Physical activity and risk of age-related cataract

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Abstract

● **AIM:** To summarize quantitatively the prospective association between physical activity and age-related cataract (ARC) risk.

● **METHODS:** PubMed, Embase, Web of Science, and Cochrane Library were systematically searched for all relevant follow up studies until July 2019. Multivariable-adjusted relative risks (RRs) and corresponding 95% confidence intervals (CIs) from individual studies were used to calculate the overall summary estimates. The dose-response relationship was assessed using generalized least-squares trend estimation.

● **RESULTS:** Six prospective cohort studies, involving 19 173 cases in 6.2-12.1y follow up of 171 620 participants, were included in the analysis. Increased physical activity was significantly associated with reduced risk of ARC by 10% (RR: 0.90; 95%CI: 0.81, 0.99, *P*=0.04). Stratified analysis by assessment method for physical activity suggest that studies using metabolic equivalent (MET) per day tended to report a slightly stronger association with ARC (RR: 0.85; 95%CI: 0.81, 0.90, *P*<0.001) than studies which assessed activity by weekly activity (RR: 0.96; 95%CI: 0.89, 1.03, *P*=0.24). Dose-response analysis indicated that the risk of ARC decreased by 2% (RR: 0.98; 95%CI: 0.98, 0.99, *P*<0.001) for every 6 METs per day increase in activity.

● **CONCLUSION:** The findings from this Meta-analysis provide additional evidence that increased physical activity is inversely associated with ARC risk dose-responsively.

● **KEYWORDS:** physical activity; age-related cataract; lens; Meta-analysis

INTRODUCTION

Age-related cataract (ARC) is one of the most-common cause of vision impairment and blindness throughout the world[1]. The number of blind patients caused by ARC is anticipated to reach to 13.4 million (34.8% of blindness) by the year 2020[2]. Although cataract extraction surgery is effective in recover vision, the high therapeutic costs and increasing demands for therapy have conferred a considerable financial burden to healthcare organization and society in general[3]. Therefore, identification of the factors associated with ARC pathogenesis and implementation of interventions to modify these factors will be urgently required to prevent ARC or delay its progression.

Although the exact pathogenic mechanisms underlying ARC has not been completely understood, aging and oxidative damage have been implicated as playing a crucial role in the development of this disease[4]. An increasing number of evidence supports the positive effects of physical activity on attenuating oxidative damage by increasing the activity of antioxidant enzymes, and inhibiting inflammation by modulating high-density lipoprotein (HDL), which may contribute to a lower risk of certain age-related eye diseases[5-7]. A recent Meta-analysis by McGuinness *et al*[8] found a protective association of physical activity on age-related macular degeneration (AMD). Since AMD shared common oxidative stress or inflammation-related mechanisms with ARC, indicating that physical activity might also can serve as a strategy for preventing of ARC. Several studies have revealed that higher physical activity level was associated with a reduced incidence of cataract; however, the association were not consistently observed in other studies[9-11]. Moreover, heterogeneity in study design and the method to assess

physical activity may also have differential impacts on the association of physical activity with ARC risk; thus, it is essential to investigate the potential effects of these variants. We, therefore, performed a dose-response Meta-analysis across identified prospective cohort studies to assess the relation between physical activity and ARC risk. Furthermore, subgroup analyses were also conducted to explore whether this association was differed by study characteristics.

MATERIALS AND METHODS

We adhered to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) reporting guidelines[12].

Search Strategy We searched PubMed, Embase, Web of Science, and Cochrane Library until July 2019 for studies that investigated the association between physical activity and ARC risk using a predefined search strategy. No language restriction was applied. We also manually checked the reference lists of all retrieved articles, published reviews and Meta-analyses to identify potential additional studies not captured by electronic searches. Furthermore, experts in the field were also contacted to obtain any additional studies.

Study Selection Included studies had to meet the following prespecified inclusion criteria: 1) Prospective cohort studies were published as original articles; 2) The exposure of interest was physical activity; 3) The primary outcome of the study was the incidence of ARC, including total cataract, subtype cataracts or cataract extraction; 4) The studies reported relative risks (RRs) or odds ratios or hazards ratios with 95% confidence intervals (CIs) or reported sufficient data to calculate them for each outcome. In the case of multiple publications, only the most recent or informative study was selected. Three authors (Jiang H, Wang LN and Liu Y) independently screened the search results and assessed the eligibility of the studies. Any discrepancies were settled by consensus, with the involvement of an author (Wu CR).

