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ORIGINAL ARTICLE

Venous thromboembolism among physically active young adult females

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Abstract

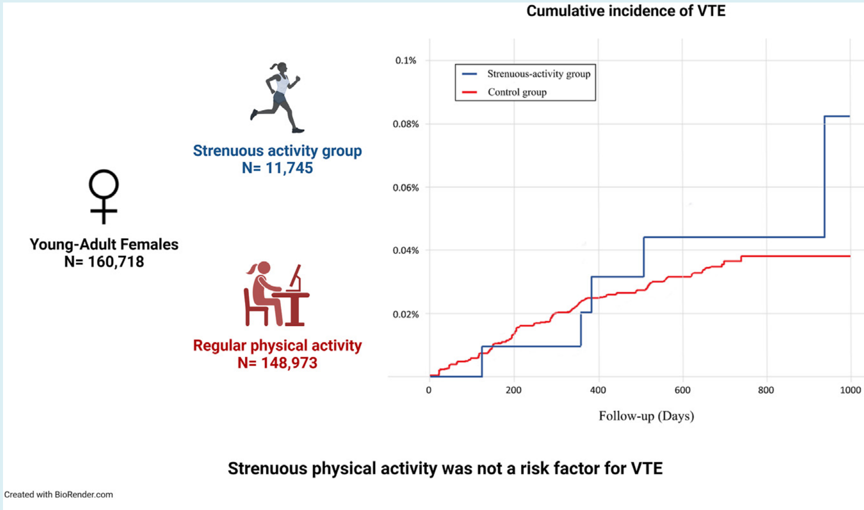
Background: Young adult females are at risk of venous thromboembolism (VTE) due to various acquired and transient factors. In recent years, a growing number of females have engaged in strenuous physical activity, but its role as a risk factor for VTE is uncertain.

Objectives: To determine the incidence of VTE in young adult females engaged in strenuous physical activity.

Methods: A large national cohort of female individuals enlisted in the Israeli Defense Forces between 2012 and 2019 was analyzed. The study group consisted of participants undergoing strenuous physical training during their military service, while the control group maintained regular activity levels. We compared the incidence of VTE between the groups and adjusted for potential risk factors using a multivariate Cox analysis.

Results: The cohort included 160,718 female individuals aged 18 to 21years, of whom 11,745 engaged in strenuous physical activity and 148,973 served as controls. During a mean follow-up of 1.7 years, VTE occurred in 5 individuals (0.04%) in the strenuous activity group and 47 individuals (0.03%) in the control group. The incidence per 10,000 person-years was 2.41 (95% CI, 0.78-5.62) for the strenuous activity group and 1.82 (95% CI, 1.34-2.42) for the controls. Strenuous activity did not increase the risk for VTE in univariate or multivariate regression, with a hazard ratio (HR) of 1.27 (95% CI, 0.49-4.22). Use of oral contraceptives was the only significant risk factor, demonstrating dose effect; HR 1.95 (95% CI, 1.06-3.57) for low dose and HR 3.62 (95% CI, 1.40-9.37) for medium estrogen dose contraceptives.

Conclusion: Strenuous physical activity did not increase the risk for VTE among a large cohort of young adult female individuals.



KEYWORDS

exercise, female, military personnel, pulmonary embolism, venous thromboembolism, young adult

Essentials

- The effect of strenuous physical activity on venous thromboembolism (VTE) in young females is uncertain.
- We examined VTE incidence among physically active females aged 18 to 21 years vs matched controls.
- Strenuous physical activity did not increase the risk for VTE.
- Oral contraceptives contributed to a higher VTE risk and correlated with estrogen dose.

1 | INTRODUCTION

Venous thromboembolism (VTE) is a major contributor to global disease burden and is among the most common cardiovascular diseases across different age groups [1–3]. VTE is a multifactorial disease involving interactions between acquired and/or inherited predispositions to thrombosis and various daily-life risk factors [4,5]. The occurrence of VTE has remained constant in recent decades despite significant advances in understanding the pathophysiology and efforts extended at VTE prevention [6].

