

Original Article

Influence of metabolic syndrome on cataract risk: a meta-analysis of observational studies

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Abstract: The purpose of this article was to conduct the association between metabolic syndrome (MetS) and the risk of cataract. PubMed, Web of Science, Google Scholar, and Cochrane Library were searched for observational studies published before March 2015. Two authors independently extracted information from all included studies. STATA (version 12.0) software was used for data analysis. Fixed-effects or random-effects methods were used for the risk estimates. Publication bias was assessed qualitatively. Heterogeneity was examined using the I^2 statistic. Six independent studies were chosen for analysis, with a total of 54398 participants. This meta-analysis confirmed that MetS was associated with increased prevalence of cataract among cohort/case-control studies (RR 1.58, 95% CI: 1.4-1.77) and cross-sectional studies (OR 1.23; 95% CI, 1.05-1.44). In the subgroup meta-analysis by cataract types, MetS was found to be associated with an increased incidence of cataract extraction (OR 1.75; 95% CI, 1.49-2.06). However, no significant association was observed between MetS and all three cataract subtypes. MetS was significantly associated with cataract only in women (OR 1.29; 95% CI, 1.02-1.63). All individual components of MetS, including obesity, high glucose levels, high blood pressure (HBP), high triglycerides, and low high-density lipoprotein (HDL), were also found to correlate with an increased estimated risk of cataract. The ORs with 95% CI were 1.30 (1.09-1.55), 1.37 (1.1-1.71), 1.39 (1.08-1.79), 1.10 (1.0-1.20), 1.17 (1.04-1.32), respectively. In addition, cataract prevalence tended to increase with the number of MetS components. Overall, our results suggested that MetS was associated with a high risk of cataract.

Keywords: Metabolic syndrome, cataract, meta-analysis, observational studies

Introduction

According to data provided by the World Health Organization (WHO), cataracts, including nuclear cataract (NC), cortical cataract (CC) and posterior subcapsular cataract (PSC), are responsible for 51% of worldwide blindness [1]. With the development of an aging population around the world, the prevalence of cataract has tended to increase. The growing need for cataract surgery imposes a heavy personal and social economic burden [2]. Thus, preventing or delaying the progression of cataract through the avoidance of risk factors is a crucial strategy that could improve quality of life and lessen enormous personal economic burdens. Many risk factors are associated with cataract, and these are not completely understood. Several

factors associated with an increased risk of cataract have been confirmed, such as smoking [3], alcohol consumption [4], myopia [5], and use of vitamin supplements [6]. In previous systematic reviews and meta-analyses of the literature, we found that some metabolic abnormalities, such as hypertension, obesity, and type 2 diabetes, were also associated with cataracts [7-9].

Metabolic syndrome (MetS) represents a cluster of these metabolic abnormalities including central obesity, dyslipidemia, hyperglycemia, and HBP [10]. A joint statement by several major organizations defines MetS as with the presence of any three abnormal findings out of the above-mentioned metabolic disorders [11]. MetS appears to be a risk factor in several ocu-

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Table 1. Search strategy for PubMed (up to March 2015)

Search Strategy	Search Terms
#1	Cataract
#2	Cataracts
#3	crystalline opacity
#4	lens opacification
#5	lens opacities
#6	lens opacity
#7	cataract extraction
#8	cataract surgery
#9	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8
#10	Metabolic Syndrome X
#11	Metabolic Syndrome
#12	MetS
#13	x syndrome
#14	metabolic abnormalities
#15	dysmetabolic syndrome
#16	insulin resistance
#17	insulin resistance syndrome X
#18	insulin resistance syndrome
#19	#10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18
#20	#9 AND #19

lar diseases, including age-related macular degeneration (AMD) [12], high intraocular pressure or glaucoma [13, 14], and anterior ischemic optic neuropathy [15]. Previous epidemiologic studies also have been published to investigate the relationship between MetS and the risk of developing cataracts. Nevertheless, the results are not consistent. Evidence for the association between MetS and the risk of cataract has not been systematically assessed. Therefore, a meta-analysis was conducted to investigate this association.

