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Association of statins with peak oxygen consumption in 4,941 adults: A cross-sectional study

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ABSTRACT

Background and aims: Cardiovascular disease remains a leading cause of mortality, with statins widely used to reduce its risk. Despite extensive research, the nuanced impact of statin therapy on cardiorespiratory fitness, particularly the reduction in peak oxygen consumption (VO_2), is still an open question. This study aims to contribute fresh insights to the ongoing discussion, highlighting the unresolved nature of this clinical matter.
Methods: We retrospectively analyzed maximal cardiopulmonary exercise test (CPET) in male and female participants over 18 years of age who were under statins treatment. They were categorized as physically active or inactive according to self-report of physical activity. From 33,804 CPET, 4,941 participants (76 % men, age 42 ± 13 years; and 24 % women, age 41 ± 13 years) were included in the study.
Results: The multivariate linear regression model showed that statins were associated with a significant reduction in VO_2 peak (−4.2 [-4.8, −3.5] mL/kg/min, $p < 0.01$) after adjusting for age, sex, use of beta-blockers, antiarrhythmics, presence of diabetes, and weekly level of physical activity. This reduction in VO_2 peak was attenuated in participants with higher weekly physical activity volume (150 to 300 min/week: 3.2 [2.7; 3.7] mL/kg/min; 301 to 600 min/week: 4.5 [3.7; 5.3] mL/kg/min; and > 600 min/week: 6.9 [5.4; 8.4] mL/kg/min, all $p < 0.01$).
Conclusions: Statin use is associated with a lower VO_2 peak in adults. However, this adverse effect appears to be mitigated by engaging in regular physical activity (>150 min/week). Future research should explore the mechanisms behind this interaction and identify optimal exercise regimens for individuals on statin therapy.

1. Introduction

Statin therapy is widely used for the prevention and treatment of cardiovascular disease (CVD), which continues to be the leading cause of death worldwide [1,2]. Although statins have demonstrated effectiveness in reducing low-density lipoprotein cholesterol levels and decreasing the incidence of CVD events, their usage appears to be linked to potential side effects, including a reduction in cardiorespiratory fitness (CRF)[3,4]. Some studies report impaired exercise training adaptations in CRF following statin therapy [5–7], while others have found no significant effect on CRF [8–10]. Despite the extensive research on the effects of statins on exercise performance and mitochondrial function, there remains a significant research gap in understanding the long-term implications of statin use on muscle health and exercise adaptation. Most studies have focused on short-term outcomes, leaving the chronic effects largely unexplored. Additionally, there is a lack of consensus on the mechanisms by which statins may impair exercise capacity and whether these effects are reversible with supplementation or cessation of statin therapy. Therefore, this issue remains unclear and, undoubtedly, warrants further investigation.

Statins cause mitochondrial dysfunction in skeletal muscle, leading to blunted exercise fat oxidation [11], reduced adenosine triphosphate (ATP) production and oxidative phosphorylation capacity. This process increases the concentration of reactive oxygen species, causing

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heightened oxidative stress, and decreases mitochondrial biogenesis due to the reduced activity of peroxisome proliferator-activated receptor-gamma coactivator-1α (PGC-1α) [12–16]. These responses appear to be contributing to the reduced CRF in patients undergoing statin treatment.

Aerobic exercise training significantly improves VO_2 peak in patients with metabolic syndrome; however, co-administration of simvastatin (40 mg/day) attenuates this response [6]. Further investigation has demonstrated that the attenuation in CRF gain after exercise training in patients with type 2 diabetes treated with simvastatin is linked to reduced skeletal muscle mitochondrial content [7]. It is noteworthy that the blunted VO_2 peak associated with statin use is more prevalent in men than in women [17]. Contrary to these finds, high-dose atorvastatin for 6 months does not decrease average muscle strength or exercise performance in healthy, previously untreated subjects [18]. The interaction between different types of statins and various forms of exercise has not been thoroughly investigated. It is unclear if certain statins might have less detrimental effects on exercise performance or if specific exercise regimens could mitigate the negative impacts of statins. Exploring these uncharted areas could pave the way for tailored medical strategies that enhance cardiovascular well-being while maintaining optimal physical performance and quality of life. Therefore, it is critical to consider the potential impact of statin therapy on CRF when evaluating the overall risk–benefit balance of this treatment, particularly in individuals who are at risk of CVD and could benefit from exercise interventions.