VTE is a significant cause of morbidity in the young adult female population [7,8] due to the risk of recurrence, particularly during pregnancy, and the long-term sequelae, such as postthrombotic syndrome and chronic thromboembolic pulmonary hypertension. The prolonged use of anticoagulants has also been implicated in abnormal uterine bleeding, especially heavy menstrual bleeding, with detrimental effects on quality of life [9–12]. The incidence of first VTE in a population-based study [13] conducted in Norway demonstrated a rate of 1.3 and 3.5 per 10,000 person-years in the 20 to 24 years age group for men and women, respectively, compared with 14.3 per 10,000 person-years in all the age groups (the general population). The influence of sex on the risk of developing VTE has been extensively studied in recent years [14–17]. Women have been found to carry a lower baseline risk [18,19], with an overall age-adjusted annual incidence of 1.1 per 1000 compared with 1.3 per 1000 for men [20]. However, in the young adult population, women experience more VTE [7,13] due to hormonal risk factors, namely pregnancy and use of oral contraceptives [13,17,19–21].

While the benefit of moderate physical activity for cardiovascular health [22,23] and VTE prevention [24] is well established, there are diverging results as to the effects of strenuous exercise on the incidence of VTE and their association with sex [25–28]. Several reports [29–33] explore VTE in previously healthy, fit young individuals, suggesting that athletes may be exposed to unique risk factors producing a thrombogenic milieu [34–36]. Some studies [37–39] demonstrated an increased risk, particularly among women [39]. In recent decades, female individuals have been progressively introduced into a growing number of military units in the Israeli Defense Forces (IDF) [40], engaging in strenuous training, including daily high-intensity aerobic and anaerobic physical activity. In this study, we aimed to determine the incidence of VTE in a large cohort of this previously unexamined population and discuss the role of strenuous physical activity as an independent risk factor for VTE among young adult females.

2 | METHODS

2.1 | Study design and population

We studied all female individuals who enlisted in the IDF between 2012 and 2019. Participants in the control group were followed up until the end of their military service. For individuals who discontinued the strenuous activity position prior to completion of military service, follow-up ended on the last day of the strenuous activity role. We excluded participants who had a history of VTE prior to enlistment and who received any form of antiplatelet and/or anticoagulant therapy, namely aspirin, clopidogrel, ticagrelol, prasugrel, dipyridamole, warfarin, dabigatran, rivaroxaban, apixaban, edoxaban, heparin, enoxaparin, and fondaparinux. Individuals who manifested abnormalities on a complete blood count, except for mild anemia, and participants who volunteered for service despite a serious medical condition (ie, inflammatory bowel disease or malignancies) were also excluded.

2.2 | Definition of physical activity

Study participants were stratified according to the level of physical activity required by their military role. Individuals with an active combat position engaged in strenuous training vs those whose military role did not entail physical training and who maintained a regular level of physical activity. Of note, combat positions are voluntary for female individuals. Participants who served in combat positions participated in strenuous physical training during the first 4 months of service, followed by duty that included daily high-intensity activity. During training, physical activity encompasses daily aerobic and anaerobic exercises. Aerobic activities included 3 to 5 km runs, marches of up to 20 km with weight-carrying of up to 33% of body weight (twice a week), and obstacle course training. Additional anaerobic activities to increase muscle mass occurred daily within dedicated time slots. Similar physical regimens continued in various forms throughout the active service.

2.3 | Clinical and demographic characteristics collection

The study variables were accrued from the military electronic medical records and included age, body mass index (BMI), health status, and contraceptive use. The type of military service, combat vs regular, was determined according to the allocated code by IDF human resources. This indicator is used in various aspects of military service and determines the soldier's salary, and is thus regarded as highly accurate. The IDF provides free health care without deductibles for enlisted soldiers, including contraceptives; thus, most soldiers obtain these from military pharmacies. We determined the user status and type of oral contraceptives according to the prescriptions or procurement from a military pharmacy during the first 3 months of service. The cohort participants used combined oral contraceptives containing either desogestrel, gestoden, or drospirenone (third and fourth-generation progestins), conferring a similar prothrombotic risk [41]. Levonorgestrel, a low-risk progestin, is not routinely used in Israel. The oral contraceptives were categorized as low and medium doses according to the estrogen component, 15 to 20 μg and 30 to 35 μg, respectively, since they contribute to different levels of prothrombotic risk [42,43].

