (13). Big data analytics and diverse modeling approaches and tools – beyond mining and patterning longitudinal data – may advance the translation of asthma phenotypic discovery into mechanistic insights and actionable solutions such as better diagnostic decision-making and clinical practice (65). For example, by investigating the extent of within-phenotype variations and delineating more precisely the characteristics of the individual trajectories assigned to each phenotype. These findings would have significant medical, financial and healthcare implications, at both the individual and national levels.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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References

1. Masoli M, Fabian D, Holt S, Beasley R. The global burden of asthma: executive summary of the GINA Dissemination Committee report. *Allergy* 2004;59: 469–478. Epub 2004/04/15. doi:10.1111/j.1398-9995.2004.00526.x.
2. Asher I, Pearce N. Global burden of asthma among children. *Int J Tuberc Lung Dis* 2014;18:1269–1278. Epub 2014/10/10. doi:10.5588/ijtld.14.0170.
3. Bateman ED, Jithoo A. Asthma and allergy - a global perspective. *Allergy* 2007;62:213–215. Epub 2007/02/15. doi:10.1111/j.1398-9995.2007.01324.x.
4. Palomares O, Akdis M, Martin-Fontecha M, Akdis CA. Mechanisms of immune regulation in allergic diseases: the role of regulatory T and B cells. *Immunol Rev* 2017;278:219–236. Epub 2017/06/29. doi:10.1111/imr.12555.
5. Miyasaka T, Dobashi-Okuyama K, Takahashi T, Takayanagi M, Ohno I. The interplay between neuroendocrine activity and psychological stress-induced exacerbation of allergic asthma. *Allergol Int* 2017;67: 32–42. Epub 2017/05/26. doi:10.1016/j.alit.2017.04.013. PubMed PMID: 28539203.
6. Chung KF. Defining phenotypes in asthma: a step towards personalized medicine. *Drugs* 2014;74: 719–728. Epub 2014/05/07. doi:10.1007/s40265-014-0213-9.

7. Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk PJ, Adcock IM, Bateman ED, Bel EH, Bleecker ER, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J* 2014;43:343–373. Epub 2013/12/18. doi: [10.1183/09031936.00202013](https://doi.org/10.1183/09031936.00202013).
8. Fitzpatrick AM, Teague WG, Meyers DA, Peters SP, Li X, Li H, Wenzel SE, Aujla S, Castro M, Bacharier LB, et al. Heterogeneity of severe asthma in childhood: confirmation by cluster analysis of children in the National Institutes of Health/National Heart, Lung, and Blood Institute Severe Asthma Research Program. *J Allergy Clin Immunol* 2011;127:382–389 e1–13. Epub 2011/01/05. PubMed PMID: 21195471; PubMed Central PMCID: PMC3060668. doi: [10.1016/j.jaci.2010.11.015](https://doi.org/10.1016/j.jaci.2010.11.015).
9. Haldar P, Pavord ID, Shaw DE, Berry MA, Thomas M, Brightling CE, Wardlaw AJ, Green RH. Cluster analysis and clinical asthma phenotypes. *Am J Respir Crit Care Med* 2008;178:218–224. Epub 2008/05/16. PubMed PMID: 18480428; PubMed Central PMCID: PMC3992366. doi: [10.1164/rccm.200711-1754OC](https://doi.org/10.1164/rccm.200711-1754OC).
10. Sonnappa S, Bastardo CM, Wade A, Saglani S, McKenzie SA, Bush A, Aurora P, et al. Symptom-pattern phenotype and pulmonary function in preschool wheezers. *J Allergy Clin Immunol* 2010;126:519–526 e1–7. Epub 2010/06/29. doi: [10.1016/j.jaci.2010.04.018](https://doi.org/10.1016/j.jaci.2010.04.018).
11. Savenije OE, Granell R, Caudri D, Koppelman GH, Smit HA, Wijga A, de Jongste JC. Comparison of childhood wheezing phenotypes in 2 birth cohorts: ALSPAC and PIAMA. *J Allergy Clin Immunol* 2011;127:1505–1512. e14. Epub 2011/03/18. doi: [10.1016/j.jaci.2011.02.002](https://doi.org/10.1016/j.jaci.2011.02.002).
12. Pite H, Gaspar A, Morais-Almeida M. Preschool-age wheezing phenotypes and asthma persistence in adolescents. *Allergy Asthma Proc* 2016;37:231–241. Epub 2016/04/15. doi: [10.2500/aap.2016.37.3955](https://doi.org/10.2500/aap.2016.37.3955).
13. Carr TF, Bleecker E. Asthma heterogeneity and severity. *World Allergy Organ J* 2016;9:41. Epub 2016/12/17. doi: [10.1186/s40413-016-0131-2](https://doi.org/10.1186/s40413-016-0131-2). PubMed PMID: 27980705; PubMed Central PMCID: PMC5129643.
14. Lee E, Lee SH, Kwon JW, Kim YH, Yoon J, Cho HJ, Yang SI, Jung YH, Kim HY, Seo JH, et al. Persistent asthma phenotype related with late-onset, high atopy, and low socioeconomic status in school-aged Korean children. *BMC Pulm Med* 2017;17:45. Epub 2017/02/25. PubMed PMID: 28231776; PubMed Central PMCID: PMC5324247. doi: [10.1186/s12890-017-0387-5](https://doi.org/10.1186/s12890-017-0387-5).
15. Reinke SN, Gallart-Ayala H, Gomez C, Checa A, Fauland A, Naz S, Kamleh MA, Djukanović R, Hinks. Metabolomics analysis identifies different metabolotypes of asthma severity. *Eur Respir J* 2017;49:1601740. Epub 2017/03/31. PubMed PMID: 28356371; PubMed Central PMCID: PMC5399350. doi: [10.1183/13993003.01740-2016](https://doi.org/10.1183/13993003.01740-2016).
16. Zoratti EM, Krouse RZ, Babineau DC, Pongracic JA, O'Connor GT, Wood RA, Khurana Hershey GK, Kercksmar CM, Gruchalla RS, Kattan M, et al. Asthma phenotypes in inner-city children. *J Allergy Clin Immunol* 2016;138:1016–1029. Epub 2016/10/11. PubMed PMID: 27720016; PubMed Central PMCID: PMC5104222. doi: [10.1016/j.jaci.2016.06.061](https://doi.org/10.1016/j.jaci.2016.06.061).
17. Boulet LP, FitzGerald JM, Reddel HK. The revised 2014 GINA strategy report: opportunities for change. *Curr Opin Pulm Med* 2015;21:1–7. Epub 2014/11/19. doi: [10.1097/mcp.0000000000000125](https://doi.org/10.1097/mcp.0000000000000125).
18. Garden FL, Simpson JM, Mellis CM, Marks GB. Change in the manifestations of asthma and asthma-related traits in childhood: a latent transition analysis. *Eur Respir J* 2016;47:499–509. Epub 2015/10/24. doi: [10.1183/13993003.00284-2015](https://doi.org/10.1183/13993003.00284-2015).
19. Corren J. Asthma phenotypes and endotypes: an evolving paradigm for classification. *Discov Med* 2013;15:243–249. Epub 2013/05/03.
20. Pembrey L, Barreto ML, Douwes J, Cooper P, Henderson J, Mpairwe H, Ardura-Garcia C, Chico M, Brooks C, Cruz AA, et al. Understanding asthma phenotypes: the World Asthma Phenotypes (WASP) international collaboration. *ERJ Open Res* 2018;4. Epub 2018/08/29. PubMed PMID: 30151371; PubMed Central PMCID: PMC6104297. doi: [10.1183/23120541.00013-2018](https://doi.org/10.1183/23120541.00013-2018).
21. Spycher BD, Silverman M, Kuehni CE. Phenotypes of childhood asthma: are they real? *Clin Exp Allergy* 2010;40:1130–1141. Epub 2010/06/16. doi: [10.1111/j.1365-2222.2010.03541.x](https://doi.org/10.1111/j.1365-2222.2010.03541.x).
22. Just J, Bourgoin-Heck M, Amat F. Clinical phenotypes in asthma during childhood. *Clin Exp Allergy* 2017;47:848–855. Epub 2017/04/20. doi: [10.1111/cea.12939](https://doi.org/10.1111/cea.12939).
23. Eguiluz-Gracia I, Tay TR, Hew M, Escribese MM, Barber D, O'Hehir RE, Torres MJ. Recent developments and highlights in biomarkers in allergic diseases and asthma. *Allergy* 2018;73:2290–2305. Epub 2018/10/06. doi: [10.1111/all.13628](https://doi.org/10.1111/all.13628).
24. Weatherburn CJ, Guthrie B, Mercer SW, Morales DR. Comorbidities in adults with asthma: population-based cross-sectional analysis of 1.4 million adults in Scotland. *Clin Exp Allergy* 2017;47:1246–1252. Epub 2017/07/01. doi: [10.1111/cea.12971](https://doi.org/10.1111/cea.12971).
25. Gershon AS, Wang C, Guan J, To T. Burden of comorbidity in individuals with asthma. *Thorax* 2010;65:612–618. Epub 2010/07/16. doi: [10.1136/thx.2009.131078](https://doi.org/10.1136/thx.2009.131078).
26. Zhang T, Carleton BC, Prosser RJ, Smith AM. The added burden of comorbidity in patients with asthma. *J Asthma* 2009;46:1021–1026. Epub 2009/12/10. doi: [10.3109/02770900903350473](https://doi.org/10.3109/02770900903350473).
27. Ferkh KE, Nwaru BI, Griffiths C, Patel A, Sheikh A. Healthcare costs of asthma comorbidities: a systematic review protocol. *BMJ Open* 2017;7:e015102. Epub 2017/06/02. PubMed PMID: 28566366; PubMed Central PMCID: PMC5730013. doi: [10.1136/bmjopen-2016-015102](https://doi.org/10.1136/bmjopen-2016-015102).
28. de Groot EP, Duiverman EJ, Brand PL. Comorbidities of asthma during childhood: possibly important, yet poorly studied. *Eur Respir J* 2010;36:671–678. Epub 2010/10/12. doi: [10.1183/09031936.00185709](https://doi.org/10.1183/09031936.00185709).
29. Boulet LP, Boulay ME. Asthma-related comorbidities. *Expert Rev Respir Med* 2011;5:377–393. Epub 2011/06/28. doi: [10.1586/ers.11.34](https://doi.org/10.1586/ers.11.34).
30. Cazzola M, Calzetta L, Bettoncelli G, Novelli L, Cricelli C, Rogliani P. Asthma and comorbid medical

