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A Nationwide Cohort Study on the Association Between Past Physical Activity and Neovascular Age-Related Macular Degeneration in an East Asian Population

Tyler Hyungtaek Rim, MD, MBA; Hong Kyu Kim, MD; Ji Won Kim, MD; Jihei Sara Lee, MD; Dong Wook Kim, PhD; Sung Soo Kim, MD, PhD

IMPORTANCE It has been suggested that physical activity (PA) is associated with reduced risk for early age-related macular degeneration (AMD). Systematic evaluation has been examining the association between lifestyle and neovascular AMD in an East Asian population, with a particular focus on past vigorous PA.

OBJECTIVE To investigate the association between neovascular AMD and past PA, particularly a history of vigorous exercise, in the overall study population and among 2 a priori–defined subgroups.

DESIGN, SETTING, AND PARTICIPANTS In this propensity score–matched cohort study, individuals between ages 45 and 79 years who were included in the South Korean National Health Insurance Service database from 2002 through 2013 were evaluated. Physical activity and incident neovascular AMD were recorded at baseline (2002-2003) and at follow-up (August 1, 2009, to December 31, 2013), respectively. Using a 1:1 propensity score-matched analysis, the incidence of neovascular AMD was compared using hazard ratios (HRs) for neovascular AMD between 105 980 participants who did and 105 980 who did not (no-PA) engage in vigorous PA. The data analysis was performed from April 19, 2017, to June 5, 2017.

EXPOSURES Physical activity.

MAIN OUTCOMES AND MEASURES Incident cases of neovascular AMD.

RESULTS Of the 211 960 participants (92 036 [43.4%] women; mean [SD] age, 55.1 [7.8] years), neovascular AMD was detected at follow-up in 250 (0.24%) individuals who engaged in past vigorous PA and in 198 (0.19%) of those who did not (HR, 1.23; 95% CI, 1.02-1.49). In subgroup analysis, vigorous PA was associated with a greater HR for neovascular AMD in participants aged 45 to 64 years (HR, 1.30; 95% CI, 1.04-1.63) and in men (HR, 1.36; 95% CI, 1.09-1.69). In the high-PA (≥5 times/wk: HR, 1.54; 95% CI, 1.15-2.06) and moderate-PA (1-4 times/wk: HR, 1.28; 95% CI, 1.01-1.63) groups, there was a greater incidence of neovascular AMD in the vigorous PA than in the no-PA group for men; no association was found for women.

CONCLUSIONS AND RELEVANCE Self-reported past vigorous PA in men aged 45 to 64 years was associated with an increased risk for neovascular AMD. To our knowledge, no previous study has reported such an association; replication of the results would seem warranted to strengthen the likelihood of a cause and effect relationship.

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Invited Commentary
Supplemental content

Author Affiliations: Department of Ophthalmology, Severance Hospital, Institute of Vision Research, Yonsei University College of Medicine, Seoul, South Korea (Rim, H. K. Kim, J. W. Kim, Lee, S. S. Kim); Department of Policy Research Affairs, National Health Insurance Service Ilsan Hospital, Goyang, Gyeonggi-do, South Korea (D. W. Kim); Yonsei Healthcare Big Data Based Knowledge Integration System Research Center, Yonsei University College of Medicine, Seoul, South Korea (S. S. Kim); Institute of Convergence Science, Yonsei University College of Medicine, Seoul, South Korea (S. S. Kim).

Corresponding Author: Sung Soo Kim, MD, PhD, Department of Ophthalmology, Severance Hospital, Institute of Vision Research, Yonsei University College of Medicine, 50 Yonsei-ro, Seodaemun-gu, Seoul 03722, South Korea (semekim@yuhs.ac).

