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To cite this article: Yossy Machluf, Rivka Farkash, Daniel Fink & Yoram Chaite (2017): Asthma severity and heterogeneity: Insights from prevalence trends and associated demographic variables and anthropometric indices among Israeli adolescents, Journal of Asthma, DOI: [10.1080/02770903.2017.1373809](https://doi.org/10.1080/02770903.2017.1373809)

To link to this article: <http://dx.doi.org/10.1080/02770903.2017.1373809>



Accepted author version posted online: 05 Sep 2017.



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Asthma severity – prevalence trends and relationships among Israeli adolescents

Asthma severity and heterogeneity: insights from prevalence trends and associated demographic variables and anthropometric indices among Israeli adolescents

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Abstract

Objectives: While 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 paper presents a cross-sectional study of 113,671 Israeli adolescents. Prevalence rates of mild and moderate-to-severe asthma over a 24-year period were calculated and multivariate regression models (outcomes: different asthma severity, reference: subjects without asthma) were performed to analyze associations with anthropometric indices and socio-demographic variables, in males and females separately. **Results:** The prevalence of mild asthma increased until birth years 1976--1980 and then steadily decreased. In contrast, the prevalence of moderate-to-severe asthma was relatively stable until birth years 1976--1980, then rose steeply until 1986--1990 and subsequently plateaued in the early 1990s. Obesity was positively associated with both mild and moderate-to-severe asthma in males (Odds Ratio [95%CI]: 1.61 [1.37-1.89] and 1.63 [1.34-1.98], respectively) and females (1.54 [1.10-2.16] and 1.54 [1.20-1.98], respectively). Family size greater than 3 siblings was negatively associated with both mild and moderate-to-severe asthma in males (0.62 [0.56-0.68] and 0.59 [0.52-0.68]) and females (0.71 [0.60-0.83] and 0.73 [0.63- 0.83]). In contrast, in males, underweight was only associated with mild asthma (1.54 [1.22-1.94]) but not with moderate-to-severe asthma. In females, overweight was only associated with moderate-to-severe asthma (1.21 [1.00-1.46]) and rural residence was only associated with mild asthma (1.26 [1.09-1.47]).

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

Introduction

Asthma is a heterogeneous, complex and common chronic respiratory disease that affects over 300 million people worldwide, resulting in a considerable clinical and socio-economic burden. Asthma is driven by diverse mechanisms of immune regulation of allergic, inflammatory and neuroendocrine responses (1-3). It is characterized by airway hyper-responsiveness and reversible airway obstruction, yet it can present in various clinical forms and with different levels of severity. Owing to its clinical and pathophysiological heterogeneity, there have been numerous attempts to define asthma phenotypes (4-14). Each phenotype is defined by (some or all of) a unique interaction between genetic and environmental factors, clinical severity, age of onset, physiological indicators and the inflammatory cells involved in the pathophysiologic pathway, treatment, persistence of wheezing (treatment responsiveness), triggers and trigger-related phenotypes, and comorbidities. These phenotypes can vary over time in relation to changes in the principal triggers involved in the etiology of the disease (15). Classification of asthma phenotype, which is now merely based on symptoms severity (16), while in the future will be based on pathophysiologic mechanisms (endotypes) and the biomarkers attached to these endotypes (15, 17), is important for understanding, and perhaps in the future for predicting, the prognosis and response to treatment, and may lead to targeted therapy.

Although many asthma risk factors are well-documented, thus far predicting the outcome of an individual patient has not been possible. This is mainly attributed to the complicated, dynamic and multifactorial processes in which socio-demographic and lifestyle factors, environmental influences, genetic and epigenetic factors interact through the development and progression of asthma (18-21). Some studies indicate that the disparities in asthma prevalence and morbidity among the world's geographic locations are more likely to be associated with environmental exposure than genetic differences (22). Genetic and environmental factors can exert different influences in different countries, at different developmental stages and between males and females (23-25). The factors of high interest to this study are: gender, body mass index, and factors related to the "hygiene theory".

