

The higher serum endocan levels may be a risk factor for the onset of cardiovascular disease

A meta-analysis

Tianming Zhao, MM^a, Yao Kecheng, MM^b, Xuelei Zhao, BN^c, Xuehua Hu, MM^a, Jing Zhu, MD^a, Yingnan Wang, MD^a, Jixiang Ni, MD^{a,*}

Abstract

Objective: Endothelial dysfunction was widely regarded as the initial lesion in the multifactorial pathogenesis of cardiovascular disease (CVD). Serum endocan, a novel endothelial dysfunction biochemical marker, is involved in the development of CVD. Here, we fulfilled a meta-analysis to evaluate the association between CVD and serum endocan levels.

Method: The relevant published literature was searched through large literature databases, including PubMed, Embase, Cochrane Library, SinoMed, and Web of Science, up to June 1, 2018. The data were extracted from the studies. Stata software was used to perform a meta-analysis.

Result: Fifteen original studies with a total of 1839 patients and 1258 controls fulfilled the inclusion criteria and were included in the study dataset. Meta-analysis showed that the levels of serum endocan in patients with hypertension, coronary artery disease, and coronary slow flow were higher than those in the control group. The pooled standardized mean differences and 95% confidence intervals of endocan concentrations in those 3 groups were 0.53 [0.19–0.86], $P < .01$; 0.99 [0.51–1.39], $P < .01$; and 0.62 [0.45–0.78], $P < .01$, respectively. Further analysis showed that the level of serum endocan in hypertension patients with coronary artery disease was higher than that in patients with hypertension (0.61 [0.30–0.92], $P < .01$). Sensitivity analysis and subgroup analysis were used to confirm the above results.

Conclusions: In this meta-analysis, we further confirmed that serum endocan level was significantly increased in the CVD population. The high serum endocan level may be one of the risk factors for CVD.

Abbreviations: CAD = coronary artery disease, CI = confidence intervals, CSF = coronary slow flow, CVD = cardiovascular disease, ESM-1 = endothelial cell-specific molecule 1, NCF = normal coronary flow, NOS = Newcastle–Ottawa scale, SD = standard deviation, SMD = standard mean differences.

Keywords: cardiovascular disease, endocan, meta-analysis, risk factor

1. Introduction

Cardiovascular disease (CVD) has become a worldwide public health problem with high morbidity and mortality, measuring

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^a Department of Respiratory and Critical Care Medicine, ^b Department of Gerontology, ^c Department of Gastroenterology, The People's Hospital of China Three Gorges University, The First People's Hospital of Yichang, Yichang, 443000, Hubei Province, China.

* Correspondence: Jixiang Ni, Department of Respiratory and Critical Care Medicine, The People's Hospital of China Three Gorges University, The First People's Hospital of Yichang, 2# Jiefang Road, Yichang 443000, Hubei Province, China (e-mail: jxnee77@163.com).

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1.32% and 0.27%, respectively.^[1] It was reported that, in 2010, the number of people suffering from CVD was approximately 230 million, of which 200 million had hypertension, 2 million had acute myocardial infarction, and 4.2 million were heart failure patients. Every year, approximately 3 million people die from CVD, and the mortality rate of CVD is higher in rural areas than in cities.^[1,2] Traditional risk factors for CVD usually include age, genetics, obesity, dyslipidemia, diabetes, and aspects of an unhealthy lifestyle such as high salt intake or smoking. Recently, more and more newly risk factors have gradually been found to be related to CVD, such as endocan, homocysteine, soluble suppression of tumorigenicity 2, high-sensitive C reactive protein, and lipoprotein-associated phospholipase A2.^[3,4] Although the molecular mechanisms of CVD pathogenesis are not completely clear, myriads of candidates that may be involved in the genesis of CVD have been identified, including endocan.^[5]

Endocan, also known as endothelial cell-specific molecule-1, is secreted by vascular endothelial cells and is widely involved in a variety of biological processes including cell proliferation, migration, and neovascularization.^[6,7] It has also been reported that endocan plays a key role in endothelial dysfunction and inflammatory reaction.^[6,8] Some evidence has noted that a high level of endocan may be closely related to the development and progression of CVD, and serum endocan levels were higher than those of control subjects,^[9–23] which initially revealed an association between serum endocan levels and CVD. However, there were differences in the sample size due to the small number of individual studies. In this study, meta-analysis will be used to assess the association between serum endocan and the occurrence

of CVD, which will provide the basis for further related basic studies and may make endocan a potential biomarker and therapeutic target for CVD.