Individuals enlisting in the IDF undergo a thorough examination by a military physician that includes a review of medical history, an interview, and a physical examination. In addition, everyone must provide a report by a board-certified pediatrician regarding his\her current health status and medical history. In the present study, the general health status was categorized into 2 groups: A: no disease or mild medical condition causing minimal effect on the ability to perform physical activity, such as low-level myopia (up to -6 diopters), mild pes planus, past bronchial asthma, not requiring current treatment; and B: moderate medical condition that hinders physical activity. This category includes all medical conditions necessitating chronic treatment and/or follow-up, such as asthma treated with bronchodilators, obesity, and unbalanced hypothyroidism.

2.4 | Diagnosis of venous thromboembolic disease

We screened the medical records for International Classification of Diseases codes for VTE diagnosis as well as prescriptions of anticoagulants (low-molecular-weight heparin, direct oral anticoagulants [apixaban, dabigatran, rivaroxaban, and edoxaban], or warfarin), which were deemed as potential VTE cases. The full list of International Classification of Diseases-9 codes is available in Supplementary Table S1. To ensure accuracy, we manually validated each case by examining the electronic medical records to verify the presence of radiological evidence supporting the VTE diagnosis, namely ultrasound Doppler for deep vein thrombosis (DVT), pulmonary computed tomography angiography for pulmonary embolism, and magnetic resonance venography\computed tomography venography for cerebral vein thrombosis.

2.5 | Statistical analysis

Continuous values are presented as mean ± SD, while the categorical values are presented as percentages. Continuous variables were compared using a *t*-test, and categorical variables using the chi-squared test. The cumulative incidence and corresponding 95% CI for VTE events were calculated for the strenuous activity and control groups and compared using the log-rank test. The survival curve was drawn using the Kaplan–Meier method. To assess risk factors for VTE, a multivariate Cox proportional hazard test was performed with the time to event calculated from enlistment until the earliest date of diagnosis or initiation of anticoagulation treatment. Hazard ratios (HR) and 95% CI were calculated, with a P value below .05 considered statistically significant. Multivariate analysis included age, health status at enlistment, level of physical activity, and the use and dose of contraceptives. To minimize potential residual confounding, a secondary cohort was created of controls individually matched with the strenuous activity group based on age, BMI, contraceptive use, and health status in a 1:5 ratio. The previously mentioned multivariable Cox regression was used for analysis. The data were analyzed using SPSS version 25 statistical software (SPSS Inc).

