Review Article
The role of systemic sclerosis on the coronary artery disease risk: a systematic review and meta-analysis

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Abstract: Several studies assessed the association between systemic sclerosis (SSc) and coronary artery disease (CAD) risk. However, the results were controversial. We searched PubMed, Embase, and Wanfang databases to find relevant articles. The association of SSc and CAD risk was estimated by OR with 95% CI. Nine studies with 5247 cases and 383468 controls were eventually included. SSc was significantly associated with CAD risk (OR = 2.37, 95% CI 1.72-3.26, $P < 0.00001$; I^2 = 79%). In the subgroup analysis by race, SSc was significantly associated with CAD risk in Caucasians (OR = 2.20, 95% CI 1.57-3.07, $P < 0.00001$; I^2 = 79%) and Asians (OR = 4.24, 95% CI 1.06-16.90, P = 0.04; I^2 = 67%). When the studies without adjustment were excluded, the result was still positive (OR = 2.23, 95% CI 1.57-3.17, $P < 0.00001$; I^2 = 86%). In conclusion, this meta-analysis suggested that SSc patients might have higher CAD risk.

Keywords: Systemic sclerosis, coronary artery disease, association

Introduction

Coronary artery disease (CAD) is a major disease of morbidity and mortality [1]. Previous studies have found some risk factors for CAD, including smoking and inflammation [1]. Ridker et al. found that base-line plasma concentration of C-reactive protein predicts the risk of future myocardial infarction and stroke [2]. Inflammation may modulate the thrombotic responses by upregulating procoagulants, downregulating anticoagulants and suppressing fibrinolysis [3]. Reduction in inflammatory levels was associated with a proportional reduction in cardiovascular events [4]. Thus, inflammation play an important role in the development of CAD.

Systemic sclerosis (SSc) is a disease with unknown etiology. Inflammation play an important role in the development of SSc. Several studies assessed the association between SSc and CAD risk [5-13]. However, the results were controversial. Thus, we decided to perform a meta-analysis to determine the association between SSc and CAD risk.

Methods

Publication search

We used the following electronic databases to search for eligible literature: PubMed, Embase, and Wanfang, and the searching keywords included: "systemic sclerosis" and "coronary artery disease". We additionally searched the references of all articles retrieved. There was no language restriction.

Inclusion and exclusion criteria

We considered studies meeting the following criteria eligible for included in the present meta-analysis: (1) estimation the association between SSc and CAD risk; (2) with a case-control or cohort study; (3) sufficient original data for calculating odds ratio (OR) with its 95% confidence interval (CI). The major reasons for exclusion included: (1) comment, review, or abstract; (2) animal study; and (3) duplicates. As for publications containing same data series, we only selected the latest one.

24 records identified through database searching

22 records after duplicates

6 records excluded

16 full-text articles assessed for eligibility

7 full-text articles excluded: 1 overlapping study, 2 not relevant to CAD, 2 reviews or abstracts, 2 animal studies