2. Materials and methods

2.1. Literature research

We systematically searched on PubMed, Embase, Cochrane Library, SinoMed, and Web of Science, including all articles published up to June 1, 2018. We used the following search terms: “endocan” or “endothelial cell-specific molecule 1” or “ESM-1.” Since there is little published literature about endocan, we implemented the search without the term “cardiovascular disease.” Furthermore, we hand searched for additional usable studies from the reference lists of original studies or review articles. Meanwhile, we skimmed the titles and abstracts of potential papers to determine their relevance and eliminate any apparently unrelated studies. Finally, only relevant studies with full-text articles containing useful data were included. If studies were carried out with overlapped subjects, we only retained those published studies that disseminate the most versatile information.

2.2. Inclusion and exclusion criteria

According to the research objectives of this paper, we formulated the following inclusion and exclusion criteria. Inclusion criteria: Published in English or Chinese; eligible studies of human serum endocan and CVD; directly extracted or calculated the mean, standard deviation, and sample size. There are 4 main reasons why some studies were excluded: duplicated studies; summary and review of the literature; unpublished sources of data; unable to extract the mean, standard deviation (SD) and sample size.

2.3. Data extraction and quality assessment

After reviewing the papers, we excluded unrelated and duplicate studies. At the same time, 2 investigators carefully and independently decided whether each single study was applicable to this meta-analysis. We extracted the relevant information from each effective study. Through great efforts of comparison, disagreement analysis and rigorous discussion, we finally reached a consensus. The following information was sought and recorded from each study: first author, year of publication, ethnicity of participants, CVD type, sample size, and the mean \pm SD about serum endocan level.

We used the Newcastle–Ottawa scale (NOS) to evaluate the quality of the included studies.

2.4. Statistical analysis

We used the statistical software Stata version 13 (Stata Corporation, College Station, TX) to analyze the relevant data. The standard mean differences (SMD) and the corresponding 95% confidence intervals (CI) were used to assess the association between serum endocan level and the risk of CVD, and $P < .05$ was statistically significant. The Q test was used to assess the heterogeneity of each study. If the P value of the Q test was $> .05$ or $I^2 < 50\%$, study heterogeneity was regarded as insignificant. When heterogeneity existed, a random-effects model was used to calculate the SMD and its 95% CIs; otherwise, a fixed-effects model was selected. Additionally, both a funnel plot and Egger’s test were used to assess publication bias. If P value $> .05$, the

publication bias was nonexistent. Sensitivity analyses were carried out to estimate the stability of the results.

3. Results

3.1. Characteristics of studies

We identified 353 potentially relevant publications in several databases by using the search terms “endocan” or “endothelial cell-specific molecule 1” or “ESM-1.” Among these, 173 papers were excluded because they were duplicates. Of the remaining 201 articles, 175 were excluded because the papers were reviews, case reports, conference articles, or non-CVD studies. Thus, 26 studies were selected based on the title and abstract, but 11 of these were excluded because they had no controls or data on serum endocan levels. Finally, 15 articles involving a total of 3097 subjects met the inclusion criteria for our meta-analysis.^[9–23] Of these, there were 8 papers about coronary artery disease (CAD),^[10,12–18] 6 about hypertension,^[9,11,15,16,22,23] and 3 about coronary flow slow^[19–21] (Table 1). A flowchart of the study selection progress with specific reasons for exclusion is displayed in Figure 1. All eligible studies with sufficient data were published from 2013 to 2018. The NOS scores for study quality assessment revealed that the most of the publications were of high quality (Table 1).

3.2. Quantitative data synthesis

The meta-analysis examined the relationship between serum endocan and cardiovascular disease, including hypertension, coronary artery disease, and coronary slow flow (CSF).

3.3. Meta-analysis of serum endocan levels in patients with hypertension compared with levels in normotensive patients

Six studies (7 data sets) investigated the association between serum endocan levels and hypertension. The analysis was performed with a random-effects model for the evidence of $I^2 = 82.8\%$ and $P_{\text{heterogeneity}} < .01$. It was found that serum levels of endocan in hypertension cases were significantly higher than those in normal blood pressure controls (SMD = 0.53, 95% CI = 0.19–0.86, $P < .01$) (Fig. 2A, Table 2). As the heterogeneity was significant, we tried to seek heterogeneity sources through stratification analysis. The results showed that age were not sources of heterogeneity, but there was significant difference in serum endocan levels between the newly diagnosed hypertensive patients and those treated with antihypertensive agents. Stratified analysis based on area can significantly reduce heterogeneity. There may be differences between Chinese and other country with hypertensive populations in the level of endocan expression (Table 3).

3.4. Meta-analysis of serum endocan levels in patients with CAD compared with those in non-CAD patients

There were 8 eligible studies involving 1213 subjects, and those studies determined that serum endocan levels in CAD cases were significantly higher than those in non-CAD controls (SMD = 0.99, 95% CI = 0.58–1.39, $P < .01$; $I^2 = 89.8\%$, $P_{\text{heterogeneity}} < .01$) (Fig. 2B, Table 2). Similarly, in order to investigate potential sources of heterogeneity, we performed subgroup analysis by contrasting the area of included subjects and resource of controls. The results showed neither area nor controls could significantly reduce heterogeneity. The detailed results were presented in Table 3.

