Asthma in Active Military Aircrew: Long-term Health and Flight Performance

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ABSTRACT **Background:** Asthma poses unique challenges in aviation medicine. While strict criteria typically dictate waiver approvals in military aviators with asthma, the Israeli Air Force (IAF) applies a more individualized approach. Still, evidence to guide correct management is scarce.

Objectives: To assess the characteristics and long-term outcomes of military aircrew diagnosed with asthma.

Methods: This retrospective study included active and reserve aircrew who were diagnosed with asthma during annual assessments at the Israeli Aeromedical Unit between 1998 and 2024. Baseline characteristics, treatment regimes, pulmonary function tests (PFTs), and asthma exacerbations were analyzed.

Results: Thirty-two aircrew personnel (median age 30 years at diagnosis) were included in the study, with 44% serving at high-performance platforms. Six participants (19%) were classified as Global Initiative for Asthma step 4 or 5. Over an average follow-up period of 18.5 years, seven exacerbations were documented (4.0 per 100 patient-years), with no safety incidents reported. Participants' pulmonary function remained stable. Forced expiratory volume in 1 second (FEV_1) and FEV_1/forced vital capacity (FVC) declined around asthma diagnosis (median of 82% predicted and 0.73, respectively) but recovered remarkably while on treatment (median 91% predicted and 0.78, respectively). Aircrew who experienced exacerbations had no statistically significant differences in demographics, disease severity or baseline PFTs.

Conclusions: With individualized management and regular monitoring, a new diagnosis of asthma in military aircrew was not associated with a significant impact on service. Our study supports a flexible, individualized approach to aeromedical management of aircrew with asthma.

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KEY WORDS: aircrew, asthma, aviation, Israeli Air Force (IAF), military

Asthma is the most prevalent chronic lung disease, affecting approximately 8% of adults worldwide [1,2]. Diagnosis is usually made in early childhood, but rates of adult-onset asthma are persistently increasing, in part due to occupational exposures [3,4]. Individuals with asthma who need maintenance therapy are generally disqualified from any sort of combat training in the Israeli Defense Forces (IDF). Recruits are considered eligible for combat training only when diagnosed with controlled asthma, without recent exacerbations, and with a Global Initiative for Asthma (GINA) severity of 1 or 2 (i.e., using reliever therapy only). Still, among eligible trainees, exacerbations occurred up to twice as frequently compared to their counterparts performing clerical duties, suggesting that a high-risk environment may lead to asthma worsening regardless of symptoms [5,6].

Aircrew training candidates are subject to stricter criteria to be accepted to flight academy [7]. Aviators are exposed to severe physiological stressors. Under extreme conditions of high G forces, stress, and fast maneuvers, any change or decline from optimal conditions could result in rapid compromise, especially in a vulnerable person [8,9]. In addition, acute hypobaric hypoxia (HH), which is a major hazard in aviation, occurs at lower altitudes (below 3000 meters) in susceptible individuals [10]. Recent data from the Israeli Aeromedical Center suggests asthma remains the second most common reason for disqualification of candidates even when completely asymptomatic [11].

Considering that aircrew personnel are required to be in service for many years, asthma can develop during this time frame. Renewal waivers in these cases are occasionally considered. Some official guidelines demand applicants meet

specific requirements, such as a relatively high forced expiratory volume in 1 second (FEV_1) and no evidence of airway hyper-responsiveness [9]. In the IDF, waivers are granted on a case-by-case basis and often rely on expert opinions. One study followed 19 Israeli aviators with asthma who resumed flying, most were treated with controller therapy. Over 90% had satisfactory disease control during service, with nearly no grounding cases due to disease worsening, even among aviators with higher GINA classifications [8]. This preliminary evidence suggests asthma control may be feasible in the aviation environment in a broader group of patients, with a wider range of disease severity.

Permitting aviators with active asthma to resume flying under certain conditions, creates unique circumstances in the Israeli Air Force (IAF). However, to the best of our knowledge, no comprehensive long-term study has been conducted in the last two decades on this topic, and the existing literature lacks documentation of trends in objective measures, particularly pulmonary function tests (PFT).

To address the mentioned gap in knowledge, in this study, we characterized new-onset asthma in IAF aviators, examined PFTs trends in this group, and explored the potential effects of asthma on flight performance.

