**Lower risk of fractures under methylphenidate treatment for ADHD: a dose-response effect**

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**Abstract**

**Background:** Methylphenidate (MP), a widely used and abused stimulant medication for ADHD, has adverse effects on bone mass. However, previous epidemiological studies demonstrate that MP is not associated with increased incidence of fractures in children, and may even have a protective effect due to behavior modification. This study aimed to investigate the association between MP and fracture risk in young adults.

**Methods:** A retrospective cohort study of healthy military recruits, aged 18 – 25, representative of the general population, with at least one year of service between 2008 and 2017, was conducted. Baseline demographic data included sex, age, weight, height, origin, socioeconomic status, and education. Subjects were divided into five groups: subjects without ADHD; untreated subjects with ADHD; and subjects with ADHD and prescriptions of 1 – 90, 91 – 180, or 181+ tablets during the study period. The primary outcome was at least one diagnosis of fracture during the study.

**Findings:** Among 682,110 subjects (409,175 men [60%]), 50,999 (7·5%) had fractures, and MP was used by 1681 (0·4%) men and 2828 (1%) women. The fracture rates in the no ADHD, untreated ADHD, ADHD 0 – 90, ADHD 91 – 180, and ADHD 181+ groups were 10·4%, 16·4%, 8·7%, 4·8%, and 5·8% in men, and 3·6%, 7·1%, 4·6%, 4·4%, and 3% in women, respectively. Multivariate regression analysis confirmed an inverse dose-response association between MP and fractures in men (p < 0·001). In women, untreated ADHD was associated with a significantly higher fracture risk, compared to healthy controls (OR = 1·82, p < 0·001)

**Interpretation:** The results imply that fracture risk among young, healthy individuals is primarily determined by behavior, and could therefore be modified by stimulant treatment. The study confirms previous literature that demonstrates an inverse dose-response association between MP and fracture risk.

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**Introduction**

Methylphenidate (MP) is the most effective and most recommended medication class in the pharmacologic treatment of attention deficit/hyperactivity disorder (ADHD). Worldwide prevalence of ADHD in the population aged ≤ 18 is about 7·2%. The prevalence of MP use is even higher.1 Recent studies have shown the prevalence of MP prescriptions to be 7·5% in children aged 6 – 18 in Israel,2 5% in children of the same age group in the United States, and 2·5% – 4·0% in adults in the United States.3 Stimulants like MP have been estimated to be abused (used without prescription) in 5% – 10% of high school students and 5% – 35% of college students in the United States.4

A diagnosis of ADHD has been shown to increase the risk of a traumatic fracture, probably because of the behavioral characteristics associated with the disorder, which include reckless behavior, clumsiness, an increased tendency to disregard rules of games or sports, and neglect safety precautions.5 The use of stimulants such as MP, has been shown to reduce bone density in children and adolescents, and this effect is thought to be mediated by an increase in sympathetic tone that results in the inhibition of osteoblasts and activation of osteoclasts. Nevertheless, it is not clear whether this reduction in bone density results in an increased risk of fractures. In fact, several studies have demonstrated the opposite. The treatment of ADHD with MP and other stimulants has been shown to reduce the risk of traumatic fractures in several studies.[REF – Chou, Guo] Studies on military recruits have shown that a history of MP use during adolescence is associated with a higher risk of stress fractures during military service.[REF – Schermann et al, AJSM] However, MP use is reportedly not associated with an increased risk of traumatic fractures, when compared to subjects with untreated ADHD.6

The goal of this study was to investigate the associations between treated and untreated ADHD and the risk of fracture, and to evaluate the dose-response relationship. A relatively large cohort of military recruits, representative of general population, and precise prescription data were used to achieve this goal.