Table 1
Characteristic of published studies included in this meta-analysis.

Study	Area	Age (year) case/control	Sample case/control	Assay method	Definition of control	Type of CVD	Quality score
Balta 2013 ^[8]	Turkey	47.2 ± 8.2/43.6 ± 10.3	18/23	ELISA	Normotensive	Newly diagnosed HT	7
Cimen 2016 ^[9]	Turkey	65.0 ± 10.0/64.0 ± 13.0	40/53	ELISA	Non-CVD	Angina	7
		65.0 ± 10.3/64.0 ± 13.0	120/53	ELISA	Non-CVD	CAD	
Cimen 2016 ^[10]	Turkey	46.2 ± 9.3/50.0 ± 6.4	35/35	ELISA	Normotensive	Dipper HT	9
		48.4 ± 7.2/50.0 ± 6.4	35/35	ELISA	Normotensive	Non-Dipper HT	
Kose 2014 ^[11]	Turkey	56.0 ± 11.00/56.0 ± 10.0	53/30	ELISA	Non-CAD	CAD	7
Kundi 2016 ^[12]	Turkey	64.0 ± 12.0/62.0 ± 15.0	88/45	ELISA	Non-CAD	STEMI	7
Qiu 2016 ^[13]	China	65.3 ± 12.7/63.8 ± 8.8	216/60	ELISA	27 healthy 23 HT 10 diabetes	AMI	5
Wang 2015 ^[14]	China	62.3 ± 8.5/61.2 ± 9.2	72/55	ELISA	Healthy	HT with CAD	7
		60.6 ± 8.0/61.2 ± 9.2	92/55	ELISA	Healthy	HT without CAD	
Xiong 2016 ^[15]	China	62.1 ± 8.4/61.3 ± 9.1	94/58	ELISA	Healthy	HT with CAD	5
		61.8 ± 9.9/61.3 ± 9.1	96/58	ELISA	Healthy	HT without CAD	
Ren 2015 ^[16]	China	64.1 ± 11.9/63.5 ± 9.6	85/80	ELISA	HT	HT with CAD	5
Ren 2015 ^[17]	China	61.2 ± 8.6/56.4 ± 8.6	84/92	ELISA	Healthy	CAD	5
Han 2015 ^[18]	China	55.0 ± 11.1/56.0 ± 9.6	82/184	ELISA	NCF	CSF	7
Kundi 2015 ^[19]	Turkey	59.0 ± 15.0/56.0 ± 13.0	53/25	ELISA	NCF	CSF	7
Ye 2016 ^[20]	China	59.6 ± 8.7/58.6 ± 9.7	93/206	ELISA	NCF	CSF	7
Turgunova 2018 ^[21]	Kazakhstan	54 ± 8.9/41 ± 15.6	379/291	NA	Normotensive	HT	6
Musialowska 2018 ^[22]	Poland	54 ± 51.8/51.5 ± 23.0	104/21	ELISA	Normotensive	HT	7

AMI = acute myocardial infarction, CAD = coronary artery disease, CSF = coronary slow flow, CVD = cardiovascular disease, HT = hypertension, NCF = normal coronary flow, NOS = the Newcastle-Ottawa scale.

