Vigorous Physical Activity as a Risk Factor for Central Serous Chorioretinopathy

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• PURPOSE: To evaluate whether frequent vigorous physical activity (PA) is significantly associated with active central serous chorioretinopathy (CSCR) and may represent a risk factor for CSCR.

• DESIGN: Case-control study.

• METHODS: This was a multicenter study. The patient population comprised consecutive patients with active CSCR and a comparable control group of healthy participants. Both groups were interrogated about their PA using a shortened version of the International Physical Activity Questionnaire. The Ainsworth Compendium of Physical Activities was taken as a reference for the activities requiring vigorous effort and to quantify the energy expended, expressed in metabolic equivalent of task (MET). As a main outcome measure, a moderate/high practice of vigorous PA was opposed to an absent/low practice of vigorous PA in the 2 groups.

• RESULTS: A total of 105 patients with CSCR and 105 healthy controls were included in the study. Moderate/high vigorous PA was observed in 63.5% of the patients with CSCR and in 26% of the controls (P = .0001). The MET values of vigorous PA were 2173.2 ± 2081.5 in the CSCR group and 1216.3 ± 524 in the control group (P = .029). The potential risk of disease associated with moderate/high vigorous PA was 5.58 (odds ratio; 95% confidence interval 3.01-10.69, P = .0001).

• CONCLUSIONS: This study demonstrates a significant association of vigorous PA with CSCR, indicating an increased probability of disease by 5.58 times. Frequent and intense PA, with the hypertensive episodes that it entails, can break the precarious hemodynamic balance in the choroid of individuals predisposed to CSCR, thereby favoring choroidal vascular decompensation and active disease. **(Am J Ophthalmol 2022;244: 30–37.**

Central serous chorioretinopathy (CSCR) is an idiopathic chorioretinal disorder characterized by neurosensory retinal detachment located at the posterior pole associated with retinal pigment epithelium and choroidal alterations.[1] Even if the pathophysiology underlying this disease is not yet clearly defined, there is general consensus in considering the choroid as the site of the primary changes.[2] The existence of an underlying choroidal pathology that eventually leads to the serous macular detachment is demonstrated by a large number of studies, particularly those using indocyanine green angiography (ICGA) and optical coherence tomography (OCT).

In patients with CSCR, ICGA revealed choroidal vascular filling delays, dye leakage from the inner choroid, congestion of veins, and vortex vein anastomosis.[3–5] In the same patients, OCT showed a thickened choroid with dilated choroidal vessels and other structural alteration, which caused CSCR to be included in a spectrum of disorders that share a pachychoroid condition.[6,7] These ICGA and OCT findings can be detected bilaterally in active and inactive disease, attesting to the basic impairment of choroidal vascularity and choroidal blood flow in people affected by CSCR.[3]

A sizable amount of literature has revealed a functional dysregulation of choroidal vasculature in CSCR.[8,9] The authors recently added other experimental findings in support of such a dysfunctional condition by using OCT angiography performed during hand-grip exercise.[10] They observed that an abrupt elevation of blood pressure induced by the isometric stress test increased the blood flow of the choriocapillaris in patients with CSCR but not in a control group of healthy participants. These results are in agreement with the concept that a defect in the mechanisms controlling the homeostasis of choroidal circulation in CSCR makes the vascular district more vulnerable to systemic hemodynamic variations.

Hypertension is already considered a risk factor for CSCR.[11,12] In the aforementioned study by Cardillo Piccolino et al, in which hypertensive patients were excluded, the baseline values of systolic and diastolic blood pressure

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were significantly higher in patients with CSCR than in controls.[10] Moreover, in response to the physical effort, patients with CSCR had a significant greater elevation of blood pressure that reached values definitely in the range of hypertension. We hypothesized that patients with CSCR may have a target vascular tissue in their choroids that is susceptible to hypertension, which may be basal or exercise induced.[10]

Recreational physical activity (PA) is performed with different intensities and frequencies by people within the age range of being at risk for the occurrence of CSCR. We can infer that the episodes of hypertension occurring during a vigorous PA session may have an accentuated hemodynamic impact on the choroidal microcirculation, when compensatory mechanisms are defective, as happens in CSCR, and can produce choroidal damage if protracted for a long time. To the best of our knowledge, vigorous PA was not previously taken into consideration as a risk factor for CSCR.

