

Metabolic syndrome risk factors and dry eye syndrome: a Meta-analysis

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Abstract

• **AIM:** To explore the relationship between metabolic risk factors and dry eye syndrome (DES).

• **METHODS:** Retrieved studies on the association of metabolic syndrome risk factors (hypertension, hyperglycemia, obesity, and hyperlipidemia) and DES were collected from PubMed, Web of Science, and the Cochrane Library in December 2015. Odds ratio (OR) with 95% confidence interval (CI) were pooled to evaluate the final relationship. Subgroup analyses were conducted according to diagnostic criteria of DES.

• **RESULTS:** Nine cross-sectional studies and three case-control studies were included in this Meta-analysis. The pooled results showed that people with hypertension, hyperglycemia, and hyperlipidemia had a higher risk of suffering from DES ($P < 0.05$), especially the typical DES symptoms. On the other hand, obesity did not increase the risk of DES.

• **CONCLUSION:** The present Meta-analysis suggests that all metabolic risk factors except obesity were risk factors for DES.

• **KEYWORDS:** dry eye syndrome; hypertension; hyperglycemia; obesity; hyperlipidemia; Meta-analysis

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INTRODUCTION

Dry eye syndrome (DES) is well recognized as a global health problem with a high prevalence ranging from

7.8% to 33.7%^[1-3]. DES is also the most common reason among patients for visiting ophthalmology clinics^[1]. The concept of DES has been consistently understood as an ocular surface disorder characterized by eye discomfort, visual disturbance, tear film instability, destruction and inflammation of the ocular surface, and high tear osmolarity^[4-5]. In addition to increased health care costs, physical discomfort, impaired vision-related quality-of-life issues and visual dysfunction^[6], DES patients also suffer from a higher risk of psychological problems such as anxiety and depression^[7]. In order to prevent the disease from the source, during the past decades, numerous etiological studies have been conducted to explore the potential risk factors of DES, many of which have indicated that DES might be related to metabolic syndrome and its risk factors^[2-3,8-17].

Metabolic syndrome risk factors consist of four different disorders: obesity, hypertension, hyperglycemia, and hyperlipidaemia^[18]. The relationship between these four disorders and DES remains unclear and even controversial among studies published so far^[8-17]. Additionally, single studies may be limited by sample size. We therefore performed this Meta-analysis to quantitatively explore the relationship between metabolic syndrome risk factors and DES, both of which are public health issues of common concern.

MATERIALS AND METHODS

This Meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement checklist^[19].

Search Strategy and Study Selection PubMed, Web of Science, and the Cochrane Library databases were searched for original articles, published until December 2015. The search strategy keywords included DES ("dry eye syndrome", "DES", "xerophthalmia" and "keratoconjunctivitis sicca"), hypertension ("hypertension" and "high blood pressure"), hyperglycemia ("hyperglycemia", "hyperglycemia mellitus", "hyperglycemia" and "high blood glucose"), obesity ["obesity" and "high body mass index (BMI)"], hyperlipidemia ("hyperlipidemia", "high cholesterol" and "high blood lipids") and human studies. Taking the PubMed database as a sample, the search item for DES and hyperlipidemia was "hyperlipidemia (Title/Abstract)" OR "high cholesterol (Title/Abstract)" OR "high blood lipids (Title/Abstract)" AND "dry eye (Title/Abstract)" OR

"xerophthalmia (Title/Abstract)" OR "keratoconjunctivitis sicca (Title/Abstract)" AND "Human (Mesh)". The reference lists of selected papers were manually screened for potentially missing papers.

DES patients were divided into two groups in terms of diagnostic criteria: patients with typical DES symptoms and patients with clinically diagnosed DES. The former were usually diagnosed through a questionnaire or an interview containing typical DES symptoms (such as dryness, foreign body sensation, burning, fatigue, discomfort, *etc.*); and the later were diagnosed according to both typical DES symptoms and objective tests (such as tear film breakup time, Schirmer I test, *etc.*).

The primary selection of studies was based on titles and abstracts. Then two investigators (Shentu XC and Tang YL) independently screened the full text of each selected study using the following detailed inclusion criteria: 1) original research papers reporting independent data on the relationship between metabolic syndrome risk factors and DES; 2) case-control or cross-sectional studies. To avoid double publication, only the most recent or most informative studies were included. The studies involving two separate sets of data were considered to be two independent studies; and for the studies involving two separate case groups and the same control group, the data from the larger sample size was used. No specific language restriction was imposed on the selection of publications.

