

ORIGINAL ARTICLE

Atopy as a risk factor for the development of asthma in young recruitsShlomo Moshe, MD, MOccH^{1,2}, Dan Slodownik, MD³, Yaron Yagev, MD, MOccH⁴, Noa Segal, MD²,
Michal Tavor, MD, MOccH⁴, Arnon Afek, MD, MHA⁵, and Oren Zack, MD, MOccH^{1,6}

¹Department of Environmental and Occupational Medicine, Tel Aviv University, Tel Aviv, Israel, ²Occupational Medicine Department, Maccabi Healthcare Services, Holon, Israel, ³Department of Dermatology, Sackler Faculty of Medicine, Sourasky Medical Centre, Tel Aviv University, Tel Aviv, Israel, ⁴Department of Occupational Medicine, Ben-Gurion University Medical School, Beer-Sheva, Israel, ⁵Department of Pathology, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel, and ⁶Medical Corps, Occupational Medicine Branch, Israel Defense Forces

Abstract

Objective: Asthma is one of the most common chronic diseases globally. Atopy, and especially allergic rhinitis (AR), was found as an important risk factor for asthma. The purpose of this study was to examine the association between different atopic parameters and military professions to the incidence of asthma. **Methods:** In a retrospective study, we included 128 591 Israel Defense Forces soldiers drafted between the mid-nineties to the early-2000s. We examined the incidence rates of asthma in relation to atopic background and to military profession. **Results:** The relative risk (RR) for the development of asthma in persons with a history of AR and the RR for asthma in atopics vs. nonatopics was 1.86 (95% CI: 1.57–2.21) and 1.73 (95% CI: 1.47–2.04), respectively. The RR for the development of asthma in persons with a history of AR was higher in Combat Units (CU) and Administrative and Driving units (ADU) (RR = 2.80; 95% CI: 2.09–3.76 and RR = 1.58; 95% CI: 1.19–2.12, respectively) than in Maintenance Units (MU) (RR = 1.27; 95% CI: 0.93–1.74). When comparing the risk for asthma amongst persons with AR, we found it lower in MU compared to ADU (RR = 0.65; 95% CI: 0.43–0.97). In atopics vs. non-atopics, the risk for asthma was higher in ADU as compared to other occupations. **Conclusions:** Atopy, particularly AR, is a risk factor for the development of new-onset asthma in young adults. Atopy has the highest significant effect in CU where the physical demands are higher.

Keywords

Environmental development, epidemiology, pathophysiology, rhinitis/sinusitis

History

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Introduction

Asthma is a heterogeneous disease underlined by the interaction between genetic and environmental factors and one of the most common chronic diseases globally affecting 10–12% of adults and 15% of children in affluent countries [1]. According to World Health Organization estimates, 300 million people suffer from asthma, and 255 000 people died of asthma in the year 2005 [1]. Amongst the known risk factors for asthma are atopy including allergic rhinitis (AR) [2] and atopic dermatitis (AD), which have been used as effective criteria in the asthma predictive index [3–5]. Prevalence of occupational asthma (OA) ranges from 9% to 15% of the asthmatic population [6].

It is now generally accepted that the workplace environment can lead to the development of different types of work-related asthma, including OA (i.e. asthma caused being at work) and work-exacerbated asthma (i.e. pre-existing or

coincident asthma exacerbated by non-specific stimuli at work). OA may result from either immunologically-mediated sensitization to occupational agents (i.e. “allergic occupational asthma” or “occupational asthma with a latency period”) or from exposure(s) to high concentrations of irritant compounds (i.e. “irritant-induced asthma”), which is best typified by “reactive airways dysfunction syndrome” [7].

Atopy has been consistently documented as a major risk factor for the development of IgE-mediated sensitization and OA in response to high-molecular weight agents that induce the production of specific IgE antibodies [7]. A multitude of studies have proven the association between the development of OA and a history of AR [5,8–10]. Several studies provide evidence linking the development of asthma, AR and AD in what was coined in the review of Spergel and Paller as the “atopic march” [11]. Nevertheless, the identification of atopy is not regarded as a reliable marker for excluding potentially susceptible workers from exposed jobs because it is a highly prevalent trait in the general population and thus yields only a weak positive predictive value for sensitization to low-molecular weight agents and OA [7].

