

Smoking and the risk of dry eye: a Meta-analysis

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INTRODUCTION

Dry eye is a multifactorial disease characterized by ocular surface changes which result in tear film impairment, eye itchiness, redness, light hypersensitivity, blurred vision, and other symptoms and/or discomforts^[1-2]. Dry eye is estimated to affect 5% -35% of worldwide population at various ages with increasing frequency^[3]. In the United States, moderate and/or severe dry eye affected more than 3.2 million of female and 1.6 million of male population at the age of above 50 years old^[4-5]. In China, the incidence of dry eye is also increasing because of air pollution, the popularization of computer and mobile phone, and rapid aging of the population, which is becoming an increasingly significant public health problem.

Dry eye is associated with many risk factors such as environment, lifestyle, age, sex, drug history, and systemic diseases, among which the lifestyle factors may play an important role^[3]. Smoking is already known as an important risk factor for many chronic diseases and however is still an unclear risk factor of dry eye^[3]. A number of studies evaluated the association between smoking and dry eye risk^[6-19], which show that smoking could increase the risk of dry eye^[12-13,17-18]. However, other researches showed disputed results^[7-8,10-11,14-15,19]. The definition of dry eye was suggested according to tear break-up time (TBUT) and Schirmer score^[2], and smoking was found to decrease TBUT in some of the studies^[6,9,16], in which Sayin *et al*^[9] found the decreasing of Schirmer score in smokers. Among the analyses, most of them showed their investigations were performed in specific populations. However, these results may not be representative of the larger population. Therefore, this Meta-analysis aims to summarize the association between smoking and the risk of dry eye, and to provide useful evidence for this association.

MATERIALS AND METHODS

Literature Search The PubMed, EMBASE, The Cochrane Central Register of Controlled Trials (CENTRAL, last issue), CBM (Chinese BioMedical Literature Database) and CNKI (China National Knowledge Infrastructure/Chinese Academic Journals full-text Database) were searched for relevant articles published from January 1964 to December 2015. Our

Abstract

• **AIM:** To collect the evidence to estimate the correlation between smoking and the incidence of dry eye.

• **METHODS:** The PubMed, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL, last issue), CBM (Chinese BioMedical Literature Database), and CNKI (China National Knowledge Infrastructure/Chinese Academic Journals full-text Database) were searched for eligible studies published from January 1964 to December 2015 to investigate the association of smoking with the risk of dry eye. The odds ratio (OR) and 95% confidence interval (CI) were summarized and calculated. The extracted studies were pooled by the fixed-effects model or a random-effects model.

• **RESULTS:** Two cohort studies and eight cross-sectional surveys were included in our Meta-analysis. There was no statistically significant relationship between current (OR=1.32; 95% CI: 0.99-1.76; $P=0.055$) or ever smoking (OR=1.12; 95% CI: 0.98-1.28; $P=0.107$) and the risk of dry eye among the studies, even when age and gender were adjusted (OR=1.16; 95% CI: 0.83-1.64; $P=0.383$). In the sensitivity analysis in which only general population were included, the association was significant between smoking and dry eye (OR=1.50; 95% CI: 1.08-2.09; $P=0.016$).

CONCLUSION: This Meta-analysis suggests that smoking may associate with the risk of dry eye in general population.

KEYWORDS: dry eye; smoking; Meta-analysis

Table 1 PubMed search strategy

No.	Search strategy ¹
1	“Tobacco”[Mesh] OR “Smoking”[Mesh]
2	Smok*[tiab] OR tobacco[tiab] OR cigarette[tiab] OR nicotiana*[tiab] OR lifestyle*[tiab]
3	1 OR 2
4	“Dry Eye Syndromes”[Mesh] OR “Meibomian Glands”[Mesh]
5	dry eye*[tiab] OR xerophthalmi*[tiab] OR meibomian gland dysfunction[tiab] OR MGD[tiab]
6	4 OR 5
7	“Case-Control Studies”[Mesh] OR “Cohort Studies”[Mesh] OR “Cross-Sectional Studies”[Mesh]
8	Case control [tiab] OR case comparison[tiab] OR case compeer[tiab] OR case referrent*[tiab] OR case base [tiab] OR retrospective stud*[tiab] OR cohort[tiab] OR concurrent stud*[tiab] OR incidence[tiab] OR longitudinal stud*[tiab] OR follow up[tiab] OR prospective stud*[tiab] OR cross sectional[tiab] OR disease frequency[tiab] OR prevalence[tiab]
9	7 OR 8
10	3 AND 6 AND 9

