

# Young Adults with Mild Asthma in a High-Risk Occupation: Incidence and Risk Factors for Exacerbation

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## Keywords

Asthma · Young adults · High-risk environment

## Abstract

**Background:** The effects of high-risk environment on young adults with mild asthma were never fully tested in practice, as most high-risk occupations do not welcome them. This study examines the effect of combat training on asthma worsening in the Israeli Defense Forces. **Methods:** Persons with asthma in remission and mild intermittent asthma who underwent combat training between 2014 and 2017 were compared in terms of disease worsening to their counterparts performing clerical duties during a follow-up of 8 months. Among combat trainees, exposure to known triggers for asthma exacerbation and health status on enlistment were assessed as risk factors for asthma exacerbation. **Results:** Asthma worsening among persons with asthma in remission was twice as common among those who are undergoing training compared to persons performing clerical duties. This difference was smaller among mild intermittent asthmatics. For both asthma severities, rates of asthma exacerbation requiring emergency room treatment were several

times higher among the training group. Among individuals undergoing training, mild intermittent asthma was a significant risk factor for asthma worsening compared to asthma in remission (OR 1.99 [1.44–2.75]) while age (OR 0.67 [0.53–0.85]) and immigration to Israel (OR 0.55 [0.31–0.95]) were significant protective factors. **Interpretation:** Young adults with mild asthma are at significant risk for severe exacerbations when exposed to high-risk environment even among individuals who have long been symptom free. No single risk factor was found to have an independent effect suggesting a synergistic mechanism that is harder to mitigate.

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## Introduction

Asthma is a chronic airway disease causing recurrent reversible obstruction due to exogenous and endogenous triggers. The disease is usually diagnosed during childhood and may become inactive later in life. Though usu-

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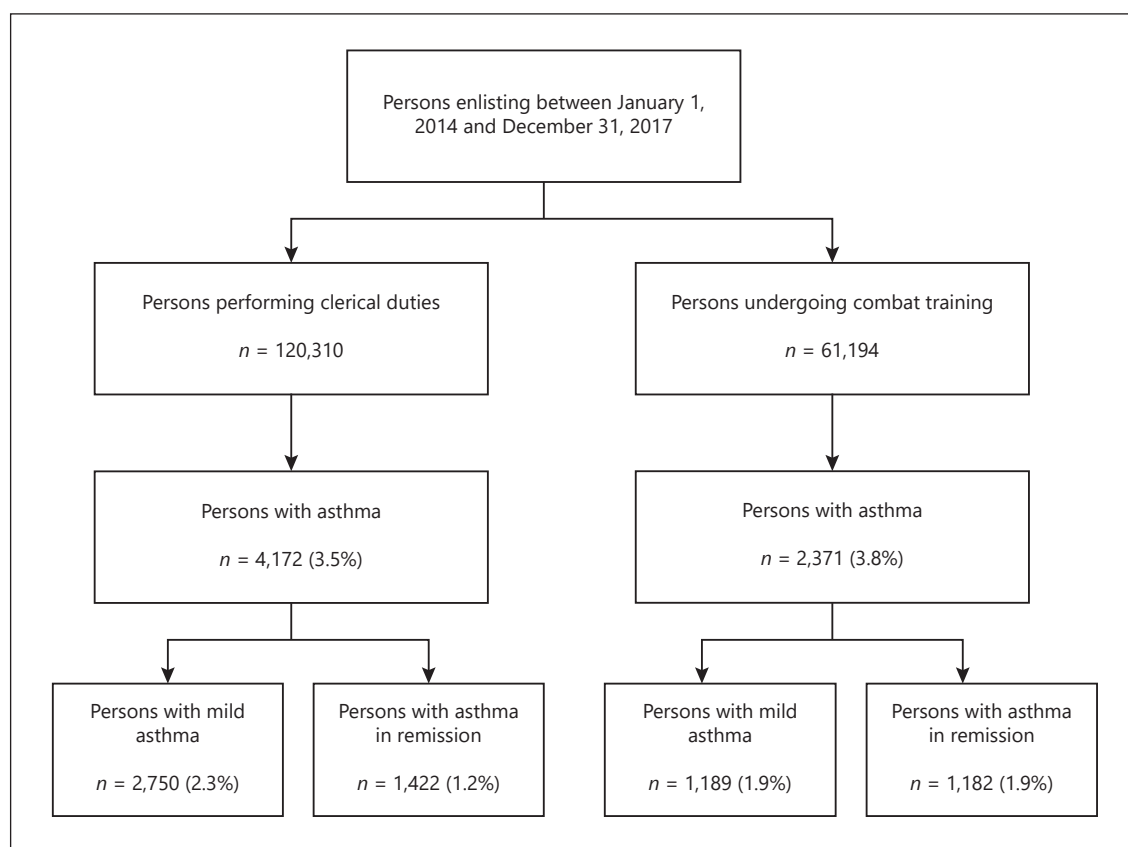