Correspondence: Dr. Shlomo Moshe, MD, Environmental and Occupational Medicine, Tel Aviv University, Tel Aviv, Israel. E-mail: shlomo.moshe@gmail.com

The aim of this study was to determine the relative risk (RR) for the development of new-onset asthma in different occupational settings and in a large population of young adults, atopic and nonatopic, in their early vocational history.

Methods

Study population

This study involved all-male recruits (aged 18–21 years) drafted between mid-nineties to early-2000s to the Israel Defense Forces (IDF) for their obligatory three-year service. The precise service years of the study group cannot be disclosed as this information is classified. The follow-up period was three years, i.e. soldiers who did not complete the full period of obligatory service were excluded from the study. The study was approved by the military ethics committee.

Health data

The health examination at the recruitment centers includes the taking of full medical history, self-reported disease status, a review of medical documentation provided by the family physician and a complete physical examination. The definition of asthma was in accordance with updated Global Initiative for Asthma guidelines [12]. Conscripts who reported a positive history of asthma or claimed they suffered from recurrent wheezing, nocturnal cough, cough or wheeze after exertion were referred for further professional examination. Subjects were instructed not to take any medication for asthma on the day of the examination that included further detailed history review, physical examination and spirometry at rest. All subjects, except those with explicit clinical signs and spirometric evidence of severe airway obstruction, underwent a physical exercise test comprised of six minutes of treadmill running at a speed of 5 km/h up to an incline of 10° while breathing room air (22 °C, 50% relative humidity). Lung function was measured 5 and 10 minutes after the exercise to determine the percentage of decline in forced expiratory volume in one second. It seems from the bellows spirometer protocol that historical data were collected in a very similar manner to the more recent measurements, i.e. in accordance with ATS/ERS guidelines [13]. The atopic background was determined based on clinical examination at the draft office and medical records based on the relevant specialist (ENT in case of AR, ophthalmologist in case of allergic conjunctivitis (AC), dermatologist in case of AD and allergologist usually in cases of AR and less frequently in cases of AC or AD). The diagnosis in case of rhinitis was either allergic or non-allergic rhinitis. The atopic background was not based on positive immediate type hypersensitivity or skin testing or specific *in vitro* blood allergy tests. Any conscript with prior asthma, even inactive, at the starting point of the study was excluded from the analysis.

A positive diagnosis according to the above criteria resulted in medical status assessment by a military medical committee, which assigned the applicable medical profile pertaining to the disease and its severity. A change in medical status during the service period resulted in reevaluation of the medical profile in light of the new evidence. The study endpoint per subject was defined as a change in the medical

profile to include asthma, diagnosed as explained and approved by a pulmonology expert and a medical military committee. This process was supervised and monitored by a trained physician stationed at the headquarters of the IDF medical corps.

Occupational categories

The soldiers' assignments were categorized into Combat Units (CU), Driving Units (DU), Maintenance Units (MU) and Administrative Units (AU). The CU includes both infantry with strenuous physical activity and high mental stress and mobile units with less strenuous physical activity and shorter training durations. The DU includes all soldiers in driving professions. The MU is characterized by moderate physical activity and mental stress, and a mild exposure to organic solvents (~10% of threshold limit value). The service in AU is predominantly characterized by sedentary office work, low mental stress and no hazard exposure. These categories were applied as markers of occupational stress. We later merged the DU and AU into one study group designated as administrative and driving unit (ADU).

Statistical analysis

Incidence of asthma during the study period was presented for each occupational category and atopic background. RR (95% CI) of asthma was calculated for atopic vs. non-atopic subjects by diagnosis and occupation as well as for comparison of occupational contribution to the development of asthma by atopic background. Analyses were performed using IBM SPSS Statistics for Windows, Version 21.0 (IBM Corp, Armonk, NY).