A notable sex disparity has been observed in asthma prevalence, incidence, severity, hospitalization rate and duration: it is more common and severe in boys during early childhood, equalizes during adolescence, and switches to female predominance in adulthood (26-30). The role of sex hormones in airway inflammation, smooth muscle contraction, mucus production and airway mechanics associated with asthma pathogenesis has been demonstrated, as has the influence of genetic predisposition and comorbidities (31, 32). Identifying sex-specific risk factors for asthma (33) may have potential diagnostic, therapeutic and prognostic implications.

Numerous large cross-sectional and prospective studies performed on adults, adolescents, and children throughout the world support a weak, yet significant relationship between high body weight and asthma (34-38). The relationship seems to be stronger in females (39-42). A causal relationship between obesity and asthma has been suggested (35, 41, 43, 44) as well as possible mechanisms driving this association (45). Scott and colleagues claimed that “there are multiple obese-asthma phenotypes, with varied aetiologies and clinical consequences” (45). Nevertheless, some questions regarding this relationship remain unanswered, as viewed by Hancox and colleagues (40).

There is evidence to support the “hygiene theory”, according to which exposure to a significant amount and diverse types of infection factors in early childhood accelerates the development of immune system protection against asthma (46).

Secular trends of asthma and associated risk factors may vary with country, population, age, and asthma phenotype (such as subjects with mild (intermittent) vs. more severe, persistent asthma). However, no study has investigated heterogeneity of asthma among males and females separately based on secular trends and association with individual and environmental risk factors. This approach may shed light on the origin and development of diverse asthma phenotypes, and could have an impact on asthma management.

Objectives

The objective of this study was to examine similarities and differences between mild asthma and moderate-to-severe asthma, regarding:

I. secular trends in asthma prevalence;

II. relationships/associations between asthma and anthropometric indices (Body Mass Index – BMI) and socio-demographic variables.

Hypothesis

If asthma in childhood initially develops as mild symptoms and then aggravates into moderate-to-severe symptoms if not properly managed and treated, one would expect similar trends and associations with anthropometric indices (BMI) and socio-demographic variables. However, if these two clinical asthma groups are differentially associated with anthropometric indices and socio-demographic variables then we may be dealing with sub-populations that are more susceptible to developing moderate-to-severe asthma.

Methods

Data source

Military service is compulsory in Israel, though various minorities are exempt, as are religious women. Mandatory pre-induction medical examination of all Israelis takes place at regional recruitment centers. The examinees undergo a comprehensive medical interview and physical examination by medical board physicians and are referred for further investigation as necessary. At the end of the medical process, a medical profile and appropriate Functional Classifications Codes (FCCs), which describe the medical status and its severity as well as an element of occupational medical 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 by diverse quality control and assurance means (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 to 19. No selection criteria (neither inclusive nor exclusive) were applied. Only the northern recruitment center was chosen, as for many years the medical examinations at this center were performed by a small group of highly-trained medical personnel, and consequently it is characterized by the 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 previous medical documentation from the primary physician and thorough medical history, physical examination and spirometry results together with an expert pulmonologist's examination. **Active asthma** included wheezing, chronic cough, dyspnea on effort, asthma attacks upon exposure to allergens during the last three years and use of medication. This was further subdivided into **mild asthma** (those with normal rest and exercise spirometry and administration of medication only as needed, not on a daily basis) and **moderate-to-severe asthma** (those with evidence of airway hyper-reactivity on spirometry and administration of medication on a daily basis). This separation into different asthma severity groups also relies on an additional criterion: the lack of confirmed reversible airflow obstruction or bronchial hyper-reactivity in the mild asthmatics, as opposed to the moderate-to-severe asthma, where reversible airflow obstruction or bronchial hyper-reactivity was confirmed. The "mild" and "moderate-to-severe" asthma groups correspond to GINA classifications of "intermittent and mild" and "moderate and severe" persistent asthma groups, respectively. The criteria for asthma severity classification were in use at the time the database was created, and did not change during the period of the study, highlighting the stability of definitions for classification over the study period.

