Original Article
Plasma fibrinogen lever and risk of coronary heart disease among Chinese population: a systematic review and meta-analysis

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Abstract: Coronary heart disease (CHD) remains the leading causes of death and disability for men and women in most developed countries. It may soon become the leading cause of death in developing countries. Several studies have examined the role of fibrinogen levels in the prediction of atherosclerosis and CHD events. The aim of this study was to explore the effects of plasma fibrinogen levels in Chinese patients with CHD and to examine the relationship of fibrinogen. We performed this meta-analysis of prospective studies of plasma fibrinogen level in relation to CHD risk in electronic database of Medline, EMBase, the Cochrane Library and CNKI (China National Knowledge Infrastructure). Plasma fibrinogen levels were calculated by mean difference with 95% confidence intervals (CI) in patients with CHD and related controls without CHD. The selected 23 studies included 2984 CHD cases and 2279 controls. Our results found that plasma fibrinogen levels of patients were significantly higher than control group (P<0.0001). The predicted odds ratio (OR) for a 1 g/L higher plasma fibrinogen level was 0.94 (95% CI=0.78-1.10). Furthermore, fibrinogen levels were slightly related to age-related CHD patients. The plasma fibrinogen lever was correlated with CHD in the Chinese population, and may be a risk factor and predictor of CHD. Further studies assessing any causal relevance of fibrinogen levels to disease are required.

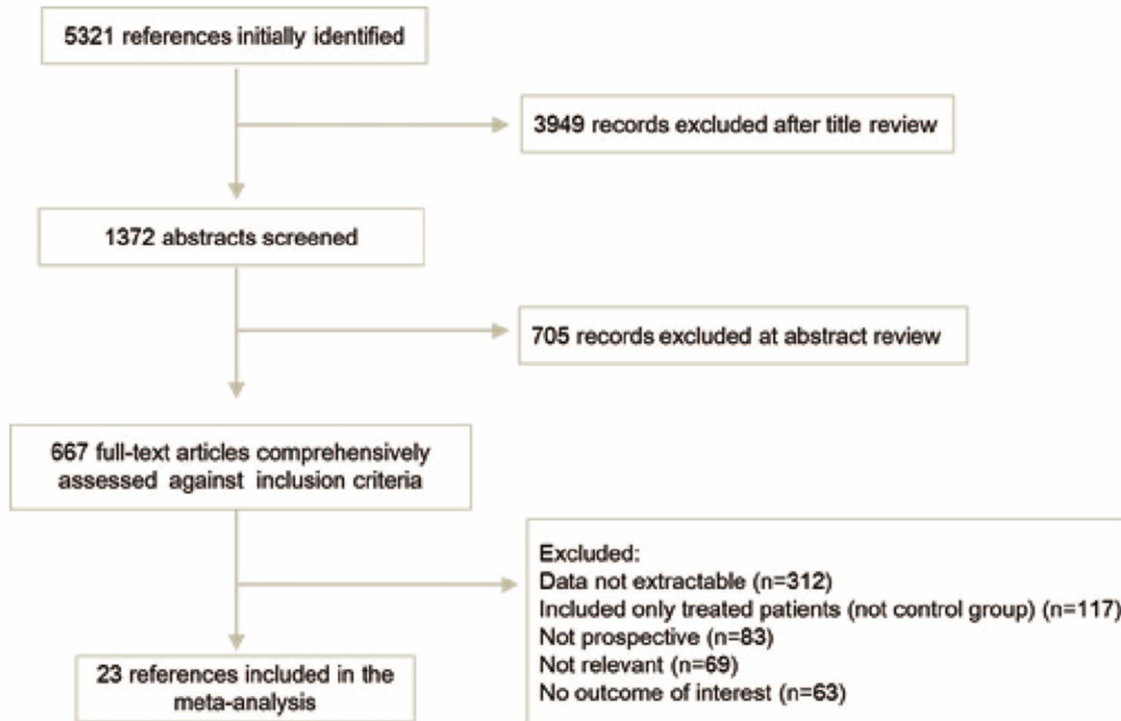**Keywords:** Coronary heart disease, plasma fibrinogen lever, meta-analysis

Introduction

Cardiovascular disease is the leading cause of global mortality, with coronary heart disease (CHD) its major manifestation in today's clinical practice. CHD is a multifactorial disease results from a complex interplay between environmental and genetic factors [1]. Every year, more than 16.3 million adults have CHD, and an estimated 935 000 heart attacks occur in the United States alone [2]. It remains not only the leading cause of death in most developed and developing countries, but also complicates the identification of the causal pathways, and delaying the development of new treatments [3, 4]. In the last few decades novel risk factors for CHD have been identified in previously healthy subjects, such as inflammatory markers (C-reactive protein), and prothrombotic markers (fibrinogen) [5, 6]. Although prospective cohort studies have examined fibrinogen in large populations with long periods of follow-up, whether these markers are a cause or consequence of CHD remains debatable.