Therefore, the aim of this study was to evaluate whether frequent and vigorous PA is associated with active CSCR and is able to represent a risk factor for CSCR. We compared the degree of PA performed by patients with CSCR with that performed by an age-, sex-, and education-matched control group, referring to the international guidelines to collect, process, and analyze the obtained data.[13–16]

METHODS

• **STUDY DESIGN:** This was a multicenter, observational, case-control study based on a written survey. The study was performed in accordance with the Declaration of Helsinki and approved by the Institutional Ethics Committees (IEC; central IEC: Hopital Ophtalmique Jules Gonin, Lausanne, Switzerland; Swiss Federal Health Department, Authorization CER-VD 2016-01861). Informed written consent was obtained from patients and controls before enrollment.

Consecutive patients with active CSCR and a control group of healthy subjects were asked about their PA in the previous 12 months using the International Physical Activity Questionnaire (IPAQ) simplified for the purposes of this study.[13] Participants were recruited from February 2019 to February 2020 from the following centers: Fondazione per la Macula Onlus (Genova, Italy), S. Maria Della Misericordia Hospital (Perugia, Italy), Policlinic S.Martino Hospital (Genova, Italy) and Hopital Ophtalmique Jules Gonin (Lausanne, Switzerland).

• **PATIENT POPULATION:** Patients that were diagnosed with active CSCR were enrolled; diagnosis was established on the basis of actual idiopathic serous macular detachment associated with typical fluorescein and indocyanine green angiographic findings and choroidal thickening documented by OCT.

Only those patients who had an onset of new symptoms within the past 6 months were included. Patients who had angiographic signs attributable to polypoidal choroidal vasculopathy were excluded. Other exclusion criteria were concomitant chorioretinal disorders confounding the diagnosis and an age greater than 50 years. Controls were individuals not having any chorioretinal disease or other ocular pathology causing low visual acuity; they were selected by matching for sex, age, and educational level with patients having CSCR, during routine visits to the same center where the related matched CSCR patient had been recruited. Physical disability, obesity, and any other systemic factor that could prevent patients from performing PA were exclusion criteria for enrollment.

• **DATA COLLECTION:** Face-to-face interviews were held by research assistants to gather the data. These data included age, sex, highest educational level completed ("1-4" or ">4" according to the International Standard Classification of Education),[17] use of steroids in the past 12 months, hypertensive state, history of the disease and duration of new visual symptoms, and type, intensity, and frequency of PA usually performed during leisure and occupation starting 6 months before the onset of symptoms. To collect data on PA, we referred to the Compendium of Physical Activities by Ainsworth et al[14–16] and to the guidelines of the IPAQ.[13] We used the short form of the IPAQ questionnaire and the sections related to vigorous-intensity PA. Participants were informed about the meaning of "vigorous-intensity" PA; it was defined as "that activity which requires hard physical exertion and that makes you breathe at a much more frequent rate than normal."[12] For each of the specific activities requiring vigorous effort, participants were asked about how many minutes per day per week they performed this kind of activity, in a typical week of the considered period.

• **DEFINITION OF LEVEL OF PHYSICAL ACTIVITY:** The Compendium of Physical Activities by Ainsworth et al, along with its updates, was taken as a reference for considering the activities that may require vigorous effort.[13–15] To each type of activity, the Compendium associates the values of energy requirements expressed in metabolic equivalent of task (MET). The MET values are defined as the ratio of the working metabolic rate relative to a standard resting metabolic rate of 1 kcal/kg per hour. One MET is considered the energy cost of a person at rest. The form used to collect data was taken from the short version of the IPAQ, by extrapolating the portion relating to the vigorous type of PA.[13] Adhering to the simplification proposed by the IPAQ guidelines, we attributed a value of 8.0 METs per minute to all types of vigorous-intensity PA.[13] A measure of the volume of activity was computed on the basis of the MET-minutes per week. In accordance with the IPAQ guidelines, the vigorous PA of participants was categorized into 3 levels: level 1, labeled "none or casual," referred to a PA that