Secular trends

To investigate secular trends of prevalence rates of each asthma severity group, among males and females separately, the study population was grouped into five separate five-year periods according to birth year (only 3.5 years for the last group), due to sample size considerations. Noteworthy, as each individual has only one observation in the database and individuals were

grouped according to birth year, the change across birth years in the prevalence rates of each asthma severity group among sub-populations (males and females) was analyzed, rather than the change of an individual's asthma severity across years.

Definitions of anthropometric indices and socio-demographic variables

In addition to anthropometric and medical data, the computerized database contained further personal, educational, and socio-demographic information about each recruit and his/her family, as recorded by the Ministry of Internal Affairs, and validated (and updated) by interviews and questionnaires. Key variables, which were used in the univariate analysis and/or multivariate logistic regression models, are described in more detail in **Appendix 1**.

Statistical method

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

As this study aims to investigate the independent associations between demographic characteristics and anthropometric indices and the development of either of the two clinical asthma groups (mild or moderate-to-severe asthma – the outcome) within each gender separately (males and females), a three-step process was applied:

First, a distinct univariate analysis was conducted for each combination of clinical asthma group and gender (total of four analyses: mild asthma among males, moderate-to-severe asthma among males, mild asthma among females, and moderate-to-severe asthma among females), where the reference group comprised subjects of the corresponding gender without asthma (total of two reference groups: 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 T-test for continuous variables.

Subsequently, a distinct multivariable logistic regression model was conducted for each combination of clinical asthma group and gender. As in the univariate analyses, in each of the four models the reference group comprised subjects of the corresponding gender without asthma. Covariates in each model included variables which were found to be significantly associated with the outcome in the univariate analysis (described briefly in **Appendix 2**). Co-linear

variables were excluded from the models, which were adjusted to control for potentially confounding effects.

To deal with variables that included more than two categories, dummy variables were created for all categories except the reference group and were added to the model as covariates. For example, three BMI-related dummy variables were created: (1) underweight BMI, (2) overweight BMI, and (3) obesity BMI, and were added to the model, where “normal BMI” was the reference group.

Lastly, the associations of each of the two clinical asthma groups were compared to each other, treating each gender separately. Odds Ratios (OR) and 95% confidence intervals (95% CI) were calculated. The statistical tests were two-tailed. Statistically significant (p value <0.05) odds ratios greater than 1 indicate positive relationships, namely increased risk for asthma, whereas odds ratios smaller than 1 indicate negative relationships, namely reduced risk for asthma (protective effect).

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

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--19 years of age. Of these, 3,308 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.

Secular trends

To investigate secular trends in asthma prevalence, the study population was grouped into five separate five-year periods of birth year (only 3.5 years for the last group).

Among males (**Figure 1A**), an inverse U-shape trend in the prevalence of mild asthma was observed – it increased until birth years 1976--1980 and then steadily decreased to its baseline

level. In contrast, the prevalence of moderate-to-severe asthma was relatively stable until birth years 1976--1980, then rose steeply until 1986--1990 and subsequently plateaued in the early 1990s.

Interestingly, relatively similar trends were also observed among females (**Figure 1B**). The prevalence of mild asthma increased until birth years 1976--1980 (though less pronouncedly than among males) and then steadily decreased far below its baseline level. In contrast, the prevalence of moderate-to-severe asthma was relatively stable until birth years 1976--1980, then rose steeply until 1986--1990 and subsequently plateaued in the early 1990s.

The baseline prevalence rates (among those born until 1975) of mild asthma (~2.2%) and moderate-to-severe asthma (~0.85%) were similar among males and females. However, after two decades the prevalence of mild asthma (among those born after 1990) was much higher among males (2.1%) than females (0.6%), whereas the prevalence of moderate-to-severe asthma was higher among females (3.3%) than males (2.4%).