**Methods**

After receiving approval from the Institutional Review Board, an automated query of military medical records was performed. The retrospective cohort included all subjects aged 18 – 25, who served for at least 12 months in the Israel Defense Forces (IDF) between 2007 and 2017. For subjects who became older than 25 during the study, only data specifically related to that period between the ages of 18 and 25 were queried, with respect to the military service period. Subjects who were enlisted for voluntary service, with severe chronic medical conditions or a history of recent malignancy were excluded. Likewise, subjects with missing baseline data (age, weight, and height) were regarded as false or error entries in the database, and were therefore excluded.

Baseline information included age (at the time of the first fracture diagnosis); sex; height (cm); weight (kg); body mass index (BMI) (kg/m2); education level (duration of ≤ 12 years, or > 12 years); socioeconomic level (a measure used by the state’s Central Bureau of Statistics that is calculated from the mean income of the subject’s area of residence and is graded on a scale from 1 – 10); origin (defined as father’s country of birth, and grouped by developed countries (North America, Europe, and former Soviet Union), developing countries (Africa, Middle East, and South America), and Israel (including subjects with missing origin data)); occupation (combat and non-combat); and duration of follow-up in months.

Exposure to MP throughout the study period was calculated using medication prescription data. Although dosing information (in mg) was available, we considered that dosing would be reflective of the body weight of the subjects, severity of ADHD symptoms, and metabolic factors that may not have been accounted for in multivariate analysis. Thus, we considered that duration of treatment (derived from the number of tablets prescribed) would be a simple and reliable indicator of MP exposure.

All ICD-9 (International Classification of Diseases, Ninth Revision) diagnoses, including the word ‘fracture’ and excluding stress fracture diagnoses (Code M84·3\*), were counted once per subject during the study period. This choice of outcome was considered optimal, because a higher number of repeated fracture diagnoses does not necessarily indicate severity of the condition. Moreover, some diagnoses were recorded because of administrative entries and renewal of referral notes, and did not necessarily represent a new fracture, or even a face-to-face encounter between the subject and physician.

Statistical analyses included descriptive statistics, unadjusted dose-dependent risk estimates, and multivariate logistic regression. Men and women were evaluated separately, considering their inherently distinct risk of fractures,7,8 and evidence of the sex-dependent effect of MP on bone metabolism.9 Categorical data (education, origin, socioeconomic level, and occupation) were presented as percentages and analyzed using the chi-squared test. Continuous data (age, height, weight, BMI, and duration of follow-up) were presented as mean ± standard deviation, and analyzed using the Student’s *t*-test.

To estimate the unadjusted dose-dependent risk of fractures, subjects were divided into five groups: subjects without ADHD (no ADHD); subjects with ADHD, who did not receive MP treatment (untreated); and subjects who had a total of 0 – 90 (ADHD 0 – 90), 91 – 180 (ADHD 91 – 180), or more than 180 tablets (ADHD 180+) prescribed during the study period. Fracture incidence in these five groups was presented as the percentage of subjects with fractures within each group. In addition, the unadjusted odds ratio (OR) of fractures was calculated for each group using logistic regression. In the regression, the above grouping of variables was the only predictor of fracture diagnosis, with ‘no ADHD’ subjects representing the reference group. Odds ratios were calculated from the regression coefficients and their respective confidence intervals (CI) were estimated by the profile likelihood method.10

Furthermore, multivariate logistic regression was fitted to adjust the prediction of fracture risk for possible confounding variables. Those variables that differed significantly between study groups were included in the model. Multilevel ordinal variables were grouped as two- or three-level variables, after consideration of the results of bivariate analysis and interpretability of the results. The relationship between predictors was reviewed to exclude autocorrelation above 0·8. Study results were reported according to the guidelines for reporting observational studies.11

**Results**

The initial cohort evaluation was based on data of the IDF recruits between the years of 2008 and 2017, and comprised 862,742 cases. After the exclusion of 106,673 subjects who served for less than 12 months during the study period, 31,519 subjects who were older than 25 at the start of the study period, 92 volunteers, and 6348 (1%) cases with missing important baseline data, 682,110 (79%) subjects remained in the final cohort (Figure 1). Among these, 409,175 (60%) subjects were men. A total of 50,999 subjects (7·7%; 10·5% of men and 3% of women) had one or more fractures during the study period. The prevalence of ADHD was 2·2% among men and 2·5% among women, and MP was used by 1681 (0·4%) men and 2828 (1%) women.