9 studies included in meta-analysis
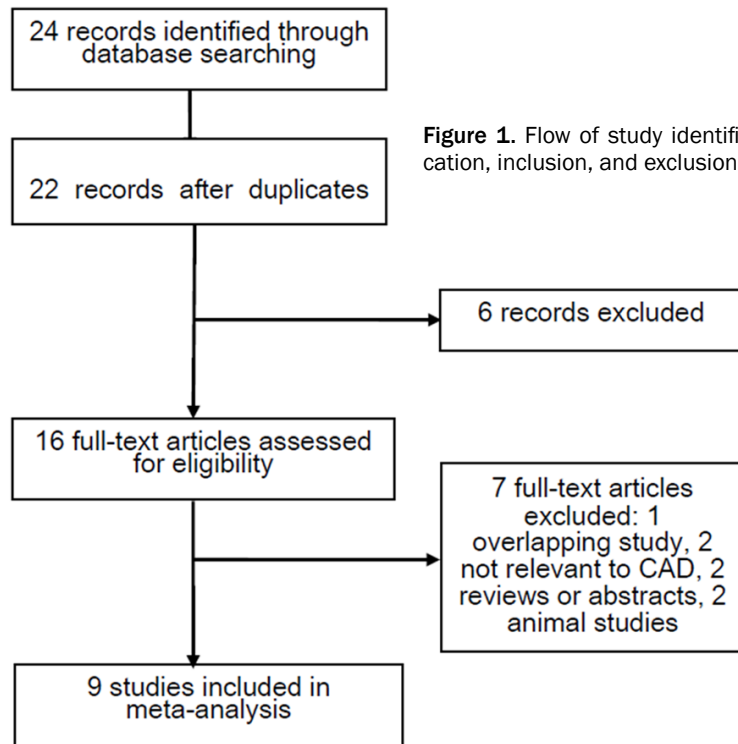
Figure 1. Flow of study identification, inclusion, and exclusion.

Data extraction and quality assessment

Two independent reviewers extracted the data utilizing a standard approach. Any discrepancy was resolved through discussion. The following data were extracted: name, year of publication, race, age, gender, smoking, number of cases, number of controls, and covariates.

The included studies were assessed independently by two authors using the Newcastle-Ottawa Scale (NOS). Scores ranged from 0 to 9 stars.

Statistical analysis

Statistical analysis was conducted by using STATA statistical package (version 11, STATA, College Station, TX) and Review Manager (Version 5.0, Copenhagen, Nordic Cochrane Centre, The Cochrane Collaboration, 2010). We used ORs and 95% CIs to measure the association of SSc and CAD risk. Heterogeneity across studies was examined with the Chi-square-based Q-statistical test. The significance of the pooled OR was determined by the Z test. Subgroup analysis was conducted by race. The

cumulative meta-analysis and sensitivity analysis were performed. Publication bias was investigated with Egger's test. The statistically significant level of all tests was set at $P < 0.05$.

Results

Study characteristics

A total of 24 studies were retrieved from the literature databases (**Figure 1**). Among them, 2 duplicate studies were excluded on the basis of their abstracts. After further reading the full text of each study, 13 additional studies were excluded for not meeting the inclusion criteria. As a result, 9 studies were eventually included. Two studies were included Asians and other studies included Caucasians. A total of 5247 cases and 383468 controls were included in this meta-analysis. The general characteristics of the included studies are shown in **Table 1**. The quality assessment demonstrated that the included studies had high quality.

Quantitative synthesis

The main results were shown in **Table 2**. SSc was significantly associated with CAD risk (OR = 2.37, 95% CI 1.72-3.26, $P < 0.00001$; I^2 = 79%; **Figure 2**). In the subgroup analysis by race, SSc was significantly associated with CAD risk in Caucasians (OR = 2.20, 95% CI 1.57-3.07, $P < 0.00001$; I^2 = 79%) and Asians (OR = 4.24, 95% CI 1.06-16.90, $P = 0.04$; I^2 = 67%). When the studies without adjustment were excluded, the result was still positive (OR = 2.23, 95% CI 1.57-3.17, $P < 0.00001$; I^2 = 86%). When the studies with adjusting for age and gender were included, we also found positive result (OR = 3.10, 95% CI 2.09-4.60, $P < 0.00001$; I^2 = 39%).