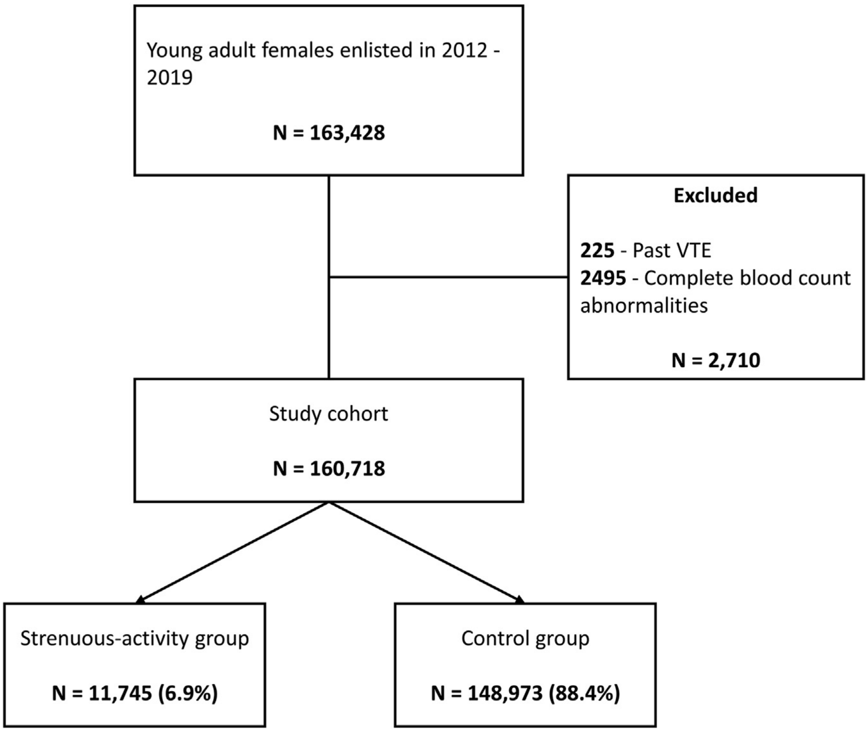


FIGURE 1 Study proliferation.

2.6 | Ethics approval

The study was approved by the Israel Defense Forces Institutional Ethics Committee.

3 | RESULTS

3.1 | Baseline data

The study flowchart is presented in Figure 1. We enrolled 160,718 female individuals who enlisted in the IDF between 2012 and 2019. The cohort included 11,745 participants in a combat position, taking part in strenuous physical training, and 148,973 females who served in nonphysically active duties, aged 18 to 21 years. The participants' characteristics are presented in Table 1. Age and BMI were similar across the study groups. Individuals in the strenuous activity group were less likely ($P < .001$) to suffer from comorbidities (Supplementary Table S2) and more likely to use contraceptives ($P = .02$) compared with individuals in the control group.

3.2 | Venous thromboembolism incidence

Both groups were followed for a mean duration of 1.7 years, amounting to 20,752 and 258,599 person-years for the strenuous activity and control groups, respectively (Table 2). During this period, 5 participants (0.0426%) in the strenuous activity group and 47 (0.0315%) in the control group experienced VTE. The incidence per 10,000 person-years was 2.41 (95% CI, 0.78-5.62) compared with 1.82 (95% CI, 1.34-2.42) for the strenuous activity and control groups, respectively. The results for the matched control group were similar, with an incidence per 10,000 person-years of 1.80 (95% CI, 1.07-2.85) (Supplementary Table S3). The VTE rate among the groups was similar when compared using the log-rank test ($P = .23$). The Kaplan–Meier

TABLE 1 Baseline characteristics of the study population.

Parameter	Strenuous activity *N* = 11,745	Controls *N* = 148,973
Age (y), mean ± SD	18.7 ± 0.6	18.8 ± 0.7
Mean (IQR)	18.6 (18.4, 18.9)	18.57 (18.4, 18.9)
BMI (kg/m^2), mean ± SD	23.0 ± 3.5	22.3 ± 4.1
Mean (IQR)	22.3 (20.5, 24.8)	21.5 (19.5, 24.1)
Health status, *N* (%)		
A: no disease or mild medical condition	11,639 (99.1)	118,136 (79.3)
B: moderate medical condition	106 (0.9)	30,837 (20.7)
Contraceptive use, *N* (%)		
None	8339 (71.0)	119,923 (80.5)
Low-dose (15-20 μg)	2971 (25.3)	25,177 (16.9)
Medium (30-35 μg)	435 (3.7)	3873 (2.6)

BMI, body mass index; Health status, A: no disease or mild medical condition causing minimal effect on the ability to perform physical activity; B: moderate medical condition that hinders physical activity.

TABLE 2 Follow-up duration and incidence of venous thromboembolism.