**Fig. 1.** Study population.

ally mild to moderate in nature, asthma could be fatal in some patients [1]. Disease prevalence varies between 1 and 16% in different countries [2], and the incidence of persistent asthma in young adults is on the rise in the Western world [3, 4]. Data published by the Israeli National Health Service showed that between 1999 and 2008, about 9% of adolescents in Israel had mild to moderate asthma [5].

Traditionally, it is believed that strenuous situations, both physically and mentally, might deteriorate asthmatic patients. Weather conditions, including cold weather and high temperature fluctuation [6, 7], exposure to airborne irritants and pollen [8–10], and strenuous physical and psychological stress [11, 12] are known triggers for asthma exacerbations.

This study aims to examine the effect of stressful conditions on the disease activity of young adults with inactive or mild intermittent asthma. This goal is achieved by first comparing individuals with asthma who underwent combat training, thus being exposed to a high-risk environment, to asthmatics with similar disease severity who per-

formed clerical duties. Next, we examined the various exposures of the high-risk environment to determine their significance in inducing asthma worsening among individuals with mild asthma. Our research is unique to answer this question, as most civilian high-risk occupations and armed forces do not accept mild intermittent asthmatics.

## Materials and Methods

### Study Population

We collected data regarding all adolescents who enlisted to the Israeli Defense Force between January 1, 2014, and December 31, 2017, and were diagnosed with asthma in remission or mild intermittent asthma on pre-enlistment evaluation. The final study population included 6,503 individuals with mild intermittent or in-remission asthma, with 4,172 serving in clerical jobs and 2,331 underwent combat training (shown in Fig. 1). Both groups were followed up for 8 months.

### Asthma Diagnosis

Roughly a year and a half before enlistment, Israeli adolescents undergo a medical examination and provide information about past and current illnesses, for the purpose of assessing his or her

**Table 1.** Baseline characteristic by asthma severity among combat trainees

| Characteristics                            | Asthma in remission | Mild asthma       | <i>p</i> value |
|--------------------------------------------|---------------------|-------------------|----------------|
| <i>N</i>                                   | 1,182               | 1,189             |                |
| Age, mean $\pm$ SD, years                  | 19.01 $\pm$ 0.77    | 18.86 $\pm$ 0.68  | <0.001         |
| Female, %                                  | 5.7                 | 3.3               | 0.005          |
| BMI, mean $\pm$ SD, kg/m <sup>2</sup>      | 22.90 $\pm$ 4.11    | 22.75 $\pm$ 4.13  | 0.375          |
| Cognitive performance score, mean $\pm$ SD | 59.47 $\pm$ 17.03   | 58.72 $\pm$ 16.91 | 0.285          |
| Quality group score, mean $\pm$ SD         | 52.45 $\pm$ 2.76    | 52.22 $\pm$ 2.67  | 0.045          |
| Health status on enlistment, %             |                     |                   |                |
| A                                          | 62.8                | 0                 | <0.001         |
| B                                          | 30.1                | 0                 |                |
| C                                          | 7.1                 | 100               |                |
| Unit type, %                               |                     |                   |                |
| Infantry                                   | 58.4                | 4.6               | <0.001         |
| Armor & artillery                          | 20.3                | 55.6              |                |
| Other                                      | 21.3                | 39.7              |                |
| Rural residence, %                         | 15.8                | 14.6              | 0.420          |
| Training season, %                         |                     |                   |                |
| Spring                                     | 30.8                | 29.7              | 0.761          |
| Summer                                     | 31.3                | 32.5              |                |
| Fall                                       | 37.9                | 37.8              |                |
| Born outside of Israel, %                  | 9.8                 | 8.3               | 0.219          |
| Training base location, %                  |                     |                   |                |
| Southern Negev                             | 23.5                | 47.2              | <0.001         |
| Northern Negev                             | 51.5                | 39.2              |                |
| Non-Negev                                  | 25.5                | 13.6              |                |