Fibrinogen, the precursor of fibrin, was the first described blood coagulation factor [7, 8]. The mature fibrinogen protein is made up of two chains, each of which has three different polypeptides, alpha, beta, and gamma, encoding by three genes located in a cluster of 51 kb on chromosome 4 at q23-q32 [9]. Fibrinogen is an acute-phase inflammatory protein involved in blood clotting and is also a potentially suitable target for CHD [10]. Many studies had demonstrated that the plasma fibrinogen concentration was associated with CHD [11]. These associations indicated that fibrinogen might be a possible causal factor, a therapeutic target, and a risk predictor in not only healthy persons but also those with cardiovascular diseases. Observational studies show that an increase of

Figure 1. Summary of article selection process.

1 g/L of plasma fibrinogen is associated with more than a two-fold increase in CHD and fibrinogen lever may predict the development, the course, and negative prognosis of coronary heart disease (CHD) [12, 13]. However, the relevance of circulating levels of plasma fibrinogen to CHD risk remains uncertain.

Moreover, Okwuosa et al. have demonstrated that fibrinogen tracked longitudinally with changes in traditional risk factors over 13 years through middle age among young black and white men and women with few baseline cardiovascular risk factors [14]. Considering the diversity between age, sex and ethnicity, and the necessity to improve prevention strategies in CHD patients, we conducted this meta-analysis and aimed to evaluate the prognostic implications of fibrinogen in a unique and relatively large cohort of Chinese patients with acute coronary syndrome.

Materials and methods

Search strategy for identification of studies

Four major electronic databases, Medline, EM-Base, the Cochrane Library and China National

Knowledge Infrastructure (CNKI) were searched for related reports between 2005 and 2013 using the following medical subject heading terms and keywords: coronary heart disease, CHD, plasma fibrinogen and risk factors. All eligible studies were retrieved. And references were retrieved for other relevant publications.

Criteria for article screening

Studies were defined as eligible if: 1) they were prospective cohort studies evaluating fibrinogen level to CHD risk; 2) adult patients with longer than 1 year of follow-up; 3) all CHD patients accorded with the diagnosis standard of WHO in 1999, and coronary angiography results show that at least one coronary artery lumen diameter was stenosed more than 50% [15]; 4) the two groups of subjects have no significant difference in such aspects as age and gender. No language restrictions were applied.

The excluded criteria were: 1) patients with diabetes, podagra, and immune system diseases; 2) patients with blood disease, malignant tumor, and heart kidney function; 3) patients have anticoagulant therapy prior to admission to hospital.

Table 1. Main characteristics of included studies in this meta-analysis

First author-published year	Cases			Controls		
	Age	Total	FB level	Age	Total	FB level
Li Y-2005	66.1±7.4	58	3.82±0.56	62.5±8.3	22	2.92±0.32
Xia HJ-2005	68.3±19.2	109	3.99±1.17	65.7±12.3	162	3.32±1.05
Zhou BR-2005	63.8±7.5	100	4.82±0.46	-	36	3.46±0.57
Zhao Y-2005	70.65±11.35	75	3.69±0.81	67.62±10.60	65	3.33±0.86
Hao JH-2006	71.02±15.56	78	5.74±2.54	68.35±14.83	60	3.82±1.70
Ma ZX-2006	58.4±7.8	46	3.72±1.08	51.3±7.5	82	3.31±0.74
Zhang ZL-2006	68.6±4.6	91	3.48±0.96	67.4±4.9	72	2.65±0.38
Chen SA-2007	66.4±13.88	80	4.25±0.32	50.53±9.01	78	3.21±0.65
Sun AJ-2008	64.2±10.2	836	3.43±2.03	59.7±11.1	418	3.11±0.68
Tian CL-2008	62.5±11.2	120	3.64±0.76	58.7±10.3	100	2.89±0.62
Bai CW-2009a	43± 4	60	3.27±0.54	41±6	74	2.67±0.30
Bai CW-2009b	65±6	105	3.15±0.49	41±6	74	2.67±0.30
Li GT-2009	67.1±8.4	106	4.04±0.49	64.5±7.3	50	2.91±0.36
Li JQ-2010	69.8	83	4.91±0.51	63	54	3.21±0.54
Liu CF-2010	41-75	112	4.01±0.51	23-67	150	3.17±0.73
Lv LS-2010	44.1	103	4.03±0.43	43.6	108	3.19±0.25
Hu YW-2011	62.16±8.72	100	3.50±1.06	56.00±10.25	100	2.83±0.46
Sun RL-2011	46	76	3.51±0.52	44	82	2.21±0.32
Wang YH-2011	62.5±11.2	120	3.64±0.76	58.7±10.3	100	2.89±0.62
Zhang YQ-2011	60±12	128	4.94±1.87	-	32	3.06±0.58
Rong YZ-2012	63.25±8.06	50	4.76±0.25	59.31±4.79	50	3.22±0.43
Du MY-2013	68.5±5.6	112	4.35±0.55	68.0±5.2	100	3.58±0.48
Liang ZH-2013	63.2±1.4	80	3.4±0.6	62.7±1.9	80	2.4±0.4
Zhang Y-2013	42.5	156	4.12± 0.58	43.1	130	3.20±0.27