Associations with socio-demographic variables and anthropometric indices

In order to investigate the independent associations between demographic characteristics and anthropometric indices and the development of either of the two clinical asthma groups within each gender, 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 multivariate logistic regression models as described above in the Methods section. The comprehensive results of the univariate analysis are shown in the **Supporting table S1** and **Appendix 2**, while the multivariate analysis findings are shown in the **Supporting table S1**.

Among males, the multivariable logistic regression models conducted for each clinical asthma group revealed five associations with mild asthma (**Figure 2A**) and four with moderate-to-severe asthma (**Figure 2B**) – only three were common to both clinical asthma groups (family size greater than 3 siblings, rural residence and obesity BMI), one unique to mild asthma (underweight BMI), and one with contrasting effects in the two clinical asthma groups (birth year).

Among females, the multivariable logistic regression models conducted for each clinical asthma group revealed four associations with both mild asthma (**Figure 2C**) and moderate-to-severe asthma (**Figure 2D**) – only two were common to both clinical asthma groups (family size greater than 3 siblings and obesity BMI), one unique to mild asthma (rural residence), one unique to moderate-to-severe asthma (overweight), and one with contrasting effects in the two clinical asthma groups (birth year).

In summary, in both males and females, obesity BMI and family size greater than 3 siblings were positively and negatively associated with both clinical asthma groups, respectively, whereas birth year was negatively associated with mild asthma and positively associated with moderate-to-severe asthma. In contrast, underweight BMI in males as well as overweight BMI and rural residence in females were positively associated with only one of the clinical asthma categories, therefore indicating differences in variables associated with their development.

Discussion

The disparities between mild and moderate-to-severe asthma, among both males and females, with regard to secular trends of prevalence as well as association with risk factors, are indicative of varied etiologies, and further strengthen the growing body of evidence supporting this notion. There are conflicting reports regarding secular trends of asthma prevalence in Israel: a small drop from 7% in 1997 to 6.4% in 2003 among self-reporting eighth graders, as evidenced by questionnaires distributed by the National Center for Disease Control (52, 53), compared to a dramatic and consistent increase from 1.02% in 1957--61 to 11.16% in 2003--04 among males aged 17--18 years, based on physical examination (54). Nevertheless, little is known about trends of asthma, stratified by clinical asthma severity criteria. Changes in asthma prevalence during the last decades could be partly attributed to changes in diagnostic criteria for asthma (55) and increased awareness of asthma diagnosis, potentially resulting in a reversal phenomenon: in the past asthma was undoubtedly underdiagnosed but in the present it is probably overdiagnosed (56-58). The main strengths of this study are the uniform diagnostic criteria used throughout the research period, and the high-quality diagnosis which was made by experts in pulmonology based on pulmonary tests and supported by medical history anamnesis and documentation.

Furthermore, although objective evidence, such as exhaled nitric oxide (FeNO) and methacholine bronchial challenge (MBC), was collected only partially (and not systematically for all asthmatic subjects), in almost all cases this evidence was aligned with the reported physician-diagnosed asthma, and supported its determined severity (data not shown).

Here, we have demonstrated that from the 1976--1980 birth year period to 1986--1990, a downward trend in the prevalence of mild asthma was observed, while an upward trend in the prevalence of moderate-to-severe asthma was observed; both subsequently plateaued by the early-mid 1990s. This was valid for both genders (**Figure 1**). Given the secular decrease in the prevalence of mild asthma, and improved treatment and management protocol, one would also expect a parallel decrease in the prevalence of moderate-to-severe asthma. The contrasting trends of mild and moderate-to-severe asthma might indicate differences in etiology between the two severity groups. The latter category might represent a more pro-inflammatory based asthma, while the former category might involve less inflammation and might also be more dependent on reporting asthma, with less objective findings to substantiate diagnosis (no spirometry findings). Also, it is possible that changes in management protocols over the years have led to a shift in classification such that some of the asthma cases that were classified as mild asthma in early years are chronically treated with medications in recent years and therefore are considered to be moderate-to-severe asthma.