Results

Our study population included 128 591 subjects. Over the three-year follow-up period, 1984 soldiers (1.54% of the study group) were diagnosed with *de-novo* asthma. The annual incidence rate for new onset asthma calculated in our study was 5.15/1000 person-yr⁻¹. Table 1 summarizes the rates for newly diagnosed asthma by profession and atopic background. Incidence rates for participants with atopic diagnoses and for non-atopics are provided including total asthma incidence rate for either occupational category and for all categories combined. The respective asthma incidence rates amongst total participants for AR, AC, AD, non-atopics and overall participants are 2.78%, 1.33%, 2.16%, 1.49% and 1.54%. As demonstrated in Table 1, one should note that 271 of the total participants and 14 of the newly diagnosed asthmatics had multiple atopic diagnoses. The highest overall incidence rate was noted for the ADU group, whereas participants with a background of AR had the highest reported rates encompassing all occupational categories.

Table 2 lists the RR for asthma in atopic vs. non-atopic subjects by atopic diagnosis and occupation. The overall RR for asthma in AR, AC, AD and overall atopics vs. non atopics were 1.86 (95% CI: 1.57–2.21), 0.89 (95% CI: 0.46–1.70), 1.45 (95% CI: 0.61–3.45) and 1.73 (95% CI: 1.47–2.04), respectively. The RR for the development of asthma in AR diagnosed soldiers was significant in CU and ADU

Table 1. Newly diagnosed asthma by profession and atopic background.

Occupational categories	Atopic background	Subjects	Newly diagnosed asthma (%)
Administrative + Driving (ADU)	Allergic rhinitis	1419	48 (3.38%)
	Allergic conjunctivitis	203	2 (0.99%)
	Atopic dermatitis	89	1 (1.12%)
	Non atopics	26 921	575 (2.14%)
	Participants	28 417 ^a	623 (2.19%) ^b
Maintenance (MU)	Allergic rhinitis	1878	41 (2.18%)
	Allergic conjunctivitis	275	5 (1.82%)
	Atopic dermatitis	70	3 (4.29%)
	Non atopics	38 488	661 (1.72%)
	Participants	40 366 ^c	702 (1.74%) ^d
Combat (CU)	Allergic rhinitis	1594	47 (2.95%)
	Allergic conjunctivitis	199	2 (1.01%)
	Atopic dermatitis	72	1 (1.39%)
	Non atopics	58 214	612 (1.05%)
	Participants	59 808 ^e	659 (1.10%) ^f
All occupational categories	Allergic rhinitis	4891	136 (2.78%)
	Allergic conjunctivitis	677	9 (1.33%)
	Atopic dermatitis	231	5 (2.16%)
	Non atopics	123 623	1848 (1.49%)
	Participants	128 591 ^g	1984 (1.54%) ^h

^aThe exact number of participants is 28 417 since 215 had multiple atopic diseases.

^bThe exact number of participants is 623 since 3 had multiple atopic diseases.

^cThe exact number of participants is 40 366 since 345 had multiple atopic diseases.

^dThe exact number of participants is 702 since 8 had multiple atopic diseases.

^eThe exact number of participants is 59 808 since 271 had multiple atopic diseases.

^fThe exact number of participants is 659 since 3 had multiple atopic diseases.

^gThe exact number of participants is 128 591 since 271 had multiple atopic diseases.

^hThe exact number of participants is 1984 since 14 had multiple atopic diseases.

Table 2. The relative risk for asthma in atopic vs. non-atopic subjects by diagnosis and occupation.

Occupational categories	Allergic rhinitis vs. non-atopics RR (95% CI)	Allergic conjunctivitis vs. non-atopics RR (95% CI)	Atopic dermatitis vs. non-atopics RR (95% CI)	Atopics vs. non atopics RR (95% CI)
Administrative + Driving (ADU)	1.58 (1.19–2.12)	0.46 (0.12–1.84)	0.53 (0.08–3.70)	1.40 (1.05–1.85)
Maintenance (MU)	1.27 (0.93–1.74)	1.06 (0.44–2.53)	2.50 (0.82–7.57)	1.28 (0.96–1.71)
Combat (CU)	2.80 (2.09–3.76)	0.96 (0.24–3.80)	1.32 (0.19–9.27)	2.55 (1.92–3.39)
Total	1.86 (1.57–2.21)	0.89 (0.46–1.70)	1.45 (0.61–3.45)	1.73 (1.47–2.04)

(RR = 2.80, 95% CI: 2.09–3.76; RR = 1.58, 95% CI: 1.19–2.12, respectively). The RR for asthma in atopics vs. non-atopics was significantly higher in ADU, CU and total participants (RR = 1.40, 95% CI: 1.05–1.85; RR = 2.55, 95% CI: 1.92–3.39; and RR = 1.73, 95% CI: 1.47–2.04, respectively).