Data Extraction and Study Quality Assessment Two investigators (Tang YL and Cheng YL) independently extracted the data using a standardized data extraction format including the following data: first author's name, publication year, country, study design, sample size, hypertension status, hyperglycemia status, obesity status, hyperlipidemia status, adjusted variables, and odds ratio (OR) values with corresponding 95% confidence intervals (CI). Any disagreement was settled by consensus of the investigators.

Qualities of all selected studies were evaluated according to the Newcastle-Ottawa scale (NOS, Figure 1)^[20], and studies scoring five or more points were deemed to be of high quality.

Statistical Analysis All statistical analyses were performed using Stata version 12.0 software (StataCorp, College Station, TX, USA). The significance level of the statistics was set to $P < 0.05$, except in the case of heterogeneity. The OR values with corresponding 95% CI served as the valid estimate for all qualified studies to obtain a pooled OR with 95% CI. Potential heterogeneities among the included studies were evaluated using Cochran's Q statistic and an I^2 index score, and a P -value less than 0.10 or an I^2 score greater than 50% was considered to be significant^[21]. When high heterogeneity was detected, the random-effects model based

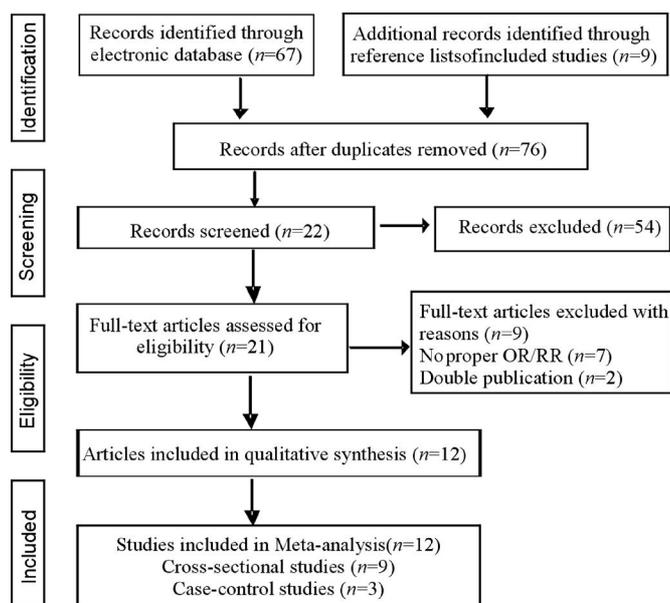


Figure 1 Qualities of all selected studies were evaluated according to the NOS.

on the DerSimonian and Laird method was used; otherwise, the fixed-effects model based on the inverse variance method was used^[22]. Subgroup analysis was performed according to diagnostic criteria and adjusted factors. And only if more than one study contained the same adjusted factors, subgroup analysis would be performed. The sensitivity analysis was used to assess the robustness of the main Meta-analysis results by sequentially omitting individual studies. Meta-regression analysis was used to analyze the source of heterogeneity. Egger's linear regression test and Begg's test were used to evaluate the potential publication bias^[23].

RESULTS

Characteristics of Included Studies Seventy-six unique articles were identified through searching three electronic databases and reference lists of the selected articles. Twenty-two articles were retrieved for the final review after the primary screen based on titles and abstracts. Ten articles were excluded for the following reasons: seven articles did not provide proper OR values with 95% CI, two articles provided data that had been used in other studies, and the full text of one article was not available. Finally, twelve articles met all the predefined inclusion criteria, including nine cross-sectional studies and three case-control studies. The characteristics of the selected studies are summarized in Table 1.

Hyperglycemia and Dry Eye Syndrome Three case-control studies and six cross-sectional studies involving 10 separate sets of data reported hyperglycemia data^[2-3,9,11-16]. Since significant heterogeneity was found among the included studies ($I^2=50.6\%$, $P=0.033$), the random-effects model was adopted. Based on the forest plot shown in Figure 2, hyperglycemia patients have a higher risk of suffering from DES (OR: 1.18, 95% CI: 1.04-1.35).