¹Database: PubMed (inception to December 2015).

Table 2 EMBASE search strategy

No.	Search strategy ¹
1	Exp tobacco/ OR exp smoking/
2	(smok* OR tobacco OR cigarette OR nicotiana* OR lifestyle*).mp
3	1 OR 2
4	Exp dry eye/ OR exp xerophthalmia/ OR exp meibomian gland/
5	(Dry eye* OR xerophthalmi* OR meibomian gland dysfunction OR MGD).mp
6	4 OR 5
7	Exp case control study/ OR exp cohort analysis/ OR exp cross-sectional study/
8	(Case control OR case comparison OR case compeer OR case referrent* OR case base OR retrospective stud* OR cohort OR concurrent stud* OR incidence OR longitudinal stud* OR follow up OR prospective stud* OR cross sectional OR disease frequency OR prevalence).mp
9	7 OR 8
10	3 AND 6 AND 9

¹Database: EMBASE (OvidSP) (1974 to 2015 December).

search strategies of PubMed and EMBASE are provided by Tables 1 and 2. We also searched the references which listed in the retrieved studies to find additional related articles.

Study Selection For our Meta-analysis, articles fulfilled these inclusion criteria were selected: 1) cross-sectional, case-control or cohort study design; 2) estimation of the association between smoking and dry eye risk; 3) reporting of data adequate to estimate relative risk (RR) and/or odds ratio (OR) with a 95% confidence interval (95% CI). And the exclusion criteria were as follows: 1) repeated publications; 2) non-original literature (*e.g.* comment, letter, review, *etc.*). In cases of the publication overlapped, we only used the studies with the largest sample size. And it had no language limitations for the publications.

Data Extraction The following information from each included studies were extracted: first author, publication year, country, years of follow-up or the study period, study design, age range, the sample size, smoking exposure status, the ORs with corresponding 95% CIs, and the adjusted variables. The status of smoking exposure (*i.e.* current and/or ever smoking) was taken from each of the articles directly.

The data extraction was performed independently by two authors (Xu L and Zhu XY) who resolved the disagreements

by discussions between them. The final decision was made by a third investigator (Zhang W) if no consensus could be achieved.

Statistical Analysis In our Meta-analysis, the association of smoking with dry eye was investigated, with or without the adjustment of age and gender. Then, to pool a risk estimate, we extracted the ORs of dry eye related to smoking from individual studies and weighted log risk estimates by the inverse of their variances. Among the included studies, heterogeneity was detected using Q -test. Studies were pooled using a Mantel-Haenszel fixed-effects model or a DerSimonian and Laird random-effects model depending on the heterogeneity [20]. In addition, for the control of potential bias, sensitivity analysis was performed. Egger's regression asymmetry test was performed to examine the possible publication bias with a funnel plot of log [OR] against its standard error (SE) visually.

All statistical analyses were completed by the statistical analysis software STATA 11.2 (Stata Corporation, College Station, TX, USA). A P value less than 0.05 was defined as statistically significance for the pooled ORs, while the significance level was 0.10 for the test of heterogeneity and publication bias. All the tests were two sided.