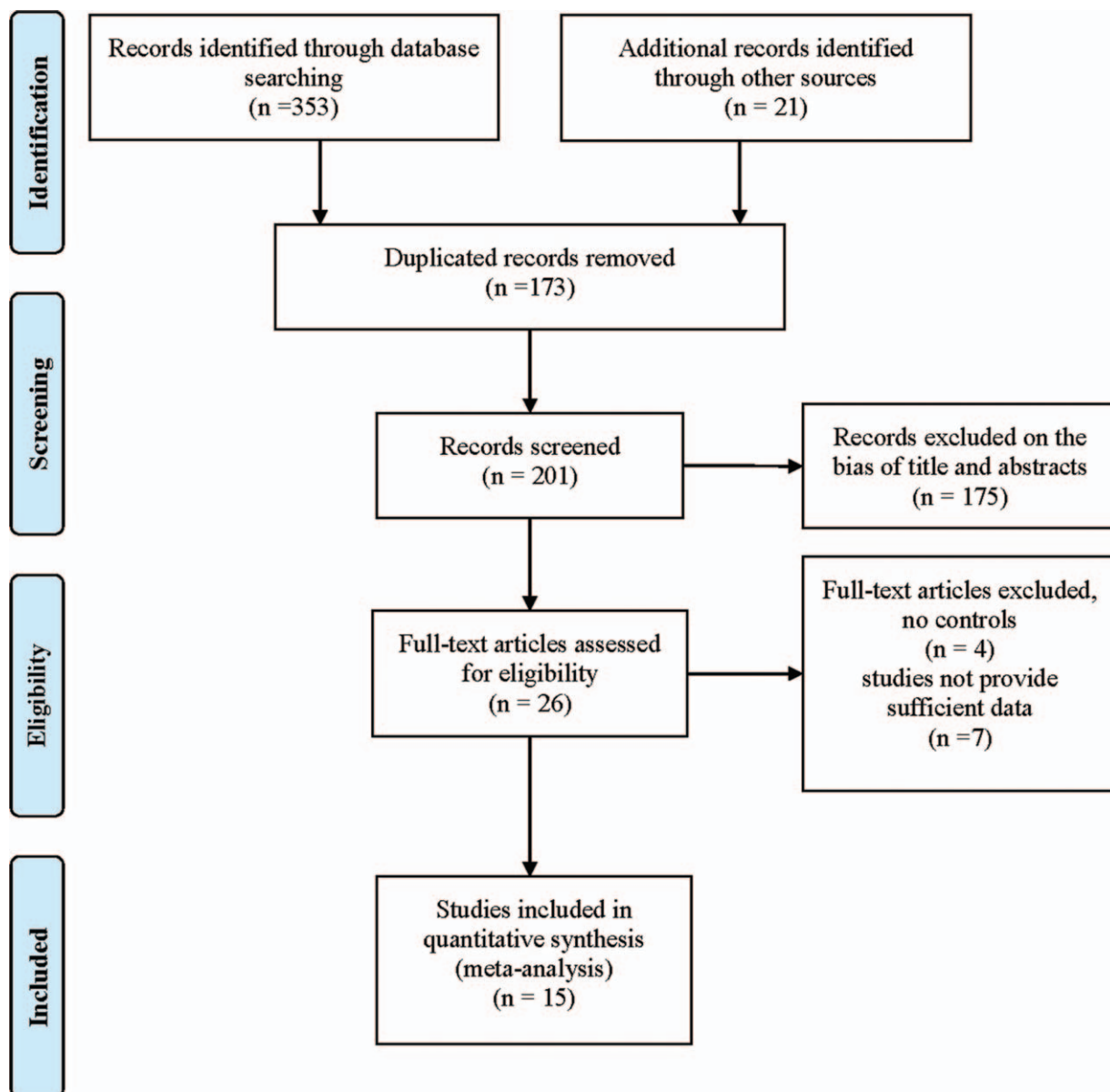


Figure 1. Flow chart of the identification and inclusion of articles.

Table 2

Meta-analysis of the association between serum endocan and CVD.

Variable	No	Cases/Controls	SMD (95%CI)	P _{value}	I ² (%)	P _{heterogeneity}	P _{Begg's}	Pooling model
HT vs NT	7	759/518	0.53[0.19–0.86]	.00	82.8	.00	.72	Random
CAD vs non-CAD	8	767/446	0.99[0.51–1.39]	.00	89.8	.00	.36	Random
CSF vs NCF	3	227/425	0.62[0.45–0.78]	.00	0.0	.51	.66	Fixed
HT with CAD vs HT	3	251/268	0.61[0.30–0.92]	.00	67.0	.05	.68	Random

CAD = coronary artery disease, CSF = coronary slow flow, HT = hypertension, NCF = normal coronary flow, No = number of studies, NT = normotensive, P_{Begg's} = for publication bias; 0.00 mean value < .01. P_{heterogeneity} = for heterogeneity test

3.5. Meta-analysis of serum endocan levels in patients with CSF compared with those having normal coronary flow (NCF)

Three studies were included to assess the relationship between serum endocan levels and CSF. We did not find significant heterogeneity among these studies (I² = 0.0%, P = .51); therefore, a fixed-effects model was selected. The results of this meta-analysis suggested that serum endocan levels in coronary slow flow cases were also significantly higher than those in NCF controls (SMD = 0.62, 95%CI = 0.45–0.78, P < .01) (Fig. 2C, Table 2).

3.6. Meta-analysis of serum endocan levels in hypertension with CAD compared with those in patients with simple hypertension

We compared hypertensive patients with CAD and simple hypertension. Three relevant studies were included. The results showed that the serum endocan levels in hypertensive patients with CAD were significantly higher than those in patients with hypertension (SMD = 0.61, 95%CI = 0.30–0.92, P < .01; I² = 67%, P_{heterogeneity} = .05) (Fig. 2D, Table 2).