Finally, Table 3 compares the occupational contribution for asthma in either atopic diagnosis. Comparison of CU to MU and CU to ADU yielded a lower risk in CU (RR = 0.61, 95% CI: 0.55–0.68 and RR = 0.49, 95% CI: 0.44–0.55, respectively). When comparing MU with ADU, we found lower risk for AR and non-atopics (RR = 0.65, 95% CI: 0.43–0.97 and RR = 0.80, 95% CI: 0.72–0.90, respectively).

Discussion

In this retrospective study, we evaluated 128 591 subjects over a three-year follow-up period. This study clearly demonstrates that atopic background is a risk factor for the development of

new onset asthma (RR = 1.73; 95% CI: 1.47–2.04). A history of AR confers a RR of 1.86 (95% CI: 1.57–2.54) for the development of de novo asthma. It was shown that the RR for the development of asthma in persons with a positive history of AR is high amongst CU and ADU (RR = 2.80, 95% CI: 2.09–3.76 and RR = 1.58, 95% CI: 1.19–2.12, respectively).

The annual incidence rate for new onset asthma calculated in our study was 5.15/1000 person-yr⁻¹. There have been few studies of asthma incidence rates among adults; published rates by studies from the USA, Scandinavia, Spain and Italy, show incidence rates from 1 to 5 cases per 1000 person-yr⁻¹ [14] with the closest incidence rate to our results shown by the northern Swedish study reporting a mean annual incidence rate of 0.5% [15]. We assume that the rigorous physical efforts carried out in CU could partially explain the higher incidence of asthma in this group as shown by our previous works [16,17].

We found that the RR for the development of asthma in patients diagnosed with AR was 1.86 (95% CI: 1.57–2.54)

Table 3. Comparison of occupational contribution to the development of asthma by atopic background.

	Allergic rhinitis RR (95% CI)	Allergic conjunctivitis RR (95% CI)	Atopic dermatitis RR (95% CI)	Non-atopics RR (95% CI)
Combat (CU) vs. Maintenance (MU)	1.35 (0.89–2.04)	0.55 (0.10–2.82)	0.32 (0.04–3.04)	0.61 (0.55–0.68)
Combat (CU) vs. Administrative and Driving (ADU)	0.87 (0.59–1.30)	1.02 (0.145–7.17)	1.24 (0.08–19.42)	0.49 (0.44–0.55)
Maintenance (MU) vs. Administrative and Driving (ADU)	0.65 (0.43–0.97)	1.85 (0.36–9.42)	3.81 (0.40–35.88)	0.80 (0.72–0.90)

(Table 2). Results shown by our research are comparable (lower range of the spectrum) to results published by other studies showing RR of between 1.6 and 5 [5,9,10,18–20]. The advantages in our study include a bigger population, two-magnitudes-of-order in size, compared with other studies, asthma diagnosis based on strict criteria in accordance with published guidelines and evaluations by medical specialists in contrast to other studies, which were based on questionnaires. We thus believe that our study represents a more accurate assessment of RR for the development of asthma in young adults with AR.

AD, usually the first manifestation of the atopic march, has also been identified as a risk factor for asthma. In our study, we found a non-significant RR for the development of asthma (RR = 1.45; 95% CI: 0.61–3.45). Gustafsson et al. found AD as a specific risk factor for developing asthma with up to 30% of patients with severe AD presenting with asthma [21]. Rhodes et al. [22,23] studied 100 infants from atopic families with rates of AD peaking at 20% by age one and the rates of wheezing extended to 40% by the age 22 years. The German Multicenter Atopy Study showed that by five years of age, 50% of children with early AD and a strong family history of allergy had allergic airway disease or asthma compared with 12% in patients without AD or history of atopy [24]. Ohshima et al. noted a greater risk for developing signs of asthma in 169 Japanese children with AD [25]. We assume that the age differences, the presence of a small group and a short follow-up period may explain why no significant correlation was found.