Methods

Literature search strategy and selection criteria

This meta-analysis was performed according to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines [16]. PubMed, Web of Science, Google Scholar, and The Cochrane Library databases were searched to retrieve related articles published before March 2015, without any language restrictions. The search terms comprised the following keywords: (“cataract” or “cataracts” or “crystalline opacity” or “lens opacification” or “lens opaci-

ties” or “lens opacity” or “cataract extraction” or “cataract surgery”) AND (“Metabolic Syndrome X” or “Metabolic Syndrome” or “MetS” or “metabolic abnormalities” or “dysmetabolic syndrome” or “insulin resistance” or “insulin resistance syndrome X” or “insulin resistance syndrome” or “X syndrome”) (**Table 1**). Titles and abstracts were read to exclude any clearly irrelevant studies. The full texts of the remaining articles were screened independently by two reviewers (YR. Du and MM. He) use the inclusion criteria. In addition, the reference lists of all identified articles were checked by hand to include other potentially

eligible studies. This process was performed iteratively until no additional articles could be identified.

In our meta-analysis, the articles were included if they met the following criteria: (1) the outcome of interest was the prevalence of MetS in patients with cataract; (2) observational studies included a control group; (3) the study reported risk estimates such as odds ratio (OR) or relative ratio (RR) with 95% confidence intervals (CIs) or sufficient data to calculate the ORs or RRs. When authors reported two or more publications on the same study population, only the largest study was selected.

Data extraction and quality assessment

Two authors (YR. Du and MM. He) independently extracted the following data: publication data (name of first author, country, and year of publication), study name, race, study design, study period, age range of subjects, sample size, prevalence of cataract in the study population, prevalence of MetS in the study population, prevalence of cataract in groups with MetS, cataract definitions, MetS criteria, cataract types including NC, CC, and PSC, and confound-

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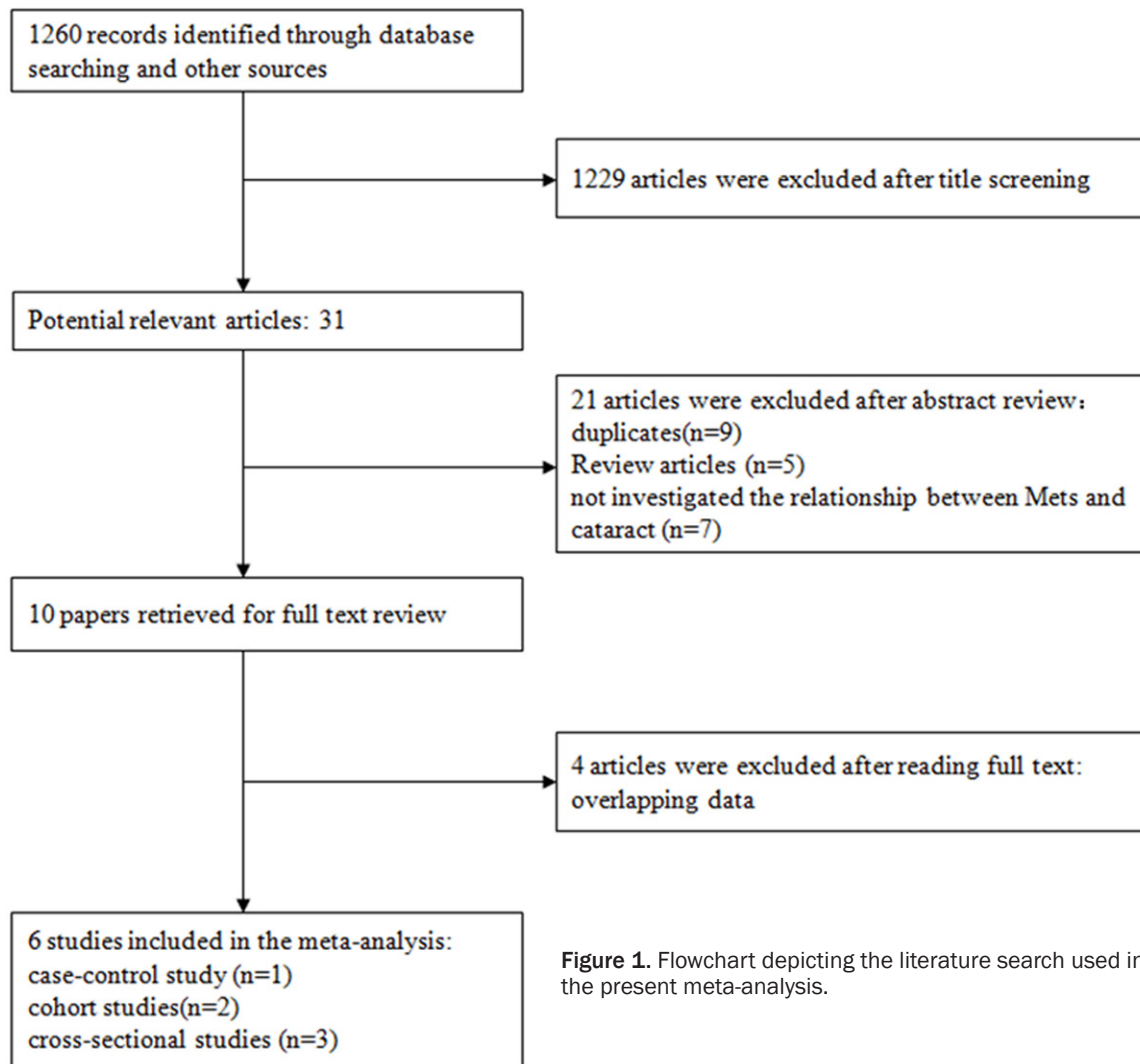