SD, standard deviation.

health status. If the person presents a report from a board-certified pediatrician of an asymptomatic asthma disease, requiring no treatment for >3 years, no further investigation will be conducted, and the individual is considered as having asthma in remission. Otherwise, persons reporting a history of asthma undergo exercise challenge testing with pulmonary function measurements and an evaluation by a board-certified pulmonologist. Individuals who experience rare and mild symptoms and have a FEV1 variability of <10% following exercise were categorized as having mild intermittent asthma. The results of the test were available to the examining pulmonologist but were not available to the researchers of this study.

#### Study Variables

We examined the medical files of all individuals from enlistment up to a period of 8 months postenlistment, the length of the typical training period. The demographic characteristics of age, gender, BMI, and birth country as well as psychotechnic test scores were collected from the records.

We also collected information regarding exposure to known triggers for exacerbation of asthma. These included the geographic location of the base, the training season, and unit type. The location was divided into 3 regions: Southern Negev with desert-like, dry climate and abundant sand dust; Northern Negev with a desert-like climate but more moderate temperatures and less sand dust; and outside the Negev, mostly coastal and humid climate. The training periods in our study included 3 seasons: spring, sum-

mer, and fall in which subjects began their training. The unit types in our study are divided into 3 categories: infantry, armor, & artillery and other units not falling into the first 2 categories. Individuals serving in the armored corps are likely to be exposed to higher levels of air pollution during training, mainly due to heavy vehicle exhaust fumes.

The general health status on enlistment is the overall assessment given to each individual by the army medical committee, representing the overall health condition. In our study, it is used to adjust for other comorbidities except asthma. The general health status of the subjects in our study was determined by a medical committee during the pre-enlistment examination and is divided into 3 groups: (A) trivial disease with no effect on physical activity; (B) very mild medical condition with minor effect in daily life; and (C) mild medical condition affecting daily life.

#### Outcome Definitions – Asthma Exacerbation

To provide a full analysis of asthma worsening, we defined it by the occurrence of at least one of the following: (1) emergency room (ER) visits due to asthma exacerbation as listed in the ER referral letter and examined by hand by the researchers; (2) medications upgrade: stepping up of asthma medication beyond short-acting inhaled beta agonists or low-dose inhaled corticosteroids. This corresponds to moving from step 1 or 2 to higher steps of the GINA treatment guidelines [13]; (3) medical profile change: undergoing a medical fitness committee due to worsening of asthma.

**Table 2.** Asthma worsening among trainees with asthma in remission or mild asthma

| Characteristics                              | Odds ratio | 95% confidence interval | <i>p</i> value |
|----------------------------------------------|------------|-------------------------|----------------|
| Age                                          | 0.673      | 0.531–0.853             | 0.001          |
| Gender                                       | 1.368      | 0.752–2.486             | 0.304          |
| Cognitive performance score                  | 0.987      | 0.974–1.001             | 0.08           |
| Quality group score                          | 1.024      | 0.938–1.119             | 0.591          |
| BMI                                          | 0.992      | 0.961–1.024             | 0.627          |
| Born abroad vs. Israel born                  | 0.552      | 0.319–0.953             | 0.033          |
| Mild asthma vs. asthma in remission          | 1.99       | 1.440–2.749             | <0.001         |
| Unit type (vs. infantry)                     |            |                         |                |
| Armor and artillery                          | 0.857      | 0.571–1.286             | 0.458          |
| Light infantry, antiair, and search & rescue | 0.825      | 0.549–1.241             | 0.356          |
| Training season (vs. spring)                 |            |                         |                |
| Summer                                       | 0.899      | 0.662–1.221             | 0.499          |
| Fall                                         | 0.747      | 0.551–1.012             | 0.059          |
| Training base location (vs. Sothorn Negev)   |            |                         |                |
| Northern Negev                               | 0.981      | 0.736–1.309             | 0.898          |
| Outside the Negev                            | 1.08       | 0.738–1.580             | 0.691          |