Table 1 Characteristics of 12 case-control/cross-sectional studies included into the present Meta-analysis

Source (Published year)	Country	Study design	Sample size	Age (a)	Diagnostic criteria	Adjusted factors	NOS scores
Yang <i>et al</i> (2015)	China	Case-control	1908	20-89	Typical symptoms	Age, sex, atherosclerosis, <i>etc</i>	7
Vehof <i>et al</i> (2014)	British	Cross-sectional	3824	20-87	Both	Age, glaucoma, asthma, <i>etc</i>	7
Ahn <i>et al</i> (2014)	South Korea	Cross-sectional	11666	19-95	Both	Age, gender, education, <i>etc</i>	6
Schaumberg <i>et al</i> (2009)	USA	Cross-sectional	25444	50-80+	Typical symptoms	Age, race, region of residence, <i>etc</i>	5
Malet <i>et al</i> (2014)	France	Cross-sectional	963	73-80+	Typical symptoms	Age, gender, smoking, <i>etc</i>	8
Uchino <i>et al</i> (2013)	Japan	Cross-sectional	672	22-65	Clinical diagnose	Sex, age, systemic disease, <i>etc</i>	8
Galor <i>et al</i> (2012)	USA	Case-control	2454458	21-100	Clinical diagnose	Gender, age	7
Uchino <i>et al</i> (2011)	Japan	Cross-sectional	3294	40-80+	Both	None	7
Viso <i>et al</i> (2009)	Spain	Cross-sectional	654	40-96	Both	Age, sex, computer use, <i>etc</i>	6
Moss <i>et al</i> (2000)	USA	Cross-sectional	3722	48-91	Typical symptoms	Age, sex, smoking status, <i>etc</i>	7
Chia <i>et al</i> (2003)	Australia	Cross-sectional	1174	50-90	Typical symptoms	Age, sex	7
Jie <i>et al</i> (2008)	China	Case-control	5324	40-101	Typical symptoms	None	7

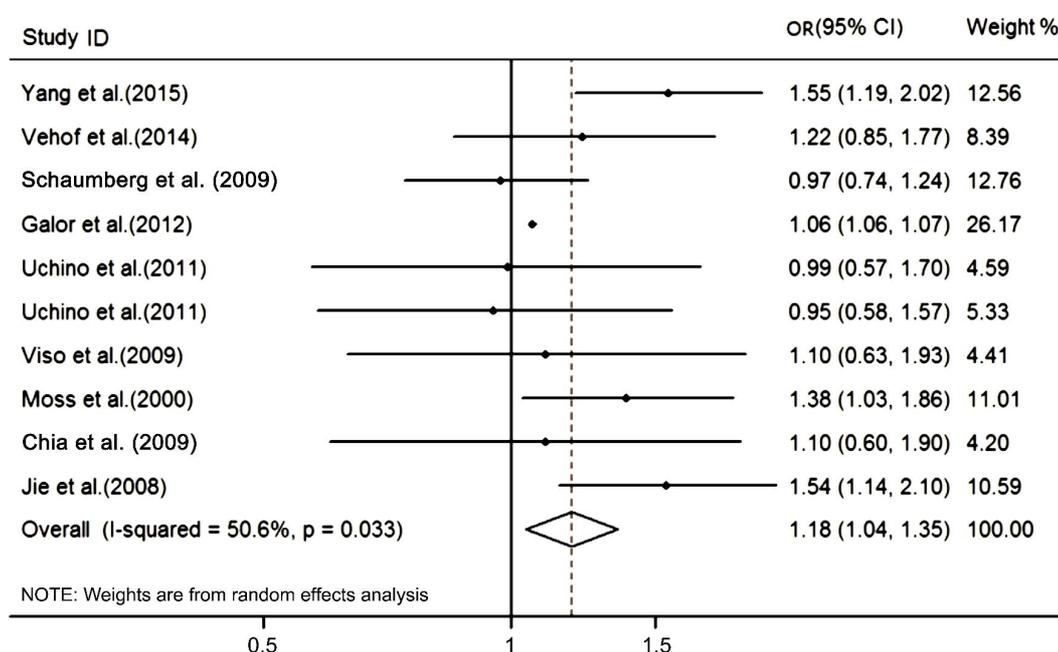


Figure 2 The association of hyperglycemia with DES.

Results from patients with typical DES symptoms were consistent with the pooled OR values above, while results from patients with clinically diagnosed DES were not (Figure 3; clinically diagnosed DES: OR: 1.28, 95% CI: 0.99-1.66; $I^2=62.5%$, $P=0.035$; typical DES symptoms: OR: 1.24, 95% CI: 1.08-1.42; $I^2=30.0%$, $P=0.210$).

Hypertension and Dry Eye Syndrome Nine separate sets of data from two case-control studies and six cross-sectional studies reported hypertension data [2-3,8-13]. The pooled results indicated that no significant relationship between hypertension and DES was detected in the random effects model (Figure 4, OR: 1.18, 95% CI: 0.93-1.50; $I^2=94.2%$, $P=0.000$).