Figure 1. Flowchart depicting the literature search used in the present meta-analysis.

ing factors that were adjusted for in the analysis. When more than one estimate of effects (OR/RR) was presented, we selected the model in which the OR/RR values were adjusted to the maximum extent for potentially confounding variables. Extracted data were checked by another author (PC. Liu). Any disagreements were resolved by discussion and consensus.

The Strengthening Reporting of Observational Studies in Epidemiology (STROBE) Statement with a checklist of 22 items was employed for quality assessment [17].

Data analysis

Preliminary analysis across all included studies was performed to seek an association between MetS and cataract. Because of the high incidence of cataract and MetS, RR is not equal to

OR. According to the formula $RR = OR / [(1-P_0) + P_0 \times OR]$ where P_0 stands for the incidence of cataract in the non-MetS group, RRs were transformed into ORs [18]. The pooled effect of each exposure on MetS was estimated using the OR values and 95% CIs. If the ORs were provided in the studies, they were used for the pooled estimate. Otherwise, the ORs were calculated according to the data provided in the articles.

The meta-analysis was conducted using either the fixed-effects method or the random-effects method. To assess whether the outcomes across the studies were homogeneous, the I^2 statistic was employed [19]. If statistical heterogeneity ($P < 0.10$ or $I^2 \geq 50\%$) was identified, the heterogeneity between studies was considered statistically significant. In the absence of

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Table 2. Characteristics of the six studies included in the present meta-analysis

Publication data	Study	Race	Study design	Study period	Age	Size (n)	Cataract (%)	MetS (%)	Cataract (% in MetS)	Cataract definition	MetS criteria	Cataract types	Adjustment for covariates	STROBE
Paunksnis A, Lithuania, 2007	WHO MONICA	Caucasians	cross-sectional	2001-2002	45-64 y	879	24.91	27.30	30.83	LOCS III	NCEP-ATP III	CC, PSC, NC	age, sex	18
Sabanayagam C, Singapore, 2011	SiMES	Mongolians	cross-sectional	non shown	40-80 y	2794	45.40	42.70	50.20	LOCS III	NCEP-ATP III	CC, PSC, NC	age, sex, education, and smoking status	18
Park YH, Korea, 2014	KNHANES	Mongolians	cross-sectional	2008-2010	≥40 y	11076	39.40	38.50	non shown	LOCS III	AHA/NHLBI	CC, NC	age, survey year	20
Galeone C, Italy, 2010	non shown	Caucasians	case-control	1991-2003	36-78 y	2283	33.30	6.40	48.30	non shown	IDF	AC	Sex, quinquennia of age, study center, year of interview, education, and smoking habit	19
Lindblad, BE, Sweden, 2008	SMC	Caucasians	cohort	1997-2005	49-83 y	35369	12.75	0.35	non shown	the Swedish National Cataract Register	IDF	AC	age, smoking, alcohol consumption, steroid medication use, vitamin supplement use, educational level	20
Ghaem MH, Australia, 2013	BMES	Mongolians	cohort	1992-2002	63.9±8.3	1997	42.90	12.30	51.60	Wisconsin	IDF	CC, PSC, NC	Age, sex, eye disease at baseline, preexisting disease at baseline, and family history of blindness	20