As shown in **Figures 3** and **4,** cumulative meta-analysis and sensitivity analysis suggested that

Table 1. Characteristics of the included studies

First author	Year	Race	Mean age	Female (%)	Smoking (%)	No. of case	No. of control	Adjusted for	NOS
D'Angelo	1969	Caucasian	NA	NA	NA	58	58	NA	6
Youssef	1995	Caucasian	63	100	13	31	31	NA	5
Khurma	2008	Caucasian	51	82	6	17	17	NA	5
Mok	2011	Asian	53	94	11	53	106	Age, sex, dysglycemia, hypertension, LDL and HDL cholesterol levels	8
Ngian 1	2012	Caucasian	48	14	20	850	8802	Age, sex	8
Ngian 2	2012	Caucasian	57	54	9	850	15787	Hypertension, hypercholesterolemia, diabetes, smoking and body mass index.	8
Man	2012	Caucasian	59	86	14	865	8643	Body mass index, smoking, hypertension, diabetes, hyperlipidaemia, NSAID and glucocorticoid use.	8
Zoller	2012	Caucasian	NA	42	NA	1068	336479	Age, period, socioeconomic status, hospitalization of chronic lower respiratory diseases, obesity, alcohol, hypertension, diabetes, arterial flutter, heartfailure, and renal disease	8
Nordin	2013	Caucasian	61	90	NA	111	105	NA	6
Chu	2013	Asian	51	76	20	1344	13440	Age, sex, and underlying comorbidities	8

HDL, high-density lipoprotein; LDL, low-density lipoprotein; NSAID, non-steroidal anti-inflammatory drugs; NOS, Newcastle-Ottawa Scale; NA, not available.

Table 2. Results of this meta-analysis

	Test of association		Heterogeneity	
	OR (95% CI)	P Value	I^2 (%)	P Value
All studies	2.37 (1.72-3.26)	< 0.00001	79	< 0.00001
Race				
Caucasian	2.20 (1.57-3.07)	< 0.00001	79	< 0.0001
Asian	4.24 (1.06-16.90)	0.04	67	0.08
Adjust	2.23 (1.57-3.17)	< 0.00001	86	< 0.0001
Adjust for age and gender	3.10 (2.09-4.60)	< 0.00001	39	0.19

the result was stable. The shape of the funnel plot showed symmetry (**Figure 5**). Egger's test found no evidence of publication bias (P = 0.44).

Discussion

This meta-analysis study with 5247 cases and 383468 controls assessed the association of SSc and CAD risk. We observed that SSc was significantly associated with CAD risk. In the subgroup analysis by race, SSc was significantly associated with CAD risk in Caucasians and Asians, respectively. When the studies with adjustment were included, the result was still positive. Additionally, cumulative meta-analysis and sensitive analysis indicated that the results of this meta-analysis were reliable.

A meta-analysis found that carotid intima-media thickness was significantly increased in SSc population compared with controls [14]. Timar et al. found that augmentation index and pulse wave velocity were both elevated in SSc patients than that in controls [15]. Many inflammatory factors, such as tumor necrosis factor-alpha, interleukin-6, and C-reactive protein, have been demonstrated to be increased in patients with SSc [16]. Inflammation is a component of the pathophysiology of both SSc and CAD. Therefore, SSc patients may have higher CAD risk.

Some advantages of this studys were noted. First, cumulative meta-analysis and sensitivity analysis were well investigated. Result from cumulative meta-analysis and sensitivity analysis suggested that results of this study is stable. Second, funnel plots and Egger's tests were used to find potential publication bias. The results indicated that there was no significant publication bias. Third, more than 39000 subjects were included in this study.