Subgroup analysis was performed according to diagnostic criteria. According to Figure 5, patients with hypertension were more likely to suffer from typical DES symptoms (OR: 1.17, 95% CI: 1.00-1.37; $I^2=56.7%$, $P=0.055$), while they had no significant relationship with risk of clinically

diagnosed DES (OR: 1.03, 95% CI: 0.66-1.60; $I^2=93.3%$, $P=0.000$).

Obesity and Dry Eye Syndrome One case-control study and three cross-sectional studies reported obesity data [2,8,12,17]. Based on the forest plot shown in Figure 6, no significant relationship was detected between DES and obesity in the fixed-effects model (OR: 0.98, 95% CI: 0.94-1.02; $I^2=12.2%$, $P=0.336$). The results of subgroup analysis were consistent with the results in Figure 7 (clinically diagnosed DES: OR: 0.76, 95% CI: 0.55-1.04; $I^2=0.0%$, $P=0.796$; typical DES symptoms: OR: 0.98, 95% CI: 0.94-1.02; $I^2=0.0%$, $P=0.440$).

Hyperlipidemia and Dry Eye Syndrome One case-control study and two cross-sectional studies were included [3,8,11]. Two of them reported hypercholesterolaemia data; one reported lipid metabolism disorder data. In the random effects model ($I^2=58.2%$; $P=0.092$), a statistically significant relationship was detected (Figure 8, OR: 1.46, 95%CI: 1.30-1.65).

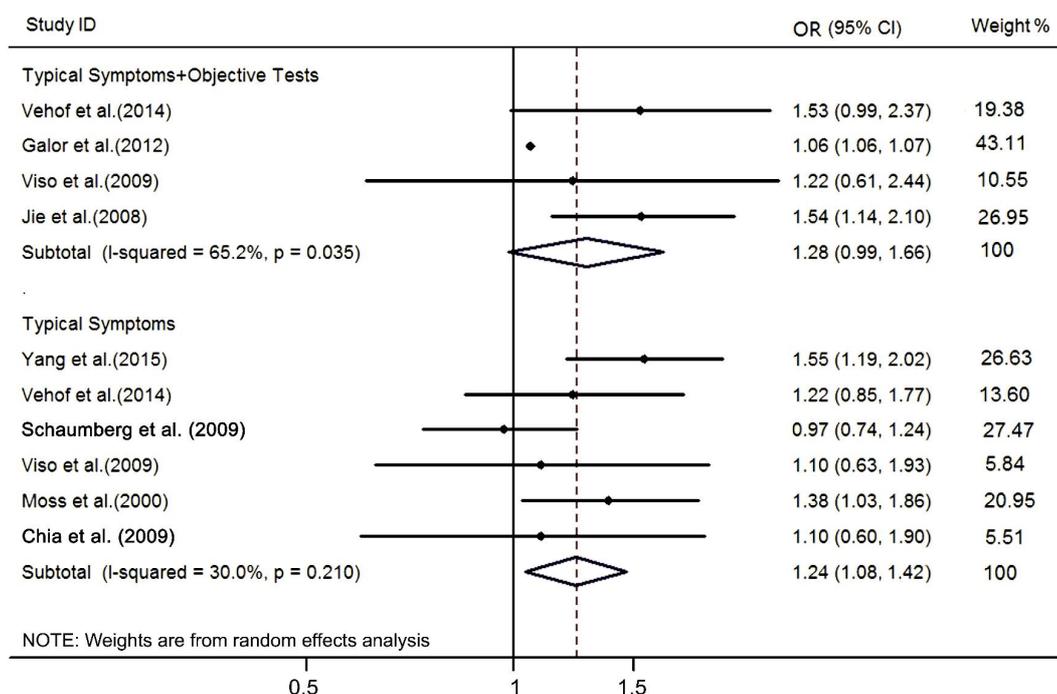


Figure 3 The association of hyperglycemia with typical DES symptoms and clinically diagnosed DES.