MetS: metabolic syndrome, STROBE: the Strengthening Reporting of Observational Studies in Epidemiology, WHO: the World Health Organization, MONICA: monitoring of trends and determinants in cardiovascular disease, LOCS III: Lens Opacity Classification System III, NCEP-ATP III: National Cholesterol Education Program Adult Treatment Panel III, CC: cortical cataract, PSC: posterior subcapsular cataract, NC: nuclear cataract, AC: any cataract, NA: not applicable, IDF: International Diabetes Federation, SiMES: the Singapore Malay Eye Study, KNHANES: the Korea National Health and Nutrition Examination Survey, AHA/NHLBI: the American Heart Association/National Heart, Lung, and Blood Institute, BMES: the Blue Mountains Eye Study, SMC: The Swedish Mammography Cohort.

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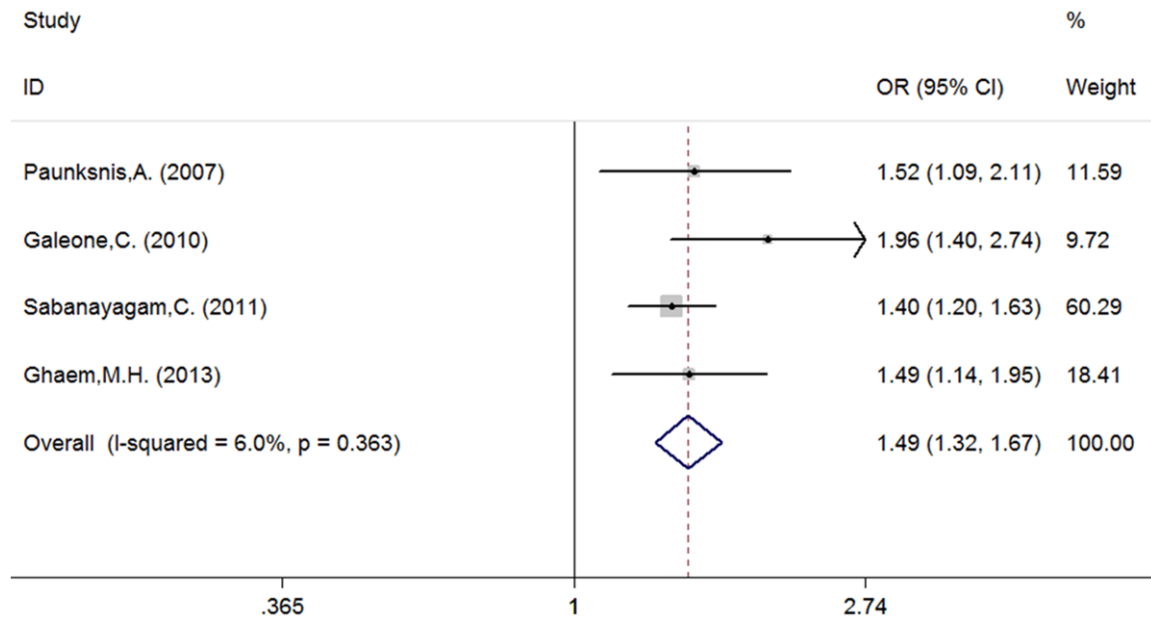


Figure 2. Fixed-effects meta-analysis evaluating the association between metabolic syndrome and the risk of cataract.

substantial heterogeneity, ORs among studies could be pooled using the fixed-effects model; otherwise, a random-effects model was applied. When the heterogeneity was high, subgroup analyses were performed to identify the source of heterogeneity.

Sensitivity analysis was used to evaluate the robustness of the meta-analysis outcome. The “leave-one-out” [20] method was used to evaluate the key studies with substantial impact on between-study heterogeneity.

Publication bias was assessed using Begg’s test [21], which is a statistical analogue of the visual funnel graph. Publication bias was considered to be significantly asymmetric if $P < 0.05$. The absence of significant correlation suggests that the studies were selected in an unbiased manner. All statistical analyses were performed with STATA version 12.0 (Stata Corporation, College Station, TX).