- illness. *Eur Respir J* 2011;38:42–49. Epub 2010/12/24. doi:[10.1183/09031936.00140310](https://doi.org/10.1183/09031936.00140310).
31. Ullmann N, Mirra V, Di Marco A, Pavone M, Porcaro F, Negro V, Onofri A, Cutrera R. Asthma: differential diagnosis and comorbidities. *Front Pediatr* 2018;6:276. Epub 2018/10/20. PubMed PMID: 30338252; PubMed Central PMCID: PMC6178921. doi:[10.3389/fped.2018.00276](https://doi.org/10.3389/fped.2018.00276).
 32. Tay TR, Hew M. Comorbid “treatable traits” in difficult asthma: current evidence and clinical evaluation. *Allergy* 2018;73:1369–1382. Epub 2017/11/28. doi:[10.1111/all.13370](https://doi.org/10.1111/all.13370).
 33. Bardin PG, Rangeswamy J, Yo SW. Managing comorbid conditions in severe asthma. *Med J Aust* 2018; 209:S11–S17. Epub 2018/11/21.
 34. Oïelea MR, Raşcu A, The Asthma Obese Phenotype. In: Huang K-HG, ed. *Asthma diagnosis and management*. London, UK: IntechOpen; 2018:165–184.
 35. Graif Y, Shohat T, Machluf Y, Farkash R, Chaïter Y. Association between asthma and migraine - a cross-sectional study of over 110,000 Adolescents. *Clin Respir J* 2018;12:2491–2496. Epub 2018/07/14. doi:[10.1111/crj.12939](https://doi.org/10.1111/crj.12939).
 36. Labor M, Labor S, Juric I, Fijacko V, Grle SP, Plavec D. Mood disorders in adult asthma phenotypes. *J Asthma* 2018;55:57–65. Epub 2017/05/11. doi:[10.1080/02770903.2017.1306546](https://doi.org/10.1080/02770903.2017.1306546).
 37. Adamia N, Jorjoliani L, Khachapuridze D, Katamadze N, Chkuaseli N. Allergic diseases and asthma in adolescents. *Georgian Med News* 2015;243:58–62. Epub 2015/06/20.
 38. Ross MK, Romero T, Sim MS, Szilagyi PG. Obese- and allergic-related asthma phenotypes among children across the United States. *J Asthma* 2018;1–10. Epub 2018/04/20. doi:[10.1080/02770903.2018.1466317](https://doi.org/10.1080/02770903.2018.1466317).
 39. Fischer GB, Sarria EE, Mattiello R, Mocelin HT, Castro-Rodriguez JA. Post infectious bronchiolitis obliterans in children. *Paediatr Respir Rev* 2010;11: 233–239. Epub 2010/11/27. doi:[10.1016/j.prrv.2010.07.005](https://doi.org/10.1016/j.prrv.2010.07.005).
 40. Skobeloff EM, Spivey WH, St CSS, Schoffstall JM. The influence of age and sex on asthma admissions. *JAMA* 1992;268:3437–3440. Epub 1992/12/23.
 41. Meurer JR, George V, Subichin S, Yauck J, Layde P. Asthma severity among children hospitalized in 1990 and 1995. *Arch Pediatr Adolesc Med* 2000;154: 143–149. Epub 2000/02/09.
 42. Chen Y, Dales R, Stewart P, Johansen H, Scott G, Taylor G. Hospital readmissions for asthma in children and young adults in Canada. *Pediatr Pulmonol* 2003;36:22–26. Epub 2003/05/29. doi:[10.1002/ppul.10307](https://doi.org/10.1002/ppul.10307).
 43. Raghavan D, Jain R. Increasing awareness of sex differences in airway diseases. *Respirology* 2016;21: 449–459. Epub 2015/12/19. doi:[10.1111/resp.12702](https://doi.org/10.1111/resp.12702).
 44. Fuseini H, Newcomb DC. Mechanisms driving gender differences in asthma. *Curr Allergy Asthma Rep* 2017; 17:19. Epub 2017/03/24. doi:[10.1007/s11882-017-0686-1](https://doi.org/10.1007/s11882-017-0686-1).
 45. Tse SM, Rifas-Shiman SL, Coull BA, Litonjua AA, Oken E, Gold DR. Sex-specific risk factors for childhood wheeze and longitudinal phenotypes of wheeze. *J Allergy Clin Immunol* 2016;138:1561–1568.e6. Epub 2016/06/02. PubMed PMID: 27246527; PubMed Central PMCID: PMC6178921. doi:[10.1016/j.jaci.2016.04.005](https://doi.org/10.1016/j.jaci.2016.04.005).
 46. Machluf Y, Farkash R, Fink D, Chaïter Y. Asthma severity and heterogeneity: insights from prevalence trends and associated demographic variables and anthropometric indices among Israeli adolescents. *J Asthma* 2018;55:826–836. Epub 2017/09/06. doi:[10.1080/02770903.2017.1373809](https://doi.org/10.1080/02770903.2017.1373809).
 47. Machluf Y, Navon N, Yona A, Pirogovsky A, Palma E, Tal O, et al. From a quality assurance and control system for medical processes, through epidemiological trends of medical conditions, to a nationwide health project. In: Eldin AB, ed. *Modern approaches to quality control*. Rijeka, Croatia: InTech; 2011:259–282.
 48. Chaïter Y, Machluf Y, Pirogovsky A, Palma E, Yona A, Shohat T, Yitzak A, Ash N, Cohen A, Chaïter Y. Quality control and quality assurance of medical committee performance in the Israel Defense Forces. *Int J Health Care Qual Assur* 2010;23:507–515. Epub 2010/09/18.
 49. Chaïter Y, Palma E, Machluf Y, Yona A, Cohen A, Pirogovsky A, Shohat T, Yitzak A, Tal O, Ash N. Quality-assuring intervention for technical medical staff at medical committees. *Int J Health Care Qual Assur* 2011;24:19–30. Epub 2011/04/05.
 50. Machluf Y, Pirogovsky A, Palma E, Yona A, Navon A, Shohat T, Yitzak A, Tal O, ash N, Nachman M, et al. Coordinated computerized systems aimed at management, control, and quality assurance of medical processes and informatics. *Int J Health Care Qual Assur* 2012;25:663–681. Epub 2013/01/02. doi:[10.1108/09526861211270622](https://doi.org/10.1108/09526861211270622).
 51. Machluf Y, Fink D, Farkash R, Rotkopf R, Pirogovsky A, Tal O, Shohat T, Weisz G, Ringler E, Dagan D, et al. Adolescent BMI at Northern Israel: from trends, to associated variables and comorbidities, and to medical signatures. *Medicine (Baltimore)* 2016;95:e3022. Epub 2016/03/26. doi:[10.1097/md.0000000000003022](https://doi.org/10.1097/md.0000000000003022).
 52. Bousquet J. Global initiative for asthma (GINA) and its objectives. *Clin Exp Allergy* 2000;30: 2–5. Epub 2000/06/13.
 53. Amelink M, de Nijs SB, de Groot JC, van Tilburg PMB, van Spiegel PI, Krouwels FH, Lutter R, Zwinderman AH, Weersink EJ, ten Brinke A, et al. Three phenotypes of adult-onset asthma. *Allergy* 2013;68:674–680. Epub 2013/04/18. doi:[10.1111/all.12136](https://doi.org/10.1111/all.12136).
 54. Moore WC, Fitzpatrick AM, Li X, Hastie AT, Li H, Meyers DA, Bleecker ER. Clinical heterogeneity in the severe asthma research program. *Ann Am Thorac Soc* 2013;10:S118–S124. Epub 2013/12/01. PubMed PMID: 24313761; PubMed Central PMCID: PMC6178921. doi:[10.1513/AnnalsATS.201309-307AW](https://doi.org/10.1513/AnnalsATS.201309-307AW).
 55. Chen MH, Su TP, Chen YS, Hsu JW, Huang KL, Chang WH, Chen TJ, Bai YM. Asthma and attention-deficit/hyperactivity disorder: a nationwide population-based prospective cohort study. *J Child Psychol Psychiatry* 2013;54:1208–1214. Epub 2013/06/05. doi:[10.1111/jcpp.12087](https://doi.org/10.1111/jcpp.12087).