Some limitations of this study should be acknowledged. First, lacking of the original data of the eligible studies limited the evaluation of the subgroup analyses by gender, age, and other factors. Second, all the studies were
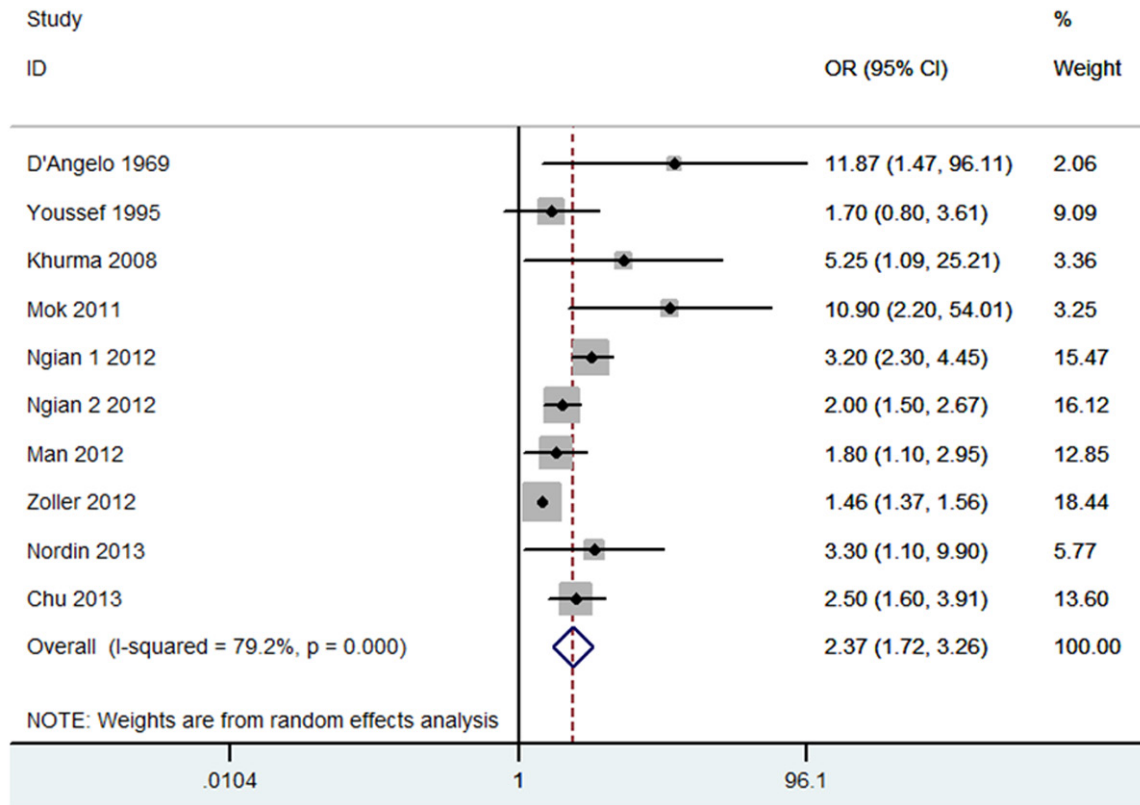
Systemic sclerosis and coronary artery disease

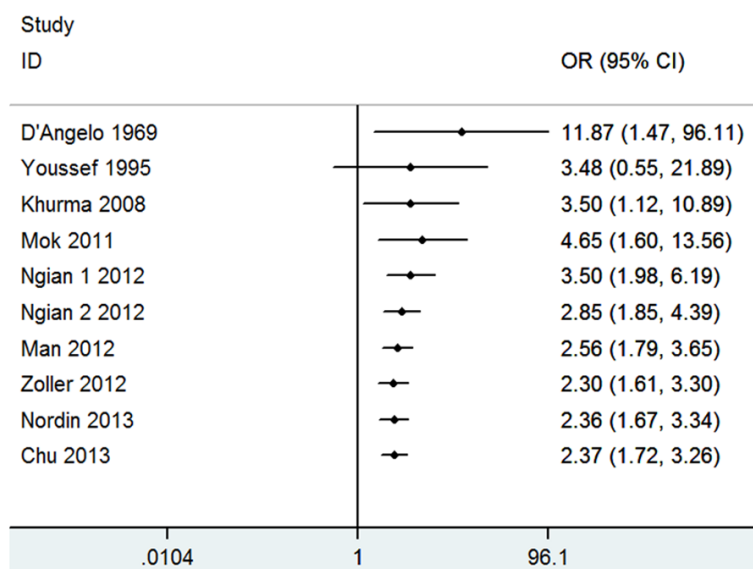**Figure 2.** Meta-analysis for the association between SSc and CAD risk.