Results

Literature search and study characteristics

The literature search process is depicted in **Figure 1**. The search yielded 1260 potentially relevant articles through the electronic database and from the checking of references in retrieved articles. After carefully screening all

included titles, 1229 articles were excluded as they were clearly irrelevant. Of the remaining 31 papers, 21 were excluded because they did not investigate the relationship between MetS and cataract, or they identified as a review or duplicate report during screening of the abstracts. Following a full text review, 4 articles with same population were excluded. Ultimately, 6 studies were included in this meta-analysis, including 3 cross-sectional studies (Paunksnis A et al., 2007 [22]; Sabanayagam C et al., 2011 [23, 24]), 1 case-control study (Galeone C et al., 2010 [25]), and 2 cohort study (Ghaem MH et al., 2013, Lindblad BE et al., 2008) [26, 27].

The main characteristics of all included studies for analysis are summarized in **Table 2**. These studies were conducted in Lithuania, Italy, Singapore, Korea, Sweden, and Australia. The population size ranged from 879 to 35369, with a total of 54398 participants involved. These studies were published between 2007 and 2014. All participants were at least 36 years old. Cataract definitions were different across the studies and were based on standardized criteria such as the Wisconsin grading system (Ghaem MH et al., 2013), the Lens Opacity Classification System III (LOCS III) (Paunksnis A et al., 2007; Sabanayagam C et al., 2011; Park YH et al., 2014), and the Swedish National Cataract Register (Lindblad BE et al.,

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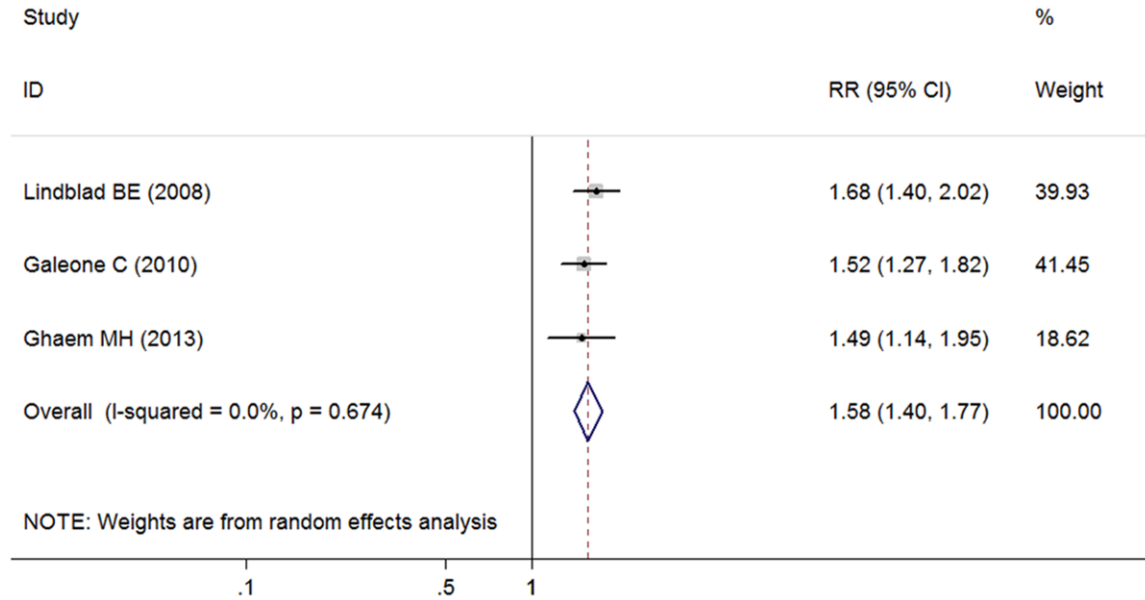


Figure 3. The association of metabolic syndrome with cataract risk after adjustment for confounders in cohort/case-control studies.