### Statistical Analysis

The data were analyzed using SPSS version 25 using a logistic regression model. The choice was made not to use a time-dependent analysis due to delays and variation in medical committee scheduling while the follow-up period was the same for all participants. The first analysis compared the rate of asthma worsening between individuals undergoing strenuous training and those who performed clerical jobs. The comparison was made using  $\chi^2$  test with Bonferroni correction for multiple comparisons. The second analysis included only training individuals with asthma on enlistment. The goal of the analysis was to assess the risk factors for worsening of asthma using a multivariate logistic regression and included potential risk factors for asthma exacerbation. The variables used in the regression included both variables that were different between the 2 group but also known variables that influence asthma exacerbation such as age and BMI.

### Results

Our study included 181,504 persons, 61,194 (34%) of them underwent training while 120,310 (66%) performed clerical duties. Both populations contained similar percentages of persons with mild and in-remission asthma, 2,331 (3.8%) and 4,175 (3.5%) for the training and clerical groups, respectively. The training group had a similar number of persons with mild or in-remission asthma while the clerical group had twice as many mild asthmatics (shown in Fig. 1). The length of combat training was 8 months, and asthma worsening were recorded during this period for the combat training group. The clerical group were followed for the same period.

The baseline characteristics of the 2,371 persons with asthma who underwent training are shown in Table 1. Age, BMI, and cognitive performance scores were similar across the groups. As mild asthma assigned the individual a health score of C, all individuals in that group were classified similarly. Additionally, there was a difference in the type of units the 2 groups were stationed in. Persons who were exposed to high-risk environment during training were much more likely to experience significant exacerbations requiring ER treatment than their counterparts performing clerical duties. For individuals with asthma in remission who performed clerical duties, this was an extremely rare event (0.1%) rising twenty-fold for those undergoing training (2.2%). For persons with mild asthma, training resulted in 4 times more ER visits due to asthma compared to their counterparts on clerical duty, 4.0 versus 1.2%, respectively (shown in Fig. 2).

The overall worsening rate was also more prominent for persons with asthma in remission. Persons undergoing training experienced a worsening rate of 9.1% compared to 4.9% among those performing clerical duties ( $p < 0.001$ ). For persons with mild asthma, this rate was similar between the groups, 16.1 and 14.5% ( $p$  value = 0.210) for the training and clerical groups, respectively (shown in Fig. 2).

Among the combat training population adjusted regression model for asthma worsening yielded OR 1.99 (95% CI 1.44–2.75) for mild asthma compared to asthma in remission. Older age (OR 0.67, 95% CI 0.53–0.85) and