Table 3 Summary of the ten studies included in this Meta-analysis with regard to the smoking status and dry eye risk

First author	Year	Country	Population	Study design	Age range (a)	n	Smoking exposure status	OR (95% CI)	Adjusted age and gender
Uchino ^[7]	2009	Japan	Office workers who use visual display terminals	Cross-sectional survey	22-60	3549	Current	0.77 (0.53-1.12)	Y
Sahai ^[8]	2005	India	Hospital-based population	Cross-sectional survey	>20	500	Current	1.42 (0.89-2.27)	-
Moss ^[10]	2008	USA	Population-based	Cohort study	43-86	2414	Current	0.89 (0.65-1.20)	-
							Ever	1.06 (0.86-1.30)	-
Chia ^[11]	2003	Australia	Population-based	Cross-sectional survey	≥49	1075	Current	0.70 (0.40-1.10)	Y
Lee ^[12]	2002	Indonesia	Households	Cross-sectional survey	≥21	1058	Current	1.50 (1.00-2.20)	Y
							Ever	1.20 (0.60-2.40)	-
Moss ^[13]	2000	USA	Population-based	Cohort study	43-84	3703	Current	1.44 (1.13-1.83)	Y
							Ever	1.16 (0.96-1.39)	-
Uchino ^[14]	2013	Japan	Office workers who use visual display terminals	Cross-sectional survey	22-65	561	Current	0.86 (0.54-1.35)	Y
Xiao ^[17]	2011	China	Smoker and non-smoker (man)	Cross-sectional survey	25-75	2385	Current	2.24 (1.78-2.81)	-
Su ^[18]	2012	China	Students	Cross-sectional survey	19-26	1168	Current	2.57 (1.41-4.67)	-
Hua ^[21]	2014	China	Population-based	Cross-sectional survey	12-88	2600	Current	2.26 (1.50-3.40)	Y

Table 4 Statistical results of the included studies

Groups	Reference No.	OR (95% CI)	P	Heterogeneity test	
				Q	P
Current smoking	7-8,10-14,17-18,21	1.32 (0.99-1.76)	0.055	55.42	0.000
Sensitivity analysis (1)	7,11-14,21	1.16 (0.83-1.64)	0.383	23.24	0.000
Sensitivity analysis (2)	6,10-13	1.50 (1.08-2.09)	0.016	38.45	0.000
Ever smoking	9,11-12	1.12 (0.98-1.28)	0.107	0.45	0.800

Sensitivity analysis (1): Only the studies which adjusted age and gender were included; Sensitivity analysis (2): Only general population were included.

RESULTS

Ten studies ^[7-8,10-14,17-18,21] which fulfilled the inclusion criteria were identified (refer to the flow diagram in Figure 1), including two cohort studies ^[10,13] and eight cross-sectional surveys ^[7-8,11-12,14,17-18,21]. Two cohort studies ^[10,13] were both from the United States. Three of the eight cross-sectional surveys included ^[17-18,21] were from China, two ^[7,14] from Japan, one^[8] from India, one^[11] from Australia, and one^[12] from Indonesia. The study samples included in the Meta-analysis were summarized in Table 3.

Current Smokers All ten studies ^[7-8,10-14,17-18,21] in which two cohort studies ^[10,13] and eight cross-sectional surveys ^[7-8,11-12,14,17-18,21] were included in the analysis of the relationship between current smoking and the risk of dry eye, among which six studies ^[7,11-14,21] adjusted variables including age and gender, and seven studies ^[10-13,17-18,21] were population-based studies (Table 4). It was found that the association between current smoking (OR=1.32; 95% CI: 0.99-1.76; P=0.055) and increased risk of dry eye was not statistically significant (Figure 2). Statistically significant heterogeneity (Q=55.42, P=0.000) was found across the studies.