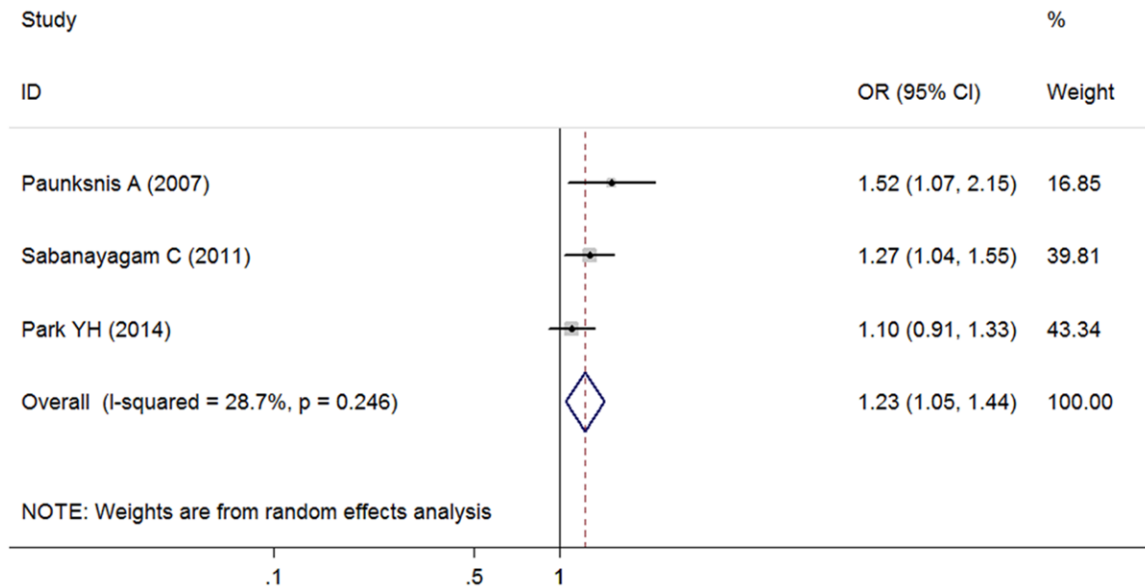


Figure 4. The association of metabolic syndrome with cataract risk after adjustment for confounders in cross-sectional studies.

2008). MetS definitions also varied across studies as follows: Two included studies (Paunksnis A *et al.*, 2007; Sabanayagam C *et al.*, 2011) [22, 23] used the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) criteria, while three studies (Galeone C *et al.*, 2010; Ghaem MH *et al.*, 2013; Lindblad BE *et al.*, 2008) [25-27] used the crite-

ria of the International Diabetes Federation (IDF), and the final study (Park YH *et al.*, 2014) [24] used the American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI) criteria. The percentages of cataract in groups with MetS were 25.2%, 48.3%, 50.2%, and 51.6% in four studies (Paunksnis A *et al.*, 2007; Sabanayagam C *et al.*, 2011; Galeone C

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Table 3. Metabolic syndrome and the risk of cataract in subgroup meta-analysis

Risk Factors	No. of Studies	Pooled OR (95% CI)	I^2 (%), P_h
Gender			
Female	2	1.29 (1.02-1.63)	23.7, 0.25
Male	2	1.04 (0.85-1.28)	6.8, 0.3
Type of Cataract			
CC	4	1.14 (0.81-1.62)	78.2, 0.03
PSC	3	1.14 (0.80-1.61)	18.4, 0.29
NC	4	1.06 (0.80-1.42)	67.3, 0.027
Surgery	3	1.75 (1.49-2.06)	0, 0.61
Definition of MetS			
IDF	3	1.58 (1.40-1.77)	0, 0.674
AHA/NHLB	1	1.1 (0.91-1.33)	non shown
NCEP-ATP III	2	1.33 (1.12-1.58)	0, 0.39
Individual Component of MetS			
Obesity	5	1.3 (1.09-1.55)	67.9, 0.014
High Glucose Levels	5	1.37 (1.10-1.71)	71.8, 0.007
High Blood Pressure	5	1.39 (1.08-1.79)	80.5, 0
High Triglycerides	5	1.1 (1.00-1.20)	0, 0.74
Low HDL Levels	4	1.17 (1.04-1.32)	0, 0.96
Number of components of MetS			
1	1	1.23 (0.98-1.54)	non shown
2	3	1.45 (1.12-1.88)	73.6, 0.023
≥3	3	1.7 (1.04-2.79)	87.6, 0.0

OR: odds ratio, CI: confidence interval, CC: cortical cataract, PSC: posterior subcapsular cataract, NC: nuclear cataract, IDF: International Diabetes Federation, AHA/NHLBI: the American Heart Association/National Heart, Lung, and Blood Institute, NCEP-ATP III: National Cholesterol Education Program Adult Treatment Panel III, HDL: high-density lipoprotein, P_h : P value of heterogeneity.

et al., 2010; Ghaem MH *et al.*, 2013), respectively. According to our predefined quality score for all studies, the scores of 6 studies were between 18 and 20.