56. Borschuk AP, Rodweller C, Salorio CF. The influence of comorbid asthma on the severity of symptoms in children with attention-deficit hyperactivity disorder. *J Asthma* 2018;55:66–72. Epub 2017/05/02. doi:[10.1080/02770903.2017.1306549](https://doi.org/10.1080/02770903.2017.1306549).
57. Carlson SM, Kim J, Khan DA, King K, Lucarelli RT, McColl R, Peshock R, Brown ES. Hippocampal volume in patients with asthma: Results from the Dallas Heart Study. *J Asthma* 2017;54:9–16. Epub 2016/05/18. PubMed PMID: 27187077; PubMed Central PMCID: PMC4560255. doi:[10.1080/02770903.2016.1186174](https://doi.org/10.1080/02770903.2016.1186174).
58. Al-Amin M, Zinchenko A, Geyer T. Hippocampal subfield volume changes in subtypes of attention deficit hyperactivity disorder. *Brain Res* 2018;1685:1–8. Epub 2018/02/11. doi:[10.1016/j.brainres.2018.02.007](https://doi.org/10.1016/j.brainres.2018.02.007).
59. Chatzikonstantinou A. Epilepsy and the hippocampus. *Front Neurol Neurosci* 2014;34:121–142. Epub 2014/04/30. doi:[10.1159/000356435](https://doi.org/10.1159/000356435).
60. Klein B, Mrowetz H, Thalhamer J, Scheibelhofer S, Weiss R, Aigner L. Allergy enhances neurogenesis and modulates microglial activation in the hippocampus. *Front Cell Neurosci* 2016;10:169. Epub 2016/07/23. PubMed PMID: 27445696; PubMed Central PMCID: PMC4923262. doi:[10.3389/fncel.2016.00169](https://doi.org/10.3389/fncel.2016.00169).
61. Lee LY, Gu Q. Role of TRPV1 in inflammation-induced airway hypersensitivity. *Curr Opin Pharmacol* 2009;9:243–249. PubMed PMID: PMC2704095. doi:[10.1016/j.coph.2009.02.002](https://doi.org/10.1016/j.coph.2009.02.002).
62. Rosenberg SL, Miller GE, Brehm JM, Celedon JC. Stress and asthma: novel insights on genetic, epigenetic, and immunologic mechanisms. *J Allergy Clin Immunol* 2014;134:1009–1015. Epub 2014/08/19. PubMed PMID: 25129683; PubMed Central PMCID: PMC4252392. doi:[10.1016/j.jaci.2014.07.005](https://doi.org/10.1016/j.jaci.2014.07.005).
63. van der Schans J, Pleiter JC, de Vries TW, Schuiling-Veninga CC, Bos JH, Hoekstra PJ, Hak E. Association between medication prescription for atopic diseases and attention-deficit/hyperactivity disorder. *Ann Allergy Asthma Immunol* 2016;117:186–191. Epub 2016/06/19. doi:[10.1016/j.anai.2016.05.025](https://doi.org/10.1016/j.anai.2016.05.025).
64. Reddy AP, Gupta MR. Management of asthma: the current US and European guidelines. *Adv Exp Med Biol* 2014;795:81–103. Epub 2013/10/29. doi:[10.1007/978-1-4614-8603-9_6](https://doi.org/10.1007/978-1-4614-8603-9_6).
65. Oksel C, Haider S, Fontanella S, Frainay C, Custovic A. Classification of pediatric asthma: from phenotype discovery to clinical practice. *Front Pediatr* 2018;6:258. Epub 2018/10/10. PubMed PMID: 30298124; PubMed Central PMCID: PMC6160736. doi:[10.3389/fped.2018.00258](https://doi.org/10.3389/fped.2018.00258).