To elucidate the association between statins and VO_2 peak, we conducted a retrospective analysis of a substantial database comprising 4,941 maximal cardiopulmonary treadmill tests. This extensive dataset ensures a robust sample size and relevant information for our investigation. Our primary objective was to ascertain the relationship between statin use and VO_2 peak in adults exhibiting both sufficient and insufficient levels of physical activity. In this case-control study, we hypothesized that use of statins would reduce VO_2 peak when compared to patients not taking this medication.

2. Materials and Methods

2.1. Experimental design

This study was approved by the Human Subject Protection Committee of the Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo (HCFMUSP), São Paulo, SP, Brazil (CAAE: 21658619.6.0000.0068). As it is a retrospective study, there was no need for participants to provide written informed consent. The study was also registered at ClinicalTrials.gov under the number NCT04986241. This study adopts a retrospective, cross-sectional, case-control design, utilizing a comprehensive database to compare the impact of statin use on VO_2 peak associations. Our inclusion strategy had the following criteria: 1) adults with sufficient levels of physical active and insufficient levels of physical activity (based on the World Health Organization guidelines on physical activity and sedentary behavior), 2) with normal cardiac function, 3) use of statins and other medications or no medication, 4) and a maximum cardiopulmonary exercise test on a treadmill characterized by respiratory exchange ratio (RER) > 1.10. The study description followed the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) checklist for observational studies. The study analyzed data collected from individuals who underwent cardiopulmonary exercise test between 1998 and 2017.

2.2. Participants

Inclusion criteria encompassed individuals over 18 years old (men and women) in two distinct groups: the statin group, comprising participants using statins and other medications, and the non-statin group, comprising healthy individuals without any medication use. Only those who achieved a maximum cardiopulmonary exercise test (RER > 1.10) on a treadmill were included in the study. Exclusion criteria were incomplete exam data and any information that raised doubts about the clinical information. Patients with heart failure, previous heart transplantation were not included. Additionally, patients with unstable angina, myocardial infarction, stroke, cardiovascular revascularization within 6 weeks prior to the test were not included in the study.

2.3. Cardiopulmonary exercise test

Prior to conducting the test, the participants underwent an anamnesis session with an exercise physiologist. Participants self-reported any pre-existing diseases, medications they were taking, and their regular physical activity habits. This information was documented in the cardiopulmonary exercise test record and used to establish the suitable test protocol.

VO_2 peak (the main outcome of the present study) was assessed through the cardiopulmonary exercise test on a treadmill, with SensorMedics equipment (Vmax Analyzer Assembly and Encore 29S). All participants underwent individualized ramp protocols. The 12-lead electrocardiogram was recorded during the exercise test (Micromed – Cardio PC 13). Ventilation was measured by the breath-by-breath method, and all data were expressed as a 30-second mean. Test completion occurred when, despite verbal encouragement, the participant could no longer maintain the exercise intensity, and the RER was greater than or equal to 1.10. VO_2 peak was determined by the relative value (mL/kg/min).

2.4. Physical activity, sedentary behavior, and medication use

Data on the type of physical activity, weekly frequency, and volume were obtained from the anamnesis records of the cardiopulmonary exercise test. Participants engaging in aerobic exercise training (e.g., walking, running, cycling, swimming) as well as resistance training (e.g., weight training) were classified as physically active. For ease of comparison, individuals with a weekly physical activity volume below 150 min were categorized as having insufficient levels of physical activity [19]. Additionally, the anamnesis process included the collection of information regarding the type and dosage of administered medications.

2.5. Clinical information

We retrospectively collected clinical information from participants by cross-referencing the cardiopulmonary exercise test database with the institutional information system to collect clinical data of interest (eg. blood biomarkers – cholesterol, HDL-C, LDL-C, fasting glucose, glycated hemoglobin, hemoglobin, triglycerides, sodium, potassium, creatinine, aspartate transaminase transaminase, alanine transaminase; echocardiogram – left ventricular ejection fraction). Therefore, the data collection for the cardiopulmonary exercise test and clinical information did not occur simultaneously.