Ever Smokers Three studies ^[10,12-13] in which two cohort studies and one cross-sectional survey was included in the analysis of the relationship between ever smoking and dry eye risk (Table 4). It was found that the association between ever smoking (OR=1.12; 95% CI: 0.98-1.28; P=0.107) and increased risk of dry eye was also not statistically significant

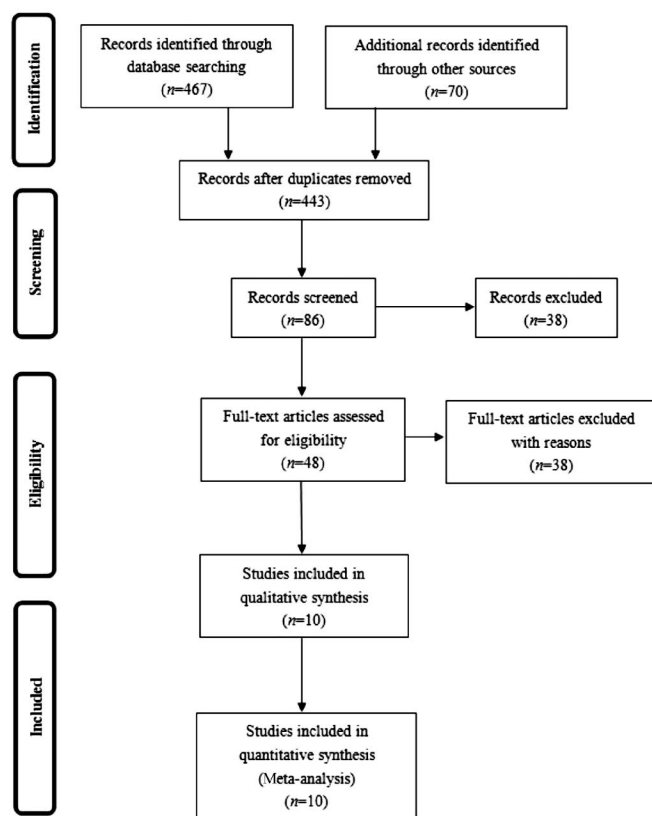


Figure 1 PRISMA flow diagram.

(Figure 3). Statistically significant heterogeneity (Q=0.45, P=0.800) was not found across the studies.