Data Extraction and Quality Assessment Data extraction and validity assessment were reviewed independently by three authors (Jiang H, Wang LN, and Liu Y), and inconsistencies were sorted out by discussion with the senior investigator (Wu CR). Information from each study were extracted by using a standardized manner in duplicate, including the characteristics of the study (first author, publication year, country, sample size, number of ARC cases, follow-up, measurement method of physical activity, level of activity, ascertainment of outcome), characteristics of the participants (age and gender), covariates adjusted for in the analysis, the overall estimate of interest and in each subclass. If studies reported more than one risk estimates, the maximally adjusted estimate was extracted. Moreover, when different subtypes of ARC were present in a single study, we combined the study-specific estimates to obtain the summary value of total ARC before pooling with

other studies. The quality of each selected study was assessed using of the Newcastle-Ottawa Scale scoring 0-9 based on three domains: four for selection of the study groups, two for comparability of cohorts, and three for the ascertainment of the outcome of interest. Studies scored five or more were considered as high quality, otherwise as low quality[13].

Statistical Analysis RR was used as the measure of the association between physical activity and ARC. The possible heterogeneity was evaluated with the use of Q statistic and the I^2 statistics, with Q statistic P value less than 0.10 and I^2 value greater than 50% indicative of significant heterogeneity and RR from random-effects model was presented; otherwise, a fixed-effects model was applied[14]. We further investigated the potential source of heterogeneity by stratification and Meta-regression analysis including the following study characteristics: sex (women vs both sex), diagnosis method of ARC (lens photography vs medical record review vs self-reported), study location (United States vs other countries), population source (population-based vs volunteer-based), physical activity assessment method [metabolic equivalents (MET) hours vs weekly activity], cataract type (total cataract or nuclear cataract), and length of follow-up (≤10y vs >10y). To assess the potential dose-response relation, the method described by Greenland and Longnecker was used to determine the trend from the correlated estimates for logarithm RR across categories of physical activity[15].

The midpoint (median/mean level) physical activity level of each category was used as the corresponding RR for each study, and the midpoint of upper and lower bounds was assumed the dose of each category when the exposure was provided as a range. If the extreme category was open ended, we estimated approximate upper or lower bound by using the width of the adjacent interval. In addition, a sensitivity analysis was applied to explore the influence of individual study by removing one study in each turn. Potential publication bias was evaluated by the application of funnel plot, Egger's and Begg's tests, with P values less than 0.10 indicates significance[16]. All analyses were performed with Stata 15.1 statistical software (Stata Corporation, College Station, TX, USA).

RESULTS

The literature search identified 5183 potentially relevant citations, 1771 of which were duplicates and subsequently removed. After independently assessing the title and abstract of individual study records, 3410 were irrelevant and therefore excluded. The remaining 83 publications were obtained for full-text evaluation. Finally, six prospective cohort studies deemed suitable for analysis[9,11,17-20] (Figure 1).

Study Characteristics Table 1 summaries the characteristics of the six studies. The number of people from the selected studies varied between 1808 and 52 660. A total of 19 173

Table 1 Characteristics of studies included in this Meta-analysis

First author, publication year, country	Age (y)	Participants/ Cases	Male/Female	Follow-up (y)	Physical activity[a]	ARC ascertainment	Covariate	Study quality[b]
Klein et al, 2003, USA[17]	43-86	4926/1535	NR	10.1	0 vs ≥3 times/wk	Medical record	Age, sex	Good
Christen et al, 2008, USA[18]	≥45	35 551/2031	0/35 551	10	Rarely/never vs >4 times/wk	Medical record	Age, smoking, alcohol, BMI, history of hypertension, diabetes, hypercholesterolemia, eye examination history	Good
Mares et al, 2010, USA[11]	50-79	1808/736	0/1808	7	< 3 vs ≥21 METs per day	Lens photography	Age, smoking, BMI, pulse pressure, iris pigmentation, Healthy Eating Index score, energy	Good
Appleby et al, 2011, UK[19]	≥40	27 670/1484	7493/20 177	10	Inactive vs active[c]	Medical record	Age, smoking	Good
Williams 2009, USA[9]	NR	49 005/1807	20 332//28 673	6.2	≤1.57 vs ≥6.57 METs per day	Self-report	Age, sex, race, education, smoking, alcohol, meat and fruit intake	Poor
Zheng selin et al, 2015, Swedish[20]	45-83	52 660/11 580	28 807/23 853	12.1	<38.4 vs >45.5 METs per day	Medical record	Age, sex, education, smoking, abdominal obesity, hypertension, corticosteroid use	Good

ARC: Age-related cataract; BMI: Body mass index; MET: Metabolic equivalent; NR: Not reported. [a]Physical activity was expressed as the lowest vs the highest categories; [b]Study quality was evaluated based upon Newcastle-Ottawa Scale; [c]The average number of hours each week was used to characterized the physical activity level as either inactive or active.