Neovascular age-related macular degeneration (AMD) is the leading cause of blindness in developed countries.[1] Its incidence is increasing, particularly in Asia, where more than one-half of individuals with AMD globally are projected to reside by 2040.[1] Smoking cessation is generally accepted to be a modifiable lifestyle risk factor for reducing the risk of neovascular AMD.[2-4] Physical activity (PA) is one of the most frequently evaluated positive influential factors for health and can lower morbidity and mortality.[5] Because there are no effective means of primary prevention of AMD other than smoking cessation, other modifications to lifestyle, including changes in PA, acquire more importance.

The incidence of neovascular AMD is low; consequently, longitudinal studies evaluating the association between PA and neovascular AMD are scarce.[6-9] Current evidence regarding the influence of PA on neovascular AMD is inconclusive: sample sizes in some studies have been too small to have adequate statistical power,[7-9] some have reported a protective association,[6,10] and others have shown no association[7,8] or varying associations according to sex.[9,11]

Previous case-control studies[10,11] and cross-sectional studies[12] that investigated the causal associations of current PA with AMD[13] may have some drawbacks. There is a possibility of reverse causality between exposure and outcome because fear of falling is predictive of reduced PA[14] and AMD-associated vision loss is associated with fear of falling.[15] Against this background, large, adequately powered longitudinal studies with sufficient numbers of participants with incident neovascular AMD as well as a PA history are required to assess the association of PA with AMD adequately.

The National Health Insurance Service (NHIS) database of South Korea provides a unique opportunity for evaluation of the development of neovascular AMD among the general population according to PA history. Systematic evaluation of the association between lifestyle and neovascular AMD using the NHIS database has previously confirmed smoking as a risk factor for neovascular AMD.[16] In the present study, we evaluated the association between neovascular AMD and past PA, particularly a history of vigorous exercise, in a propensity score–matched sample comprising 211 960 individuals selected from the South Korean NHIS.

Key Points

Question How are healthy lifestyle and frequent vigorous physical activity associated with the onset of neovascular age-related macular degeneration?

Findings In a propensity score–matched cohort of 211 960 participants, self-reported past vigorous physical activity in men aged 45 to 64 years of age was associated with an increased risk for neovascular age-related macular degeneration, compared with the no physical activity group.

Meaning These findings cautiously suggest that physical activity may be a predictive factor for neovascular age-related macular degeneration; however, because there is no strong biological rationale for this finding to date, further studies that replicate these findings would seem warranted to strengthen the likelihood of a cause and effect relationship.

Methods

Database

The South Korean NHIS developed the Health Screening Cohort for research purposes. The Health Screening Cohort database includes approximately 510 000 randomly selected individuals aged 40 to 79 years who were enrolled in the South Korean National Health Screening Program in 2002 and 2003. These selected participants were followed up until 2013. The data include variables regarding health care utilization, health screening, and sociodemographic factors; a detailed cohort profile has been published previously.[17] The study protocol was approved by the institutional review board of Severance Hospital, Yonsei University College of Medicine, Seoul, South Korea, and informed consent was waived.

Study Cohort

At baseline (2002-2003), participants attended the National Health Screening Program in which demographic and lifestyle information, including that on PA, was collected and anthropometric measurements were performed. Individuals who met the following eligibility criteria were included in the present study: response to questions regarding PA; age 45 to 79 years in 2002; and available data regarding continuous variables, including body mass index (BMI [calculated as weight in kilograms divided by height in meters squared]), blood pressure, and other variables, except for age, within the top and bottom 1%. Patients exhibiting any stage of AMD based on diagnostic code in 2002 and 2003 were excluded. A detailed diagram of the study population and those excluded is presented in **Figure 1**.