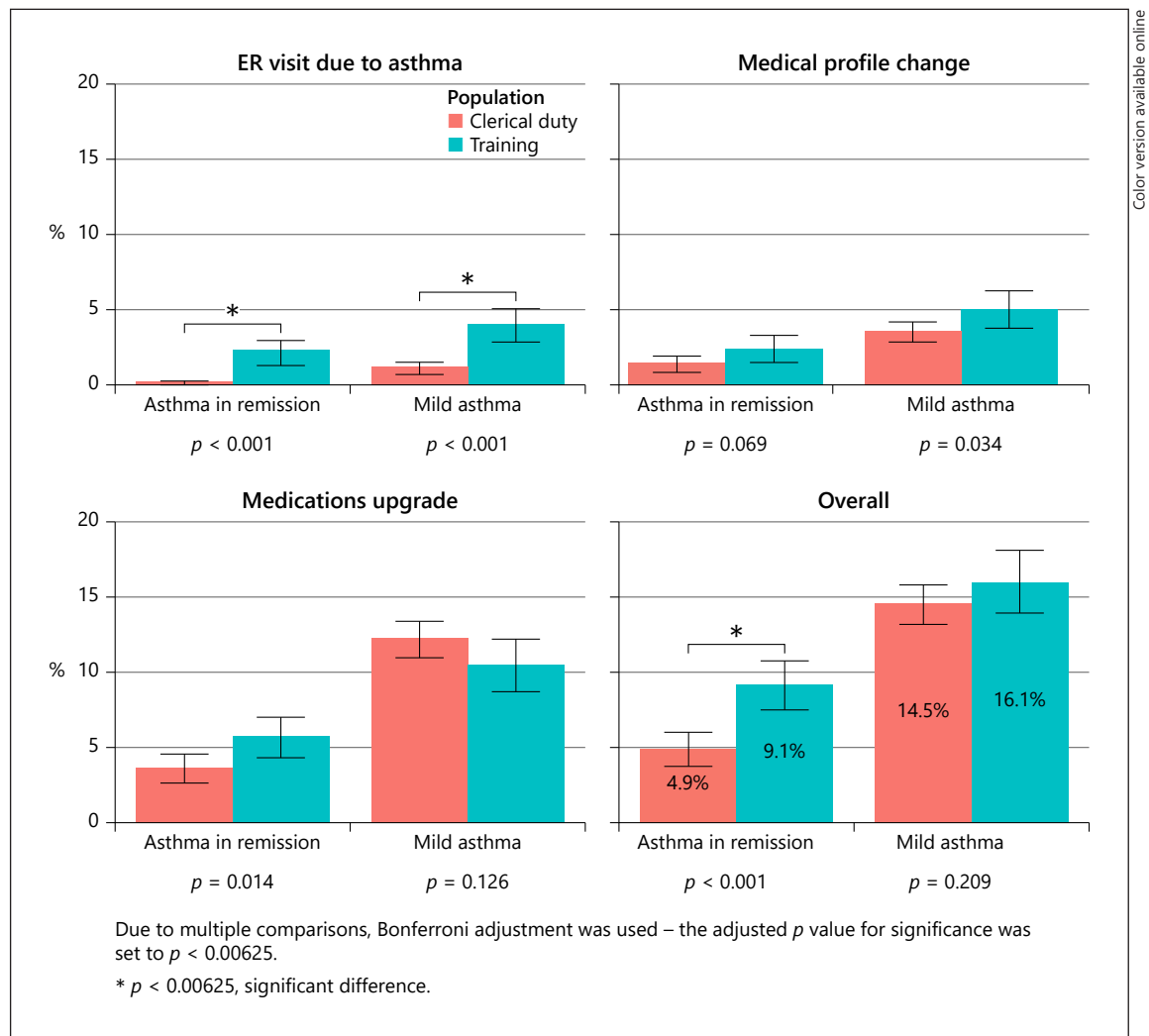


**Fig. 2.** Asthma worsening among training and clerical duty groups. This figure depicts the 3 types of asthma exacerbation that were examined in our study: ER visits, medication upgrade, and medical profile change due to asthma. The outcomes are presented for individuals who underwent combat training versus those who performed clerical duties both severities of asthma included in this study – asthma in remission and mild asthma. ER, emergency room.

immigration (OR 0.55, 95% CI 0.32–0.95) were significant protective factors for asthma exacerbations (shown in Table 2).

The geographic location of the training bases is shown in Figure 3. While the climate conditions were significantly different in the 3 areas examined, the rate of asthma worsening was similar, with no region being consistently favorable or worse for both severity levels of asthma (shown in Fig. 3). The map presented in Figure 3 depicts the approximate location of the training bases and was created by the researchers by editing a freely licensed map of Israel.

## Discussion/Conclusion

In this study, we examined the risk for exacerbation of otherwise healthy young adults diagnosed with mild intermittent asthma or asthma in remission while engaging in a high-risk occupation. Such study is not possible in civilian setting and even in most armed forces as they do not approve mild intermittent asthmatics to work in such vocation.