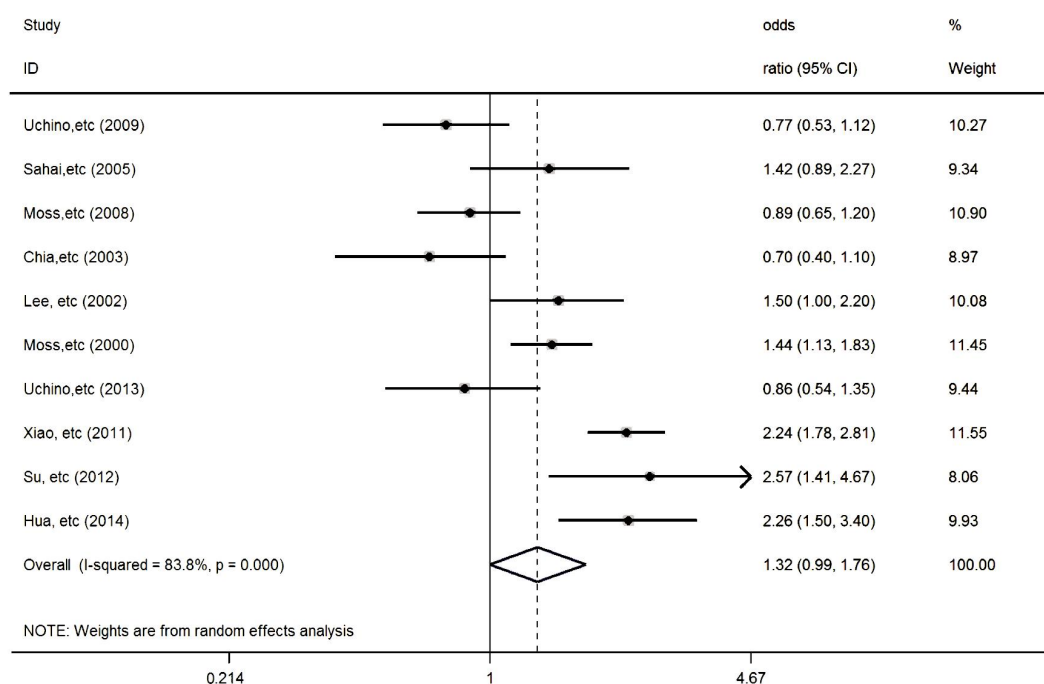


Figure 2 In ten included studies (two cohort studies and eight cross-sectional surveys), risk estimates of dry eye associated with current cigarette smoking. Squares indicate study-specific risk estimates (size of square reflects study-specific statistical weight, *i.e.* inverse of the variance); horizontal lines indicate 95% CIs; diamonds indicate summary risk estimates with its corresponding 95% CI.

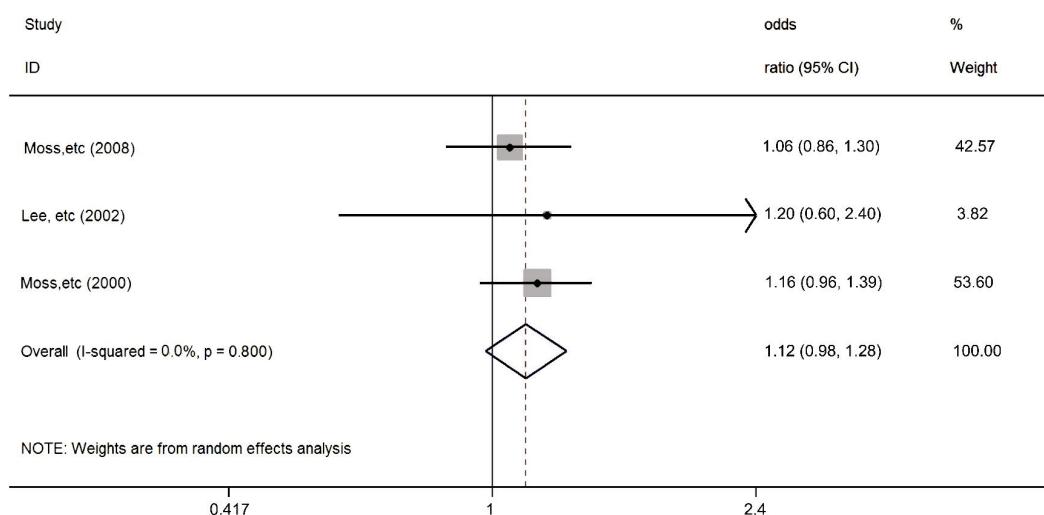


Figure 3 In three included studies (two cohort studies and one cross-sectional survey), risk estimates of dry eye associated with ever cigarette smoking. Squares indicate study-specific risk estimates (size of square reflects study-specific statistical weight, *i.e.* inverse of the variance); horizontal lines indicate 95% CIs; diamonds indicate summary risk estimates with its corresponding 95% CI.

Adjusted Age and Gender When only the studies which adjusted age and gender were included [7,11-14,21], the result showed no statistically significant relationship between current smoking and dry eye (OR=1.16; 95% CI: 0.83-1.64; $P=0.383$) (Figure 4). The heterogeneity across the studies was not significantly changed by Q test ($Q=24.23$, $P=0.000$).

General Population In the sensitivity analysis in which only general population were included [10-13,17-18,21], the result showed statistically significant relationship between current smoking and dry eye (OR=1.50; 95% CI: 1.08-2.09; $P=0.016$) (Figure 5). The heterogeneity across the studies was not significantly changed by Q test ($Q=38.45$, $P=0.000$). Furthermore, Egger's regression asymmetry test was

performed to detect the possible publication bias. It revealed no statistically significant publication bias for the association between current smoking and dry eye ($P=0.397$) (Figure 6), even when only the studies which adjusted age and gender ($P=0.383$) or in the sensitivity analysis in which only general population were included ($P=0.706$). No statistically significant asymmetry was also not detected for association between ever smoking and dry eye ($P=0.875$) which indicating an absence of substantial publication bias (Figure 7).