Propensity score matching of the study cohort was performed according to propensity scores based on 42 potential baseline confounders, including age, medical history and examination results, history of prescription drug use, and utilization of medical care (variables in the eTable in the Supplement). Details regarding diagnostic codes for comorbidity are provided elsewhere.[16]

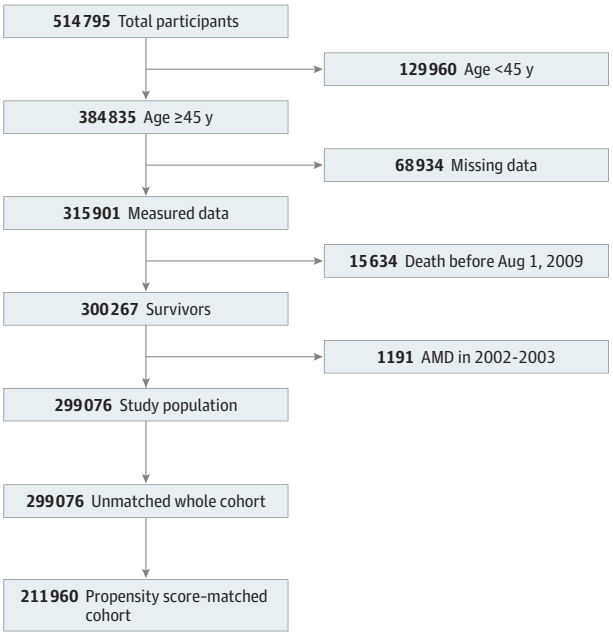
PA Status

The South Korean National Health Screening Program used a standardized questionnaire for ascertaining PA status.[18] Participants were asked the question, "On average, how many times a week do you exercise vigorously? 'Vigorously' means 'making you sweat.'" Possible responses were never, 1 to 4 times, or 5 or more times per week. Participants were classified into 1 of 2 groups (no-PA or PA) according to their responses. For evaluation of a dose-dependent association, individuals in the PA group were further subdivided according to whether exercise was performed 1 to 4 times (moderate-PA) or 5 or more times (high-PA) per week.

Follow-up and Study End Points

Participants who enrolled between 2002 and 2003 were followed up from August 1, 2009, until the date of the first instance of 1 of the following factors: loss to follow-up because

Figure 1. Study Population



Of the unmatched whole cohort, 173 437 were not physically active and 125 639 were physically active. Of the propensity score–matched cohort, 105 980 were not physically active and 105 980 were physically active. AMD indicates age-related macular degeneration.

of disqualification by the NHIS (mainly death), incidence of neovascular AMD, or last visit to any medical care facility within the end of the study period (December 31, 2013) (eFigure in the Supplement). If enrolled participants did not visit any medical practitioner throughout the study period, the database did not include information about disease. The primary end point of the study was the incidence of neovascular AMD. For incidence estimates, the date of the earliest claim with the registration code and ranibizumab use was defined as the index date. Registration of a copayment assistance policy and ranibizumab use for treatment of newly diagnosed neovascular AMD in South Korea has been described in detail elsewhere.[16,19] Briefly, from August 1, 2009, onward, patients with neovascular AMD benefited from a copayment assistance policy from the NHIS in which patient expenses were decreased to 10% of the total cost. The South Korean Health Insurance Review and Assessment Service reviews the necessity of ranibizumab use based on the findings of fundus photography and fluorescein angiography and reimburses 90% of the cost to the medical practitioner. Therefore, ranibizumab use from August 1, 2009, indicated a diagnosis of recently developed active (wet) neovascular AMD by an ophthalmologist.

Statistical Analysis

A propensity model for vigorous PA (yes/no) was developed. Propensity scores for individuals in the PA group were estimated using logistic regression of 42 potential confounders (eTable in the Supplement). The PA group and no-PA group were then matched according to propensity scores in a 1:1 ratio based on 8→1 digit matching. Descriptive statistical analysis of the entire and propensity score–matched cohorts was performed to estimate the incidence of neovascular AMD per 10 000 person-years, as well as age- and sex-adjusted hazard ratios (HRs) from Cox proportional hazards regression models. Cumulative incidence of neovascular AMD from August 1, 2009, to December 31, 2013, was described using a Kaplan-Meier survival curve.