Records identified through literature search n=5183
PubMed: 10249
Web of Science:3094 7
Embase:76 29
Cochrane: 189

Excluded n=1771
Duplicate references

Records screened based on tittles or abstracts n=3410

Excluded n=3327
Review article or technique summary
Correspondence or editorial
Not original human research
Clearly irrelevant
Did not address the association between PA and cataract

Records retrieved for full-text review n=83

Excluded n=77
Outcome was not cataract: 16
Non-PA exposure: 38
Review articles: 5
multiple papulations:1
Unusable results: 4
Cross-section study: 1
Case-control study: 1
No relevant comparisons: 11
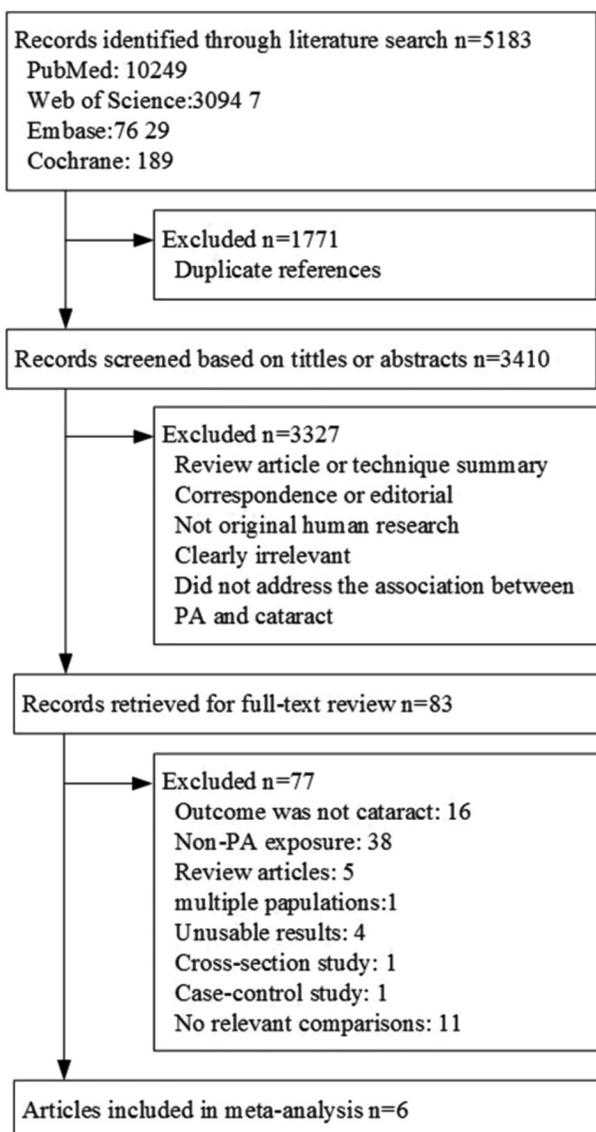
Articles included in meta-analysis n=6

Figure 1 Process of literature selection.

incident ARC cases were identified among 0.17 million participants during 6.2-12.1y of follow up. Four studies were conducted in the United States, and one each in Swedish and the United Kingdom. Among these studies, four comprised both sexes and two were performed only in women. Four studies were population-based cohorts, whereas two studies consisted of volunteers. Physical activity was collected by questionnaires. Half of the studies reported physical activity in METs per day while others in hours per week. ARC was ascertained by photography in one study, by medical record review in four study, by self-report in one study. The association was adjusted for age in all studies; while gender, education, smoking, alcohol consumption were adjusted in some studies. Five studies were scored good, and one rated low in quality.