Parameter	Strenuous activity N = 11,745	Controls N = 148,973
Follow-up in years		
Mean ± SD	1.74 ± 0.83	1.71 ± 0.68
Median (IQR)	1.94 (1.19, 2.42)	1.99 (1.40, 2.0)
Total follow-up in person-years	20,752	258,599
Venous thromboembolism, *N* (%)	**5 (0.04)**	**47 (0.03)**
Upper extremity DVT	1 (20)	2 (4.3)
Lower extremity DVT	3 (60)	35 (74.5)
Pulmonary embolism	1 (20)	7 (14.9)
Cerebral vein thrombosis	0	3 (6.4)
VTE per 10,000 follow-up years		
N (95% CI)	2.41 (0.78–5.62)	1.82 (1.34–2.42)

DVT, deep vein thrombosis; VTE, venous thromboembolism.

survival curves for the 2 groups are presented in Figure 2. The 95% CIs were omitted due to significant overlap and for visual clarity.

The adjusted Cox regression models did not show a statistically significant effect of strenuous physical activity on VTE with an HR of 1.02 (95% CI, 0.40-2.66). Oral contraceptives were the only significant risk factor demonstrating an estrogen dose effect with an HR of 1.95 (95% CI, 1.06-3.57) and 3.62 (95% CI, 1.40-9.37) for the use of low and medium-dose contraceptives, respectively (Table 3). These findings persisted when a control subgroup was used, consisting of participants individually matched at a 1:5 ratio (11,745 women in the strenuous activity group and 58,725 matched controls) for age, BMI, contraceptive use, and health status. In this matched analysis, the HR for engaging in strenuous activity was 1.30 (95% CI, 0.47-3.60).

The characteristics of individuals who experienced VTE are shown in Table 4. Similar to the multivariable Cox analysis, the use of contraceptives was the only significant difference between the groups.

4 | DISCUSSION

In this study, we assessed the incidence of VTE among young adult females engaged in strenuous physical activity and investigated its role as an independent risk factor for VTE. We found no increased risk of VTE for active female individuals compared with similar age controls. Among females who experienced VTE, known risk factors such as combined oral contraceptives exhibited the expected estrogen dose-dependence with similar progestin components. Most studies assessing VTE incidence have been performed in the adult and elderly age groups, demonstrating that the risk for VTE increases dramatically with age [44]. The risk of VTE in the young adult population has been demonstrated to be low in several population-based studies [13,20,44]. Notably, in a study conducted in Norway, the incidence rate for VTE (DVT and pulmonary embolism combined) among women aged 20 to 24 years stood at 3.5 for 10,000 person-years [13].

The role of strenuous physical activity in venous thrombosis among female individuals has long been questioned [28]. Initially considered a staple in prevention of thromboembolic events, it soon became evident that frequent and high-intensity exercise might be less beneficial than moderate physical activity. The Million Women [39] and the Cardiovascular Health studies demonstrated an increased risk of VTE for women participating in strenuous physical activity daily compared with mostly inactive women. Other studies [45–47] found no such association. This discrepancy can be partly explained by differences in the examined populations and study designs, the type of activity performed, and the resulting risk for minor and major injuries [48]. Several mechanisms have been proposed to explain the association of strenuous physical activity with VTE. These include inherent characteristics of strenuous exercise, hemoconcentration secondary to dehydration, especially in the presence of athletes' bradycardia [35], activation of the innate immune system and the resulting inflammatory process [49], as well as injury to the vessel wall [4,50]. As a result, vigorous exertion causes hypercoagulability in combination with an augmented fibrinolysis. However, the fibrinolytic parameters return to baseline quickly, whereas the procoagulant parameters remain elevated [51]. For example, upper extremity DVT in the military population has been coined “effort-thrombosis” since it is assumed to arise from microtrauma to the endothelium secondary due to repetitive arm movements and weight lifting such as heavy backpacks [52,53]. These conditions were present in the participants of our active cohort. The large sample size would have emphasized even minor effects. However, we were unable to demonstrate a statistically significant increase in VTE. This might stem from the young age of the participants in our cohort (18-22 years). The healthy endothelium and low levels of coagulation proteins characteristic of young age [54] might be able to counteract the additional hypercoagulability factors outlined above. The incidence of VTE in the control group is consistent with reported rates of VTE in this population [7], which contributes to the generalizability of our results. Upper extremity DVT is considered characteristic of military activity. One female among those who experienced VTE (1/5, 20%) in the strenuous activity group manifested with upper extremity DVT, compared with 2 individuals (2/43, 4.3%) among the controls. Due to the paucity of events, we cannot determine that upper extremity DVT was more common in the strenuous activity group.