2.6. Data mining and exploratory analysis

All exploratory analyzes were performed using Python and R for Linux (version 3.4.4) and RStudio for Windows (version 4.0.3) programs. Initially, a total of 33,804 cardiopulmonary exercise test records were included in the study. Out of these, 2,407 records were excluded due to the absence of VO_2 peak values, 10,571 records were excluded for having submaximal RER (<1.10), 494 records were excluded as the participants were under 18 years of age, 3,703 records were excluded because the participants were classified as unhealthy but not taking any medication or dyslipidemic but without the use of statins, 4,339 records were excluded due to missing exercise or medication data, and 891 records were excluded as they were conducted on a different type of ergometer (such as a bicycle or rowing machine). After the initial analysis of statin use or non-use, a total of 11,399 records were selected

for further examination.

After analyzing the records, a total of 2,577 tests were excluded for the following reasons: patients who had undergone heart transplantation (n = 15), patients classified as Chagasic without conclusive evidence of ventricular dysfunction (n = 223), incomplete medication data, clinical data, or exercise information that raised uncertainties (n = 2,339). Furthermore, 3,314 records were excluded as they represented multiple tests conducted on the same individual, with only the most recent record being considered. Thus, the final sample included in the study consisted of 4,941 participants.

2.7. Statistical analysis

Data analysis was performed by two statisticians using Python, R for Linux (version 3.4.4) and RStudio for Windows (version 4.0.3) programs. Descriptive statistics of absolute (n) and relative (%) frequencies were used for qualitative measures and summary statistics of mean, median, standard deviation (SD) and quantiles for quantitative measures. A multivariate linear regression model was used to evaluate the impact of several variables, including sex, age, pre-existing diseases, use of statins and other medications, and weekly time of physical activity, on the response variable of interest (VO_2 peak). The significance of each effect was determined using the Wald test, with only those with a p-value ≤ 0.05 considered statistically significant.

3. Results

Table 1 presents data on the physical and clinical characteristics of the participants. Mean age was 41.46 ± 13.67 years old and BMI was 22.75 ± 0.61 kg/m^2; VO_2 peak was 46.19 ± 11.35 mL/kg/min, RER peak was 1.20 ± 0.07, and peak heart rate was 172 ± 20 bpm.

Table 2 presents data on the physical and exercise-related characteristics of the participants with and without the use of statins. Table 3 details the categorical variables: 76 % of the sample were men, 23 % used hydrophilic statins, and 77 % used lipophilic statins. A significant portion of the participants (81 %) were physically active.

Table 2
Physical and exercise-related characteristics of the participants with and without statin use.

	Statin users (n = 1,141)	Non-statin users (n = 3,800)
Age (years)	57.58 (56.91 – 58.25)	36.62 (36.30 – 36.94)
Height (cm)	168.87 (168.32 – 169.42)	172.47 (172.19 – 172.75)
Weight (kg)	65.52 (65.09 – 65.95)	67.74 (67.51 – 67.96)
BMI (kg/m^2)	22.9 (22.87 – 22.93)	22.71 (22.69 – 22.73)
RER peak	1.18 (1.18 – 1.19)	1.20 (1.20 – 1.21)
Resting HR (bpm)	72.31 (71.52 – 73.1)	75.71 (75.24 – 76.19)
AT HR (bpm)	111.62 (110.48 – 112.77)	133.89 (133.33 – 134.46)
Peak HR (bpm)	149.85 (148.45 – 151.25)	179.56 (179.17 – 179.96)
VO_2 at AT (L/min)	1484.19 (1453.03 – 1515.34)	1994.76 (1974.46 – 2015.06)
AT (%)	63.57 (62.99 – 64.15)	59.09 (58.74 – 59.44)
VO_2 peak (mL/min)	2360.32 (2311.99 – 2408.65)	3370.39 (3344.28 – 3396.51)
VO_2 peak (mL/kg/min)	35.62 (35.01 – 36.24)	49.37 (49.06 – 49.67)
Exercise – 0 to 149 min/wk	948 (83.09 %)	2.785 (73.29 %)
Exercise – 150 to 300 min/wk	152 (13.32 %)	685 (18.03 %)
Exercise – 301 to 600 min/week	36 (3.16 %)	256 (6.74 %)
Exercise – over 600 min/week	5 (0.44 %)	74 (1.95 %)