Physical Activity and Age-related Cataract Of the included studies, four reported a trend toward lower risk of ARC with higher physical activity level[9,17-18,20], two of which reached statistical significance[9,17]. Significant heterogeneity was detected among these studies, and the summary estimates was 0.90 (95%CI: 0.81, 0.99, P=0.04; I^2=70%, $P_{heterogeneity}$=0.006; Figure 2) for comparison of extreme categories of physical activity.

An increment of 6 METs/day was statistically significantly associated with a 2% decrease risk of developing ARC (RR: 0.98; 95%CI: 0.98, 0.99, P<0.001). Table 2 summarized the results of stratified analyses. The inverse association reached significance in studies which quantified activity by METs/day (RR: 0.85; 95%CI: 0.81, 0.90, P<0.001) compared to studies by weekly activity (RR: 0.96; 95%CI: 0.89, 1.03, P=0.24). The association between physical activity and cataract was stronger
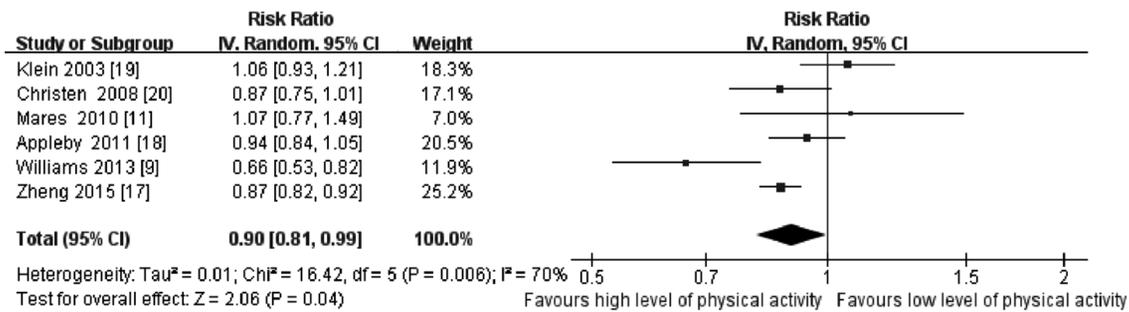
Figure 2 Pooled estimate based on random-effects Meta-analysis for the association between physical activity and ARC The diamonds and lines represents the RRs and their CIs on a log scale in each study. The square is proportional to the percentage weight of every study.

Table 2 Subgroup analyses examining the association between physical activity and ARC

Subgroup	No. of studies	RR (95%CI)	P	
			Heterogeneity	Meta-regression
Gender				0.96
Both sexes	4	0.89 (0.85, 0.93)	0.01	
Female	2	0.87 (0.76, 1.00)	0.90	
Country				0.68
USA	4	0.90 (0.83, 0.98)	<0.01	
UK	1	0.94 (0.84, 1.05)	NA	
Swedish	1	0.87 (0.82, 0.92)	NA	
Population source				0.16
Population-based	4	0.90 (0.86, 0.95)	0.06	
Volunteer-based	2	0.80 (0.70, 0.90)	0.04	
ARC ascertain method				0.34
Medical record	3	0.90 (0.86, 0.95)	0.02	
Lens photography	1	0.89 (0.64, 1.23)	NA	
Self-report	2	0.79 (0.70, 0.90)	0.04	
Physical activity measurement				0.18
METs	3	0.85 (0.81, 0.90)	0.05	
Weekly activity	3	0.96 (0.89, 1.03)	0.15	
Smoking				0.95
Adjusted smoke	4	0.92 (0.86, 0.98)	<0.01	
No adjusted smoke	2	0.87 (0.82, 0.92)	0.01	
ARC type				0.35
Cataract	3	0.87 (0.80, 0.95)	0.02	
Nuclear cataract	3	0.89 (0.84, 0.94)	0.01	
Follow-up duration				0.39
≤10y	4	0.87 (0.81, 0.95)	0.01	
>10y	2	0.90 (0.85, 0.95)	0.01	

ARC: Age-related cataract; MET: Metabolic equivalent.

from volunteer-based studies (RR: 0.80; 95%CI: 0.70, 0.90, *P*<0.001) than population-based studies (RR: 0.90; 95%CI: 0.86, 0.95, *P*<0.001) but the difference was not significant. Other prespecifed subgroup findings were consistent with the main analysis.

Sensitivity Analysis and Publication Bias Sensitivity analysis confirmed the association was not substantially changed by excluding one study at a time. Visual inspection of

a funnel plot suggested no evidence of asymmetry, suggesting the absence of publication bias. This was also confirmed by the results from tests proposed by Egger's linear regression test (*P*=0.93) and Begg's rank correlation test (*P*>0.99).