The association between MetS and risk of cataract

Adjusted ORs and 95% CIs were provided in all included studies, while the data necessary to calculate OR were provided in four studies (Paunksnis A *et al.*, 2007; Galeone C *et al.*, 2010; Sabanayagam C *et al.*, 2011; Ghaem MH *et al.*, 2013). The pooled OR value calculated from the data provided in the four included articles indicated a significant increase in cataract incidence in patients with MetS in a fixed effects model (OR 1.49, 95% CI: 1.32-1.67). No statistically significant heterogeneity among studies was found ($I^2 = 6.0\%$, P value of hetero-

geneity (P_h) = 0.363) (**Figure 2**).

A forest plot revealing the association between MetS and cataract after adjustment for confounders is presented in **Figures 3** and **4**. A random effects model yields a combined adjusted OR of 1.58 in cohort/case-control studies ($P = 0.0$). No significant heterogeneity was observed ($P_h = 0.674$, $I^2 = 0.0\%$) (**Figure 3**). The significant positive association between MetS and cataract after adjustment for confounders was also found in cross-sectional studies (RR 1.23, 95% CI: 1.05 to 1.44, $I^2 = 28.7\%$) (**Figure 4**).

Subgroup analysis

The association between MetS and the risk of cataract in the subgroup analysis according to various factors is shown in **Table 3**. There was a significant difference in the association between MetS and the risk of cataract among female participants (OR = 1.29, $P = 0.03$), whereas such association was not found in male (OR

= 1.04, $P > 0.05$). In the subgroup meta-analysis by cataract type, MetS did increase the risk of cataract extraction (OR = 1.75, $P = 0.0$), but didn't increase the risk of three cataract subtypes.

We also performed a subgroup meta-analysis across definitions of MetS. A difference in the association between MetS and cataract risk was detected in the stratified analysis across MetS definition criteria. We identified a positive association between MetS and cataract risk in the 3 studies that used IDF (OR = 1.58), the 2 studies that used the NCEP-ATP III (OR = 1.33), but not in the study that used the AHA/NHLB (OR = 1.1, $P > 0.05$).

A subgroup analysis of the individual components of MetS also identified differences between groups. We restricted the analysis to

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obesity (body mass index/waist), high glucose levels (or reported diabetes), HBP (or reported hypertension), high triglycerides, or low HDL levels to find an independent association between each component of MetS and cataract risk. The ORs were 1.3 for obesity, 1.37 for high glucose levels, 1.39 for HBP, 1.10 for high triglycerides, and 1.17 for low HDL levels (**Table 3**).

To investigate the influence of the number of components of MetS, study participants were separated into subgroups: one MetS component, two components, and three or more components (**Table 3**). The ORs were 1.23 for participants with one component and 1.45 ($P = 0.005$) for those with two components. The presence of three or more MetS components was associated with approximately two-fold increase in cataract risk ($OR = 1.7, P = 0.034$).

Publication bias

There was no evidence of publication bias as indicated by Begg's test (P value = 0.089) in the included studies. It also revealed no significant publication bias for any of the three subgroups (two components: $P = 0.146$ for bias; three or more components: $P = 0.229$ for bias).

Discussion

With the rising prevalence of diabetes mellitus (DM), obesity, and hypertension, attention has concentrated on the influence of MetS on various diseases. Cataract may be one disease that is affected by MetS. In recent years, many observational studies have been conducted to evaluate the relationship between MetS and risk of cataract. The outcomes of those studies have been inconsistent, possibly due to their inclusion of a relatively small number of participants. In this situation, the application of a meta-analysis to describe the association is of immense value.

Our meta-analysis supports the hypothesis that a significant positive association exists between MetS and cataract risk, regardless of cataract type. This phenomenon was also observed after adjusting for confounders. Subgroup analysis and a publication bias test suggest that the results of this analysis were robust.