Our study has several limitations. First, we did not include smoking status in combination with contraceptives in our multivariate analysis. Smoking status was available for 44% of our cohort due to partial documentation in the electronic medical records. Among the persons whose smoking status was known, individuals in the strenuous activity group were significantly more likely to smoke. While reporting bias of positive smoking status is expected, it is likely similar in both groups, and the actual difference is unlikely to shift radically, thus not affecting our conclusion that strenuous exercise was not a risk factor in this age group. Additionally, immobilization status was not known but is unlikely among our cohort of young adults who were

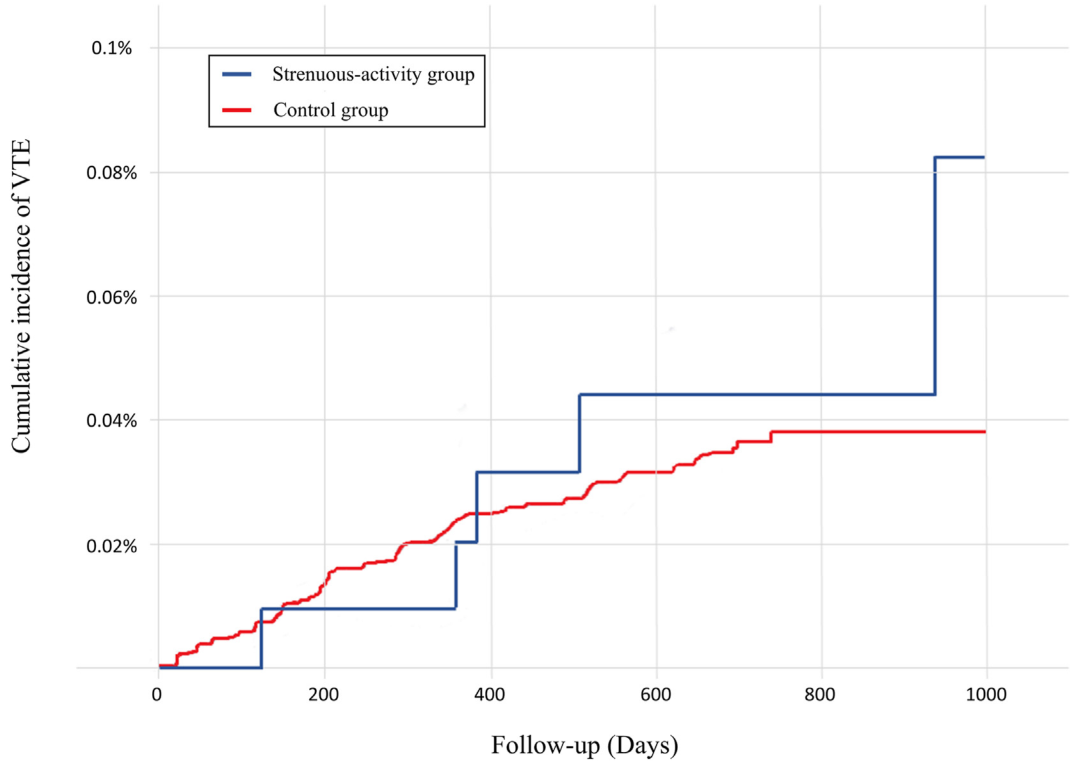


FIGURE 2 Cumulative incidence of venous thromboembolism stratified by activity level.

deemed fit for army service. Third, participants in the control group were not enrolled in a regimented exercise program, but it is conceivable that some may have been involved in physical activity outside of their military duty. Fourth, our demographic data did not include social determinants of health, such as race and/or ethnicity. However, these factors would most likely have been similar between the examined groups.