Dose-dependent association between PA status and neovascular AMD was evaluated from data obtained from the propensity score–matched cohort. In the study design phase, subgroups were defined using the baseline characteristics of the age and sex subgroups.[20,21] Furthermore, BMI is affected by PA and is considered a risk factor of neovascular AMD.[22] Thus, post hoc subgroup analyses of 2 groups divided by median BMI value (23.88 [interquartile range, 21.97-25.85]) among the total database were also performed (eAppendix 1 in the Supplement). Statistical significance was set at a level of .05. Analyses were performed from April 19, 2017, to June 5, 2017, using SAS, version 9.4 (SAS Institute Inc) and Stata/MP, version 14.0 (StataCorp).

Sensitivity analyses for PA, the International Physical Activity Questionnaire,[18] and survival bias, competing risk analysis, and survivor average causal association[23] analysis were performed in men aged 45 to 64 years. Detailed methods and results are provided in eAppendixes 2 to 4 in the Supplement.

Results

Characteristics of the Study Cohort

A total of 299 076 participants met the inclusion criteria, including 173 437 participants in the no-PA group and 125 639 in the PA group (**Table 1** and eTable in the Supplement). Patient demographic and clinical characteristics in the entire unmatched cohort varied between the 2 groups. Participants in the PA group were more likely to be younger and exhibit fewer instances of comorbid conditions or use of medical care than those in the no-PA group. However, the incidence of neovascular AMD was higher in the PA group (299 [0.24%]) than in the no-PA group (326 [0.19%]) (P = .003).

After 1:1 propensity score matching, a total of 211 960 participants, including 105 980 from the no-PA and PA groups, were included in the analysis (Table 1). In the propensity score–matched cohort, all variables except the incidence of AMD were similar between the 2 cohorts; the incidence of neovascular AMD was higher in the PA group (250 [0.24%]) than in the no-PA group (198 [0.19%]) (P = .01).

Incidence of Neovascular AMD According to PA Status

Table 2 presents the HRs for neovascular AMD in the matched cohorts. The risk for neovascular AMD among the PA group was significantly higher than that among the no-PA group in propensity score–matched cohorts (age- and sex-adjusted HR, 1.23; 95% CI, 1.02-1.49). The risk for neovascular AMD in the age subgroups (45-64 and 65-79 years) exhibited a similar result; however, HRs for the younger subgroup were greater than those

Table 1. Baseline Characteristics of the Study Population

Characteristic	Unmatched Cohort (n = 299 076)		Propensity Score–Matched Cohort (n = 211 960)	
	No Physical Activity (n = 173 437)	Physical Activity (n = 125 639)	No Physical Activity (n = 105 980)	Physical Activity (n = 105 980)
Neovascular AMD, No. (%)	326 (0.19)	299 (0.24)	198 (0.19)	250 (0.24)
Age, mean (SD), y	56.6 (8.4)	54.6 (7.6)	55.1 (7.8)	55.1 (7.8)
BMI, mean (SD)	24.0 (2.8)	24.2 (2.6)	24.1 (2.6)	24.2 (2.6)
Systolic blood pressure, mean (SD), mm Hg	128.3 (17.5)	128.2 (16.8)	128.1 (17.1)	128.1 (17.1)
Diastolic blood pressure, mean (SD), mm Hg	79.8 (10.9)	80.4 (10.8)	80.1 (10.9)	80.1 (10.8)
Charlson Comorbidity Index, mean (SD)	0.6 (1.0)	0.5 (1.0)	0.5 (1.0)	0.5 (1.0)
Annual medical care visits, mean (SD), No.	2.3 (1.3)	2.2 (1.3)	2.2 (1.3)	2.2 (1.3)
Annual ophthalmologist visits, mean (SD), No.	1.1 (0.4)	1.1 (0.4)	1.1 (0.4)	1.1 (0.4)
Women, No. (%)	96 333 (55.5)	47 312 (37.7)	46 068 (43.5)	45 968 (43.4)
Smokers, No. (%)	45 695 (26.3)	44 142 (35.1)	33 912 (32.0)	34 219 (32.3)
Hypertension, No. (%)	32 613 (18.8)	23 892 (19.0)	19 737 (18.6)	19 770 (18.7)
Cerebrovascular disease, No. (%)	3491 (2.0)	2361 (1.9)	1976 (1.9)	2050 (1.9)
Liver disease, No. (%)	9911 (5.7)	7764 (6.2)	6450 (6.1)	6323 (6.0)
Uncomplicated diabetes, No. (%)	10 483 (6.0)	9312 (7.4)	7258 (6.9)	7291 (6.9)
Complicated diabetes, No. (%)	3318 (1.9)	3020 (2.4)	2362 (2.2)	2335 (2.2)
Prescription drug use in 2002-2003, No. (%)				
Antidiabetes medication				
Metformin	5269 (3.0)	4769 (3.8)	3736 (3.5)	3713 (3.5)
Sulfonylurea	7462 (4.3)	6778 (5.4)	5285 (5.0)	5247 (5.0)
α-Glucosidase inhibitors	2488 (1.4)	2229 (1.8)	1776 (1.7)	1736 (1.6)
Antihypertensives				
Angiotensin II receptor antagonist	7536 (4.3)	6531 (5.2)	5098 (4.8)	5178 (4.9)
Angiotensin-converting enzyme inhibitor	13 055 (7.5)	9949 (7.9)	8122 (7.7)	8113 (7.7)
Calcium channel blocker	29 354 (16.9)	21 140 (16.8)	17 639 (16.6)	17 604 (16.6)