PATIENTS AND METHODS

This observational retrospective study included 32 military aircrew personnel who were diagnosed with asthma during their service between the years 1998 and 2024. To be included in the study, all the following criteria had to be met: diagnosis of asthma by a pulmonologist in Israeli Aeromedical Unit's (IAMU), active or reserve duty at the time of diagnosis and access to medical data. Of note, no patients were excluded.

The study was approved by the IDF institutional ethics review board (approval number 2127–2020) and was conducted in accordance with the Declaration of Helsinki. Informed consent was waved given the retrospective design of the study.

Asthma was diagnosed based on accepted guidelines [12], with at least one of the following: bronchodilator reversibility on spirometry: and an increase of at least 12% or 200 ml in FEV_1 or FVC following administration of salbutamol or positive methacholine challenge test (≥ 20% fall in FEV_1 at a methacholine concentration of ≤ 4 mg/ml). Asthma severity was classified retrospectively into treatment steps scored 1–5 according to the GINA 2024 guidelines [12], which was based on the treatment regime that was used for the longest duration for each patient.

Pulmonary functions were evaluated at the following time-points: at drafting or the nearest available exam, at asthma diagnosis, and the most recent exam (after treatment initiation).

Data were collected from the medical records archived at the IAMU and were based on the annual medical screening tests performed on active aircrew members.

For each participant, data collected included demographic characteristics, age at diagnosis, maximal blood eosinophil count, presence of allergy, type of treatment, and annual pulmonary function test results.

The study outcomes included asthma exacerbations and in-flight or near-flight safety events. Asthma exacerbations were defined as worsening symptoms in a diagnosed asthma patient requiring an urgent medical consultation, a change in treatment, or a grounding instruction.

Flight performance was evaluated by reviewing digital medical documentation of safety incidents and examples of grounding.

STATISTICAL ANALYSIS

Descriptive statistics were performed for the entire cohort. Continuous variables were presented as median (interquartile range [IQR]) based on their non-normal distribution (assessed by Kolmogorov–Smirnov tests). Categorical variables were presented as amount (percentage of total). Comparisons between participants with and without exacerbation were performed by Fisher's exact tests for categorical variables and Mann-Whitney U tests for continuous variables. To assess changes in PFTs, paired analyses were used by Friedman's two-way analysis of variance by ranks and Bonferroni correction for repeated measures. Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 30 (SPSS, IBM Corp, Armonk, NY, USA). A P-value < 0.05 was considered statistically significant.

RESULTS

A total of 32 aircrew members diagnosed with asthma were included in the study. The baseline characteristics are shown in Table 1. The overall median (IQR) age at asthma diagnosis was 30 (27–40) years; 3 (10%) were female; 10 (31%) had known allergies. The median (IQR) maximal eosinophil count was 327 (195–580) cells/mm³. Most were diagnosed during their reserve duty (62.5%) and 14 (44%) served at high-performance platforms.

Table 1. Cohort characteristics

Variable	Total, N=32
Age at diagnosis, years (range)	30 (27–40)
Female sex	3 (10%)
Known allergies	10 (31%)
Eosinophils, cells/mm³	327 (195–580)
Service type	
Active	12 (37.5%)
Reserve	20 (62.5%)
Profession	
High performance	14 (44%)
Non-high performance	28 (56%)
Asthma onset	
Young-adult (< 35 years)	21 (66%)
Adult (> 35 years)	11 (34%)
Mode of diagnosis	
Bronchodilator reversibility	24 (75%)
Methacholine challenge	8 (25%)
Worst GINA score	
1–2	10 (31%)
3	16 (50%)
4	5 (16%)
5	1 (3%)

GINA = Global Initiative for Asthma

Asthma was diagnosed based on bronchodilator reversibility (75%) or positive methacholine challenge (25%). Five participants (16%) had GINA severity scale of 4, which required using maintenance medium-dose inhaled corticosteroids (ICS). None of the participants were suspected of having occupational asthma, as there were no changes in symptoms in relation to work exposure, nor were symptoms severe enough to require termination of service.

PULMONARY FUNCTIONS

Trends in pulmonary functions are shown in Figure 1 and Figure 2. At baseline (first documented spirometry), participants had normal lung functions, with a median FEV_1 of 95% predicted (85–100%), FVC of 92% predicted (87–107%), and FEV_1/FVC of 0.85 (0.76–0.89). At asthma diagnosis, there was a decrease in FEV_1 compared to baseline (median 82% predicted, $P < 0.001$) [Figure 1] and in FEV_1/FVC (median 0.73, $P < 0.001$) [Figure 2] while FVC remained similar (median 89% predicted, $P = 0.081$).