Figure 3. Cumulative meta-analysis for the association between SSc and CAD risk.

conducted in Caucasians and Asians, no study from other races was included.

In conclusion, this meta-analysis suggested that SSc patients might have higher CAD risk.

Disclosure of conflict of interest

None.

Address correspondence to: Wenwei Bai, Department of Cardiology, The Second Affiliated Hospital of Kunming Medical University, No. 374 Dianmian Road, Kunming 650101, Yunnan, China. Tel: 86-0871-65351281; E-mail: tan0271612746@sohu.com

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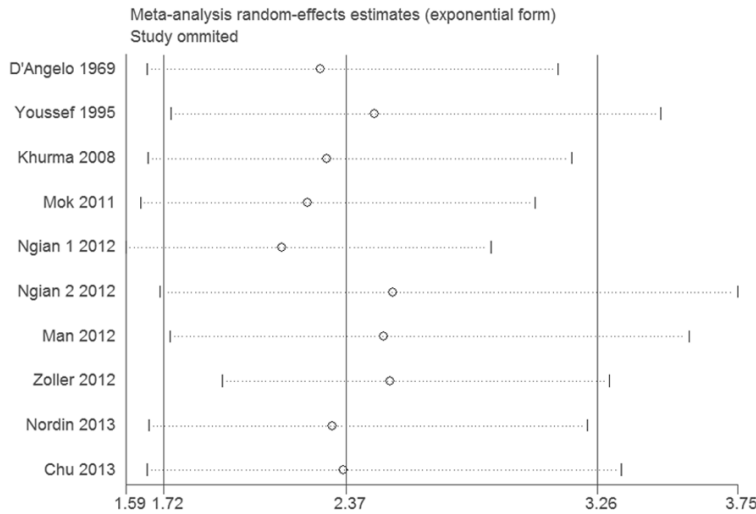
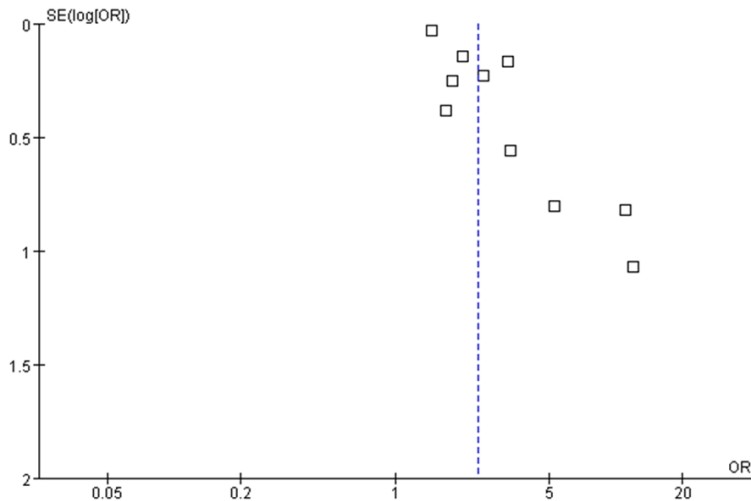**Figure 4.** Sensitivity analysis for the association between SSc and CAD risk.

Figure 5. Funnel plot for the association between SSc and CAD risk.

SE, Kissela BM, Lackland DT, Lichtman JH, Lisabeth LD, Liu S, Mackey RH, Matchar DB, McGuire DK, Mohler ER 3rd, Moy CS, Muntner P, Mussolino ME, Nasir K, Neumar RW, Nichol G, Palaniappan L, Pandey DK, Reeves MJ, Rodriguez CJ, Sorlie PD, Stein J, Towfighi A, Turan TN, Virani SS, Willey JZ, Woo D, Yeh RW, Turner MB; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics--2015 update: a report from the American Heart Association. Circulation 2015; 131: 29-322.

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