In CU, we found a RR of 2.55 (95% CI: 1.92–3.39) in atopics vs. nonatopics for the development of asthma, higher than in ADU and MU (RR = 1.40; 95% CI: 1.05–1.85 and RR = 1.28; 95% CI: 0.96–1.71, respectively). Although exercise is a known precipitant of acute asthma among patients, it is not considered as a cause *per se* of asthma among healthy individuals. In a follow-up study of IDF soldiers by Katz et al. [16], they found that asthma rates were higher among subjects serving in CU (RR = 3.7) than in either MU or AU (RR = 2.7 and RR = 1.4, respectively) suggesting that more strenuous job assignments may be correlated with a higher probability for the development of asthma. One might suggest that amongst atopic individuals, the same trigger is even more substantial, contributing to their higher risk of developing asthma and thereby explaining our findings in CU of higher rates in atopics vs. nonatopics.

In MU, representing jobs such as technicians and mechanics, we did not find a significant RR for the development of asthma in atopics vs. nonatopics (RR = 1.28; 95% CI: 0.96–1.71). Atopy is a known risk factor for IgE-mediated OA caused by exposure to high-molecular-weight agents [26,27].

The MU in our study was usually exposed to low levels of organic solvent mixtures, which are not known as classic sensitizers for OA, and we assume that may explain why no higher risk was found.

In ADU, we found a higher risk for the development of asthma in atopics vs. nonatopics (RR = 1.40; 95% CI: 1.05–1.85; Table 2). When we compared the RR for the development of asthma between occupations (Table 3), we found a lower risk in MU vs. ADU (RR = 0.65; 95% CI: 0.43–0.97), although ADU is actually the control group and the MU is the group that was exposed to low levels of organic solvents. A plausible explanation may lie in the differed severity of atopic disease in ADU since severe atopic patients are posted only in ADU, and only mild atopics are posted in either CU or MU.

Our study has several drawbacks. We lack data concerning atopic status in the study population, i.e. an allergologist evaluation was not obligatory in the diagnosis process, the levels of total serum IgE and/or specific IgE to common allergens (dust mite and skin prick allergens) and the definition of rhinitis, which includes non-allergic and AR. Due to inherent limitations with the study population, we did not differentiate populations according to ethnical origin. Another downside is the lack of data concerning the date of asthma onset relative to induction, which would have yielded a more powerful analysis. A possibility that cannot be ruled out is that lower-motivated soldiers may have higher patient–doctor encounter rates than their combat counterparts but also that higher stress can promote combat soldiers to seek a lower medical profile. We assume that the small incidence of false-positive diagnoses (malingerers) is similar to the small incidence of the false-negative diagnoses (highly motivated individuals), thus compensating for each other and representing probable true figures of recrudescence. Nonetheless, we believe it to have little limited implications on our results. This study's strength lies in its large epidemiological database, strict criteria for asthma diagnosis and the precise vocational criteria.

Conclusions

We found that atopy, and particularly AR, is a risk factor for the development of new-onset asthma in young adults, especially in CU where physical effort is demanded. However, we did not find any correlation regarding MU, which represents technical jobs characterized by occupational exposures to agents such as organic solvents but without exposure to high-risk agents for OA like flour, isocyanates, latex, persulfate salts, aldehydes, animals, wood dusts, metals, enzymes, etc., which are common in professions like

laboratory workers, pharmaceutical workers, bakery workers, laboratory animals workers and polyurethane foam workers [6,7]. As implicated by our results, it seems that AR may present as an important risk factor for asthma among young adults engaged in jobs characterized by physical work, but not technical jobs characterized by exposure to various chemical substances including organic solvent mixtures.

These findings are of high importance especially since it has been shown that self-selection into low-risk jobs seems to play a minor role in teenagers with asthma or allergies [28] – perhaps, it may even be prudent to guide such teenagers early in their vocational education and training.

More studies are required in order to validate the pathogenesis and etiology concerning the relationship between an atopic background and the development of asthma and specifically OA in high-risk jobs as mentioned above and all in accordance with accurate and precise determination of the atopic background.

Declaration of interest

The statement is accurate.

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