We found that despite experiencing no symptoms for >3 years, persons with asthma in remission who were exposed to a high-risk environment during combat training

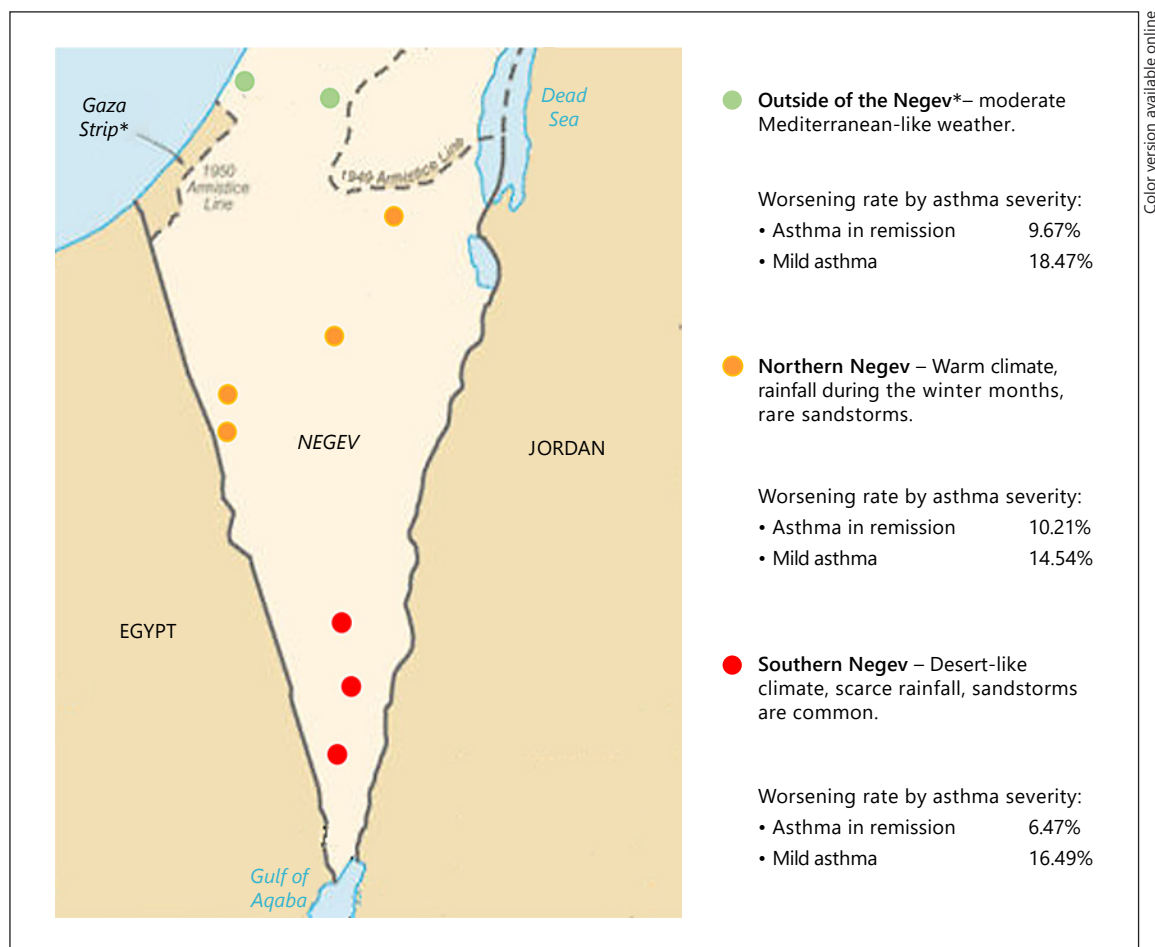


**Fig. 3.** Asthma worsening among trainees by geographic location of base. This figure depicts the approximate location of training bases included in this study, divided by climate region. The figure presents the overall asthma exacerbation rate for each region for individuals with asthma in remission and mild asthma.

were at a much higher risk for severe exacerbations requiring ER treatment than their counterparts performing clerical duties. These results suggest a potential underlying, asymptomatic inflammation, with the potential to culminate to a severe asthma exacerbation, and are consistent with previous evidence showing elevated levels of eosinophils, mast cells, as well as increased IL5 levels in persons with asthma in remission [14, 15]. Additional factors contributing to this phenomenon is the age of the individuals in our study. As depicted previously, young adults tend to experience recurrence of their asthmatic disease [16, 17].

Mild asthmatics on the other hand had overall worsening similar between the training and clerical groups while the rate of ER admission was 4 times higher in the training group and similar to previous studies [18–20]. Therefore, we believe the high-risk environment enhanced the in-

tensity of the exacerbation events, with almost a quarter of persons experiencing worsening of their disease were referral to the ER. This happened despite all persons with mild asthma undergoing exercise spirometry before enlistment.

