# The effect of previous methylphenidate use on incidence of stress fractures in military recruits: a retrospective cohort.

# Abstract

## Background

Stimulant medications used for the treatment of attention deficit hyperactivity disorder (ADHD) are associated with decreased bone density, according to previous animal and human research. Previous research has detected an increased risk of stress fractures among subjects who reported previous use of methylphenidate. Conversely, all-type stimulant medication use has been associated with traumatic fracture risk reduction, possibly due to the improved control of the ADHD symptoms. The goal of this study was to investigate the effect of previous methylphenidate use on the incidence of traumatic and stress fractures among combat soldiers with previously treated and untreated ADHD.

## Methods

The retrospective cohort included 100,000 combat soldiers recruited to the Israeli Defense Forces in 2005-2015. Diagnosis of ADHD and previous exposure to methylphenidate were determined based on self-reported recruitment questionnaires and on medical records. The cohort was divided accordingly into three groups: subjects with ADHD who were previously treated with methylphenidate (“treated”, n=698), subjects with ADHD reporting no medication use (“untreated”, n=762), and controls having no ADHD diagnosis (n=98,549). Logistic regressions were fitted to determine the odds ratios of study subjects for stress and non-stress (traumatic) fractures. Baseline characteristics including age, gender, weight, duration of service, and diagnosis of anemia at some point during the service were incorporated in multivariate analysis.

## Results

The risk of traumatic fractures was significantly increased in both treated (OR=1.03, 95% CI: 1.00-1.05) and untreated subjects (OR=1.04, 95% CI: 1.02-1.07) compared to controls, after adjustment for gender, anemia, weight, age, and duration of service. Treated subjects were at significantly high risk of stress fractures (OR=1.04, 95% CI: 1.02-1.07). Interestingly, diagnosis of anemia was an independent predictor of stress fractures (OR=1.05, 95% CI: 1.04-1.06).

## Conclusions

Methylphenidate use is associated with an increased risk of stress and traumatic fractures. These and previous findings may serve as sufficient basis for screening for other risk factors, and perhaps taking prevention measures in all those using stimulant medications, especially those planning to engage in strenuous physical activity.

Level of Evidence: III.

**Key terms:**

Methylphenidate, stress fracture, traumatic fracture; bone mineral density, attention deficit hyperactivity disorder

# Introduction

Methylphenidate (MP) prescription rates have been continuously rising in the past decade, reaching about 7.5% of children and adolescents in Israel in 2017,1⁠ and the prescription of stimulants, including MP, reached 5% of school-age children and 2.5% to 4% of adults in the United States.2 Moreover, medication abuse (without prescription) is estimated in different studies at 5% to 10% of U.S. high school students and 5% to 35% of U.S. college students.3⁠ Currently-known adverse effects of the medication on the musculoskeletal system include suppression of growth in children and osteopenia.4 Both can be partially explained by the side effects of MP, such as anorexia and loss of appetite, but a growing body of basic and animal research indicate a direct effect of MP on osteoclasts and leptin metabolism, leading to increased bone resorption.5–7 Reduced bone density is a significant risk factor for both bone fractures as a result of acute trauma and stress fractures. The scope of the problem may be significant, considering the previously mentioned staggering prevalence of the medication use.

The incidence of traumatic fractures (TF) has been found to be higher in children diagnosed with ADHD than in children without the disorder.8,9 However, receiving any type of treatment for ADHD (MP as well as non-stimulant medication and non-pharmacological methods) was in fact associated with a lower risk for traumatic fractures. It was hypothesized that fractures in children with ADHD are more common due to symptoms of the disorder, such as impulsive and restless behavior. Treatment of these symptoms lowers this risk.10⁠

In contrast, stress fractures (SF) develop due to repetitive loading of the bone, leading to micro-fractures over time in stressed areas of the bone. These types of fractures have a unique clinical presentation and course, and are known to be slow to heal.11,12⁠ Risk factors include repetitive activities — for example, runners are predisposed to stress fractures of the tibia and other weight-bearing bones, and athletes of sports involving repetitive throwing motions are predisposed to humeral fractures. Sudden increases in activity in non-athletes may also be a trigger.13⁠ Nutritional factors include anemia,14⁠ vitamin D and calcium deficiencies,15 as well as disordered eating and reduced caloric intake common in some athletes such as gymnasts.16⁠ Demographic risk factors include female sex, older age, low weight and/or low BMI, non-African-American ethnicity, and as mentioned earlier, decreased bone density.17,18⁠

A previous case-control study by the authors (in press, accepted for publication) comparing MP exposure in combat soldiers who had a bone-scan diagnosis of stress fractures and soldiers who had no known stress fractures showed that previous use of MP was associated with a significantly higher odds ratio for stress fractures (OR=1.15; 95% CI: 1.07-1.24). The present study was conducted in an effort to validate the findings of the previous study using an alternative study design and a larger sample (100,000) from the same study population of combat soldiers.