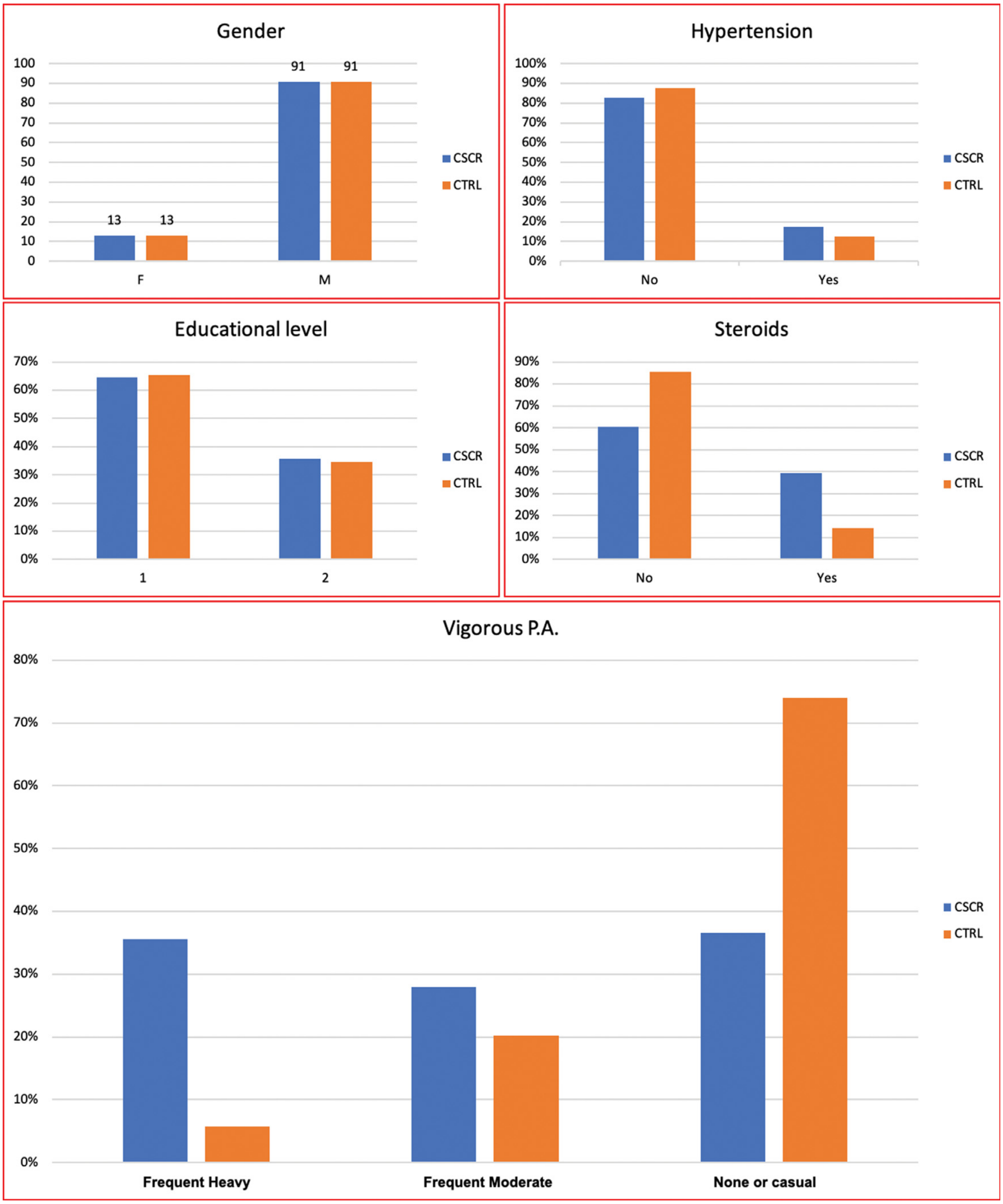

FIGURE 1. Histograms depicting the distribution of patients with CSCR and healthy controls with respect to the following factors: sex, hypertension, educational level, steroid use, and vigorous physical activity. CSCR = central serous chorioretinopathy; CTRL = healthy control; F = female; M = male; PA = physical activity; 1 = graduated; 2 = not graduated.

did not meet criteria for levels 2 and 3; level 2, labeled "frequent moderate," referred to 3 or more days per week of vigorous-intensity PA of at least 20 minutes per day, with a total score less than 1500 MET-minutes per week; level 3, labeled "frequent heavy," described a vigorous-intensity PA for at least 20 minutes per day, for at least 3 days per week, achieving a minimum total of at least 1500 MET-minutes per week. The CSCR group was compared with the control group based on the category level of PA of participants. Categories 2 and 3, corresponding to a moderate/high practice of vigorous PA, were opposed to category 1, corresponding to an absent or low practice of vigorous PA.