Values are expressed in mean and 95% confidence interval. BMI: body mass index; RER: respiratory exchange ratio; HR: heart rate; AT: anaerobic threshold; VO_2: Oxygen consumption

The multivariate linear regression analysis (Table 4) revealed that statin use was significantly associated with a reduction in VO_2 peak (−4.2 [-4.8, −3.5] mL/kg/min, $p < 0.01$), after adjusting for age, sex, use of beta-blockers, antiarrhythmics, presence of diabetes, and weekly physical activity level. This reduction in VO_2 peak was less pronounced in participants with higher levels of physical activity (150 to 300 min/

Table 1
Physical and clinical characteristics of the participants.

	Sample (n)	Mean	SD	IQR (25 %)	Median	IQR (75 %)
Age (years)	4941	41.46	13.67	31.00	39.00	50.00
Height (cm)	4941	171.64	9.03	166.00	172.00	178.00
Weight (kg)	4941	67.22	7.17	62.70	68.60	72.50
BMI (kg/m^2)	4941	22.75	0.61	22.35	22.88	23.19
RER peak	4941	1.20	0.07	1.14	1.18	1.24
Resting HR (bpm)	4420	75.00	13.89	65.00	74.00	84.00
AT HR (bpm)	4623	129.00	19.99	115.00	130.00	142.00
Peak HR (bpm)	4646	172.00	20.09	165.00	177.00	185.00
VO_2 at AT (L/min)	4903	1877.19	650.47	1397.00	1799.00	2286.00
AT (%)	4903	60.00	10.91	52.00	60.00	68.00
VO_2 peak (mL/min)	4941	3137.14	927.00	2408.00	3239.00	3832.00
VO_2 peak (mL/kg/min)	4941	46.19	11.35	38.31	47.11	54.23
Hemoglobin (g/dL)	343	14.74	1.37	13.80	15.00	15.65
Fasting glucose (mg/dL)	339	103.15	21.01	92.00	98.00	107.00
Glycated hemoglobin (%)	237	5.74	0.69	5.40	5.60	5.90
Cholesterol (mg/dL)	337	181.30	39.54	154.00	180.00	206.00
HDL-c (mg/dL)	337	53.25	14.87	43.00	51.00	63.00
LDL-c (mg/dL)	332	107.48	33.26	83.75	105.00	132.00
Triglycerides (mg/dL)	337	99.73	55.40	61.00	85.00	122.00
Sodium (mmol/L)	330	140.26	2.26	139.00	140.00	142.00
Potassium (mmol/L)	330	4.39	0.37	4.20	4.35	4.60
Creatinine (mg/dL)	343	1.01	0.23	0.89	0.99	1.11
Glomerular filtration (mL/min/1,73 m^2)	335	59.29	3.98	60.00	60.00	60.00
AST (U/L)	309	31.59	58.71	21.00	25.00	30.00
ALT (U/L)	310	41.50	22.41	31.00	38.50	47.00
Creatine kinase (U/L)	283	222.43	481.18	92.00	143.00	241.00
LVEF (%)	300	65.42	4.10	63.00	65.50	68.00

BMI: body mass index; RER: respiratory exchange ratio; HR: heart rate; AT: anaerobic threshold; VO_2: Oxygen consumption; HDL: high density lipoprotein; LDL: low density lipoprotein; AST: aspartate transaminase; ALT: alanine transaminase: LVEF: left ventricular ejection fraction.

Table 3
Categorical variables of participants.