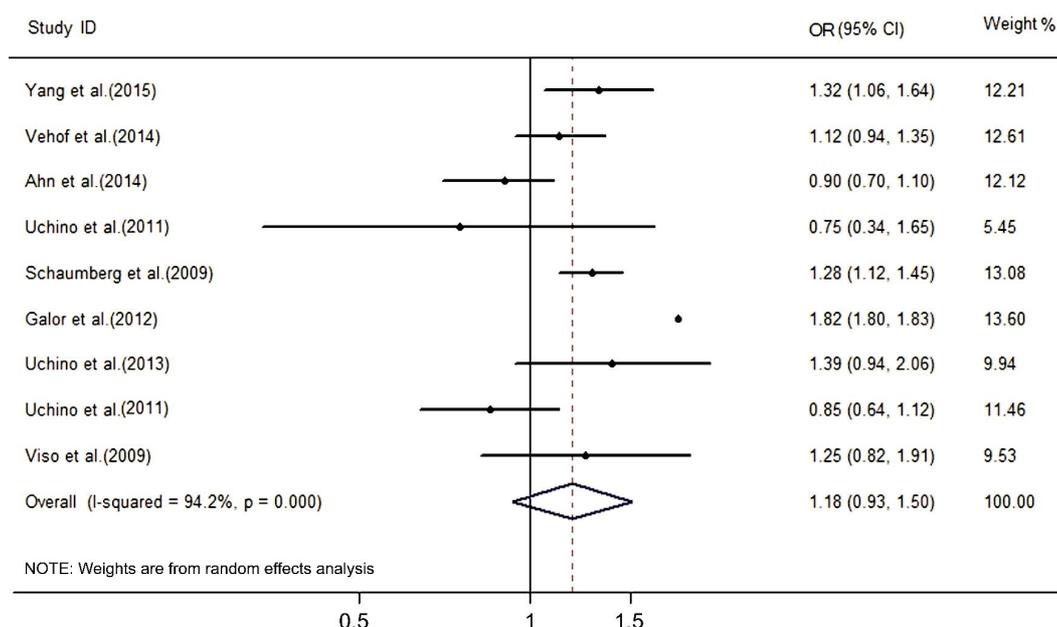


Figure 4 The association of hypertension with DES.

The pooled results of subgroup analysis according to diagnostic criteria were consistent with the main results above (Figure 9, clinically diagnosed DES: OR: 1.32, 95% CI: 1.04-1.68; $I^2=80.5\%$, $P=0.006$; typical DES symptoms: OR: 1.34, 95% CI: 1.17-1.54; $I^2=0.0\%$, $P=0.641$), and so were the results for the hypercholesterolaemia subgroup in the fixed model (OR: 1.35, 95% CI: 1.17-1.54; $I^2=0.0\%$, $P=0.630$).

Sensitivity Analysis and Publication Bias Sensitivity analysis carried out by sequentially omitting individual studies did not alter the significance of pooled OR estimates, indicating robust main Meta-analysis results. No significant publication biases were detected among the included studies,

except hypertension (Begg's test: $Z=0.10$, $P=0.917$; Egger's test: $P=0.001$).

Meta -regression Analysis We conducted a Meta-regression analysis to explore the influences of study design, publication year, study conducted area, sample size, and dry eye diagnostic criteria on explaining heterogeneity. The study conducted area was proved to be the main source of hyperglycemia data ($P<0.05$), and study design was the main source of hypertension data ($P<0.05$).

DISCUSSION

The results of the present Meta-analysis consisting three case-control studies and nine cross-sectional studies indicated that hyperglycemia, hyperlipidemia and hypertension were