• **STATISTICAL ANALYSIS:** The collected quantitative data were presented in tables as the mean and SD. In case of qualitative variables, data were reported as percentages.

TABLE 1. Distribution of Different Levels of Physical Activity Among Patients With CSCR and Healthy Controls.

Level of Physical Activity	CSCR Patients	Controls	Total	*P* Value, CSCR Patients vs Controls
Frequent heavy	35.58%	5.77%	20.67%	.0001
Frequent moderate	27.88%	20.19%	24.04%	.0001
None or casual	36.54%	74.04%	55.29%	.0001
Total	100%	100%	100%	

CSCR = central serous chorioretinopathy.

TABLE 2. Metabolic Equivalent of Task (MET) Values for Different Levels of Physical Activity Performed by Patients With CSCR and Healthy Controls.

Level of Physical Activity	CSCR Patients		Controls		*P* Value, CSCR Patients vs Controls
	Mean	SD	Mean	SD	
Frequent heavy	3113.7	2377.2	1986.7	483.8	.021
Frequent moderate	973.1	363.0	996.2	263.8	NS
Total (MET)	2173.2	2081.5	1216.3	524.0	

CSCR = central serous chorioretinopathy; NS = not significant.

TABLE 3. Distribution of Different Types of PA in Patients With CSCR and Healthy Controls

Type of PA	CSCR Patients n (%)	Controls n (%)	*P* Value
Weight lifting	18 (17.14%)	5(4.76%)	.0080
Bicycling	16(15.23%)	4(3.80%)	.0097
Running	11(10.47%)	5(4.76%)	NS
Swimming	7(6.66%)	0	NS
Gym	5(4.76%)	2(1.90%)	NS
Boxing	2(1.90%)	0	NS
Soccer	1(0.95%)	1(0.95%)	NS
Martial arts	1(0.95%)	0	NS
Skiing	1(0.95%)	1(0.95%)	NS
Rugby	1(0.95%)	0	NS
Heavy carpentry	1(0.95%)	0	NS
Forestry	1(0.95%)	0	NS
Basket	1(0.95%)	0	NS
Tennis	0	4(3.80%)	NS
Rowing	0	2(1.90%)	NS
Squash	0	1(0.95%)	NS
TOTAL	105(100%)	105(100%)	

CSCR = central serous chorioretinopathy; NS = not significant.

Some variables were represented graphically. For quantitative data, the Kolmogorov—Smirnov test was used to determine whether the data were normally distributed. Based on the result, the *t* test and the Wilcoxon (Mann—Whitney *U*) test were used to verify the differences between the 2 groups. The logistic regression and odds ratio was computed to determine the potential correlation between risk factors and the presence/absence of the disease. The analysis was performed with SAS 9.2 for Windows (SAS Institute Inc). The significance level was set at $P < .05$.

RESULTS

A total of 105 CSCR patients (13 female) and 105 healthy controls (13 female) were included in the study. The mean (±SD) age was 43.2 ± 7.4 years for CSCR patients and 43.1 ± 7.9 years for healthy controls ($P = .9423$). No statistically significant differences were observed in terms of educational level ($P > .99$) between the 2 groups (Figure 1). No patients or controls had been treated for ob-

TABLE 4. Estimation of Risk Factors in the Development of CSCR

Potential Influencing Factor for CSCR Development	Odds Ratio	*P* Value	95% CI
Vigorous PA	5.58	.0001	3.01-10.69
Steroids	4.76	.0001	2.24-9.78
Hypertension	1.33	.522	—

CSCR = central serous chorioretinopathy; PA = physical activity.

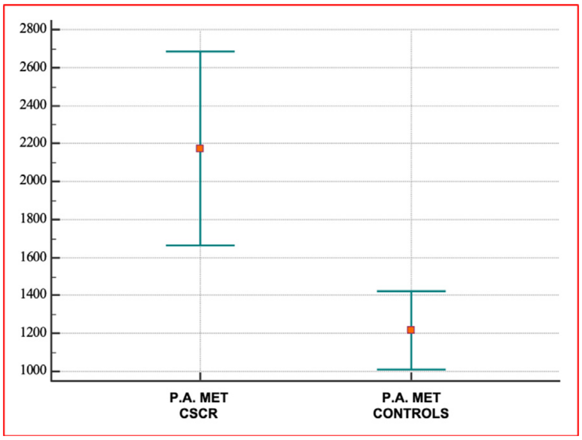

FIGURE 2. Differences in terms of physical activity expressed in metabolic equivalent of task (MET) values in patients with CSCR and in healthy controls. CSCR = central serous chorioretinopathy; MET = metabolic equivalent of task; PA = physical activity.

structive sleep apnea. Only 8 of the CSCR patients had first-episode disease with symptoms lasting for less than 4 months. In the other cases, it was a recurrent and/or chronic disease.