3.7. Sensitivity analysis and publication bias

We performed sensitivity analysis by serially deleting each single study. The influence of the omission of each individual study on

pooled SMD was assessed. No single study influenced overall effect in this meta-analysis, suggesting that results of this meta-analysis were statistically robust (Fig. 3). To determine the potential publication bias of the literature, we performed Begg's funnel plot test. Included studies about hypertension, coronary artery disease, and CSF, we did not find any existence of publication bias (P_{Begg's} > .05) (Fig. 4, Table 2).

4. Discussion

Inflammatory cytokines are produced by inflammatory cells and endothelial cells and closely related to cardiovascular diseases. Inflammatory factors, in turn, affect endothelial cell function.^[24,25] Vascular endothelial cells, especially with the inflammation reaction, can secrete endocan, which can be used as a biomarker of various diseases, such as lung cancer, kidney cancer, inflammatory diseases, and CVD.^[5,6] There was a close relationship between serum endocan levels and the severity and prognosis of disease.^[5] In the present study, we performed a meta-analysis of 3097 participants from 15 original studies, and we found that the levels of serum endocan in patients with CVD were significantly higher than those in controls.

Vascular endothelial dysfunction is the main factor in the progression of atherosclerosis.^[5] Endocan can stimulate endothelial cells to produce more kinds of inflammatory cytokines, increase vascular permeability and promote leukocyte migration,

Table 3

Stratification group analysis of serum endocan levels and hypertension and coronary artery disease.

Stratification group	n	Test of association			Heterogeneity test	
		SMD (95%CI)	Z	P _{value}	I ² %	P _{het}
HT vs NT	7	0.53[0.19–0.86]	3.10	.00	82.8	.00
Age						
>50 years	4	0.56[0.10–1.03]	2.37	.02	89.2	.00
<50 years	3	0.47[–0.10–1.05]	1.61	.11	71.9	.03
Area						
China	2	0.97[0.72–1.21]	7.69	.00	0.00	.54
Other	5	0.30[0.03–0.56]	2.21	.03	52.6	.07
Diagnosis						
New diagnosis	2	0.20[–0.14–0.53]	1.16	.25	0.0	.39
Non new diagnosis	5	0.66[0.22–1.10]	2.94	.00	87.7	.00
Definition of control						
Normotensive	2	0.97[0.72–1.21]	7.69	.00	0.00	.54
Healthy	5	0.30[0.03–0.56]	2.21	.03	52.6	.07
CAD vs non-CAD	8	0.99[0.58–1.39]	4.77	.00	89.8	.00
Area						
Turkey	4	0.90[0.40–1.40]	3.53	.00	83.7	.00
China	4	1.09[0.39–1.78]	3.05	.00	94.1	.00
Resource of controls						
Healthy	3	1.35[0.69–2.01]	4.02	.00	90.0	.00
Non-CAD	5	0.77[0.30–1.23]	3.23	.00	87.2	.00

CAD = coronary artery disease, HT = hypertension, NT = normotensive, P_{het} = for heterogeneity test; 0.00 mean value < .01, SMD = standard mean differences.