Descriptive characteristics of the cohort are presented for men and women separately in Table 1. The average time of follow-up among all study groups was between 54·6 and 58·6 months. Within the male subjects, all variables were significantly, but not substantially different between subjects who had fractures and those who had not, owing to the relatively large sample size. Among the female subjects, those with fractures were of significantly and substantially lower weight and height, and a greater number had been on combat duty, in comparison to subjects without fractures. A slightly lower percentage of subjects in the fractured groups were of North American, European, and former Soviet Union origin, in comparison to the non-fractured groups (26% vs. 29% males, 25% vs. 28% females, p < 0·001).

Table 2 shows the unadjusted odds of having a fracture, stratified by sex, and subdivided by groups treated with different doses of MP. The group without ADHD was the reference group. Among the men, the OR of having a fracture and untreated ADHD was 1·69 (p < 0·001); among the subjects with ADHD who were treated with 1 – 90 tablets during the study period, the OR was 0·82 (p = 0·02); among those treated with 91 – 180 tablets, the OR was 0.43 (p < 0·001); and among those treated with 181+ tablets, the OR was 0·53 (p < 0·001). Among the women, the OR of having a fracture and untreated ADHD was 2·08 (95% CI, 1·84 – 2·34); among cases with ADHD, who were treated with 1 – 90 tablets, the OR was 1·3 (95% CI, 1·02 – 1·61); among those treated with 91 – 180 tablets, the OR was 1·24 (95% CI, 0·77 – 1·89); and among those treated with 181+ tablets, the OR was 0·84 (95% CI, 0·52 – 1·28). In Table 2, we see a tendency of the OR to indicate a dose-response relationship between the incidence of fractures and number of MP tablets administered.

The adjusted OR analysis, as presented in Table 3, shows the persistence of a negative dose-response effect between MP use and the risk of fractures in males. No MP treatment group was associated with an odds ratio for fractures that was greater than 1·46 (p < 0·001), whereas increasing exposure to MP resulted in reduced risk of fracture, with the lowest risk being observed in the group with highest exposure to MP (OR = 0·48, p = 0·002). The dose-response effect was not observed in women; however, the groups that received no treatment for ADHD were at a significantly higher risk of fractures (OR = 1·82, p < 0·001). Among male subjects, other significant predictors of fractures included a younger age, greater weight, 12 or less years of education, low socioeconomic status, and combat service. Subjects of European or North-American origin were associated with a lower risk of fractures, in comparison to Israeli-born subjects. Among females, a younger age, greater weight, North African and Middle Eastern origin, combat service, and longer duration of follow-up were associated with a higher risk of fractures (Table 3).

**Discussion**

This study presents an inverse dose-response relationship between MP use and the risk of fractures among male subjects with ADHD. Within the study sample, subjects of both sexes with untreated ADHD had the highest risk of fractures; whereas chronic treatment was associated with a reduced risk of fractures in men. Among the women, subjects with untreated ADHD had a significantly higher risk of fractures compared to healthy controls; whereas ADHD treatment at any level was not associated with any increase in fracture risk. These findings are supported by those of several studies that report higher odds for fractures in young adults with ADHD, and in the case of men, show that treating ADHD with MP (a stimulant medication) reduces these odds to a level that is even lower than that of the population without ADHD.5,12–14