Variables	Sample (n)	%
Men	3,745	76 %
Women	1,196	24 %
Pacemaker/ICD/Resynchronizer	28	1 %
Hypertension	338	7 %
Diabetes	129	3 %
Antiarrhythmic	52	1 %
Cardiac glycoside	1	0 %
Anticoagulant	41	1 %
Antianginal	79	2 %
Mineralocorticoids	54	1 %
Antithrombotic	220	4 %
Ca2 + channel blockers	156	3 %
Antilipemic (ezetimibe, fibrates)	82	2 %
Vasodilators	8	0 %
Diuretic	183	4 %
Antiplatelet	570	12 %
ACEI/ARB	578	12 %
Hypoglycemic agents	274	6 %
Beta blockers	516	10 %
Category 1 beta blockers	19	4 %
Category 2 beta blockers	386	75 %
Category 3 beta blockers	109	21 %
Statins	1,141	23 %
Hydrophilic	260	23 %
Lipophilic	873	77 %
Physically active (>150 min/week)	3,983	81 %
Physically inactive (<150 min/wk)	958	19 %

ICD: Implantable Cardioverter Defibrillator; Ca2+- Calcium; ACEI/ARB angiotensin-converting enzyme inhibitors/angiotensin receptor blockers.

Table 4
Multivariate linear regression model (values are mL/kg/min of VO_2 peak).

Variables	Complete Model	Final Model
Age (18–27) – Ref	–	–
Age (28–37)	−1.7*** (−2.2, −1.1)	−1.7*** (−2.2, −1.1)
Age (38–47)	−3.1*** (−3.7, −2.5)	−3.1*** (−3.7, −2.5)
Age (48–57)	−5.7*** (−6.4, −5.0)	−5.7*** (−6.4, −5.0)
Age (58–67)	−10.6*** (−11.5, −9.715)	−10.6*** (−11.5, −9.7)
Age (68–77)	−15.1*** (−16.3, −13.9)	−15.2*** (−16.4, −14.0)
Age (78–87)	−18.2*** (−20.5, −15.984)	−18.2*** (−20.5, −16.0)
Age (>87)	−24.0*** (−31.461, −16.6)	−24.0*** (−31.5, −16.6)
Male sex	10.1*** (9.7, 10.5)	10.1*** (9.7, 10.5)
1st beta blocker	−8.1*** (−11.0, −5.1)	−8.0*** (−11.0, −5.0)
2nd beta blocker	−4.9*** (−5.8, −4.1)	−4.9*** (−5.7, −4.0)
3rd beta blocker	−9.8*** (−11.1, −8.5)	−9.8*** (−11.1, −8.4)
Antiarrhythmics	−4.9*** (−6.8, −3.1)	−5.0*** (−6.8, −3.1)
Statins	−4.1*** (−4.8, −3.5)	−4.2*** (−4.8, −3.5)
Exercise – 0 to 149 min/week – Ref	–	–
Exercise – 150 to 300 (min/wk)	3.2*** (2.7, 3.7)	3.2*** (2.7, 3.7)
Exercise – 301 to 600 min/week	4.5*** (3.7, 5.3)	4.5*** (3.7, 5.3)
Exercise – over 600 min/week	6.9*** (5.4, 8.4)	6.9*** (5.4, 8.4)
Diabetes	−1.7** (−2.9, −0.5)	−1.7** (−2.9, −0.5)
Constant	*43.3*** (42.7, 43.8)*	*43.3*** (42.7, 43.8)*
Observations	*4.941*	*4.941*
R^2	*0.532*	*0.532*
R^2 adjusted	*0.530*	*0.530*
Residual standard deviation	*7.778 (df = 4922)*	*7.780 (df = 4923)*
Statistical value of the F-test	*311.1*** (df = 18; 4922)*	*329.0*** (df = 17; 4923)*

*p < 0.1.
** p < 0.05.
*** p < 0.01.

week: 3.2 [2.7; 3.7] mL/kg/min; 301 to 600 min/week: 4.5 [3.7; 5.3] mL/kg/min; >600 min/week: 6.9 [5.4; 8.4] mL/kg/min, all p < 0.01).

Additional factors associated with significant reductions in VO_2 peak included age, female sex, use of beta-blockers, antiarrhythmics, and presence of diabetes.

Fig. 1 illustrates the comparison between groups with and without statin use, and between physically active and inactive participants. Fig. 2 presents a graphical representation of the multivariate linear regression model, highlighting key variables such as age, sex, and statin use.