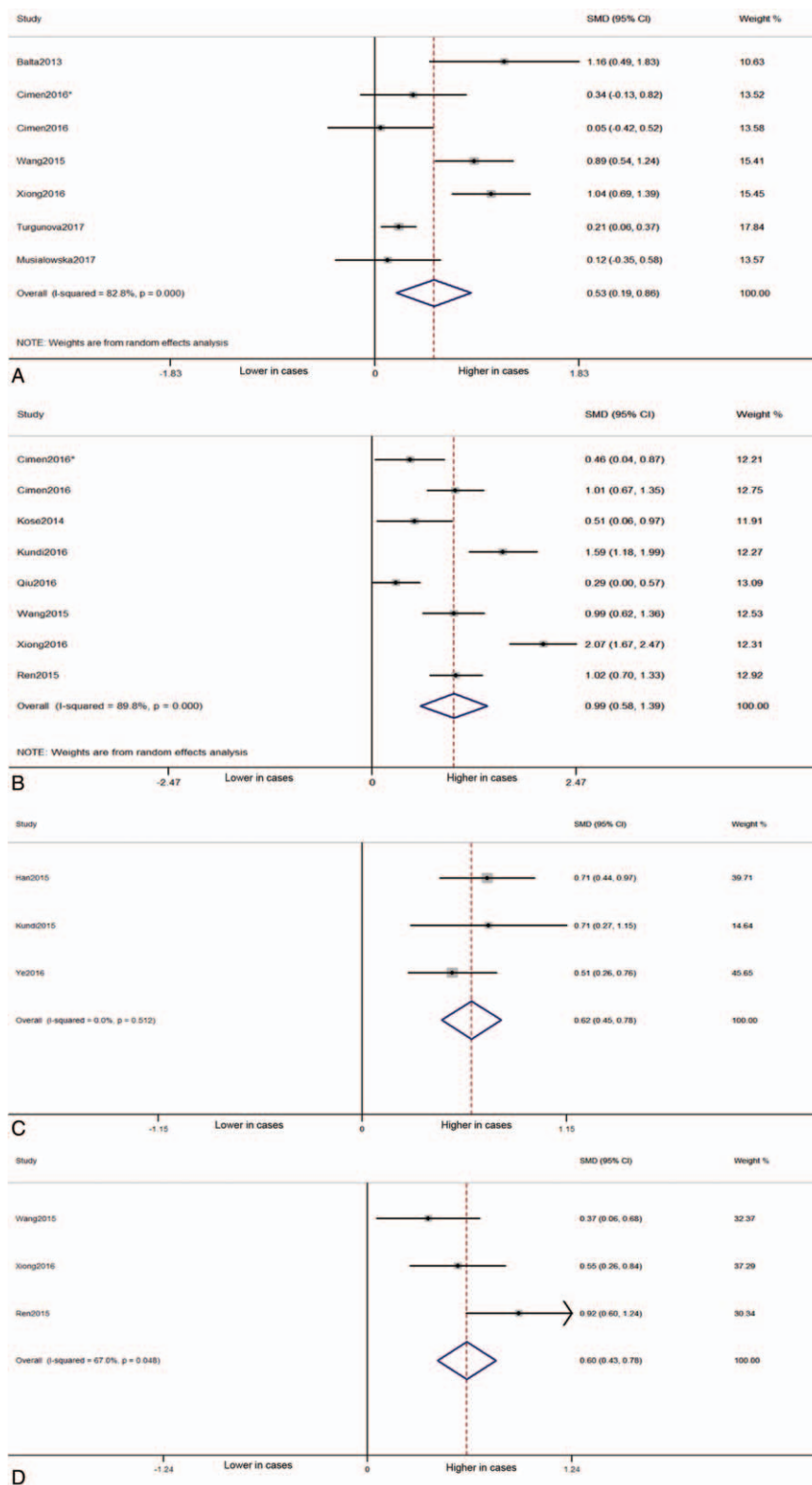


Figure 2. The forest plot for endocan levels in CVD patients: (A) hypertension and normotension, (B) coronary artery disease and non-coronary artery disease, (C) coronary slow flow and normal coronary flow, and (D) hypertension with coronary artery disease and hypertension. CVD = cardiovascular disease.

which plays a key role in the pathogenesis of various phases of atherosclerosis.^[7,26] Endocan, a new endothelial mediator, regulates vascular smooth muscle cell migration and proliferation and may thus lead to the occurrence of atherosclerosis.^[26] High

expression of endocan has been observed in the early stage of atherosclerosis by immunohistochemistry.^[5] Initially, Kose et al,^[12] comparing 53 acute coronary syndrome patients and 30 healthy controls, found that the expression levels of serum