Data extraction

All of the data were independently abstracted in duplicate by two authors. The following information was concerned: study characteristics, participant information, analyses, CHD outcome, and adjustment. Discrepancies were resolved by discussing with a third author to reach a final consensus.

Statistical analysis

The strength of association between fibrinogen level and CHD risk was assessed by the mean difference with 95% confidence intervals (95% CI). A *P*-value of the Z test less than 0.05 was considered significant, which determined the significance of the pooled mean level. The between-study heterogeneity of all the included articles was evaluated by the Cochran's Q test and the I^2 statistics. The fixed-effect model was used when the *P*-value of the Q test more than 0.1 and the I^2 less than 50%, considering no statistically significant heterogeneity among studies. Otherwise, the random-effect model was employed. The funnel plot was performed to examine the publication bias. Analyses were performed in the Review manager 5.2 (The Cochrane Collaboration). All tests were two-sided.

Results

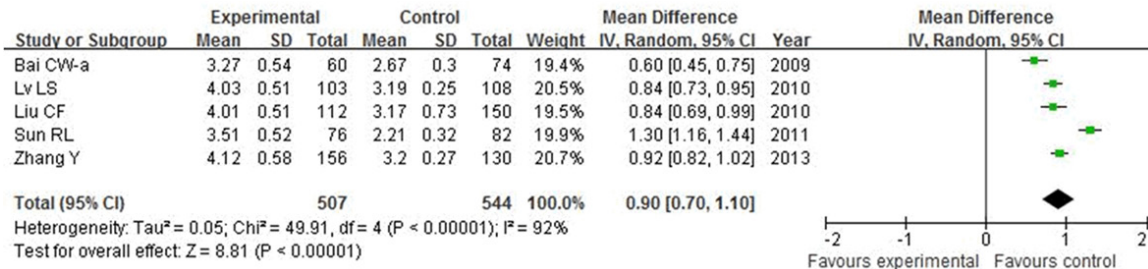*Characteristics of included studies*

The electronic database search identified 5321 references. Following the inclusion criteria for relevance, finally a total of 23 studies containing 5263 participants were included in this meta-analysis. **Figure 1** showed the study flow.

Among the 23 papers, one was written in English [16], twenty-two were published in Chinese [17-38]. All of them, including 2984 patients and 2279 healthy controls, was assessed the relationship between fibrinogen level and CHD.

Table 2. Meta-analysis of predicted association for plasma fibrinogen level and CHD risk

	OR (95% CI)	*P* value	$P_{Heterogeneity}$	Model
All studies	0.94 (0.78, 1.10)	P<0.0001	P<0.0001	Random-effect model
Studies with middle patients	0.90 (0.71, 1.10)	P<0.0001	P<0.0001	Random-effect model
Studies with old patients	0.96 (0.75, 1.16)	P<0.0001	P<0.0001	Random-effect model

