SCIENTIFIC REPORT

Physical activity and the 15-year cumulative incidence of age-related macular degeneration: the Beaver Dam Eye Study

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Background: Cardiovascular disease and age-related macular degeneration (AMD) may share common risk factors. Physical activity improves the cardiovascular risk profile; however, there have been few studies investigating a relationship between physical activity and the long-term incidence of AMD.

Methods: The 15-year cumulative incidence of AMD was determined through four examination phases at 5-year intervals of a population-based study conducted in Beaver Dam, Wisconsin, USA, initiated in 1988–90 (n = 3874 men and women between ages 43 and 86 years). Early AMD (pigment abnormalities or soft indistinct drusen), exudative AMD and geographic atrophy were determined by grading stereoscopic colour fundus photographs. Measures of physical activity were obtained through a questionnaire administered at the baseline examination.

Results: After controlling for age, sex, history of arthritis, systolic blood pressure, body mass index, smoking and education, people with an active lifestyle (defined as regular activity ≥ 3 times/week) at baseline were less likely to develop exudative AMD (odds ratio (OR) 0.3, 95% confidence interval (CI) 0.1 to 0.7) compared with people without an active lifestyle. After multivariate adjustment, increased categories of number of blocks walked per day decreased the risk of exudative AMD (OR 0.7, 95% CI 0.6 to 0.97). Physical activity was not related to the incidence of early AMD or pure geographic atrophy.

Conclusions: These data show a protective effect of physical activity for incident exudative AMD, independent of body mass index and other confounders. They also suggest a possible modifiable behaviour that might be protective against developing AMD.

Evidence suggests that regular physical activity benefits health by reducing abdominal fat, weight, blood pressure, systemic inflammation and endothelial dysfunction, and improving serum lipid lipoprotein profiles.¹ These factors have been hypothesised to have a role in the pathogenesis of age-related macular degeneration (AMD).² However, few studies have investigated an association between physical activity and AMD. Data from the Eye Disease Case Control Study showed that among patients with exudative AMD, physical activity was less frequent compared with controls; however, the difference was not statistically significant.³ In this report, we investigate physical activity and the risk of developing AMD over a 15-year period.

METHODS

A private census of Beaver Dam, Wisconsin, USA, was carried out in 1987–8, to identify all eligible residents between 43

and 84 years of age. Of the 5924 eligible people, 4926 (83%) people between 43 and 86 years of age participated in the baseline examination in 1988–90. Of these, 99% were white. The cohort was re-examined at 5-year (n = 3684), 10-year (n = 2764) and 15-year (n = 2119) follow-up examinations. All data were collected with approval from the institutional review board of the University of Wisconsin, Madison, in conformity with all federal and state laws, and the study was in adherence to the tenets of the Declaration of Helsinki.

Participants were examined at the study suite at a local hospital, nursing home or in their homes. The same procedures were used at each examination.^{4–6} Height, weight and blood pressures were measured according to protocol. Non-fasting blood samples were collected and various laboratory measurements were obtained, including serum cholesterol (total and high-density lipoprotein), glycosylated haemoglobin and white blood count. Medical and lifestyle characteristics were determined through a standardised questionnaire.

Participants were asked three questions on physical activity: “On average, how many flights of stairs do you climb each day?”; “On average, how many city blocks do you walk each day?”; “At least once a week, do you engage in a regular activity long enough to work up a sweat?” and if so, “How many times per week do you do this?” For the purpose of analyses, stair climbing was categorised as none, 1–3 flights, 4–6 flights, >6 flights/day; walking was categorised as none, 1–4 blocks, 5–12 blocks, >12 blocks/day; active lifestyle was defined as engaging in regular activity with or without sweating ≥ 3 times/week; and sedentary lifestyle was defined as regular activity <3 times/week.