DISCUSSION

The results of available prospective cohort studies suggested that increased physical activity was inversely with ARC risk; and that the association was significant in studies which

quantified the physical activity by METs compared with those by weekly activity. Dose-response analysis showed that the risk of ARC decreased by 2% for every 6 METs/day increase. Lens is highly susceptible to oxidative damage because of its high concentration of polyunsaturated fatty acid and its specific biological function; cumulatively elevated reactive oxygen species (ROS) have a toxic effect on multiple lens components, such as crystallin proteins, which in turn disturbs fundamental functions of the lens and, consequently, lead to the development of lens opacities[21-23]. Physical activity could reduce levels of oxidative stress by increasing the activity of antioxidant enzymes. In a trial among 32 elderly persons (aged 73.2y), Ong *et al*[7] showed that long-term physical activity was positively correlated with higher total antioxidant status and less oxidative injury. Moreover, physical activity could also modulate inflammation by elevating HDL, as well as HDL-associated proteins concentration, which in turn inhibits lipid peroxidation, leukocyte adhesion, and cytokine production and the release[24-25]. Studies have indicated that HDL could inhibit the oxidation of low density lipoprotein through transition metal ions and the 12/15-lipoxygenase-mediated formation of lipid hydroperoxides[26]. Furthermore, HDL plays an important role in lipophilic antioxidants transport, and elevated HDL may carried more antioxidants from plasma to lens, to prevent the human eye lens from oxidative damage and inflammation[26-27]. Physical activity could improve insulin resistance and lipid profiles, which have been observed to be associated with an increased risk of ARC[28-31].

Our stratified results indicated significant association among studies which assessed physical activity by METs compared with those by weekly activity, which was a rough estimate of the duration of physical activity but not specify the intensity and pattern. Given the prospective design of the ineligible studies, such misclassification is likely non-differential and would have biased the analyses toward null and underestimate the magnitude of the true associations. While the use of the energy cost (METs) could reasonably reflect the intensity of physical activity and reduce measurement error caused by activity variation, which helped confer a better outcomes[32]. With regard to study population, the association was evident among volunteer-based studies. It is known that lens opacities can progress without conspicuous visual impairment at an early stage over a long time, while volunteers may have more health consciousness and more likely to seek out or accept medical care for visual impairment earlier, which increases the possibility of detecting the lens opacity at an early stage and might have a direct effect on outcome analysis[33].

Our findings have important public health implications. Currently, ARC is still a major cause of severe visual impairment and blindness around the world. Although causality has not been established, the current results and available evidence indicate a beneficial effect of physical activity on ARC. Our result suggested the risk of cataract could potentially decrease by 2% for every 6 METs/day of physical activity (which is approximately equivalent to jogging or cycling for an hour)[34]. However, considering the fact that 23% of adults are inactive and a series of physical activity related diseases[35-36] including the high incidence and huge burden of ARC, encouraging physical activities such as walking, cycling in a supportive physical environment, could bring a great public health significance to prevent ARC.

By including all available prospective cohort studies with large sample size, we could assesse the dose-response relationship between activity and ARC risk. However, the potential limitations should be noted. First, the early lens opacities can progress in the absence of obvious symptoms or subjective visual impairment at long durations[27], therefore, self-reported case ascertainments might underestimate the overall incidence of cataract, driving our pooled estimate towards the null. Second, as physical activity was self-reported and assessed by questionnaire, some measurement error was unavoidable despite the consistent estimates by stratification analysis; given that the physical activity was captured prior to the incident of ARC, the classification of physical activity was unlikely to be biased with respect to ARC outcomes. Third, the observational studies are prone to residual confounders. Although several confounding factors had been adjusted in all the included studies, the possibility of other unmeasured or residual or unknown confounding could not be completely ruled out. Fourth, the generalizability of our findings to other racial and ethnic groups might be limited because the current evidence were predominantly from western populations. Finally, potential publication bias might also have an impact on the results, although only weak evidence of a publication bias in the Meta-analysis.

In summary, the present study suggests that higher physical activity level was significantly associated with significant reductions in ARC risk in a dose-response manner. Our result continues to support current guidelines advocating the benefit physical activity, as part of a healthy lifestyle, in preventing or delaying the onset of age-related diseases.

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