Nevertheless, our study is the first to examine the incidence of VTE in a large cohort of young adult females. We used standardized occupation-related physical activity measures, thereby avoiding self-reported bias. Active military positions are voluntary for women, and as a result, the strenuous activity and control group do not differ based on their baseline physiological characteristics, as can be seen in

TABLE 3 Multivariate analysis for risk factors for venous thromboembolism.

Parameter	Hazard ratio (95% CI)
Age	1.07 (0.96–1.18)
BMI	1.06 (0.99–1.09)
Health status	
Moderate medical condition (B) **vs** no disease (A)	0.88 (0.47–2.61)
Level of physical activity	
Strenuous **vs** control	1.27 (0.49–4.22)
Contraceptive use	
Low-dose estrogen 15-20 μg **vs** no use	1.95 (1.06–2.50)
Medium-dose estrogen 30-35 μg **vs** no use	3.62 (1.40–4.20)

BMI, body mass index.

TABLE 4 Patient characteristics for venous thromboembolism cases and event-free individuals.

Parameter	Venous thromboembolism *N* (%)	No event *N* (%)	*P* value
Age (y), mean ± SD	18.8 ± 1.2	18.8 ± 0.7	.465
BMI (kg/m^2), mean ± SD	23.3 ± 4.5	22.4 ± 4.1	.118
Obesity (BMI >30 kg/m^2)	4 (7.3)	8997 (5.6)	.208
Health status, *N* (%)			
A: no disease or mild medical conditions	39 (75.4)	113,591 (70.7)	.498
B: moderate medical condition	13 (24.6)	47,075 (29.3)	
Contraceptive use, *N* (%)			
None	31 (60.0)	127,408 (79.3)	<.001
Low-dose (15-20 μg)	16 (30.9)	28,759 (17.9)	
Medium (30-35 μg)	5 (9.1)	4499 (2.8)	

BMI, body mass index; Health status, A: no disease or mild medical condition causing minimal effect on the ability to perform physical activity; B: moderate medical condition that hinders physical activity.

the detailing of prevalent comorbidities. Therefore, healthy worker bias is unlikely. Moreover, participants in the strenuous physical activity group participate in a structured, high-intensity daily training program. Individuals in the control group, whose roles are primarily clerical, lack an organized exercise program. To testify to this distinction, women in combat positions have been shown to suffer commonly from overuse injuries [55], while women in the nonactive population are known to gain weight during military service [56,57]. Altogether, we conclude that the 2 groups were randomized based only on the levels of physical activity. To ensure the accuracy of VTE diagnoses, we employed a strict definition, requiring both imaging confirmation (ie, ultrasound and computed tomography angiography) and proven anticoagulation treatment and manual validation of positive cases. We followed our cohort for a long period of an average of 20 months and observed VTE rates similar to previous studies [13].

Identification of modifiable risk factors at the population level may provide a measure to reduce the burden of VTE [27]. A more nuanced understanding of the specific risk factors for VTE in young adult females and its clinical characteristics could improve the diagnostic process, therapeutic strategy, and outcomes [7]. In our case, the study's findings can serve to reassure young adult females engaged in strenuous physical activity and their physicians on the use of oral contraceptives and the management of other risk factors. These dilemmas are becoming ever more relevant as an increasing number of female individuals are being introduced to strenuous physical activity and an ever-expanding array of military positions worldwide.

5 | CONCLUSION

Strenuous physical activity did not contribute to the risk of VTE in young adult females. Further epidemiologic and mechanistic studies regarding risk factors specific to young adult female individuals will help to improve the awareness of patients, practitioners, and policymakers and inform accurate and personalized prevention management.

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ETHICS STATEMENT

The study was approved by the Israel Defense Forces Institutional Ethics Committee.

AUTHOR CONTRIBUTIONS

M.S. and A.G.S. were responsible for the study design, data collection, statistical analysis, and manuscript writing. E.N.H., A.L., R.L., and S.M. contributed to the study design, interpretation of the data, critical writing, and revising of the intellectual content. All authors approved the submitted version.

RELATIONSHIP DISCLOSURE

The authors declare no conflict of interest.

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SUPPLEMENTARY MATERIAL

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