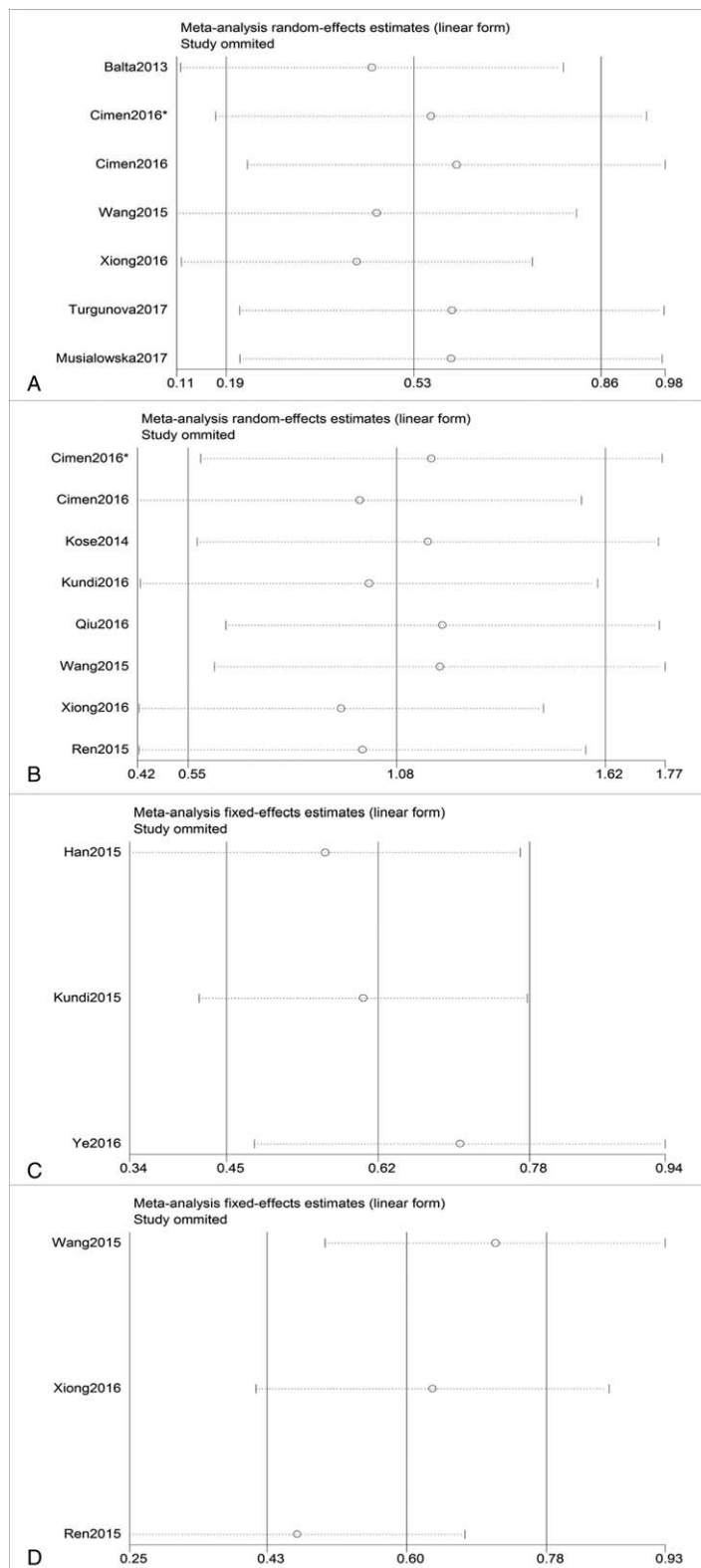


Figure 3. Sensitivity analysis for endocan levels in CVD patients. CVD=cardiovascular disease.

endocan in patients with acute coronary syndrome was significantly increased. High levels of serum endocan may be one of the independent risk factors of acute coronary syndrome.

The injury, activation, and disorder of endothelial cells are involved in the occurrence and development of hypertension.

Serum markers of inflammation are also closely related to hypertension.^[27] High levels of serum endocan can contribute to the development of reactive inflammation.^[28] A study by Balta et al,^[9] including 18 newly diagnosed, untreated hypertensive patients, found that serum endocan levels were significantly