There is a well-established relationship between asthma and body weight, and more specifically obesity. Studies have shown an overall increase in asthma incidence, prevalence and severity, as well as poorer treatment outcome, in the obese (59-61). A diversity of possible mechanisms have been proposed to explain the relationship between obesity and asthma, including mechanical properties, organ cross-talk (inflammation and adipokines), comorbidities, hormones, oxidative stress and a shared genetic basis (62-65), although human studies are still inconclusive. Some studies suggest improvements in disease symptoms with weight loss in obese asthmatic patients, which may represent a distinct phenotype of asthma. Our study demonstrated that obesity was positively associated with increased risk of both mild and moderate-to-severe asthma, in both males and females. Furthermore, overweight was only associated with moderate-to-severe asthma in females, while underweight was associated with mild asthma in males. Although it

appears contradictory, relationships of asthma with overweight and underweight have been previously observed (66, 67), and are related to BMI during childhood (68). Although further research is warranted to synthesize these observations into a cohesive understanding of the relationship between BMI and asthma, it is clear that the disparate association of BMI in the different clinical asthma groups supports the notion of varied etiologies in males and females.

Asthma and asthma-related symptoms occur more frequently in urban than in rural areas; this difference correlates with environmental risk exposure (such as dust mites and vehicle emission), socio-economic status, and healthcare access (22). As expected, in our study, rural residence was negatively associated with both clinical asthma groups (mild and moderate-to-severe) in males. However, not only was this relationship valid only in males, urban residence was unexpectedly negatively associated with mild asthma, but not with moderate-to-severe asthma, in females. The contrasting relationships in males and females might be attributed to possible gender differences in dose thresholds of endotoxin exposure to invoke atopy and allergy to dust mite and animal dander or fur. Yet, the difference between mild and moderate-to-severe asthma within females points to additional interacting factors.

A higher risk of asthma was shown to be associated with smaller family size (69). Here, in both genders, family size greater than 3 siblings was associated with a decreased risk of both mild and moderate-to-severe asthma. This and other family-related variables might also be related to the “hygiene theory”. The bigger the family, the higher the relative exposure in early childhood to a significant amount and diverse types of infection factors, which may in turn accelerate the development of immune system protection against asthma.

Concluding remarks, limitations and future directions

Whereas the symptoms of asthma severity groups are easily recognized, the incident factors, pathogenesis, prognosis, and treatment of asthma remain incompletely understood. Better characterization of asthma phenotypes is required, from both etiological and clinical perspectives. 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 (the reference was subjects without asthma) among Israeli adolescents, in males and females

separately, while examining secular trends and relationships with sociodemographic variables and anthropometric indices.

This brought to light differences, and also some similarities, based on combinatorial stratification of gender and asthma severity. The findings suggest that different mechanisms, and probably an etiological basis, might be involved in the pathogenesis of mild asthma compared to moderate-to-severe asthma, and perhaps also between males and females. A similar notion has already been proposed for asthma among obese subjects. The differences might have implications not just for our view of asthma pathogenesis and progression in different sub-populations, but also for asthma diagnosis, and potential preventive and educative actions among sub-populations, pre-determined measures and testing among at-risk sub-populations, and treatment of asthma.