DISCUSSION

In our primary Meta-analysis, the effect of smoking on dry eye was evaluated. Our results showed no significant association between current smoking and increased risk of

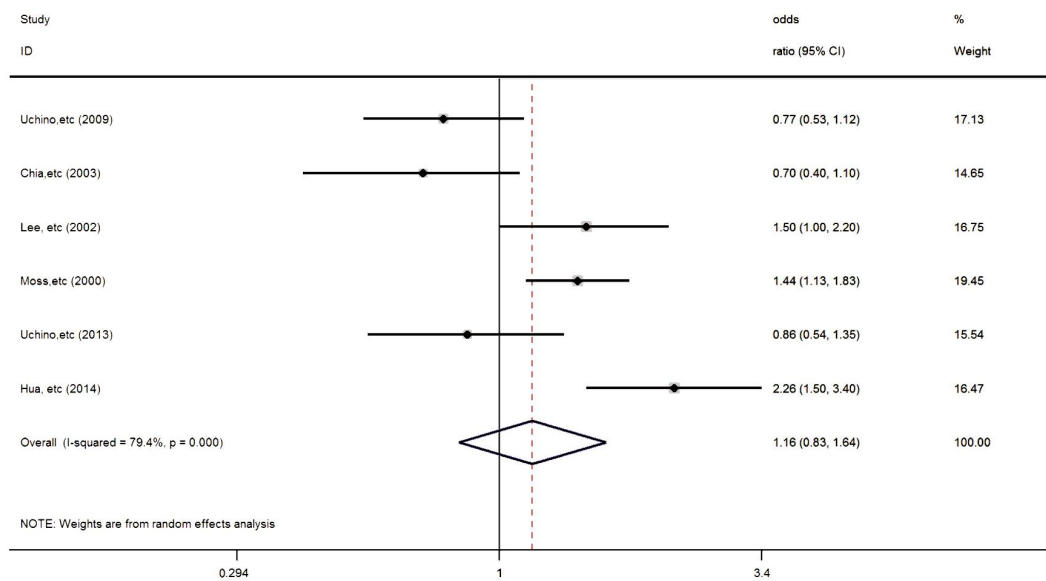


Figure 4 In six included studies (one cohort study and five cross-sectional surveys), risk estimates of dry eye associated with current cigarette smoking which adjusted age and gender. Squares indicate study-specific risk estimates (size of square reflects study-specific statistical weight, *i.e.* inverse of the variance); horizontal lines indicate 95% CIs; diamonds indicate summary risk estimates with its corresponding 95% CI.