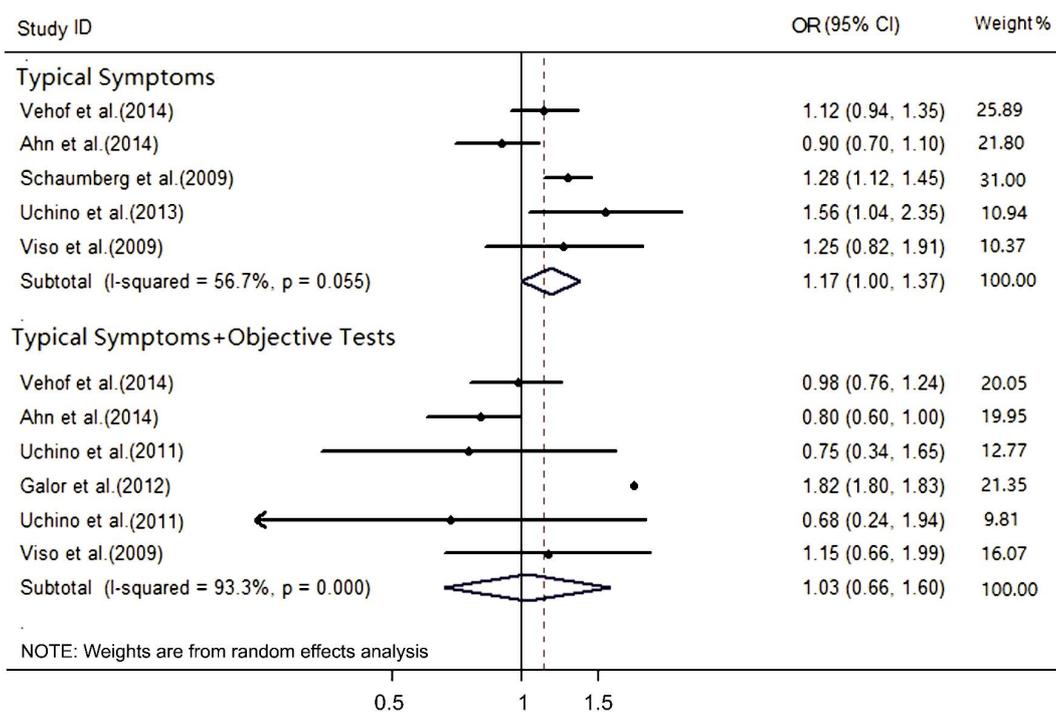


Figure 5 The association of hypertension with typical DES symptoms and clinically diagnosed DES.

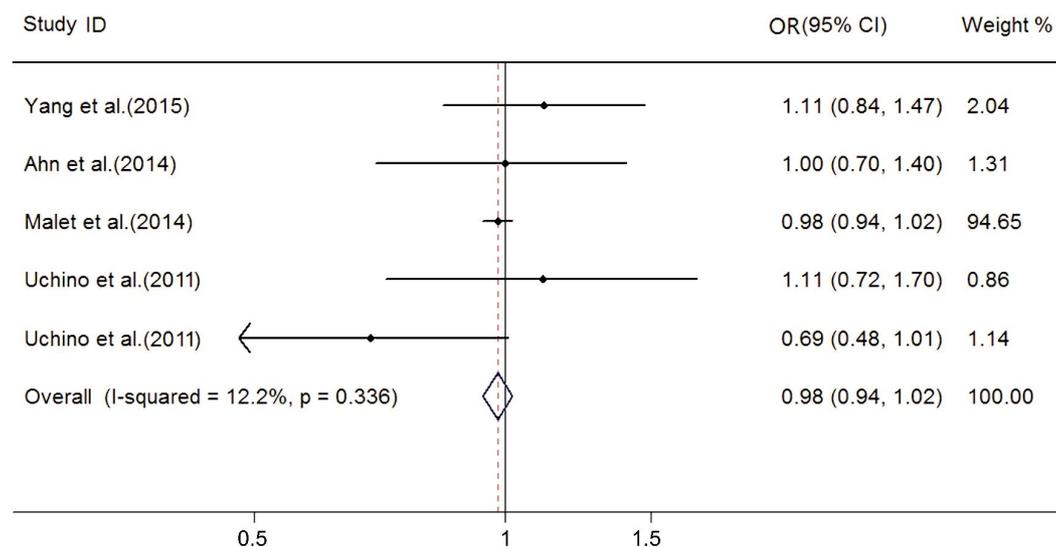


Figure 6 The association of obesity with DES.

significantly associated with an increased risk of DES, while obesity not. And the significance remained unchanged after adjustment other risk factors of DES, such as age, gender, alcohol, autoimmune disease and thyroid disease.

Our results imply that hyperglycemia could significantly increase the risk of DES, especially in the case of patients with typical DES symptoms. Diabetes could induce decrease in corneal sensation, followed by a decrease in tear production, impaired metabolic activity, and loss of cytoskeletal structure associated with cellular adhesion, which is the main mechanism of DES^[2,8,24].

According to subgroup analysis results, hyperglycemia was also a significant risk factor for patients with typical DES symptoms, and the relationship between hyperglycemia and clinically diagnosed DES reached near statistically significant

level. The minor inconsistencies of subgroup analysis might be caused by the inaccuracy of diagnostic criteria described in the included studies. Tear films consist of three layered structures: an inner mucus layer, a middle aqueous layer and an outer lipid layer^[25]. Nowadays, traditional objective tests aimed for diagnosis of DES could not comprehensively evaluate the tear film, especially for patients with reflectively increased tear secretion and reduced tear film quality^[2,26]. Besides, tear osmolarity test should also be involved in routine examination, as the progressively increased variation in tear osmolarity can well reflect the severity of DES and increase the sensitivity of current diagnosis criteria^[2-3,26]. Thus, in our opinion, the limitations of clinically diagnostic criteria for DES may influence the veracity of statistical results. Our Meta-analysis also indicated that hypertension was a risk