The large population size (113,671 adolescents), the long period of data collection (24 years), the standardized high-quality medical examination and stable criteria for defining asthma severity groups – are all key strengths of the study. Nevertheless, there were also certain limitations to this study. It was restricted to only one recruitment center, with an under-representation of certain populations (such as minorities and religious women that are exempt from service). Moreover, additional information on socio-demographic and lifestyle factors, such as socio-economic status and smoking habits, respectively, as well as genetic information, were not available for analysis. Our database also lacks information about age of asthma onset, which is directly related to some asthma phenotype classifications (11, 12). Data on atopy, a key determinant for clinicians when making appropriate decisions about both asthma etiology and treatment modalities, were only collected during the later years of the study, regarding only some atopic conditions and not differentiating their severity – therefore they were not included in the models. The database also lacks longitudinal information, therefore assessing natural history and progression of asthma after the examinations (diagnosis) was also beyond the scope of this study.

Utilizing measureable characteristics of asthmatic patients, including demographic, lifestyle and environmental factors, as well as physiological and medical measures and biological markers may shed more light on possible relationships and identify meaningful asthma phenotypes. Profiling the “medical signature” (comorbidities, namely, the accompanying medical conditions)

of asthmatic subjects, including children, adolescents and adults (males and females separately), and other systematic omics data (such as metabolomics (13), genomics, transcriptomics, proteomics etc.) may assist in defining high-resolution phenotypes (4) and leveraging toward understanding of disease state, identifying preventive strategies and improving precise and personalized therapeutics (11). These are of high interest and might have 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 the paper.

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Appendix 1 Description of variables

BMI categories – were defined according to gender-related percentiles for 17 years 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 (1). The actual definitions were as follows: Obesity – above the 95th percentile ($>28.2 \text{ kg/m}^2$ and $>29.6 \text{ kg/m}^2$ for males and females, respectively); Overweight – the 85th-95th percentiles ($25.0\text{-}28.2 \text{ kg/m}^2$ and $25.2\text{-}29.6 \text{ kg/m}^2$); Underweight – below 5th percentile ($<17.6 \text{ kg/m}^2$ and $<17.2 \text{ kg/m}^2$) (2).

Year of birth – for the univariate analysis, the study population was grouped into five separate five-year periods of birth year (only 3.5 years for the latest group). For the multivariate analysis, the continuous form of the variable was used.

Season of birth – the four astronomical seasons were defined as follows, based on birth date, in the northern hemisphere: autumn (September 22 to December 21), winter (December 22 to March 21), spring (March 22 to June 21), summer (June 22-September 21).

Country of birth – two categories, native-born (in Israel) vs. immigrants (out of Israel), were defined.

Religion – due to sample size considerations all minorities were grouped together (non-Jewish) and compared to Jewish population.

Residential environment – two categories, urban vs. rural area, were defined based on classification of Ministry of Internal affairs. The former was considered as reference in the multivariate analysis.

Socio-economic status (SES) – it was determined according to the publications of the Central Bureau of Statistics, which classifies the SES according to 10 deciles, which were further stratified into three groups: low (1-4), intermediate (5-7) and high (8-10).

Education – it takes into account both the number of years of studies, the course of study and level of educational institution. For the univariate analysis, it was stratified into five groups which correspond to primary (1-6), lower secondary (7-9), incomplete higher secondary (10-11) complete higher secondary (12), and tertiary (≥ 13) education. For the multivariate analysis (which is not described in details here), strata were combined to 1--11 and 12 or above, where the former was considered as reference.

Number of children in family / family size – for the univariate analysis, family size was stratified into four groups, according to the number of children in the family: 1, 2--3, 4--5, 6 or more. For the multivariate analysis, strata were combined to 1--3 and >3 children, where the former was considered as reference.

Birth order – a dichotomous variable. Subjects who answer the condition were compared to these who do not. Two sub-variables were considered, youngest offspring (compared to non-youngest offspring) and eldest offspring (compared to non-eldest offspring).

Advanced parental age – a dichotomous variable. Subjects who answer the condition were compared to these who do not. Two sub-variables were considered, advanced paternal age (father's age at subject's birth is at 95th percentile or higher, compared to non-advanced paternal age) and advanced maternal age (mother's age at subject's birth is at 95th percentile or higher, compared to non-advanced maternal age).