# Materials and Methods

### Study design

For this retrospective cohort study, 100,000 subjects were randomly selected from the population of combat soldiers who started and finished compulsory military service in the Israeli Defense Forces from January 1, 2005 through December 12, 2015. Medical records were reviewed and sorted according to the exposure information: diagnosis of ADHD and previous use of MP, which was self-reported by soldiers in recruitment questionnaires. Based on the above information, the cohort was divided into three groups: treated ADHD, untreated ADHD, and controls (no known diagnosis of ADHD). Additional background data collected included gender, age, weight, height, length of service, ICD-9 stress fracture diagnoses (M84.3\*), anemia diagnoses (D50.0, D63.\*, D61.9, or D64.\*), and all diagnoses including the word “fracture.” Every diagnostic code was counted once, thus allowing for incidence estimation. The study was approved by the IDF Medical Corps Institutional Review Board (No. 1666-2017).

### Statistical analysis

Statistical analyses included descriptive statistics, risk estimates, and multivariate logistic regression. Categorizing data (gender, diagnosis of anemia) was presented as percentages and analyzed using the chi-square test. Continuous data (age, height, weight, duration of service) was presented as mean ± standard deviations and analyzed using the analysis of variance and Student’s t-test.

Unadjusted incidence rates of SFs and TFs were calculated as the number of subjects with at least one respective diagnosis divided by the total number of subjects in the group. The rates were compared using the chi-square test. Adjusted incidence of SF and TF per 1000 person-months was calculated as the total number of fractures (sum of all diagnoses) divided by the total sum of duration of service in each group. Incidence rates were compared using the proportions Z-test. We also presented the adjusted incidence of all SF types and of the most common types of TFs.

Multivariate logistic regression was fitted to adjust for possible confounding variables. Those variables that differed significantly between study groups were included in the model. Odds ratios and respective confidence intervals were calculated from the regression coefficients.

## Source of funding

No funding was provided for this study.

# Results

### Background variables

A diagnosis of ADHD was found in 1,451 (1.4%) subjects, 689 (47%) of whom were prescribed stimulant medications during the course of their service. Our groups therefore included 689 subjects with treated ADHD, 762 subjects with untreated ADHD and 98,549 controls without a diagnosis of ADHD (Figure 1). The groups were of a similar age, height, and weight. However, they differed significantly with respect to the percentage who were female, which was almost twice as high in the treated ADHD group than in the other groups (p < .001), and the percentage of subjects diagnosed with anemia at some point during their service, which was high among ADHD subjects (both treated and untreated) and low among the undiagnosed controls (p < .001) (Table 1).

### Measures of risk

The percentage of subjects with SFs was higher in the treated ADHD group than among the undiagnosed controls (p < .001), but no significant difference in the percentage with SFs was found between treated and untreated subjects (p = .07), or between untreated subjects and controls (p = .31). A higher percentage of subjects with untreated ADHD had TF compared with undiagnosed controls p < .001). However, there was no significant difference between the ADHD-treated and ADHD-untreated groups (p = 0.3), or between the ADHD-treated and undiagnosed groups (p = .06).

The incidence of SF, adjusted for duration of service, among ADHD-treated subjects was significantly higher than among controls (p < .001). No difference in SF incidence was found between the ADHD-treated and ADHD-untreated subjects, or between the ADHD-untreated and the control subjects. The incidence of TF was similar between ADHD-treated and ADHD-untreated subjects, but each of the two groups had a significantly higher incidence than the controls (p = .01 and p < .001, respectively) (Table 2).

*Multivariate logistic regression*

Two logistic regression models for the prediction of stress and traumatic fractures were constructed to calculate the adjusted odds ratios for SF and TF. The main grouping variable (treated, untreated, undiagnosed) and baseline variables that were significantly different between the groups (gender, diagnosis of anemia, weight, age at conscription, and duration of service) were incorporated into the model. Height and study years were not included as predictors because their variability was low and the differences between groups were significant but not substantial. After adjustment, ADHD treatment remained an independent risk factor for both SF (OR = 1.05, p < .001) and TF (OR = 1.03, p = 0.046). Untreated ADHD was a risk factor for TF (OR = 1.04, p < .001) but not for SF (p = 0.4). As expected, female gender was a risk factor for SF (OR = 1.05, p < .001), while male gender was a risk factor for TF (OR = 1.04, p < .001). Furthermore, anemia proved to be a predictor of SF (OR = 1.05, p < .001) but not of TF (p = 0.84). Age, duration of service, and weight were significant predictors of both outcomes, but their associated risk was small (Table 3).

*Specific diagnoses*

Specific fracture diagnoses are presented in Table 4, grouped by major characteristics (open, closed, stress fracture, and location). Additionally, there were 10 pathologic fractures in the entire study population, none of them in the ADHD subjects, making comparison impossible. Incidences of the specific diagnoses followed the same trend as total fracture numbers: there were generally more stress fractures in the ADHD groups than in the controls, more stress fractures in the treated ADHD than the untreated ADHD group, and more traumatic fractures in the untreated group than in the treated group. Interestingly, a diagnosis of “fracture non-union” was more frequent in the treated ADHD group (2 cases) than in the controls (62 cases, p = 0.014), but not more frequent than in the untreated ADHD group (1 case, p = 0.7) (Table 4).