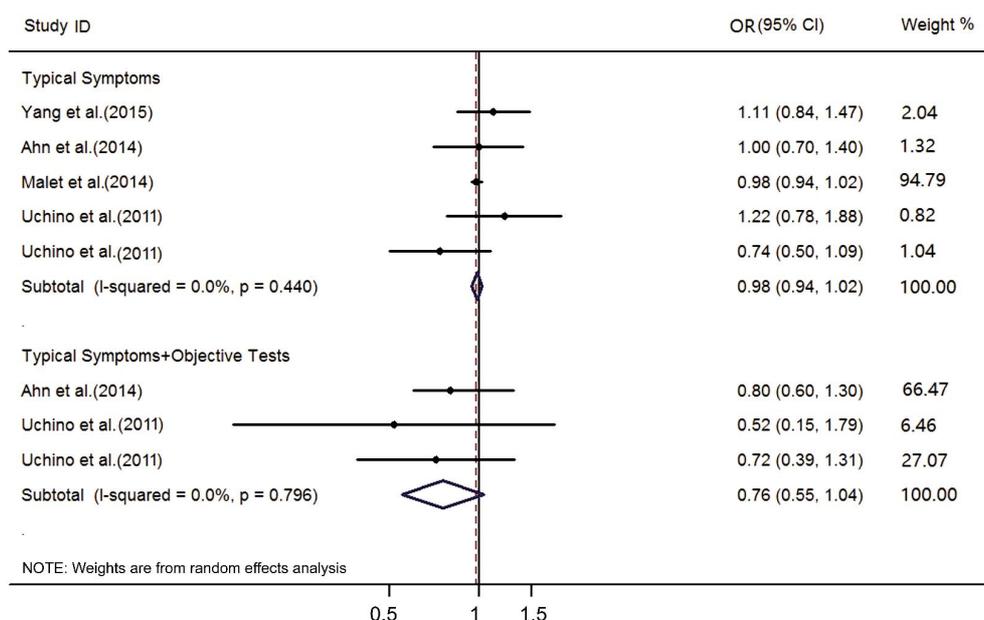


Figure 7 The association of obesity with typical DES symptoms and clinically diagnosed DES.

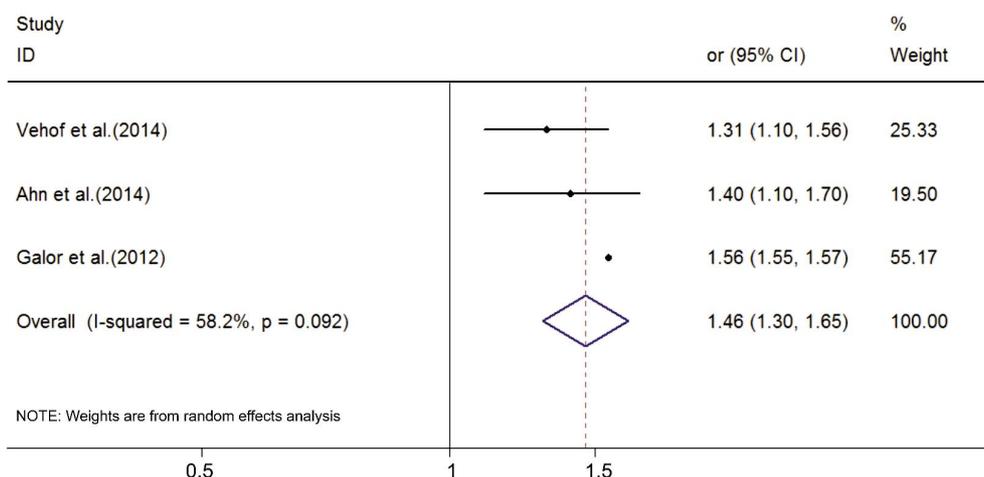


Figure 8 The association of hyperlipidemia with DES.