There was no evidence of a significant relationship between MetS and NC, CC, or PSC in the present meta-analysis, a finding that is contrary to the data from some previous studies [23, 24, 26, 28]. These studies have in some instances found a positive association of CC with MetS [23, 26], whereas the Korea National Health and Nutrition Examination Survey (KNHANES) did not confirm this association [24]. Based on previous reports of the Blue Mountains Eye Study (BMES) and KNHANES, MetS may be a predictor of NC [24, 28]. MetS was also found to be associated with an increased 5-year incidence of PSC ($HR = 1.75, 95\% CI: 1.01-3.04$) [26]. We were unable to evaluate the relationship between MetS and any cataract subtypes because of the small number of studies included.

In addition, there was a significant association between MetS and cataract in women rather than in men. This finding is consistent with those found in the study by Park YH *et al.* [24]. Several studies have reported strong association of MetS with cataract risk among women [22, 29, 30]. This may be due to different hormonal level and life-style between men and women. However, only two studies provided OR calculable data to evaluate the association between MetS and cataract in both genders, and this is not enough power to statistically detect an effect.

We also examined the association of MetS with cataract risk by MetS definition criteria. Various studies have used different criteria for defining MetS, such as IDF [31] and NCEP-ATP III [32]. Most of the definitions are based on an individual having three or more of the five above-mentioned factors, but there are clear variations. These variations of MetS definition criteria may be the potential source of heterogeneity between studies.

Our meta-analysis of MetS components provides support for a possible relationship between cataract risk and DM, obesity, HBP, high triglycerides, and low HDL levels. Moreover, our analysis shows that cataract risk increases with the number of components of MetS. Despite these results, it is still unclear whether the increase in cataract risk is in fact due to the components of MetS or to a general metabolic derangement. The mechanisms linking cata-

ract risk and MetS (or its individual components) are not clear. Inflammatory mechanisms may play a role in cataract formation, and this may explain its relationship with MetS [33]. One study has suggested that measurements of C-reactive protein (CRP), a marker of inflammation, add clinically critical prognostic information to each component of MetS [34]. In addition, elevated CRP is associated with future cataract risk in healthy people [35]. Inflammation, as a manifestation of oxidative stress, may therefore be involved in the relationship between MetS and cataract development.

Many articles have reported that cataract risk is higher in subjects with DM or hyperglycemia [23, 36, 37], and this is supported by a recent meta-analysis [9]. Increased blood glucose levels may contribute to cataractogenesis. Three possible pathogenetic mechanisms have been provided for this process: nonenzymatic glycation of lens proteins, oxidative stress, and increased osmotic stress caused by an activated polyol pathway in glucose disposition [38, 39].

Likewise, the elevated prevalence of cataract in obese patients (compared to normal) was confirmed by the Age Related Eye Study (AREDS) [40] and BMES [28], consistent with our results. A possible explanation for the positive association between cataract risk and obesity is that individuals with increased plasma levels of leptin, a cytokine expressed by adipocytes, have also been shown to have an increased accumulation of reactive oxygen species, which are a major cause or consequence of lens opacification [41, 42].

However, the relationship between hypertension and cataract risk is disputed. The study from Singapore found that hypertension was associated with an increased risk of cataract surgery [23], while the study from France reports the opposite [43]. The biological mechanism that relates hypertension and cataract risk is unclear, but the association of hypertension with increased CRP levels suggests that an inflammatory process may be involved [34]. Anti-hypertension medications also play a part role in cataract development [44].

This meta-analysis has some potential limitations. First, over- or underestimation of OR values might have occurred. This is because the

residual confounds inherent to each of the original studies cannot be controlled, even though all included studies controlled for several known risk factors, such as gender, types of cataract, and individual components of MetS. Second, all of the studies included in our meta-analysis were observational studies instead of randomized controlled trials (RCTs). It is generally recognized that observational studies are more likely to be subject to confounding and bias than RCTs, which may consequently confound the results of our analysis. Third, only six studies are included in our report. Although no publication bias was found by Begg's test, the possibility of publication bias cannot be fully ignored in a low-powered analysis. Finally, the different studies used various cataract grading systems and MetS definition criteria, which may increase the heterogeneity among the studies.

Conclusions

Our meta-analysis of six studies suggests that MetS is associated with increased cataract risk. Given the increasing global burden caused by metabolic risk factors like MetS, even a slight association of these factors with increased cataract risk can have real health consequences for the population. Therefore, the relationship between MetS and cataract risk should not be ignored. Further well-designed studies need to confirm a causal relationship.

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Disclosure of conflict of interest

None.

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