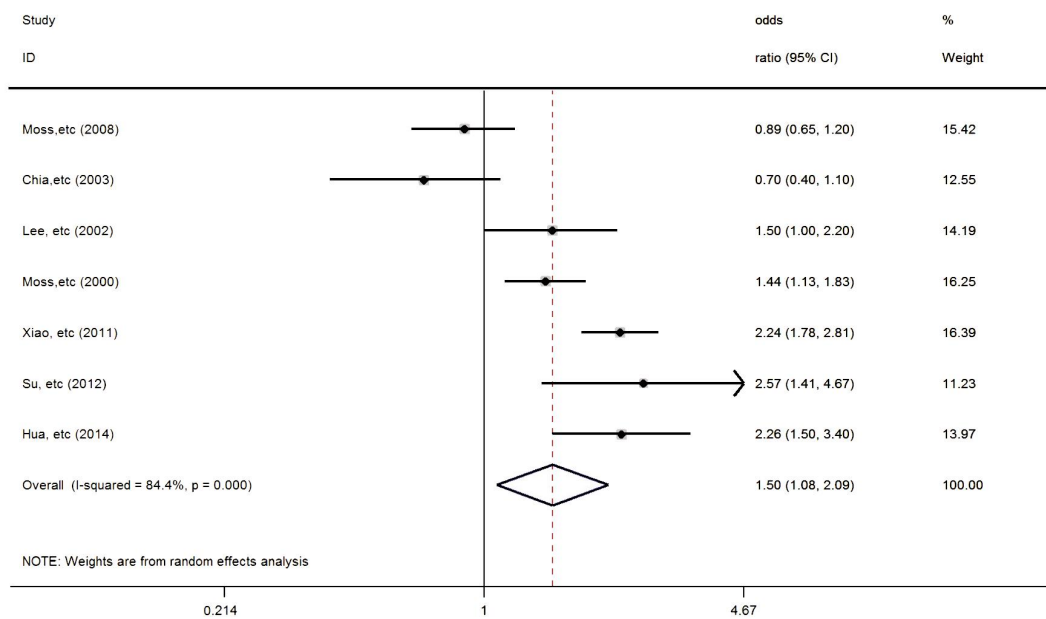


Figure 5 In seven included studies (two cohort studies and five cross-sectional surveys), risk estimates of dry eye associated with current cigarette smoking. Squares indicate study-specific risk estimates (size of square reflects study-specific statistical weight, *i.e.* inverse of the variance); horizontal lines indicate 95% CIs; diamonds indicate summary risk estimates with its corresponding 95% CI.

dry eye, but the *P* value was close to 0.05 (*P*=0.055). We also found no significant association in the analyses on ever smoking (*P*=0.107).

Several pathogenesis of dry eye including chronic inflammation of the ocular surface, decreased sensitivity of cornea and conjunctiva, reduction of production and/or stability of tears, and epithelial damage have been suggested^[1-2]. As mentioned, smoking is a well-known risk factor for many chronic diseases, which also affects the eyes. The health of the eye could be affected by smoking toxins which decrease blood flow and/or accelerate thrombus formation in ocular capillaries^[22]. Cigarette smoking may also cause a higher risk

of many eye diseases such as cataracts, age-related macular degeneration, glaucoma, diabetic retinopathy, and optic neuritis^[22], but the relationship between smoking and the risk of dry eye was still unclear. The pooled analysis by Thomas *et al*^[16], and some other studies^[6,9] found that the tear stability and the sensitivity of cornea and conjunctiva could be decreased by smoking which also showed the decreased TBUT. Also, for dry eye patients, smoking had been reported to induce discomforts including burning and foreign body sensation of the eyes^[23-24]. But for the results of Schirmer score, it showed no significant change^[6,16]. On the International Dry Eye Workshop 2007, the diagnostic criteria

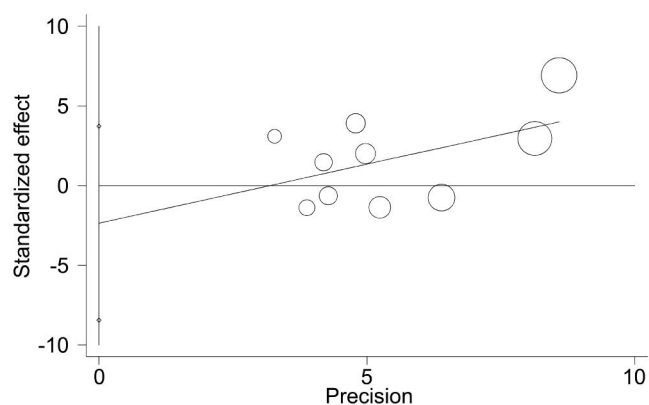


Figure 6 A funnel plot, showing no publication bias of ten included studies (two cohort studies and eight cross-sectional surveys) as assessed by Egger's test in this Meta-analysis.