Appendix A

Criteria for the diagnosis of each medical condition (variables)

This study is aimed at providing an overarching characterization of the medical signature of asthma severity phenotypes, within each gender separately. Therefore, on one hand diverse medical conditions were grouped together,

while focusing on the more common medical conditions among conscripts, such as scoliosis/kyphosis and refraction errors. Other medical conditions, such as allergy and neurologic-cognitive-mental disorders, which were shown to be associated with asthma, were separated into the sub-conditions constituting them, in order to provide a higher resolution. No self-reported measurements were used in this study. The medical conditions were as follows.

Allergies

Allergic conjunctivitis

Diagnosis was made according to previous documentation, a history of redness of conjunctiva, edema, itching and lacrimation associated with season and/or allergens and verified by an eye specialist.

Allergic rhinitis

Diagnosis was made according to previous documentation verified by ear, nose and throat (ENT) specialist or allergy specialist. Diagnosis required chronic rhinitis associated with allergens and/or season of year.

Atopic dermatitis

Diagnosis was made according to previous documentation and history of characteristic itchy, red, swollen rash of skin, associated with seasons and/or allergens according to diagnosis of a certified dermatologist or allergy specialist.

Hymenoptera/bee allergies

Hymenoptera allergy was diagnosed according to previous documentation and history of reaction to bee, yellow jacket or hornet sting accompanied by swelling, rash, angioedema or anaphylactic shock and verified by skin tests as well as specific Immunoglobulin E tests and confirmed by an allergy specialist.

Urticaria and angioedema/food allergies

Diagnosis was made according to previous documentation and characteristic history of typical general skin rash (hives) for urticaria, general swelling including swelling of the neck, face, tongue and larynx for angioedema, specific skin tests and IgE levels for specific foods allergy, verified by a specialist in allergy.

Neurologic-cognitive-mental disorders

Epilepsy

Diagnosis of epilepsy was made according to previous documentation involving recurrent general or focal seizures, a neurological workup including EEG and certified by a specialist neurologist.

Migraine

The diagnosis of migraine relied on at least 1 year's documentation of headaches with typical characteristics of a migraine, which was verified by a neurologist.

Learning disabilities

Learning disabilities were diagnosed by specific psychodiagnostic tests and verified by neurologist and or psychiatrist examination. In this analysis, only the severe learning disorders were included, such those accompanied with dyspraxia or coordination problems.

Attention-deficit hyperactivity disorder

ADD/ADHD was diagnosed according to specific psychodiagnostic tests and verified by a neurologist or psychiatrist examination. In this analysis, only severe ADD/ADHD was included, requiring daily consumption of medication (Ritalin or Concerta).

Anxiety-mood disorder/depression

Anxiety and mood disorders were diagnosed according to previous documentation from a certified psychologist or psychiatrist, relied on typical medical history and was verified by an examination by a certified psychiatrist at the recruitment center.