# Discussion

Methylphenidate is a commonly used and effective medication for ADHD in children and adults. While generally considered a safe medication, methylphenidate has some known side effects, including gastrointestinal side effects, anorexia, and increased blood pressure. Though animal and human studies have shown reduced bone density, very few studies have examined the clinical consequences of this reduced bone density, namely stress fractures. Although the incidence of traumatic fractures seems to be reduced in ADHD patients treated with MP compared with untreated ADHD patients, we hypothesized that the incidence of stress fractures would be increased by treatment with MP because the mechanisms of the two types of fractures are different. While traumatic fractures may be explained by risk-taking behavior, inattention, or sensation and balance problems, stress fractures develop over time due to the inability of the bone to sustain a repetitive submaximal load. Decreased bone density may result in a higher propensity for fracture in the latter situation than in the former. A recent study by the authors (in press, accepted for publication) revealed an association between stress fractures diagnosed by bone scans and history of methylphenidate in a sample of 8,587 combat soldiers. To confirm these findings, this study examined a much larger sample from the same population, relying on medical records for determining the exposure (ADHD and self-reported use of MP) and the outcome (stress fracture and traumatic fracture diagnoses).

The results of our present study confirmed our hypothesis of increased stress fractures in ADHD patients compared to controls, with higher odds of stress fractures in treated ADHD patients compared to untreated patients or controls after adjusting for other factors such as age, gender, weight, anemia, and length of service. The risk elevation was relatively small, with an odds ratio of 1.04 (CI 95% 1.02 - 1.06) in treated ADHD patients. However, the study population included physically active and otherwise healthy subjects, which leaves the possibility that many other populations are at a higher risk of consequences from MP treatment. This finding is consistent with the results of our previous study, despite a difference in methods, and therefore appears internally and externally valid.

A higher risk for traumatic fractures in the ADHD population, with a lower risk among those receiving stimulant treatment, is another important finding of this study. This finding is consistent with previous research, and we agree with the explanation that controlling the symptoms of ADHD may reduce the traumatic fracture incidence. The effect sizes were smaller than those found in other studies,9,10⁠ which may be attributed to incomplete exposure data and inaccurate diagnostic coding in military clinics.

**Interestingly, among recruits, there was a significantly higher prevalence of female than male soldiers who received treatment for ADHD. Unlike males, females may choose non-combat service and even have several legal options to be excused from military service altogether, i.e., marriage or pregnancy, declaration of religiosity, choice of an alternative civilian service, etc. We hypothesize that females who do choose to serve, especially in combat positions, are likely to be high achievers, and when diagnosed with ADHD in their school years, may have been more likely to use MP to improve performance.**

The association between anemia and stress fractures was first reported by Yanovich et al.19⁠ In this study, anemia is associated with a significant elevation of SF risk (OR = 1.05). The association is possibly explained by a common condition: reduced nutritional intake or a systemic inflammatory response to stress that impairs both hematopoiesis and bone metabolism.

### Study Limitations

This was an observational, retrospective study. Thus the study was vulnerable to the biases inherent in the design of such designs, and we were unable to prove causality. Our data cannot confirm how stress fractures were diagnosed, and we do not know how complete our records were. Prescription data does not include dosage or duration of treatment; nor is it possible to know whether patients indeed took these medications as prescribed. Additionally, we do not have information on whether the MP-treated stress fracture patients in fact had lower bone density, explaining their higher risk for fractures (or whether another mechanism may be responsible for such a risk). It is important also to take into consideration that the population studied consisted of healthy combat soldiers, and the findings do not necessarily generalize to populations of younger or older age, subjects at the extremes of BMI, or persons with various comorbidities (e.g., vitamin D deficiency, corticosteroid treatment, eating disorders, etc.). On the other hand, all of the latter may be more severely affected by MP than this study population, with greater clinical consequences.

### Clinical significance

Our study adds to the body of evidence of an association between stress fractures and methylphenidate treatment, which includes studies showing a biological mechanism (lower bone density) at work in the association between stress fractures and methylphenidate treatment, and a study demonstrating an association between bone-scan diagnosed stress fractures and methylphenidate treatment.

It is likely that methylphenidate is still of much benefit to patients in whom it is indicated. Indeed, the reduced risk of traumatic fractures may offset the increased risk of stress fractures; however, it is important to recognize all possible adverse effects of the medication. This may be clinically relevant in MP patients beginning exercise or athletic routines. Perhaps these patients should proceed with a more gradual onset of activity. These patients may also benefit from screening for other risk factors, such as vitamin D deficiency.

This study confirms previous studies associating MP treatment with a higher risk of stress fractures. Causality may be better evaluated using prospective studies that include accurate diagnoses of stress fractures, bone density tests, and dose-response analyses, but this and previous research may suffice to justify the introduction of prevention measures. The possibility of stress fracture risk must be recognized by prescribers and patients. Bone density scans are possibly warranted in patients treated with MP for long periods or receiving a high dose of the medication.

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# Figure legends

Figure 1: Study flow diagram