A vigorous PA (Frequent Heavy + Frequent Moderate) was observed in 63.5% of patients with CSCR and in 26% of controls ($P = .0001$). A significant difference was also detected between the 2 groups when frequent heavy and frequent moderate, and none/casual vigorous PA were examined separately ($P = .0001$) (Table 1).

The MET values of vigorous PA were 2173.2 ± 2081.5 in the CSCR group and 1216.3 ± 524 in the control group ($P = .029$) (Table 2, Figure 2).

Weight lifting, bicycling, and running were the most frequent PAs in both groups, with higher percentages of frequency in the CSCR patients. Differences between the 2 groups were statistically significant for weight lifting and bicycling (Table 3).

In the CSCR group, 17.3% of patients had treated hypertension as compared with 12.5% in the control group (Figure 1); this difference was not statistically significant ($P = .44$). Previous use of steroids was significantly more widespread in CSCR patients compared to controls (39.4% vs 14.4%, $P = .0001$).

Table 4 reports the disease risk estimation associated with hypertension, use of steroids, and vigorous PA. The logistic regression test showed an exponential value of B (odds ratio) of 4.76 (95% CI = 2.24-9.78, $P = .0001$) for steroids and 5.58 (95% CI = 3.01-10.69, $P = .0001$) for vigorous PA.

DISCUSSION

During strenuous physical exercise, the increased metabolic demand in the working muscles is fulfilled by local vasodilation and increased blood flow. An immediate boost of sympathetic activity produces increased heart rate and strengthening of the cardiac output. The latter ends up overcoming the increased vascular compliance in the active muscle districts, leading to an overall elevation of blood pressure.[17] The present study was based on the hypothesis that frequent and intense PA, with the hypertensive episodes that it entails, can break the precarious hemodynamic balance in the choroid of individuals predisposed to CSCR, thereby favoring choroidal vascular decompensation and active disease.

We specifically investigated the association between PA of vigorous intensity—which is connected to a more significant elevation of blood pressure[18]—and CSCR. To define and classify vigorous PA and to give it a quantitative value, we referred to the Compendium of Physical Activities by Ainsworth et al and its updates, in which the specific activities were categorized by rate of energy expenditure expressed in MET units.[13–15] The compendium is widely accepted in sports and exercise sciences and in public health fields.

The case-control comparative evaluation demonstrated a significant association of vigorous PA with CSCR. The odds ratio indicated that vigorous PA (heavy or moderate level) increases the risk of disease by 5.58 times. The use of corticosteroids is widely recognized as a risk factor for the onset and exacerbation of CSCR.[18] In the present study, the risk of disease appeared to be 4.76 times increased with steroid use, lower than the risk value attributable to vigorous PA. These 2 factors appeared to be independent.

We found that patients with CSCR, in comparison with controls, consumed a significantly greater amount of energy every week as a consequence of high-intensity physical exercise that was performed mostly in leisure time. Only for 2 patients, the prevalent vigorous PA was connected to a job requiring high muscular effort (forestry, carpentry). Weight lifting and bicycling were the PAs more frequently performed by patients with CSCR, with a significantly higher percentage than in controls. Weight lifting predominantly involves isometric muscle contraction (resistance training) that is particularly correlated with sharp elevation of both systolic and diastolic blood pressure.[19] In addition, during weight lifting, extremely high values of blood pressures can be reached as an effect of the Valsalva maneuver.[20] Bicycling, when performed with an intense level of exertion, also entails an elevated amount of isometric exercise.[19] Vigorous resistance training has been shown to be associated with unfavorable cardiovascular effects, ending in an increase in arterial stiffness and ventricular wall hypertrophy.[21] It could produce similar organ damage in the choroid in the form of pachychoroid, with possible consequent active CSCR.