Other diseases

Gastro-esophageal reflux disease

Diagnosis was made according to previous documentation and characteristic history of heartburn, bloating, taste of acid and food coming back to the mouth (reflux), tightness of breathing and chest characteristically after meals, and certified by a specialist gastroenterologist.

Irritable BOWEL Syndrome (IBS)

Irritable bowel syndrome was diagnosed by certified gastroenterologist after a work up including blood laboratory tests to exclude other conditions such as inflammatory bowel disease (IBD), imaging including ultrasound of abdomen, computerized tomography (CT) on GI tract, endoscopy and colonoscopy.

Inflammatory bowel disease

IBD was diagnosed by certified gastroenterologists, relying on medical history, laboratory blood workup demonstrating elevated C-reactive protein, sediment rate and fecal calprotectin levels as well as other serological indexes as well as a thorough GI workup including CT, magnetic resonance enterography and endoscopy including colonoscopy. Diagnosis was verified by results of typical findings and histopathological findings.

Lactase deficiency

Lactase deficiency was diagnosed by a certified gastroenterologist relying on medical history and laboratory workup.

Scoliosis/Kyphosis

Spine deformities included scoliosis and kyphosis as established by clinical examination and X-ray imaging.

Chest deformations

Chest deformation was diagnosed according to characteristic findings on physical examination by two physicians and included pectus excavatum, pectus carinatum and other deformations of chest wall. In cases of a moderate-to-severe deformity, a spirometry was performed to assess possible restrictive condition.

Diabetes mellitus

Diabetes mellitus diagnosis was established by fasting blood glucose levels above 126 mg/dL for those examined after 1998, and above 140 mg/dL for those examined during previous years in repeated analysis, and or 2 h post-prandial glucose levels above 200 mg/dL. The change in the fasting glucose level threshold was made according to changes in

definition as decided by the World Health Organization (WHO) and National Health Institute (NIH).

Autoimmune connective tissue diseases

This group of diseases included rheumatoid arthritis, systemic lupus erythematosus, Sjögren disease, scleroderma, mixed connective tissue disease, polymyositis dermatomyositis and psoriatic arthritis. Diagnosis of the conditions was made according to previous medical documentation, accepted criteria including complete laboratory workup and confirmation by a specialist in rheumatology.

Hyperlipidemia

Hyperlipidemia was diagnosed as low-density lipoprotein cholesterol levels above 150 mg/dL and/or triglyceride levels above 200 mg/dL.

Cardiac anomalies (heart disease)

Cardiac anomalies were diagnosed according to cardiologist examination and Echo Doppler study. Cardiac anomalies included valvar abnormalities such as bicuspid aortic valve, aortic valve insufficiency or stenosis, mitral valve insufficiency or stenosis, pulmonary stenosis or insufficiency, tricuspid valve insufficiency or stenosis. Non-valvar anomalies included patent ductus arteriosus, atrial septal defect, ventricular septal defect, coarctation of the aorta, tetralogy of Fallot, complete transposition of great vessels and dextrocardia.

Pneumothorax

Pneumothorax was diagnosed relying on findings of pulmonologist, previous documentation including discharge letters from hospital and by performing spirometry and X-ray imaging.

Hoarseness

Hoarseness was diagnosed according to examination and previous documentation and was substantiated by a certified ENT specialist following examination of the larynx and pharynx for possible pathologies.

Eating disorders

Eating disorders were diagnosed by certified psychiatrists relying on additional documentation and on a thorough psychiatric status examination verifying criteria for eating disorders by International Classification of Diseases.

Sleep disorders

Sleep disorders included mainly sleep apnea syndrome and somnambulism diagnosed at a certified sleep disorders laboratory and verified by a sleep disorders specialist.

The following anthropometric indices were included in the univariate analyses.

Body mass index

BMI groups were defined according to gender-related percentiles for 17-year old BMI on growth charts of the Israeli Ministry of Health, similarly to the approach of the U.S. Centers for Disease Control and Prevention. The actual definitions were as follows: Obesity – above the 95th percentile (>28.2 and >29.6 kg/m² for males and females, respectively); Overweight – the 85th–95th percentiles (25.0–28.2 and 25.2–29.6 kg/m²); Underweight – below 5th percentile (<17.6 and <17.2 kg/m²). The age of 17 years was chosen as

the median age [and interquartile range] of males and females was 17.35 [17.08–17.9] and 17.24 [17.02–17.63], respectively.

Blood pressure

Systolic and diastolic blood pressure (BP) measures (herein SBP and DBP, respectively) were obtained by a sphygmomanometer, in a relaxed, sitting position. Categories were defined following age (17 years old)- and height (174 and 162 cm for males and females, respectively) – adjusted definitions of Ministry of Health. Six categories were defined hierarchically based on clinical severity: Missing BP: either DBP = 0 or SBP = 0; Abnormal BP: either DBP = 1–39 or SBP = 1–79 or SBP-DBP < 20; Hypertension type II (>99th percentile + 5 mmHg): either DBP > 90 or SBP > 146/139 or males/females or recruits belonging to 1 of the 3 BP categories indicated below and having FCC indicative of taking medications due to hypertension type II; Hypertension type I ($\geq$ 95th percentile and $\leq$ 99th percentile + 5 mmHg): DBP = 86–90 or SBP = 135–146/129–139 for males/females; Pre-hypertension ($\geq$ 90th percentile and <95th percentile + 5 mmHg): DBP = 80–85 or SBP = 120–134/120–138 for males/females; Hypotension: DBP = 40–49 or SBP = 80–89; Normal BP: DBP = 50–79 or SBP = 90–119. Diagnosis of hypertension warranted also further workup including ten measurements of BP every alternate day.