4. Discussion

This study aimed to investigate the association between statin use and cardiorespiratory capacity as evaluated by VO_2 peak during a maximal cardiopulmonary exercise test on a treadmill. Physical activity levels reported by participants were assessed to determine this association. The main findings of our study are as follows: 1) Patients receiving statin treatment exhibit a decline in VO_2 peak; 2) The reduction in VO_2 peak can be alleviated by engaging in at least 150 min of physical activity per week; and 3) Besides statin use, various other factors including age, sex (female), utilization of beta-blockers and antiarrhythmics, and the presence of diabetes, were also found to be significantly associated with a decline in VO_2 peak.

Statins can negatively influence the adaptation of VO_2 peak through two mechanisms. First, they may act directly on the electron transport chain in the mitochondria, increasing the production of reactive oxygen species. Second, they may cause myalgia, thereby reducing adherence to physical activity [4]. Recent studies suggest that in symptomatic statin users, exercise improves quality of life and muscle performance without exacerbating muscle complaints [20,21]. These findings strengthen the idea that exercise training should be encouraged to patients undergoing statin treatment. This strategy based on regular exercise improves symptoms and alleviates the decline in CRF. In addition to enhancing VO_2 peak, exercise training offers further benefits. Exercise has a holistic impact on cardiovascular health, influencing factors such as endothelial function, arterial compliance, and overall cardiovascular fitness. Additionally, it may positively affect lipid profiles, glucose metabolism, and skeletal muscle function [22].

The direct effect of statins on cholesterol production, which is linked to vitamin D synthesis, suggests an association between vitamin D levels and VO_2 peak [23–25]. A randomized clinical trial showed that simvastatin uses attenuated VO_2 peak increase after 12 weeks of exercise training in vitamin D-deficient diabetic patients, indicating that vitamin D supplementation might prevent declines in CRF and mitochondrial function during statin therapy [7]. Although our study did not measure serum vitamin D concentrations, future research should explore this potential association.

Studies that did not show VO_2 peak improvement after exercise training in statin users [26–28] often included participants with diabetes or metabolic syndrome and low vitamin D levels [6,7,29]. Diabetes, which adversely affects skeletal muscle energy function, mitochondrial efficiency, and arteriovenous oxygen difference [30–32], was a significant factor in VO_2 peak attenuation in our study. This underscores the importance of thoroughly evaluating diabetic patients on statin therapy.

Coenzyme Q10 (CoQ10) levels can decrease with statin use, potentially leading to mitochondrial dysfunction and myopathy [4]. Animal studies [5] and clinical trials [33] have shown that CoQ10 supplementation can reverse reductions in aerobic capacity and mitochondrial activity and improve myopathy symptoms, enhancing physical performance and exercise adherence. However, a study by Kuhlman and collaborators [28] found that simvastatin with or without CoQ10 supplementation did not significantly differ in VO_2 peak improvements after 8 weeks of training, highlighting the complexity of statin-exercise-VO_2 peak interactions influenced by various factors like duration of intervention, training intensity, type and dosage of statins, and