Fundus photographs of the retina were obtained at each examination and graded in a blinded fashion using the Wisconsin Age-Related Maculopathy Grading System to determine the AMD status.⁷ Early AMD was defined as presence of soft indistinct drusen or pigmentary abnormalities in the presence of drusen. Geographic atrophy (pure form) and exudative AMD were defined according to the standard definitions.⁷

All those who contributed some follow-up information at the baseline examination were included in the analysis (n = 3874). Cumulative incidence was calculated using a competing risk method to account for death and was based on the more severely involved eye.⁸ Age adjustment was computed with the direct method using the baseline population with weights of 0.58, 0.26 and 0.16 for ages 43–64, 65–74 and 75–86 years, respectively. Multivariate odds ratios (ORs) adjusted for age, sex, history of arthritis, systolic blood pressure, smoking, education and body mass index were calculated with discrete logistic hazard regression. SAS V.9 was used for all analyses.

Abbreviation: AMD, age-related macular degeneration

RESULTS

In all, 25% of the population engaged in an active lifestyle, 23% climbed >6 flights of stairs/day, and 13% walked >12 blocks/day at baseline. Participants with an active lifestyle were more likely to be younger and after controlling for age, were less likely to be currently smoking, have a history of heavy drinking, less education, larger body mass index, higher systolic blood pressure, higher white blood count, and were more likely to have a history of cardiovascular disease than people with a sedentary lifestyle (table 1).

After controlling for age, increasing levels of stair climbing were related to the 15-year cumulative incidence of early AMD, but this association was not statistically significant after further multivariate adjustment (table 2). No marked relationships were found between physical activity and the 15-year cumulative incidence of pure geographic atrophy. After controlling for age and additionally for other factors, both an active versus sedentary lifestyle and increasing categories of blocks walked were associated with a reduction in the incidence of exudative AMD. Additional adjustment for history of emphysema, heavy drinking, serum lipids, vitamin use and white blood count did not alter this relationship (data not shown).

The relationship between physical activity and exudative AMD was further investigated by stratifying by age (65 years as a cut-off value), sex and body mass index (30 kg/m² as a cut-off value). The only significant interaction was with age and walking. People <65 years of age at baseline who walked did not have a decreased risk for developing exudative AMD (OR per increasing category 1.01, 95% confidence interval (CI) 0.69 to 1.47), whereas those >65 years of age at baseline did have decreased risk (OR 0.54, 95% CI 0.37 to 0.80 for those >65 years; *p* interaction = 0.04).

DISCUSSION

Engaging in an active lifestyle or walking more, independent of confounders, reduced the risk of developing exudative AMD over 15 years by 70% and 30%, respectively. Physical activity was not independently associated with incident early AMD or pure geographic atrophy. Physical activity and exudative AMD were studied previously in a case-control

study, where the authors found that after controlling for age and other systemic factors, people with exudative AMD (cases) were less likely to have above average compared with below average physical activity levels than controls (OR 0.7, 95% CI 0.4 to 1.1).³

Physical activity in the Beaver Dam population was associated with lower systolic blood pressure, lower white blood count and less obesity; factors previously found to be associated with incident AMD.^{9–11} However, the relationships of walking and an active lifestyle and lower incidence of exudative AMD remained while controlling for these factors. Physical activity also reduces systemic inflammation and endothelial dysfunction¹; both hypothesised to have a role in the pathogenesis of AMD.² It is not clear if specific inflammatory markers (eg, C reactive protein) or other unmeasured confounders are the explanation for the association.

AMD is strongly linked to ageing, which is more relevant biologically rather than chronologically. Physically active people are likely to be biologically younger than sedentary people. Adjustment for markers of biological ageing, such as frailty, may explain part of the association, but were not available for analysis. The lack of an association with physical activity and early AMD or pure geographic atrophy suggests that different pathogenetic mechanisms may be involved at different stages of AMD (early v late) and between the two late-stage outcomes. However, with the low incidence of geographic atrophy (*n* = 39 events), we cannot rule out the possibility of an association.

This study has several limitations. Physical activity was measured using a questionnaire, and we have no measurement of how long the participant may have been physically active. Also, participants with a sedentary lifestyle were less likely than those who were physically active to return for follow-up examinations. We believe that these limitations would only bias the associations with AMD towards the null. Finally, we cannot rule out the possibility of uncontrolled confounding. Despite these limitations, this report provides evidence that a modifiable behaviour, regular physical activity, such as walking, may have a protective effect for incident AMD.