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Appendix 2 Description of univariate analysis findings

Associations in males

Of the socio-demographic variables, 13 were associated with either mild asthma or moderate-to-severe asthma. Of these, 7 variables were associated with both mild and moderate-to-severe asthma (Jewish religion, urban area of residence, 2--3 children in the family, eldest offspring, and various categories of birth year, socio-economic status, and education – were associated with a higher risk), 4 variables were only associated with mild asthma (season of birth [spring and summer] and immigrant status were associated with a higher risk, whereas advanced paternal and maternal age were associated with a lower risk), and 2 variables were only associated with moderate-to-severe asthma (youngest offspring and young maternal age were associated with a higher and lower risk, respectively).

Both asthma groups were positively associated with obesity and high average weight, whereas underweight was mainly positively associated with mild asthma.

Associations in females

Of the socio-demographic variables, only 6 were associated with either mild asthma or moderate-to-severe asthma. Of these, only 2 variables were associated with both mild and moderate-to-severe asthma (6 or more children in the family and various categories of birth year were associated with a higher risk), 3 variables were only associated with mild asthma (Jewish religion, rural residence of area and eldest offspring were associated with a higher risk), and 2

variables were only associated with moderate-to-severe asthma (youngest offspring and lower socio-economic status were associated with a higher and lower risk, respectively).

Only moderate-to-severe asthma was positively associated with obesity and overweight, yet both asthma groups were positively associated with high average weight.

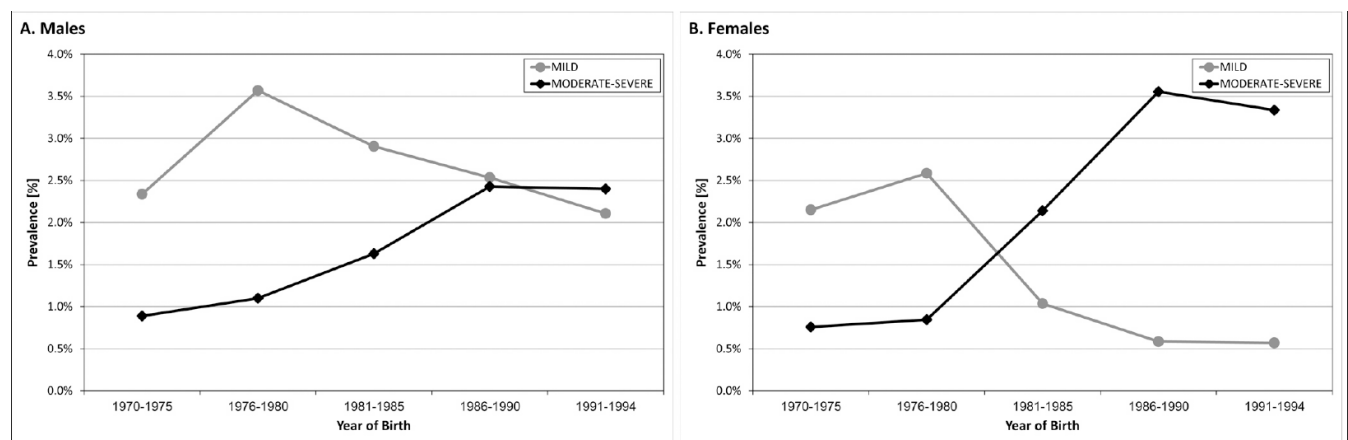


Figure 1. Secular trends of mild asthma (gray lines) and moderate-to-severe asthma (black lines) in males (A) and females (B).