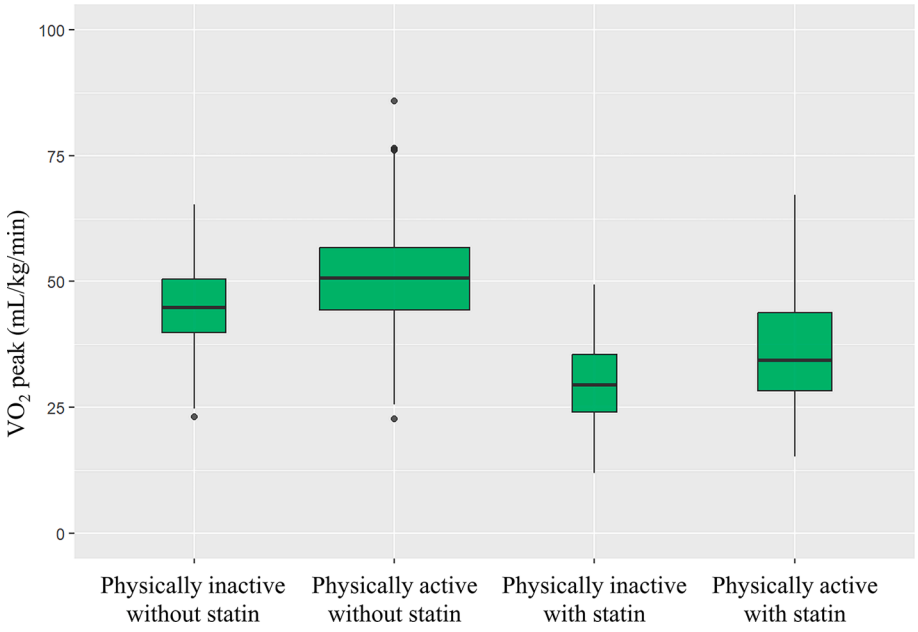

Fig. 1. Comparison between groups with and without the use of statins, physically active and physically inactive.

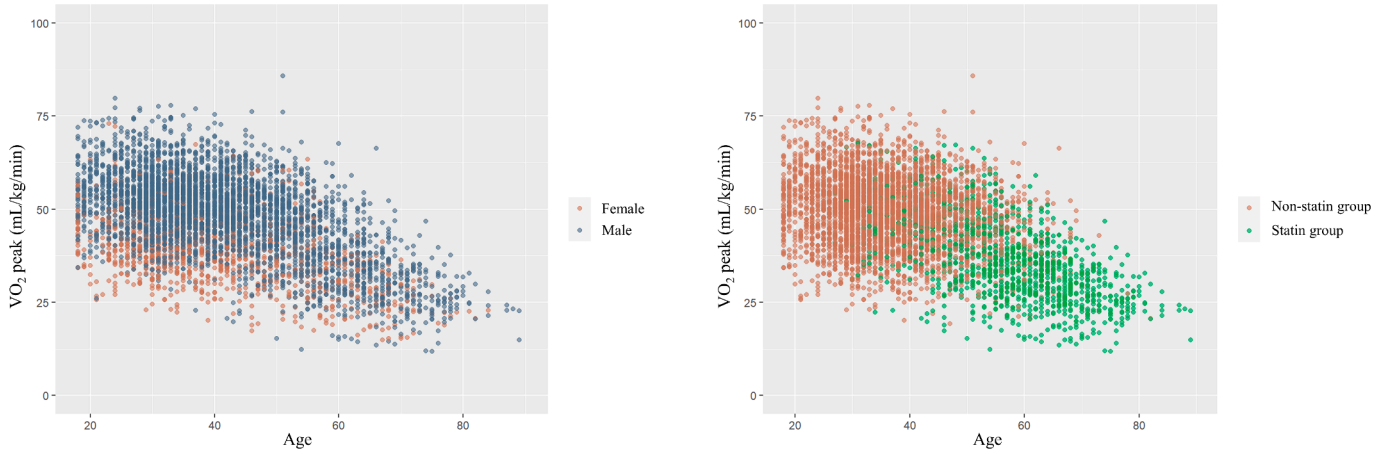

Fig. 2. Graph representation of the multivariate linear regression model (including the most representative variables such as age, sex, and the presence of statin).

individual genetic polymorphisms [4,6,7,26–29].

Beta-blockers [34,35] and antiarrhythmics [36,37], which lower heart rate and reduce cardiac output were also associated with VO_2 peak reduction. Beta-blockers differ in their specific receptor targets and effects on the cardiovascular system, with category 1 beta-blockers affecting multiple organs and category 3 beta-blockers offering additional vasodilatory effects [38]. Our findings indicate that beta-blockers significantly reduce VO_2 peak even in populations without cardiac dysfunction. Similarly, antiarrhythmics had an association with lower VO_2 peak in our sample.

Several additional factors, such as age, sex, and insufficient levels of physical activity were also found to be associated with a decrease in VO_2 peak. Interestingly, our findings indicate that this decline in VO_2 peak was mitigated among participants who engaged in higher weekly volumes of physical activity. Therefore, for patients taking statins, exercise training should be recommended to counteract this adverse effect on CRF. The combination of higher CRF and statin treatment significantly lowers the risk of mortality [39]. In this context, a higher CRF significantly contributes to the maintenance of a favorable lipid profile, potentially leading to a delay in the onset of dyslipidemia, atherosclerosis, and subsequent CVD [40]. Additionally, CVD-related mortality is reduced when CRF levels are higher, regardless of the patient's LDL [41] and HDL levels [42]. A recent *meta*-analysis of cohort studies involving 392,240 participants supports these findings. It demonstrates an inverse relationship between increased CRF and CVD mortality, highlighting the importance of exercise in public health recommendations [43].