Another retrospective cohort study from 2009 showed ADHD to be positively associated with injuries.12 That study also demonstrated that more severe injuries (fractures of the skull, neck, and trunk; intracranial injuries without skull fracture; and injuries to the nerves and spinal cord) have a significantly stronger association with ADHD than less severe injuries do.12 One study of children with fractures who were admitted to a hospital in the United States showed that those with impulsive/hyperactive behavior presented with a greater number of fractures in the lower extremities, caused by more solitary activities and more severe fractures that required open reduction.13 A case-control study in adults reported increased odds of a fracture among diagnosed cases of ADHD and related these odds to the levels of hyperactivity and impulsiveness, rather than the inattention scores.14 A population-based retrospective cohort study published in 2014 also reported an increased risk of fractures (hazard ratio [HR] 1·26; 95% CI, 1·12 – 1·42) among children with ADHD, compared to those without ADHD.5

In a longitudinal cross-sectional study that showed an association between reduced bone mineral density and content, and stimulant use in pediatric patients, stimulant treatments, such as MP, which are the first-line pharmacological agents prescribed for ADHD, were shown to have a negative effect on bone mineral density.15 Contradictory results were reported by another study, in which no significant effects of MP on bone mineral density turnover in children were observed, when administered for 1 to 2 years.16

Several studies have attempted to shed light on the association between stimulants and reduced bone mineral density. A 2012 study on rats showed that MP treatment resulted in smaller, less mineralized, and weaker bones at appendicular sites, but did not affect the axial skeleton.17 Another scientific study on rats showed the dose- and sex-dependent regulatory effects of MP on osteoclasts.9 Furthermore, another study on children with ADHD, who were treated with stimulants, reported reduced bone turnover after 3 months of treatment.18

Despite evidence of the adverse effects of MP on bone health, ADHD treatment has been consistently shown to reduce the risk of fractures. A retrospective cohort study of more than 10,000 cases concluded that three times as many patients without documented prescriptions for ADHD medication, are affected by a fracture, compared to patients with a history of two or more prescriptions for an ADHD medication.19 Another retrospective cohort study of more than 6000 cases from Taiwan, reported an adjusted hazard ratio of 0·77 (95% CI, 0·63 – 0·94) among cases with ADHD treated with MP, compared to cases with ADHD who were not treated with MP.20

The main important finding of this study is the establishment of a dose-response relationship between MP use and fracture incidence, which is one of the basic criteria for determining causation.21 In addition, the present study shows that treatment of ADHD reduces the odds for fractures, despite its reportedly adverse effects on bone mineral density. This finding suggests that ADHD itself and its associated behaviors exert a greater influence on fracture odds than on bone mineral density (BMD), at least in the age group under investigation and over the specific experimental period. Moreover, the fact that subjects with ADHD, who were treated with MP, were less susceptible to fractures than subjects without ADHD, shows the unusual ability of a stimulant like MP to improve function in a diverse scope of human abilities, even to the extent of not only eliminating pathology, but also surpassing normal human ability. This is further evidence of the role of MP in cognitive enhancement, which was been extensively studied over the last decade, and has been reviewed by Busardò et al.22 This cognitive enhancement resulting in possibly higher levels of concentration and the prevention of fractures could be considered an advantage of MP-treated subjects for employment in certain high-risk occupations.

Regarding other determinants of fracture risk, the results of the present study are consistent with those of previous studies that have shown associations between male subjects, obesity, health-damaging behavior (characteristic of a lower socioeconomic status), and fractures.23,24

The major limitations of the present study include the retrospective use of secondary data and the resulting reliability of exposure data. Although ADHD prevalence was similar to that reported for adult populations in other studies,3 it is highly possible that MP abuse could have occurred, or medications could have been purchased from private pharmacies instead of military bases. Moreover, it is possible that a relatively large number of subjects in the ‘no ADHD’ group were exposed to large quantities of MP during high school or childhood, with negative effects on bone density. Owing to the lack of exposure data prior to military service, the present study did not attribute fractures in these subjects to MP use. However, the aforementioned limitations would be common to all studies that attempt to evaluate the effects of MP on fracture risk. Thus, despite these limitations, the study findings are in line with those of the existing literature.