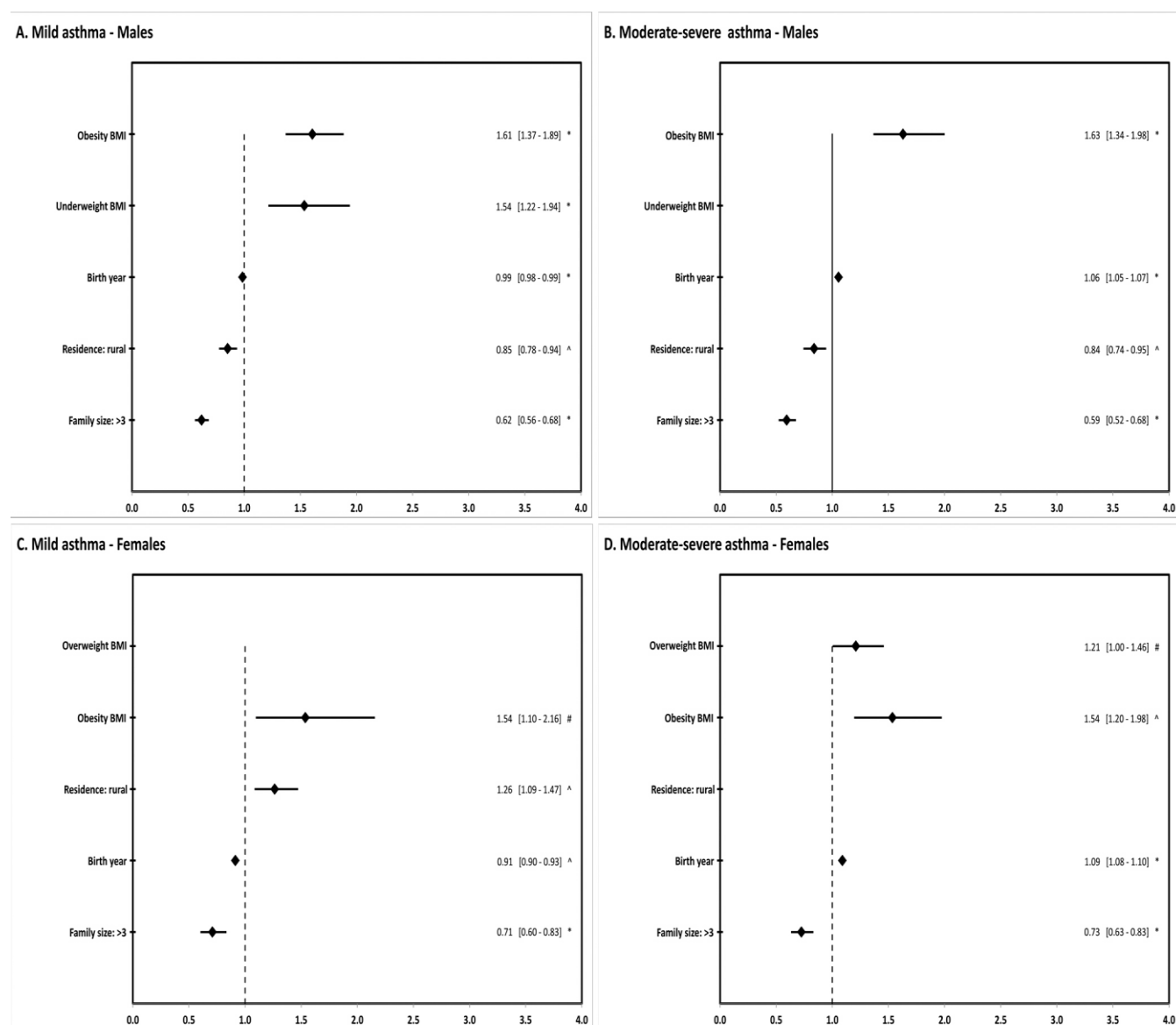


Figure 2. Correlates of mild asthma (A, in males; C, in females) and moderate-to-severe asthma (B, in males; D, in females) with socio-demographic variables in the multivariate logistic regression analysis. * $p < 0.001$; ^ $p < 0.01$; # $p < 0.05$