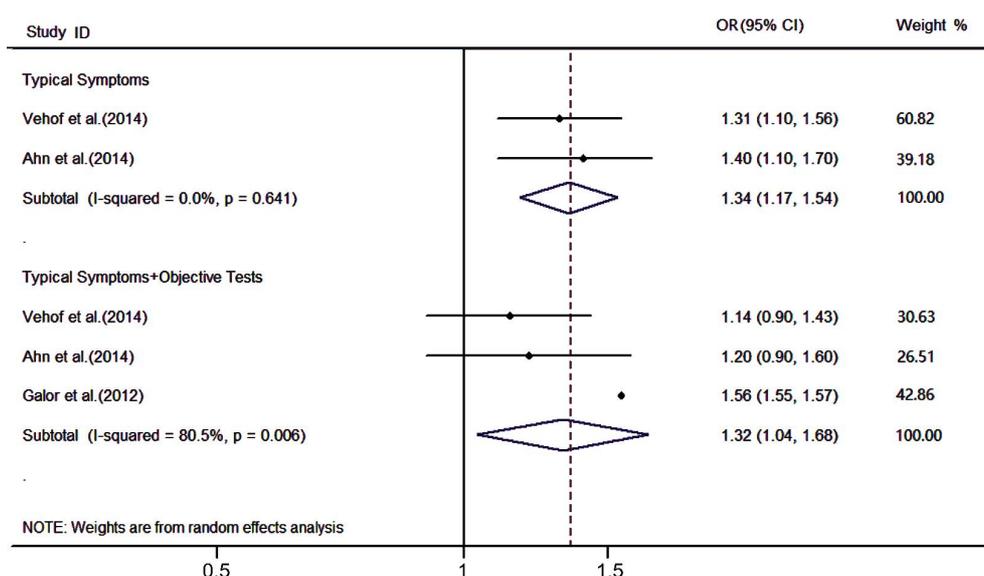


Figure 9 The association of hyperlipidemia with typical DES symptoms and clinically diagnosed DES.

factor for patients with typical DES symptoms. According to Viso *et al*^[13], hypertension may not be a direct risk factor for DES, but anti-hypertension drugs were. In terms of people

with clinically diagnosed DES, no significant association was detected. That may be because, not all hypertensive medications were DES risk factors, such as ACE inhibitors,

which were proven to be a protective factor for DES in a recent study^[16]. The controversial effect of hypertension drugs may mainly contribute to the inconsistency of our results, and none of the involved studies have grouped subjects according to the type of antihypertensive drugs, which made it impossible for us to further confirm the effect of different types of antihypertensive drugs on DES risk. What's more, the inaccuracy of diagnostic criteria mentioned above was another reason of the inconsistency of subgroup results.

According to our results, no significant relationship was detected between obesity and risk of DES, both for patients with typical DES symptoms and clinically diagnosed DES. In this meta-analysis, both normal-weight subjects and underweight subjects were considered to belong to the control group. And according to Uchino *et al*^[12], BMI less than 18.5 kg/m² was a protective factor for DES; thus, further studies should be conducted among the underweight group, the normal-weight group and the obesity group to distinguish the effect of different levels of BMI on DES risk.

Some researchers have argued that hyperlipidemia would increase the risk of DSE^[3,11], which is consistent with our results, especially for the hypercholesterolemia group. Compared with the normal meibomian lipid melting point of 30°C–34°C, increased cholesterol in the meibomian lipid with increased melting point of 46°C contributes to increased viscosity and plugging of the meibomian orifice, thus increasing the risk of DES^[13].

It was noteworthy that the sample size of one included study is larger than all the other studies^[7], which included patients from 365 eye clinics across America. And according to the results of sensitivity analysis, omitting this study did not alter the significance of the pooled results.

This Meta-analysis has several limitations. First, not all the included studies are well adjusted for other risk factors of DES. Although we have performed subgroup analysis according to some adjusted factors (including age, gender, alcohol, autoimmune disease and thyroid disease), other known risk factors (such as contact lens uses, hormone replacement therapy) were not included in this Meta-analysis, which was due to insufficient data. Second, the diagnostic criteria of the metabolic risk factors and DES are not uniform, which definitely contributed to some certain heterogeneity. Third, publication bias should be taken into consideration, as studies without statistically significant results would not be published. In addition, too few studies were included in our analysis to improve the accuracy of the Egger's linear regression test or Begg's rank correlation test. Fourth, Kawashima *et al*^[27] reported that metabolic syndrome could induce lacrimal gland hypofunction, but no published articles in the three included electronic databases reported epidemiological data on the relationship between metabolic syndrome and DES. We therefore did not

conducted Meta-analyses to ascertain whether metabolic syndrome, combining the four risk factors together, would increase the risk of DES. Lastly, compared to randomized controlled study design, the case-control or cross-sectional study design may lead to some systemic errors.

In summary, the pooled results of the 12 involved studies showed that hyperglycemia, hypertension and hyperlipidemia increase the risk of DES, while obesity does not. Although DES may be partly relieved by the use of artificial tears and other drugs, DES patients usually have poor quality of life. Thus, for ophthalmologists, the key point is to cure the disease by understanding and addressing the underlying source. These findings indicate that controlling metabolic risk factors may help to reduce DES prevalence. Based on a uniform and more comprehensive diagnostic criteria (for example, to classify tear osmolarity test as routine examination) large-scale and long-term randomized controlled trials in various populations should be designed to provide more powerful evidence to confirm the conclusions.

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Conflicts of Interest: Tang YL, None; Cheng YL, None; Ren YP, None; Yu XN, None; Shentu XC, None.

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