The last documented spirometry, after initiation of treatment, showed opposite trends. Improvements were noted in FEV_1 compared to the diagnosis ($P = 0.01$), FEV_1/FVC ($P = 0.007$), and stable FVC ($P = 0.401$). The significant differences remained following Bonferroni corrections for multiple testing. Of note, at asthma diagnosis, 13 patients (41%) had an $FEV_1 < 80\%$ predicted. Persistent reduction was observed in 6 patients during follow-up (19%).

Figure 1. Longitudinal changes in FEV_1 from baseline to asthma diagnosis and latest spirometry

[A] Changes in FEV, (liters) **[B]** Individual trajectories and mean change in FEV_1 (% predicted)
FEV_1 = forced expiratory volume in 1 second

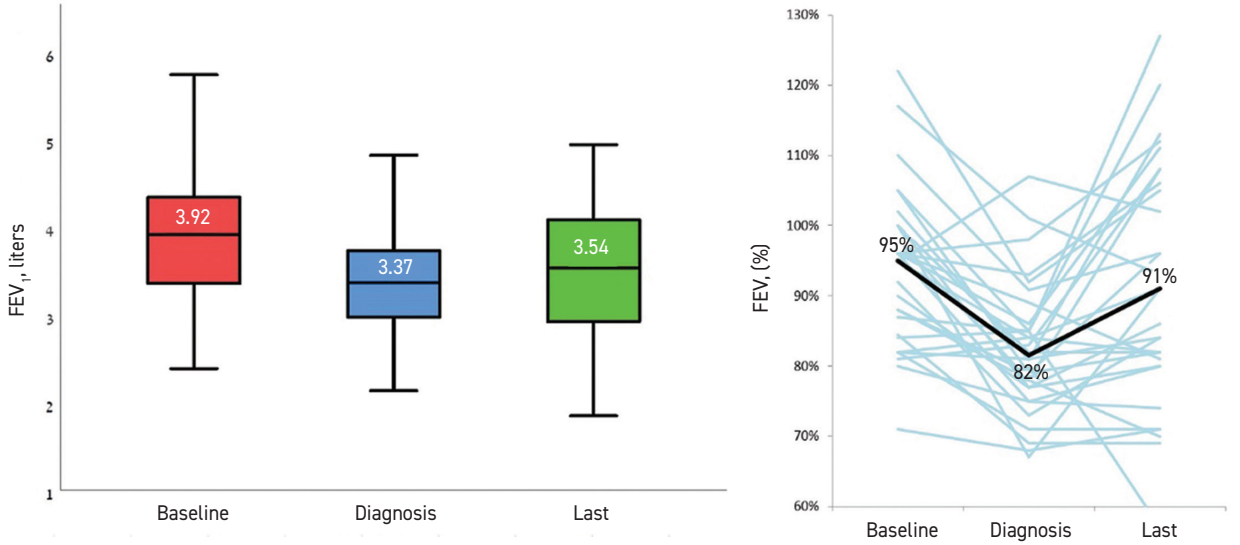

Figure 2. Changes in pulmonary function from baseline, to asthma diagnosis and latest spirometry

[A] Changes in FVC (liters) **[B]** Changes FEV_1/FVC ratio
FEV_1 = forced expiratory volume in 1 second, FVC = forced vital capacity