Abbreviations: AMD, age-related macular degeneration; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).

for the older subgroup. This association was different between the sexes, as it was only observed in men (age-adjusted HR for men, 1.36; 95% CI, 1.09-1.69; age-adjusted HR for women, 0.90; 95% CI, 0.62-1.32). The Kaplan-Meier survival curve demonstrated a clear difference in the incidence of neovascular AMD between the no-PA and PA groups in men (**Figure 2**A).

Hazard ratios for the high-PA group were greater than those for the moderate-PA and no-PA groups in the propensity score-matched cohort (HR for high-PA, 1.38 [95% CI, 1.07-1.79]; HR for moderate-PA, 1.17 [95% CI, 0.95-1.44]) (**Table 3**). In the sex-based subgroup analyses, a dose-dependent relationship was shown in men (HR for high-PA, 1.54 [95% CI, 1.15-2.06]; HR for moderate-PA, 1.28 [95% CI, 1.01-1.63] CI; $P = .002$ for trend) but not in women. This result was also reflected in the survival curve for cumulative incidence of neovascular AMD in Figure 2B.

eAppendix 1 in the Supplement summarizes BMI-based subgroup analyses in terms of the dose dependence of PA for the risk of neovascular AMD among men aged 45 to 64 years. In terms of the level of PA, in men with a BMI less than 23.88, the risk for neovascular AMD was greater in the high-PA group (HR, 2.53; 95% CI, 1.46-4.40), and a trend was also observed (HR, 1 for no-PA group as a reference group; HR, 1.88 for PA 1-4 times/wk; HR, 2.53 for PA ≥5 times/wk; $P < .001$ for trend). The sensitivity analyses are provided in eAppendixes 2 to 4 in the Supplement.

Discussion

The present study investigated the association between past vigorous PA and prospective development of neovascular AMD in a nationwide sample of 211 960 matched participants (888 466 person-years). It is generally understood that PA tends to have a positive association with health, including, but not limited to, cardiovascular disease. We revealed an unexpected association between higher levels of vigorous PA and an increased risk for neovascular AMD in men; no association was found for women. In men between ages 45 and 64 years, a clear dose-dependent relationship between intensity of past vigorous PA and neovascular AMD was observed, which was particularly pronounced among the relatively slender group (BMI <23.88).