In conclusion, the present findings show that chronic MP use is inversely associated with the risk of fractures in young adults, in a dose-dependent manner. The study sample included generally healthy young adults with a low probability of long-term intake of other medications. Therefore, it is highly likely that the association between medication and the risk of fracture reported in this study is unbiased, with a true effect size.

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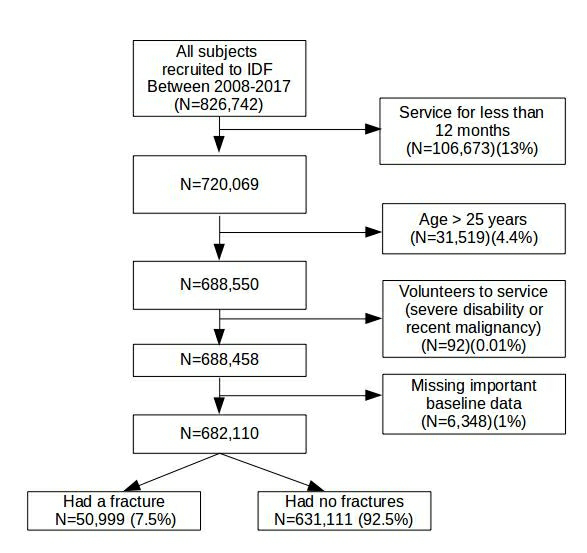
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| **TablesTable 1: Baseline characteristics of subjects** | | | | | | |
|  | **Men** (n = 409,175) | | | **Women** (n = 272,935) | | |
|  | **Fracture**  (n = 42,851; 10·5%) | **No fracture** (n = 366,324; 89·5%) | **p value** | **Fracture**  (n = 8,148; 3%) | **No fracture**  (n = 264,787; 97%) | **p value** |
| **Age** | 18·6 ± 0·9 | 18·9 ± 1·2 | < 0·001 | 18·3 ± 0·7 | 18·9 ± 1·2 | < 0·001 |
| **Weight** | 73·0 ± 14·9 | 72·1 ± 15·3 | < 0·001 | 62·3 ± 13·2 | 72·1 ± 15·3 | < 0·001 |
| **Height** | 174·7 ± 6·8 | 174·4 ± 6·8 | < 0·001 | 162·8 ± 6·3 | 174·4 ± 6·8 | < 0·001 |
| **BMI** | 23·9 ± 4·4 | 23·6 ± 4·5 | < 0·001 | 23·5 ± 4·6 | 23·6 ± 4·5 | 0·008 |
| **Education**  **< 12 years**  **12 years**  **> 12 years** | 2188 (5%)  39,032 (93%)  890 (2%) | 15,673 (4%)  332,644 (93%)  12,050 (3%) | < 0·001 | 185 (2%)  9548 (97%)  109 (1%) | 4145 (1·6%)  255326 (97·4%)  2514 (1%) | 0·02 |
| **Origin**  **North Africa**  **Asia and Middle East**  **Ethiopia**  **Israel**  **Other/Unknown**  **Former USSR**  **North America and Europe** | 7,514 (18%)  6,045 (14%)  782 (2%)  3,924 (9%)  13,745 (32%)  4,543 (11%)  6,298 (15%) | 57,200 (16%)  53,177 (15%)  9,184 (3%)  27,683 (8%)  112,362 (31%)  44,518 (12%)  62,200 (17%) | < 0·001 | 1645 (17%)  1215 (12%)  117 (1%)  590 (6%)  3845 (39%)  1038 (10%)  1440 (15%) | 38558 (15%)  36072 (14%)  4688 (2%)  16181 (6%)  93365 (35%)  31407 (12%)  42774 (16%) | < 0·001 |
| **Socioeconomic level**  **low**  **middle**  **high** | 1,842 (5%)  27,844 (75%)  7,437 (20%) | 13,529 (4%)  241,627 (76%)  64,066 (20%) | < 0·001 | 122 (1%)  6513 (75%)  2007 (24%) | 3046 (1%)  172932 (75%)  55296 (24%) | 0·27 |
| **Occupation**  **combat**  **non-combat** | 12,643 (34%)  25,044 (66%) | 95,400 (31%)  211,542 (69%) | < 0·001 | 432 (5%)  7470 (95%) | 4887 (1·5%)  323,569 (98·5%) | < 0·001 |
| **Follow-up** | 58·6 ± 18·6 | 54·6 ± 19·9 | < 0·001 | 57·9 ± 20·5 | 54·6 ± 19·9 | < 0·001 |
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BMI: body mass index