Hypertension is a recognized risk factor for CSCR.[11,12] Even without frank hypertension, higher baseline values of blood pressure can be found in patients with CSCR with respect to normal controls.[10] During an isometric hand-grip exercise, these values rise further, easily reaching the range of hypertension.[10] Exercise-induced hypertension (EIH) observed in healthy individuals with apparently normal blood pressure is a condition that is attracting increasing attention for its significant correlation with cardiovascular events, left ventricular hypertrophy, and cardiac injury.[22–24] EIH seems to be relatively common in active individuals and athletes and is favored by a higher resting blood pressure.[22] It is explained by a failure of the physiological protective sympatholytic effect that follows the first exercise-induced sympathetic vasoconstriction to counteract excessive increases in arterial blood pressure. Underlying mechanisms of EIH seem to include high sympathetic tone and increased activation of the renin—angiotensin—aldosterone system.[22–25] Moreover, it was experimentally observed that mineralocorticoid receptor antagonists attenuate the exercise hypertensive response.[26] The activation of the aldosterone/mineralocorticoid receptor pathway has also been called into question as a promoter of CSCR and choroidal vasculopathy.[27] All of these observations considered together led us to assume that patients with CSCR may fall into the category of EIH. This should be confirmed by using dynamic tests such as treadmill or bicycle ergometer, which were used to define EIH.

In patients with CSCR who are characterized by type A personality and sympathetic hyperactivity,[28,29] frequent vigorous PA could further worsen an already unstable hemodynamic condition, producing repetitive hypertensive episodes and a *de facto* hypertensive state that can fall under the definition of "blood pressure variability."[30–32] The latter is considered to be a particular phenotype of hypertension and is associated with a specific risk of organ damage similar to that of stable hypertension.[32] For individuals with defective choroidal vascular compensatory mechanisms such as those affected by CSCR, the choroid could be a target organ for possible damage.[8–10] The structural alterations detected by ICG and OCT in the choroid of these patients could be the depiction of this damage.

Several risk factors have been called into question for CSCR, and different pathophysiologic patterns have been hypothesized to be at the basis of the disease.[33] Spaide et al have recently described CSCR as a "venous overload choroidopathy" in which everything originates from an abnormality of the venous outflow from the eye, owing to scleral thickening and increased local resistances.[34] The present study offers elements to delineate a pathophysiologic model of CSCR, whereby a choroidal venous overload may be progressively produced by a frank or variable hypertension (also exercise induced) in presence of inadequate mechanisms of organ protection in the choroid.[10] The enhanced arterial input to the eye could lead to the progressive increase in the blood volume in the choroidal vessels, favored by the bottleneck effect—to which the venous outflow through the sclera is subjected, even in the absence of scleral abnormalities.[35] However, we cannot exclude a multifactorial involvement and the overlap of different pathophysiologic mechanisms, particularly when the disease evolves chronically.

This study had some limitations. First, the reliability of a data collection using questionnaires is not very high. This possible bias was minimized by the use of the synthetic version of a well-tested PA questionnaire validated by the World Health Organization and already used in several studies to evaluate the risk of the PA in other diseases.[36,38] Second, there may have been an interview bias, although we undertook measures to minimize it by entrusting the interviews to research assistants who were not involved in the design of the study and the analysis of the results. Third, hyperopia and other factors that have been associated with CSCR were not considered for adjustment of our results and could be cause of a bias.[37] They should be considered in future larger studies to better delineate the disease risk to be attributed to PA. Finally, there is a possibility of a residual confounding effect, owing to the presence of those factors that were not considered, which is attributable to any observational study.

In conclusion, this study provides evidence for a significant association between vigorous PA and CSCR, showing that vigorous PA may be a relevant risk factor for the disease. Our observations run counter to the generally accepted notion that PA has health benefits and is important in chronic disease prevention.[36] Considering how frequently young adults indulge in sports and leisure-time PA, further studies, possibly longitudinal, should be undertaken to define their impact on the occurrence of CSCR. It also remains to be clarified whether PA can influence phenotypes and duration of the disease. The effective dose—response relationship of PAs with CSCR should be further investigated, as well as the role of specific sports and activities in favoring a choroidal impairment or the disruption of an already precarious hemodynamic equilibrium in the choroid.[8–10]

DATA AVAILABILITY STATEMENT

Deidentified datasets generated/analyzed in the present study will be available upon reasonable request to the corresponding author.

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