In multivariate analysis, we found that the environmental risk factors tested did not have a significant effect on disease worsening. The rate of exacerbation was mainly determined by the initial severity of the disease, with mild intermittent asthmatics experiencing almost twice the exacerbations than those with asthma in remission. Age was a significant protective factor in our study, possibly because subjects enlisting at an older age were more mature and independent. Most of them spent time apart from their parents and were more experienced in controlling their disease on their own. Previous study found an opposite effect with older patients having a higher risk for

exacerbation [21], but the effect was significant for 10 years difference while most of the individuals in our study were 18–21 years old. Previous studies that focused on similar age-groups to our study did not find any significant effect for age, but they did not focus on mild asthma [22, 23].

Previous studies that have shown that physical exercise as well as psychological stress are significant independent risk factors for asthma exacerbations [12, 24, 25]. Weather conditions, especially extreme temperatures and large diurnal temperature shifts, are also a major concern [7]. Additional environmental factors such as rural environment, exposure to vehicle pollution, dust, and desert environment are known to contribute to asthma worsening [8, 26, 27]. In our study, we were not able to show any of these conditions to be a significant and independent risk factor for asthma worsening, despite a large cohort. We believe this discrepancy comes from the research population we examined, consisting of young, otherwise healthy adults with up to mild intermittent asthma. Our results show that they experienced more exacerbations and more ER visits when exposed to a high-risk environment but no single factor was found to be significant. We believe this supports the hypothesis that the combination of the environmental, physical, and psychological conditions was the root cause rather than a single prominent factor. Thus, it might be much harder to control and prevent exacerbations in this population in a high-risk environment.

Persons in Israel are assigned to combat training and clerical duties through a complex selection process that takes into account the individual abilities and aspirations. We did not have access to the selection criteria of the individuals in our cohort. However, to the best of our knowledge the combat training group does not differ psychologically or physically in a way that may precipitate asthma exacerbations.

This study design possesses several strengths. We examined young adults with up to mild intermittent asthma that were otherwise healthy while they engage in a high-risk environment and occupation on a large scale. Our analysis included a variety of environmental and occupational factors as well as levels of physical exercise. The disease worsening was highly sensitive, including both ER admissions as well as medication upgrades, thus providing a highly sensitive account.

This research, however, is subject to several limitations. We were unable to acquire the smoking status of the participants due to insufficient records in the army medical database. We were also unable to examine the ef-

fect of atopic comorbidities as allergic rhinitis [28], atopic dermatitis [29], and food allergies [30] that might influence the rate of exacerbations. While they are highly prevalent in population of this study [31, 32], they are poorly documented in the military health records. Further studies are needed to examine whether these conditions, when co-existing with asthma, increase the risk for exacerbations among persons with mild asthma.

Moreover, the climate risk factors examined in our study were categorized crudely using the seasons of training and geographic location as indicators for the likely climate and allergen exposures. However, no exact measurements of temperature, humidity, and rain data were available for the training bases. Exacerbation in the previous year to enlistment, an important risk factor for future exacerbations [33], were not available to the researchers. Additionally, this study population consists of only young healthy adults that diagnosed with up to mild asthma. Therefore, we cannot generalize these findings to young adults with a more severe form of asthma or additional serious comorbidities.

In summary, this study depicts a complex dynamic of mild intermittent and asthma in remission among young adults. Our study shows that this population experiences a higher rate of severe exacerbations, placing them at risk for life-threatening exacerbations requiring ER treatment. Thus, the lack of symptom is not a guarantee for safety. Our attempt to determine the specific aspects of the occupation that induce worsening was unsuccessful, suggesting a more complex relation and making it harder to mitigate the risk. We believe that further studies are needed to consolidate our results and create a better understanding of the disease progression among this population.

### Statement of Ethics

The study was approved by the Israel Defense Force Institutional Ethics Committee approval number 1996–2019.

### Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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This study did not receive any funding.

## Author Contributions

M.S. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data

analysis, including and especially any adverse effects. M.S., K.Z., Y.R., and R.L. contributed substantially to the study design, data analysis and interpretation, and the writing of the manuscript. The authors do not have any conflicts of interest.

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