5. Strengths and limitations

One of the strengths of our study lies in its large and diverse sample size, encompassing 4,941 participants, which enhances the generalizability of the findings. The rigorous use of maximal cardiopulmonary exercise testing (CPET) provides a precise and objective measure of cardiorespiratory fitness (VO_2 peak), a key indicator of cardiovascular health. Our study also benefits from a robust multivariate analysis, adjusting for critical confounding variables such as age, sex, use of beta-blockers, antiarrhythmics, presence of diabetes, and weekly physical activity levels. Additionally, the investigation into the mitigating effects of physical activity on the statin-associated reduction in VO_2 peak offers valuable insights for clinical practice, highlighting the importance of regular exercise in patients on statin therapy. Furthermore, our study addresses a significant gap in the literature by examining the complex

interplay between statin use, physical activity, and cardiorespiratory fitness, contributing to a deeper understanding of these relationships and providing a foundation for future research.

Our study has several limitations. Firstly, employing a case-control design means that caution is warranted when interpreting causal relationships. Additionally, exclusions due to missing or unclear data regarding exercise type, medications, and clinical conditions reduced our initial sample size. Furthermore, insufficient information prevented analysis of the relationship between lipophilic and hydrophilic statins, as most data pertained to the former class. The inclusion of other medications in the statin group may introduce bias and should be considered when interpreting our findings. The study is limited by the inconsistent and imprecise recording of statin-induced myalgia, which could impact the accurate assessment of VO_2 peak. In a randomized placebo-controlled trial evaluating atorvastatin (a lipophilic drug class), Parker and collaborators did not observe negative impact on muscle strength or exercise performance in healthy, previously untreated subjects [18]. Dosage and duration of statin use could not be determined due to incomplete records. Owing to the retrospective nature of our study, we encountered limitations in data retrieval, particularly regarding atherosclerotic cardiovascular disease (ASCVD) and smoking status. Despite our efforts, we were only able to retrieve ASCVD data for 20 % of our participants. Lastly, reliance on the most recent cardiopulmonary exercise test for participants with multiple records posed a limitation.

6. Conclusions

Statin use is associated with a lower VO_2 peak in adults. Additionally, several other factors, including age, sex, diabetes, use of beta-blockers, and insufficient levels of physical activity (less than 150 min per week) were also associated with a lower VO_2 peak. However, this adverse effect appears to be mitigated by engaging in regular physical activity (>150 min/week). Future research should explore the mechanisms behind this interaction and identify optimal exercise regimens for individuals on statin therapy.

Authors' contributions

MRS, CENP applied for ethics approval, designed the study, drafted and revised the manuscript, created all tables, collected all data, contributed to interpretation of findings. ER contributed to data collection and manuscript revision. CFRR, MOO ran all statistics analysis. FRS, MJNNA, CEN managed patients and contributed to the concept of the study and interpretation of findings. The final version of the manuscript was approved after input was provided by all authors.

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Data are available upon reasonable request.

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CRediT authorship contribution statement

Caio Eduardo Novaes: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Eduardo Rondon:** Writing – review & editing, Supervision, Methodology, Data curation. **Caio Fernando Ribeiro Rizzo:** Writing – review & editing, Formal analysis, Data curation. **Matheus Oscar de Oliveira:** Writing – review & editing, Formal analysis, Data curation. **Francis Ribeiro de Souza:** Writing – review & editing, Validation, Methodology. **Maria-Janieire de Nazaré Nunes Alves:** Writing – review & editing, Validation, Methodology. **Carlos Eduardo Negrão:** Writing – review & editing, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization. **Marcelo Rodrigues dos Santos:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: [Carlos Eduardo Negrao reports financial support and administrative support were provided by University of Sao Paulo Heart Institute. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.].

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