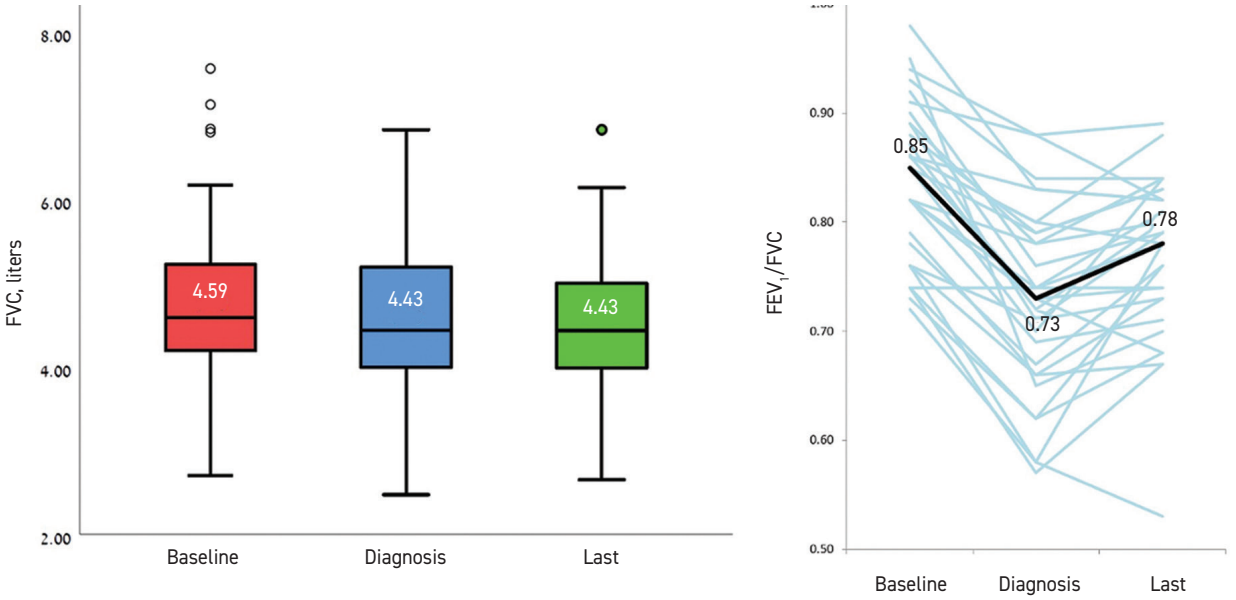

Table 2. Comparison of aircrew characteristics by asthma exacerbation

Variable	No exacerbation, n=25 (%)	Exacerbation, n=7 (%)	*P*-value
Age at diagnosis	30 (27–42)	30 (27–35)	0.929
Female sex	2 (8)	1 (14)	0.536
Eosinophils, cells/mm³	330 (190–620)	270 (200–520)	0.929
Known allergies	8 (32)	2 (29)	1
Worst GINA			
1–2	9 (38)	1 (14)	0.502
3	12 (48)	4 (57)	
4	3 (12)	2 (29)	
5	1 (4)	0 (0)	
Baseline FEV_1, %predicted	93 (85–96)	99 (96–102)	0.247
FEV_1 at diagnosis, %predicted	83 (77–88)	79 (68–85)	0.296

FEV_1 = forced expiratory volume in 1 second, GINA = Global Initiative for Asthma

ASTHMA OUTCOMES

During 174 patient-years of follow-up, seven exacerbations occurred in seven different participants, corresponding to an incidence rate of 4.0 exacerbations per 100 patient-years. Still, review of flight performance data revealed no significant safety incidents during the follow-up period. Characteristics of aircrew with exacerbations compared to those who had not experienced exacerbations are shown in Table 2. There were no significant differences in demographic or clinical characteristics between the groups, although a numerically lower FEV_1 at asthma diagnosis was observed in the exacerbated group (median 79% predicted, IQR 68–85%) compared to the rest of the cohort (median 83% predicted, IQR 77–88%).

DISCUSSION

In this study, we evaluated the long-term outcomes of 32 IAF aircrew members diagnosed with asthma either during or after completion of training. Our findings showed that while many had a significant disease requiring maintenance inhaler therapy, the vast majority were clinically stable and without sustained impact on their performance as aircrew personnel. In addition, pul-

monary functions showed improvement with treatment, even with a long follow-up period averaging 18.5 years.

Exacerbations were infrequent with an incidence rate of 4.0 per 100 patient-years, triggered primarily by respiratory viruses or an allergic flare. Exacerbations were managed in the ambulatory setting, with temporary disqualification from flying, usually for no longer than a month. No permanent disqualification was instructed.

We hypothesize that the positive outcomes observed in our cohort stem from the continuous, frequent follow-up and guidelines-based treatment provided by specialized medical personnel, which is readily available at the IAMU. This procedure is supported by prior studies that showed significantly lower rates of exacerbation and improved outcomes in patients treated by respiratory specialists [13].

PFTs trends were reassuring. The mean FEV_1 (liters) declined modestly from 3.92 L at the earliest available spirometry to 3.54 L at the most recent spirometry. Expected declines are approximately 22 ml/year in healthy individuals and 38 ml/year in asthmatic individuals [14]; hence, the observed decline in our cohort resembles that of the general healthy population.