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| **Table 2. Unadjusted dose-response association between methylphenidate and risk of fracture** | | | | | |
|  | | **Men** | | **Women** | |
| **Fracture incidence during the study period (%)** | **Odds of fracture with 95% CI\*** | **Fracture incidence during the study period (%)** | **Odds of fracture with 95% CI\*** |
| **No ADHD** | | 41,635 (10·4%) | Reference group | 9,478 (3·6%) | Reference group |
| **Untreated ADHD** | | 1,004 (16·4%) | 1·68 (1·58 – 1·81) | 294 (7·1%) | 2·08 (1·84 – 2·34) |
| **Treated ADHD** | 1 – 90 doses | 158 (8·7%) | 0·82 (0·69 – 0·96) | 78 (4·6%) | 1·3 (1·02 – 1·61) |
| 91 – 180 doses | 20 (4·8%) | 0·43 (0·27 – 0·65) | 20 (4·4%) | 1·24 (0·77 – 1·89) |
| 180+ doses | 34 (5·8%) | 0·53 (0·36 – 0·73) | 20 (3·0%) | 0·84 (0·52 – 1·28) |
| \*Odds of fracture when subjects without ADHD were used as the reference group.  CI: confidence interval | | | | | |

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| **Table 3. Odds of fractures adjusted for methylphenidate use, ADHD, and other risk factors** | | | | |
|  | **Men** | | **Women** | |
|  | **OR (95% CI)** | **p value** | **OR (95% CI)** | **p value** |
| **Untreated ADHD\*** | 1·46 | < 0·001 | 1·82 | < 0·001 |
| **ADHD 1 – 90 doses\*** | 0·74 | 0·02 | 1·23 | 0·19 |
| **ADHD 91 – 180 doses\*** | 0·53 | 0·03 | 0·88 | 0·71 |
| **ADHD 180+ doses\*** | 0·48 | 0·002 | 0·69 | 0·24 |
| **Age** | 0·84 | < 0·001 | 0·94 | 0·03 |
| **Weight** | 1·004 | < 0·001 | 1·01 | < 0·001 |
| **Origin: North Africa and Middle East\*\*** | 0·99 | 0·82 | 1·18 | < 0·001 |
| **Origin: North America and Europe, former Soviet Union\*\*** | 0·87 | < 0·001 | 0·99 | 0·92 |
| **Education > 12 years\*\*** | 0·89 | 0·001 | 0·97 | 0·76 |
| **Middle socioeconomic level\*\*\*\*** | 0·90 | 0·003 | 1·15 | 0·31 |
| **High socioeconomic level \*\*\*\*** | 0·88 | 0·001 | 1·15 | 0·32 |
| **Combat service \*\*\*\*\*** | 1·16 | < 0·001 | 2·41 | < 0·001 |
| **Duration of follow-up** | 1·0004 | 0·11 | 0·99 | 0·03 |
| \*Subjects without ADHD as reference group  \*\*\*Twelve years of education as reference group  \*\*\*\*Low socioeconomic level as reference  \*\*\*\*\*Non-combat service as reference group  The model was adjusted for interaction between ADHD + MP exposure status and type of military service. | | | | |

**Figure 1**



IDF: Israel Defence Forces