Table 1 Baseline characteristics by physical activity status, Beaver Dam Eye Study, 1988–90

Characteristics	Active* (n = 964)	Sedentary* (n = 2910)	p Value†
	%	%	
Male sex	45.3	44.7	0.90
Current smoking	13.3	21.1	<0.001
Ever heavy drinker	13.1	18.0	<0.001
<High school education	17.5	28.1	<0.001
History of arthritis	34.8	38.5	0.054
Diabetes	7.9	8.9	0.39
History of emphysema	1.9	3.2	0.052
History of gout	0.5	0.3	0.18
Hypertension	46.1	49.5	0.16
History of cardiovascular disease	15.5	12.8	0.003
	Mean (SD)	Mean (SD)	
Age (years)	60.3 (9.7)	61.3 (11.0)	0.01
Body mass index (kg/m ²)	28.2 (4.6)	29.0 (5.6)	<0.001
Systolic blood pressure (mm Hg)	129 (19.7)	132 (19.9)	0.002
Diastolic blood pressure (mm Hg)	77.5 (10.4)	77.5 (10.8)	0.36
Serum total cholesterol (mg/dl)	232 (42.6)	233 (44.1)	0.47
Serum HDL cholesterol (mg/dl)	53.0 (17.9)	51.8 (17.4)	0.07
White blood count (k/μl)	7.0 (1.9)	7.4 (2.1)	<0.001

HDL, high-density lipoprotein.

*Active lifestyle was defined as engaging in a regular activity (eg, jogging or biking) with or without sweating ≥3 times/week; sedentary lifestyle was defined as activity <3 times/week.

†p value adjusted for age.

Table 2 Physical activity and age-adjusted 15-year cumulative incidence and multivariate adjusted odds ratios of early and late age-related macular degeneration, Beaver Dam Eye Study, 1988–2005

Physical activity measure	Level	Incidence of early AMD			Incidence of geographic atrophy			Incidence of exudative AMD		
		n	% (SE)*	OR (95% CI)†	n	% (SE)*	OR (95% CI)†	n	% (SE)*	OR (95% CI)†
Exercise status	Sedentary	2303	16.5 (0.8)		2870	1.4 (0.3)		2891	2.5 (0.3)	
	Active	781	14.1 (1.5)	0.9 (0.7 to 1.1)	962	1.8 (0.6)	1.1 (0.5 to 2.3)	959	0.7 (0.3)	0.3 (0.1 to 0.7)
	p Value		0.08	0.21		0.85	0.76		0.005	0.008
Stair climbing	None	611	17.4 (1.5)		800	1.8 (0.5)		809	1.8 (0.5)	
	1–3 flights	906	16.1 (1.3)		1128	1.5 (0.4)		1131	2.1 (0.5)	
	4–6 flights	816	15.6 (1.4)		1003	0.7 (0.3)		1010	2.9 (0.6)	
	>6 flights	750	14.5 (1.7)	0.9 (0.8 to 1.0)	899	2.3 (0.8)	1.0 (0.7 to 1.3)	898	1.7 (0.7)	1.0 (0.8 to 1.3)
	p Value for trend		0.04	0.15		0.85	0.93		0.60	0.96
Walking	None	1341	16.8 (1.1)		1691	1.8 (0.4)		1703	3.0 (0.5)	
	1–4 blocks	659	14.0 (1.5)		804	0.9 (0.4)		805	1.4 (0.5)	
	5–12 blocks	658	17.7 (1.6)		818	0.9 (0.4)		821	1.5 (0.5)	
	>12 blocks	419	14.8 (2.0)	1.0 (0.9 to 1.1)	511	2.2 (0.8)	0.9 (0.7–1.2)	513	1.4 (0.6)	0.7 (0.6 to 0.97)
	p Value for trend		0.13	0.42		0.53	0.55		0.006	0.03

AMD, age-related macular degeneration. n=number at risk.

*Age-adjusted cumulative incidence (see Methods for age-adjustment weights).

†ORs shown per increasing group of the risk factor, and are adjusted for age, sex, arthritis, systolic blood pressure, body mass index, smoking and education.

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