To our knowledge, few studies have focused on past vigorous PA in association with neovascular AMD, and the con-

Table 2. Incidence of Neovascular AMD in Primary and Subgroup Analyses

Analysis	Propensity Score–Matched Cohort	
	No Physical Activity (n = 105 980)	Physical Activity (n = 105 980)
Primary analysis		
Total follow-up, person-years	443 810	444 655
Neovascular AMD, No.	198	250
Incidence, No. per 10 000 person-years	4.5	5.6
HR (95% CI)	1 [Reference]	1.23 (1.02-1.49)
P value	NA	.03
Subgroup analysis		
Age 45-64 y	*P* = .44 for interaction	
Total follow-up, person-years	384 777	384 084
Neovascular AMD, No.	131	170
Incidence, No. per 10 000 person-years	3.4	4.4
HR (95% CI)	1 [Reference]	1.30 (1.04-1.63)
P value	NA	.02
Age 65-79 y		
Total follow-up, person-years	59 034	60 571
Neovascular AMD, No.	67	80
Incidence, No. per 10 000 person-years	11.3	13.2
HR, (95% CI)	1 [Reference]	1.10 (0.79-1.52)
P value	NA	.57
Men	*P* = .003 for interaction	
Total follow-up, person-years	247 577	248 562
Neovascular AMD, No.	140	199
Incidence, No. per 10 000 person-years	5.7	8.0
HR (95% CI)	1 [Reference]	1.36 (1.09-1.69)
P value	NA	.006
Women		
Total follow-up, person-years	196 233	196 093
Neovascular AMD, No.	58	51
Incidence, No. per 10 000 person-years	3.0	2.6
HR (95% CI)	1 [Reference]	0.90 (0.62-1.32)
P value	NA	.62

Abbreviations: AMD, age-related macular degeneration; HR, hazard ratio; NA, not applicable.

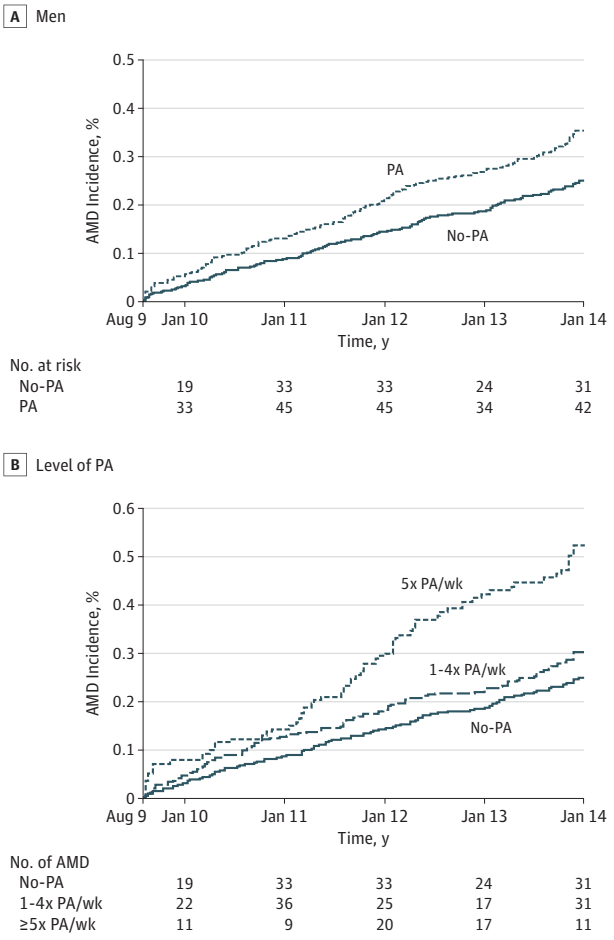
clusion remains unclear. Regular PA is generally accepted as a lifestyle factor for improving health, particularly cardiovascular health; however, the findings of this study suggest otherwise. Furthermore, this negative association between past vigorous PA and neovascular AMD was limited to men. The results of this study should be interpreted carefully given the lack of a strong biological rationale, the possibility of uncontrolled confounding factors, and the focus on a single East Asian country.