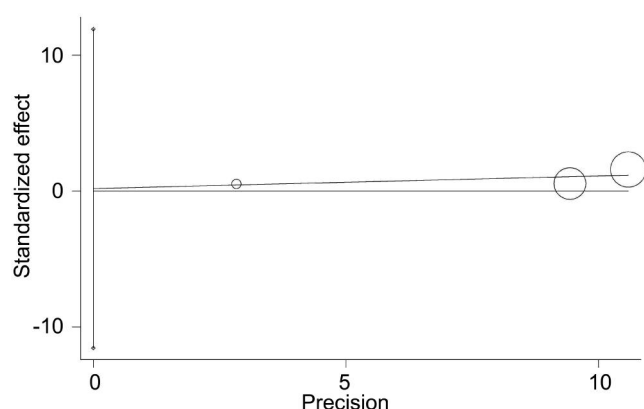


Figure 7 A funnel plot, showing no publication bias of three included studies (two cohort studies and one cross-sectional survey) as assessed by Egger's test in this Meta-analysis.

of dry eye were suggested to be TBUT ≤ 10 s and Schirmer score performed without anesthesia ≤ 5 mm in 5min [2]. The possible explanation is that there were no clear diagnostic criteria of dry eye in the studies or just using questionnaire. It may affect the association between dry eye and smoking of some studies, thus cause the bias.

Dry eye is associated with many risk factors such as environment as mentioned. Among the risk factor of dry eye, older age and female sex were two of the most inconsistent ones [3,25]. The effect of sex hormones on the homeostasis of ocular surface had been acknowledged. It was reported by Sullivan et al. that androgen levels decrease with advancing age in both males and females [26]. Clinically, patients suffering from sex hormone deficiency including congenital androgen insufficiency syndrome [27-28], Sjogren's syndrome [29], premature ovarian failure [30], and those receiving anti-androgen medications [31-33] usually had higher risk of dry eye. Also, it is known that smoking is more prevalent in male population than female. Five studies in which adjusted age and gender were included in the analysis [7,11-14]. When age and gender were adjusted, it also showed no statistically significant relationship between current smoking and dry eye (OR=1.16; 95% CI: 0.83-1.64; $P=0.383$).

Apart from age and sex, environment may also affect the incidence of dry eye. For example, the office workers who use visual display terminals (VDTs) [34] and glaucoma patient who use anti-glaucoma medication [35] were found to have higher risk of dry eye. In this Meta-analysis, the result of no significant association was changed between current smoking and dry eye when only the studies which sample is general population were included. The possible explanation for the inconsistency of the result is that some of the studies included in our primary Meta-analysis were related to the populations exposed to other risk factors of dry eye such as the use of VDTs, or the studies were related to specific population such as hospital-based population.

Several strengths and limitations of this Meta-analysis should be understood for proper interpretation of the results and findings. For the strengths, the first is this Meta-analysis included the studies in several important English databases published from January 1964 to December 2015. Second, the adjustment of age and gender and the subgroup analysis of general population were performed to avoid the bias of different age and sex, and to reduce the influence of different population including the patients of other eye diseases and/or visual display terminal users, and positive results was found in the analysis of general population. The most important is that the result of this Meta-analysis may be helpful to the ophthalmologists' suggestion of lifestyle on dry eye patients. For the limitations, the first is that most of the articles included are cross-sectional surveys which may affect the quality of this analysis. Second, our results were probably be affected by misclassification of smoking, and we did not include the studies related to passive smoking. And our results may be affected by different factors although we did sensitivity analysis of general populations and adjusted age and gender. Third, among the studies included, some of them showed different or unclear diagnostic criteria and/or types of dry eye, which may also affect our results. The statistically significant heterogeneity showed by our result could not be avoided. In addition, present data were inadequate to carry out dose-dependent risk estimation.

In summary, this Meta-analysis of all ten studies shows negative association between current and/or ever smoking and increasing risk of dry eye. But when only the studies which sample is general population were included, it showed statistically significant relationship between current smoking and dry eye. The findings would be possible to indicate that smoking may associate with the risk of dry eye in general population which may be helpful to the ophthalmologists' suggestion on dry eye patients. This Meta-analysis cannot explore the association between different types of dry eye and smoking due to the limitation of data in this study. Therefore, further investigations and Meta-analysis are needed to validate the role for smoking in the incidence of dry eye.

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