The following socio-demographic variables were included in the univariate analyses: year of birth, season of birth, country of birth, migration status, education, religion, residential area, family size (number of children in the family), birth order (place of child among children), age of parents at child's birth (advanced/young parental age) and SES.

These variables and the related findings were described in detail previously (see reference 46 and its [Supplementary Material](#)).

Appendix B

Description of univariate analysis findings

Associations in males

Of the medical conditions, 12 conditions were associated with either mild asthma or moderate-to-severe asthma – all associated with a higher risk among the asthmatic male populations (compared with the corresponding non-asthmatic ones). Of these, six variables were associated with both mild and moderate-to-severe asthma (Allergic rhinitis, allergic dermatitis, urticarial/angioedema/food allergies, learning disorders, migraine and allergic conjunctivitis), two variables were only associated with mild asthma (Hymenoptera/bee allergies and epilepsy) and four variables were only associated with moderate-to-severe asthma (ADHD/ADD, hyperlipidemia, pneumothorax and hoarseness).

Associations in females

Of the medical conditions, 12 conditions were associated with either mild asthma or moderate-to-severe asthma – all associated with a higher risk among the asthmatic female populations (compared with the corresponding non-asthmatic ones, with one exception: learning disorders was less prevalent among the mild asthma phenotype). Of these, five variables were associated with both mild and moderate-to-severe asthma (Allergic rhinitis, allergic dermatitis, urticarial/angioedema/food allergies, learning disorders and allergic conjunctivitis), one variable was only associated with mild asthma (Scoliosis/Kyphosis) and six variables were only associated with moderate-to-severe asthma (Hymenoptera/bee allergies, GERD, sleep disorder, migraine, anxiety-mood disorder/depression, ADHD/ADD).

Only these variables, which were shown to be significantly associated with either of the asthma severity-gender groups, were included in the corresponding multivariable logistic regression models.

Table S1: Prevalence of accompanying medical conditions among asthmatic versus non-asthmatic subjects- univariate analysis

Medical condition	Males (N=66,547)					Females (N=47,124)				
	N	Mild Asthma (N=1,829)		Moderate-severe asthma (N=1,091)		N	Mild Asthma (N=675)		Moderate-severe asthma (N=986)	
Scoliosis/Kyphosis	6,145	10.4% =0.070	9.2%	10.3% =0.235	9.2%	3,593	11.4% =<0.001	7.6%	6.9% =0.384	7.9%
Allergic rhinitis	3,124	25.5% =<0.001	4.1%	32.1% =<0.001	4.2%	2,024	24.4% =<0.001	4.0%	30.5% =<0.001	3.7%
Chest deformations	3,644	5.3% =0.742	5.5%	5.0% =0.525	5.5%	361	1.2% =0.208	0.8%	0.7% =0.838	0.8%
Learning disorders	1,478	4.1% =<0.001	2.2%	3.8% =<0.001	2.2%	1,035	0.7% =0.009	2.2%	7.1% =<0.001	2.1%
Migraine	627	2.5% =<0.001	0/9%	2.1% =<0.001	0.9%	833	1.2% =0.247	1.8%	5.2% =<0.001	1.7%
Heart Disease	999	1.2% =0.287	1.5%	1.6% =0.876	1.5%	510	0.9% =0.625	1.1%	1.5% =0.178	1.1%
Food allergies	599	2.7% =<0.001	0.8%	2.2% =<0.001	0.9%	603	3.9% =<0.001	1.2%	2.9% =<0.001	1.2%
Atopic dermatitis	500	2.4% =<0.001	0.7%	3.2% =<0.001	0.7%	468	2.7% =<0.001	1.0%	3.8% =<0.001	0.9%
Allergic conjunctivitis	479	3.5% =<0.001	0.6%	3.1% =<0.001	0.7%	263	2.8% =<0.001	0.5%	2.3% =<0.001	0.5%
Anxiety/depression	470	0.8% =0.555	0.7%	1.2% =0.054	0.7%	201	0.3% =1.000	0.4%	1.6% =<0.001	0.4%
Epilepsy	413	1.0% =0.021	0.6%	0.7% =0.633	0.6%	256	0.1% =0.280	0.5%	0.5% =0.876	0.5%
Bee allergies	311	0.9% =0.003	0.5%	0.8% =0.081	0.5%	114	0.3% =0.680	0.2%	0.6% =0.033	0.2%
Autoimmune connective tissue diseases	173	0.1% =0.098	0.3%	0.3% =0.763	0.3%	174	0.4% =0.741	0.4%	0.5% =0.419	0.4%
GERD	171	0.4% =0.150	0.3%	0.5% =0.064	0.3%	133	0.3% =0.716	0.3%	0.8% =0.007	0.3%
ADHD/ADD	163	0.4% =0.092	0.2%	1.2% =<0.001	0.2%	126	0.1% =1.000	0.3%	1.3% =<0.001	0.2%
IBS	156	0.2% =1.000	0.2%	0.5% =0.115	0.2%	133	0.3% =0.716	0.3%	0.6% =0.061	0.3%
Diabetes	81	0.3% =0.073	0.1%	0.1% =1.000	0.1%	58	0.1% =0.567	0.1%	0.0% =0.636	0.1%
Hyperlipidemia	74	0.2% =0.146	0.1%	0.5% =0.007	0.1%	64	0.3% =0.249	0.1%	0.1% =1.000	0.1%
Sleep disorders	85	0.1% =1.000	0.1%	0.3% =0.164	0.1%	16	0.0% =1.000	0.0%	0.2% =0.043	0.0%
Eating disorders	8	0.1% =0.200	0.0%	0.0% =1.000	0.0%	50	0.0% =1.000	0.1%	0.1% =1.000	0.1%
IBD	47	0.0% =0.641	0.1%	0.1% =0.540	0.1%	28	0.0% =1.000	0.1%	0.0% =1.000	0.1%
Pneumothorax	41	0.1% =1.000	0.1%	0.4% =0.004	0.1%	10	0.1% =0.134	0.0%	0.0% =1.000	0.0%
Hoarseness	19	0.0% =1.000	0.0%	0.2% =0.038	0.0%	25	0.1% =0.303	0.1%	0.1% =0.411	0.1%