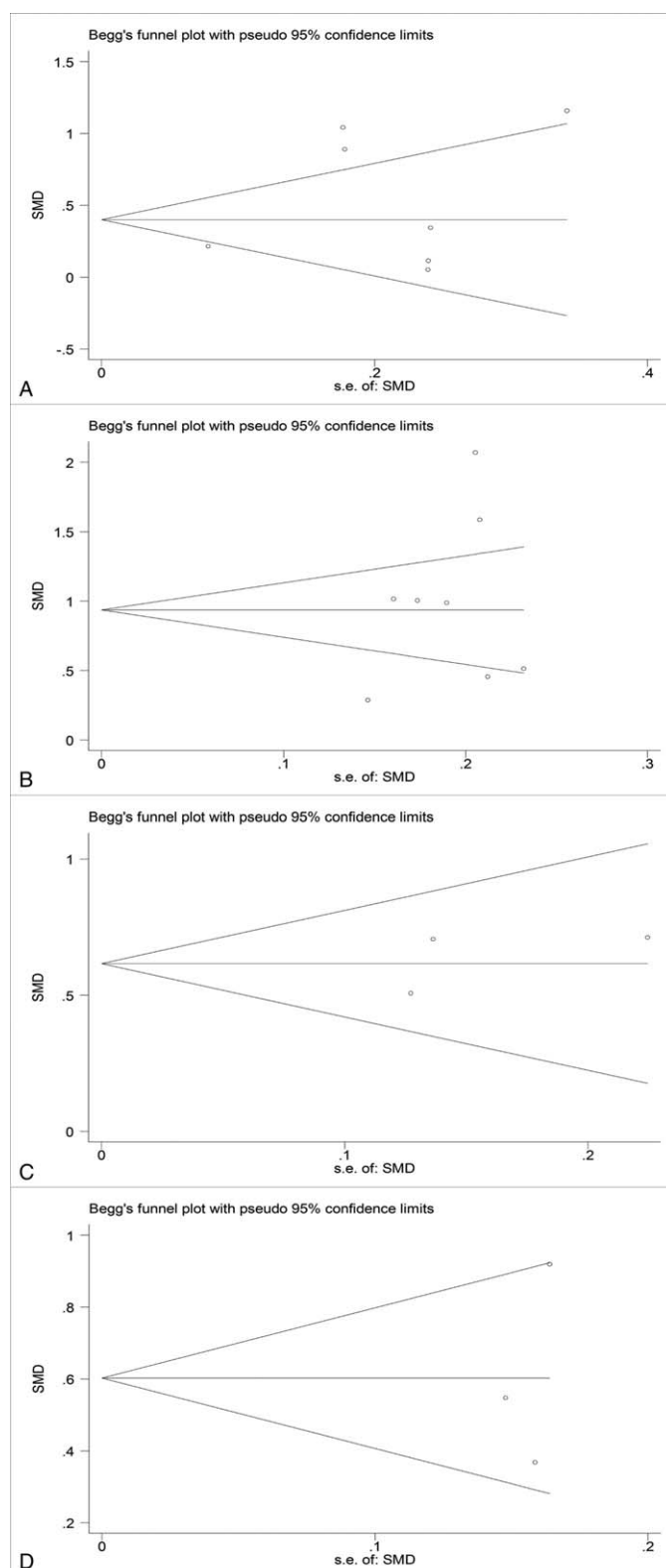


Figure 4. Begg's funnel plot for endocan levels in CVD patients. CVD = cardiovascular disease.

higher in those hypertensive patients than in the control group. It was also found that serum endocan levels were positively correlated with the intima-media thickness of the common carotid artery and were decreased in patients with hypertension treated with amlodipine and valsartan.^[29] In the present study,

we also found that serum endocan levels in hypertensive patients with newly diagnosed hypertension were significantly different from those in patients treated with drugs. The higher serum endocan level may reflect endothelial dysfunction, involving in development of hypertensive.

Coronary slow flow is an angiographic phenomenon characterized by delayed opacification of coronary vessels in an otherwise normal coronary angiogram.^[30] CSF can be associated with myocardial infarction, angina pectoris, malignant arrhythmia, or even sudden cardiac death and other adverse cardiovascular events.^[31,32] Serum endocan can lead to the occurrence of endothelial dysfunction, which plays an important role in the occurrence and development of CSF.^[33,34] Serum endocan levels were significantly higher in a sample of 93 patients than in controls, suggesting that endocan levels may be an effective biomarker for predicting the occurrence and severity of CSF.^[21]

To date, studies on the association of serum endocan and CVD have used small samples, and there may be selection bias. In this paper, we first performed a meta-analysis to generate a quantitative synthesis of related published studies to obtain more accurate conclusions. The results showed that the levels of serum endocan in patients with hypertension, CAD and CSF were higher than those in the control group, indicating that the increase in endocan was closely associated with the pathogenesis of CVD. An elevated level of endocan may be one of the key risk factors of CVD. In addition, serum endocan levels in hypertensive patients with coronary artery disease were higher than those in patients with hypertension, indicating that high levels of endocan may be a predictor of coronary artery disease in hypertensive patients. Hypertension patients with CAD may have more severe vessel damage. In addition, several methods have been reported for evaluating heart function and cancer metastasis.^[35-37] Similarly, the endocan concentration may indicate the cumulative effects of the inflammatory process and cardiac insufficiency.^[38] Serum endocan overexpression conferred cancer enhanced invasion, and metastasis.^[39]

Inevitably, this meta-analysis still has several limitations. First, we only searched the literature published in Chinese and English and failed to incorporate other languages or the gray literature. This choice may have introduced publication bias. Second, other factors such as hyperglycemia, hyperlipidemia, infection, and smoking may affect serum endocan levels. However, no further comparative analysis was found in the original study. More studies with prospective designs are needed to further clarify the relationship between endocan and CVD. Third, the heterogeneity of relevant studies about hypertension and CAD is still existence, although we have reduced heterogeneity through subgroup analysis. Thus, caution is needed in interpreting the overall outcome. Finally, we analyzed hypertension, coronary artery disease, and CSF, but the number of cases in each group is still small. Besides, the most including studies in this meta-analysis are reported from Turkey and China, which could lead to unrepresentative outcomes.

In conclusion, elevated serum endocan may be an important risk factor for hypertension, coronary artery disease and coronary slow flow. Monitoring serum endocan may be a consequential step forward in predicting the occurrence and development of these diseases. However, additional prospective studies are still needed to validate this conclusion.

Author contributions

Conceptualization: Tianming Zhao.

Data curation: Tianming Zhao, Xuelei Zhao, Kecheng Yao.

Formal analysis: Tianming Zhao, Kecheng Yao, Xuelei Zhao, Xuehua Hu.

Methodology: Tianming Zhao, Kecheng Yao, Xuelei Zhao.

Resources: Jixiang Ni, Yingnan Wang, Jing Zhu.

Software: Tianming Zhao, Kecheng Yao.

Supervision: Jixiang Ni, Yingnan Wang, Jing Zhu.

Visualization: Tianming Zhao.

Writing – original draft: Tianming Zhao.

Writing – review & editing: Jixiang Ni.

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