Based on patient inhaler therapy, 19% had GINA severity scale of 4 or 5. Importantly, stability in PFTs was observed even in this group, which required moderate to high doses of ICS. This finding suggests that granting of waivers should not rely on PFTs results alone. Additional testing, such as fractional exhaled nitric oxide (FeNO), might provide additional information for improved individual-level prognostication to optimize candidate selection [15]. Notably, given the possible devastating consequences of uncontrolled symptoms or exacerbations during flights, treatment strategy is generally more aggressive with aircrew personnel, which may explain the high rate of participants requiring maintenance ICS in our cohort. Moreover, anti-inflammatory reliever therapy was not recommended during most of the study period, unlike current guidelines where it is considered first line therapy for early GINA stages. This protocol may further explain the high use of maintenance ICS therapy.

Of note are two participants, both of whom served in high-performance platforms. Despite persistently not maintaining an FEV_1 (%predicted) value of 80% or higher as accepted for a long duration in the follow-up period (latest spirometry of 69% and 75%, accordingly), both were granted waivers to resume flying with no limitations.

The findings reinforce the unique waiver policy employed by the IDF. Unlike stricter systems worldwide [9], the IDF follows a more individualized, case-by-case approach. Our data support the safety and effectiveness of this strategy. The updated waiver policy presented in our study is more inclusive compared to the approval algorithm described in previous literature on the same population of IDF aircrew [8] with no major safety or health complications.

Several limitations should be acknowledged. First, the retrospective nature of the study could lead to missed exacerbations that were not documented in the medical files. As all military aircrew are followed regularly by IAMU physicians, we believe the odds of this are low. Second, although we included patients over a course of 20 years, the cohort size was still relatively small. Third, there was notable underrepresentation of female participants, consistent with the demographics of military aviation. Fourth, the absolute number of pilots during the study period is classified by the IDF and cannot be disclosed. Therefore, these data were not available for analysis, and we were unable to include a control group or report the overall percentage of new-onset asthma following recruitment. Last, although grounding events were rare, further exploration of flight activity variables, including flight hours, airframe type and exposure to environmental stressors, could improve understanding of factors influencing long-term outcomes.

CONCLUSIONS

A new diagnosis of asthma among aircrew members, while requiring maintenance therapy in most cases, was not found to significantly affect performance during service. Our findings have potential implications for broader populations of military and civilian aviation programs worldwide, especially considering the resources invested in aviator training and retention. Future prospective studies with a matched control group are warranted to validate these findings and dictate a change in guidelines.

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Capsule

Two PRINCEs

Controlling the duration of gene-editing activity could make gene-editing therapies safer; however, achieving precise temporal control over these platforms in situ is challenging. **Zhang** et al. developed the PRINCE CRISPR/Cas gene-editing system, in which expression of the nuclease and the guide RNA are separately inducible by small-molecule drugs, thereby maximizing temporal control. After demonstrating PRINCE's stability and temporal precision in vitro up to 2 years after genomic integration into cells, the authors established a more translational system, Little Prince, using compact nucleases that can be delivered within a single vector. In two mouse models, Little Prince ameliorated phenotypes with fewer off-target edit and lower off-target editing frequencies than constitutive nuclease expression.

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Capsule

The long noncoding RNA lnc13 restrains inflammatory responses to maintain oral tolerance to gluten

Yang-Fischer et al. investigated the role of the long noncoding RNA (lncRNA) lnc13 in maintaining immune tolerance to dietary gluten. Loss of oral tolerance to gluten is a hallmark of Celiac disease, but the molecular mechanisms regulating this process remain incompletely understood. The authors demonstrated that lnc13 acts as a critical regulator of inflammatory gene expression in intestinal immune cells. Under normal conditions, lnc13 suppresses excessive inflammatory responses and helps maintain tolerance to gluten-derived antigens. Impaired lnc13 function resulted in enhanced inflammatory signaling, increased cytokine production, and loss of immune tolerance. The authors identified lnc13 as an important molecular checkpoint in intestinal immune homeostasis and provides new insight into the pathogenesis of celiac disease. Therapeutic strategies aimed at restoring lnc13 function may offer novel approaches for treating gluten-related autoimmune disorders.

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