Medical conditions are sorted by their combined prevalence (total N).

N – Number of cases/records diagnosed with each medical condition. The prevalence shown are of asthmatic subjects diagnosed within each medical condition population (bold, on the left) compared to the corresponding prevalence among the remaining population not diagnosed with the medical condition (on the right); statistically significant relationships are marked by bold p value (<0.05)
Significance code: all significant differences marked in bold, and level of significance is color coded: $p<0.05$; $p<0.01$; $p<0.001$.

Table S2: Prevalence of medical conditions among asthmatic versus non-asthmatic subjects- multivariate analysis

	Males								Females							
	Mild asthma				Moderate-severe asthma				Mild asthma				Moderate-severe asthma			
	OR	Lower 95% CI	Higher 95% CI	P value	OR	Lower 95% CI	Higher 95% CI	P value	OR	Lower 95% CI	Higher 95% CI	P value	OR	Lower 95% CI	Higher 95% CI	P value
Underweight BMI	1.509	1.185	1.922	0.001	1.155	0.813	1.640	0.421	1.200	0.861	1.674	0.282	0.991	0.742	1.324	0.951
Overweight BMI	1.010	.854	1.193	0.910	1.054	0.858	1.295	0.614	1.079	0.841	1.385	0.550	1.218	1.002	1.480	0.047
Obesity BMI	1.644	1.388	1.946	<0.001	1.670	1.364	2.045	<0.001	1.439	1.008	2.053	0.045	1.455	1.113	1.901	0.006
Allergic rhinitis	6.804	6.025	7.683	<0.001	9.022	7.817	10.411	<0.001	8.286	6.808	10.086	<0.001	10.183	8.724	11.888	<0.001
Atopic dermatitis	1.647	1.091	2.485	0.018	2.439	1.583	3.757	<0.001	1.012	0.516	1.984	0.972	2.392	1.603	3.569	<0.001
Urticaria & angioedema	1.541	1.040	2.284	0.031	1.174	0.718	1.919	0.524	2.107	1.201	3.699	0.009	1.669	1.078	2.583	0.022
Allergic conjunctivitis	1.609	1.199	2.160	0.002	1.025	0.697	1.506	0.901	1.469	0.879	2.455	0.142	0.961	0.600	1.539	0.869
Hymenoptera allergy	1.802	1.085	2.993	0.023	1.679	0.835	3.377	0.146	-	-	-	-	2.713	1.139	6.458	0.024
Learning disability	1.528	1.195	1.955	0.001	1.588	1.146	2.200	0.005	0.414	0.169	1.012	0.053	2.566	1.963	3.354	<0.001
ADD/ADHD	-	-	-	-	3.059	1.687	5.546	<0.001	-	-	-	-	2.955	1.610	5.425	<0.001
Migraine	1.870	1.353	2.583	<0.001	1.124	0.721	1.752	0.606	-	-	-	-	1.561	1.137	2.144	0.006
Epilepsy	1.644	1.023	2.640	0.040	-	-	-	-	-	-	-	-	-	-	-	-
Anxiety-Depression	-	-	-	-	1.535	0.862	2.732	0.146	-	-	-	-	2.569	1.479	4.462	0.001
Pneumothorax	0.776	0.103	5.842	0.806	5.951	1.964	18.033	0.002	18.863	2.179	163.269	0.008	-	-	-	-

p<0.05; p<0.01; p<0.001.