Because we balanced many confounding factors between the PA and no-PA groups in this propensity score–matched analysis, our control group was relatively healthy even though they did not exercise regularly. In particular, our control group comprised participants who had a relatively healthy BMI (24.1 and 24.2 in the PA and no-PA groups, respectively), healthy physical examination values, relatively few comorbid conditions (Charlson Comorbidity Index, 0.5), and relatively less frequent use of medical resources (Table 1). The most important risk factor for neovascular AMD is age, and the fact that the no-PA group had a healthy status—despite the lack of PA—suggests that their biological age was younger than their chronologic age.

The difference in the results between men and women is notable. The prevalence of neovascular AMD has been reported to be similar for sex or higher in women of European ancestry.[24,25] However, a previous study in South Korea showed that the incidence of neovascular AMD in men was approximately 2 times higher than that in women,[26] and our present results also reflected this finding. This disparity was explained in part by the dominance of polypoidal choroidal vasculopathy in Asian men.[27,28] The sex difference in the disease type and prevalence in the Asian population, including South Korea, may cause the sex-dependent association between neovascular AMD and PA. However, the finding that PA affects only men lacks a clear biological rationale; additional studies are needed to confirm this finding.

Although PA has generally been reported to be associated with reduced risks for cardiovascular diseases, some studies

Figure 2. Cumulative Incidence of Neovascular Age-Related Macular Degeneration (AMD)



Incidence among the physical activity (PA) and no-PA groups between August 1, 2009, and December 31, 2013. There were differences in the cumulative incidence of neovascular AMD according to PA status among men (A) and according to level of PA (1-4 times per week and ≥5 times per week) (B).

have reported that strenuous or frequent PA was associated with markedly higher risks for those diseases.[29,30] A 13-year follow-up study using the Swedish National Patient Registry suggested a U-shaped association between total PA and heart failure risk among men. Another large-scale study performed in the United Kingdom also suggested a U-shaped association between various types of cardiovascular events and any frequent PA.[29] In this regard, we cautiously suggest that exercise may not always have favorable effects in terms of the development of neovascular AMD.

As mentioned above, there is a fundamental limitation in the cross-sectional approach because visual impairment is one of the most important confounders of PA.[12-14] Therefore, a large-scale longitudinal study would be indispensable for gaining understanding of any temporal relationship between PA and AMD. To our knowledge, there are only 4 previous studies that have investigated neovascular AMD rather than early AMD. First, the 15-year cumulative results of the Beaver Dam Eye Study[6] suggested that individuals with an active lifestyle, defined as regular activity 3 or more times per week, were less likely to develop exudative AMD (odds ratio, 0.3) than were those without an active lifestyle. However, in terms of average stair-climbing as a PA, an inverse U-shaped association was observed in the same study: the incidence was lower in groups in which individuals answered no to a query on climbing stairs (1.8%) or more than 6 flights (highest level, 1.7%) than in the 2 groups between these extremes (1-3 flights [2.1%] or 4-6 flights [2.9%]).[6] The Melbourne Collaborative Cohort Study[9] also used past PA, particularly vigorous exercise, similar to the present study and could not conduct an adequate analysis for late AMD due to the small number of cases of late AMD in men (n = 8) or women (n = 9) who exercised vigorously. In the same report, in terms of recreational activity, the most active recreational activity group exhibited a greater relative risk ratio (1.20); however, the 95% CI was wide (0.66-2.20). Another investigation, the Carotenoids in Age-Related Eye Disease Study,[7] did not perform analyses to examine advanced AMD due to the small number of advanced AMD cases (n = 12). Finally, the Blue Mountains Eye Study, including a total of 84 late AMD cases, concluded that PA did not influence the risk for AMD over a 15-year period.[8] Finally, when we focused on incident neovascular AMD, rather than early or intermediate AMD, the Beaver Dam Eye Study was the only adequate longitudinal study to investigate the preventive effect of exercise on exudative AMD.

Previous studies have reported that higher BMI increased the risk for progression to the advanced forms of AMD.[22] Body mass index is a major confounding factor at baseline, and our exploratory analysis of the effects of BMI on incident neovascular AMD demonstrated that BMI did not affect the incidence of neovascular AMD (eAppendix 1 in the Supplement). Because we performed a sophisticated propensity score-matching analysis using 42 confounders, we believe that we were able to evaluate the effect of PA alone. Finally, our results suggest that nonobese men (BMI <23.88) are the most likely to be at high risk for neovascular AMD when exercising vigorously (to the point of sweating) 5 or more times per week (eAppendix 1 in the Supplement).

In terms of mechanism, the choroid is a sensitive part of the eye, and thickness varies with changes in body position[31]; therefore, excessive exercise would affect the local circulation in and around the choroid, which may in turn be associated with angiogenesis. However, epidemiologic studies cannot provide any evidence for the mechanism or pathology and, therefore, experimental studies should be pursued.

Limitations

The present study has the following limitations: (1) the inaccuracies of outcome variables based on claims data and exposure variables based on self-reporting, (2) existence of survival bias, and (3) difficulty of generalization due to race/ethnicity and geographic restrictions. eAppendix 5 in the Supplement describes the limitations of the present study in detail.

Table 3. Incidence of Neovascular AMD According to Physical Activity Level

Analysis	No Physical Activity	Moderate Physical Activity (1-4 Times/wk)	High Physical Activity (≥5 Times/wk)
Total (n = 211 960)			
Participants, No.	105 980	78 224	27 756
Total follow-up, person-years	443 810	328 462	116 193
Neovascular AMD, No.	198	163	87
Incidence, No. per 10 000 person-years	4.5	5.0	7.5
HR (95% CI)	1 [Reference]	1.17 (0.95-1.44)	1.38 (1.07-1.79)
P value	NA	.14	.01
P value for trend	NA	.01	NA
Men (n = 119 924)			
Participants, No.	59 912	46 051	13 961
Total follow-up, person-years	247 577	191 178	57 385
Neovascular AMD, No.	140	131	68
Incidence, No. per 10 000 person-years	5.7	6.9	11.8
HR (95% CI)	1 [Reference]	1.28 (1.01-1.63)	1.54 (1.15-2.06)
P value	NA	.04	.004
P value for trend	NA	.002	NA
Women (n = 92 036)			
Participants, No.	46 068	32 173	13 795
Total follow-up, person-years	196 233	137 285	58 809
Neovascular AMD, No.	58	32	19
Incidence, No. per 10 000 person-years	3.0	2.3	3.2
HR (95% CI)	1 [Reference]	0.86 (0.56-1.33)	1.00 (0.59-1.67)
P value	NA	.51	.99
P value for trend	NA	.82	NA

Abbreviations: AMD, age-related macular degeneration; HR, hazard ratio; NA, not applicable.

Conclusions

The findings of our longitudinal study demonstrate an unexpected and negative link between past vigorous PA and subsequent risk for neovascular AMD in the East Asian population. We emphasize that these results were generated from a relatively healthy comparison group who are as healthy as those who exercise, even though they do not engage in any form of regular PA. This unexpected association appears to be different between men and women. Finally, frequent vigorous PA in young men aged 45 to 64 years was associated with a higher incidence of neovascular AMD. Although no strong biological rationale exists for such an effect of PA on neovascular AMD as well as the differences between the sexes, we cautiously suggest that PA needs to be re-evaluated as a predictive factor for neovascular AMD and more accurate further studies, based on precision medicine using individual sensor-based life-logging data, should be pursued.

ARTICLE INFORMATION

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Study concept and design: Rim, D. W. Kim, S. S. Kim.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: All authors.
Critical revision of the manuscript for important intellectual content: S. S. Kim.
Statistical analysis: All authors.
Study supervision: S. S. Kim.

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