Figure 2. Forest plot on the association between plasma fibrinogen level and CHD risk among middle-aged patients.
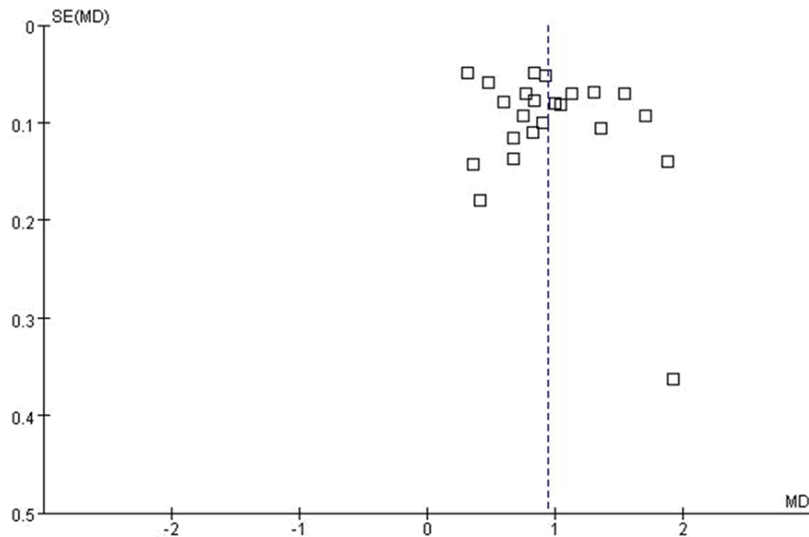
Figure 3. Publication bias for the analysis of all the studies.

The major characteristics of the eligible publications are reported in **Table 1**.

Association of fibrinogen level and CHD risk

The case-control comparison yielded a risk ratio for CHD of 0.94 (95% CI=0.78-1.10) per 1 g/L higher usual plasma fibrinogen concentration, which is equivalent to a risk ratio of middle-aged less than 50-year-old (OR=0.90, 95% CI=0.71-1.10) and old-aged (OR=0.96, 95% CI=0.75-1.16). There is a significantly association between plasma fibrinogen level and CHD risk (P<0.0001). **Table 2** shows the predicted OR for about 1 g/L increase in plasma fibrinogen, cal-culated assuming a linear-logistic relationship between plasma fibrinogen level and risk of CHD. **Figure 2** showed the relationship among middle-aged patients (less than 50-year-old). However, there is a significantly heterologous among studies.

Sensitivity analyses and publication bias

The individual study included was omitted one time to estimate the influence of the single article to the pooled ORs. The corresponding pooled ORs were not materially changed, which confirmed the stability of our overall result.

The funnel plot was conducted to assess the publication bias of the included studies. Its shape did not reveal any evidence of funnel plot asymmetry. As shown in **Figure 3**. The statistical results still did not show publication bias.

Discussion

Fibrinogen plays a key role in the final step of the coagulation cascade such as the formation of fibrin [39]. It is also a major determinant of plasma viscosity and erythrocyte aggregation [40, 41]. Fibrinogen, as well as its decomposi-

tion products, mediates the transportation of adhesion molecules in the surface of endothelium and their further migration to the intima. They can also trigger proliferation and migration of smooth-muscle cells [42]. In regard to the inflammatory aspect of fibrinogen, inflammatory process is mainly mediated by the interaction of fibrinogen-leukocytes mediated by integrins [43].

Many studies have examined the role of fibrinogen levels alone or combined with other risk factors in the prediction of atherosclerosis and CHD events. Xu et al. shown that high fibrinogen may be a possible link between job stress and cardiovascular disease [44]. Aliberti et al. found an association between fibrinogen plasma levels and platelet counts in an outpatient population and in patients with CHD [45]. In the past years, plasma fibrinogen is under debate whether it is a primary risk factor/mediator for CHD, or whether it is a marker for disease [46]. Many cohort studies showed that fibrinogen may partly mediate the effects of other risk factors on carotid atherosclerosis [47]. Molecular biology found that fibrinogen is a marker, rather than a mediator, of vascular disease [48].

The present meta-analysis involves individual participant data from 23 prospective studies of CHD among 2984 individuals with known CHD at baseline and 2279 health controls. Our results found plasma fibrinogen levels of patients were 0.94-folder higher than control group, and showed a significantly association between plasma fibrinogen level and CHD risk (P<0.0001). The predicted causal odds ratio for a 1 g/L higher plasma fibrinogen level was 0.94 (95% CI=0.78-1.10), indicating fibrinogen level is associated with the incidence rates of CHD. These data showed that throughout the range of fibrinogen levels recorded in Asian populations, the proportional differences in risk of each of these end points associated with a given absolute difference in usual fibrinogen are generally similar at all fibrinogen levels.

Studies have shown that reducing the fibrinogen level might be a potential method in reducing the CHD risk [49]. Lifestyle interventions can considerably reduce the fibrinogen level and influence levels of several established risk factors such as moderate alcohol consumption, and regular exercise, which may help in

disease prediction or prevention [50]. A previous meta-analysis which included 18 such studies and about 4000 CHD cases, indicated a relative risk of 1.8 (95% CI=1.6-2.0) per 1 g/L increase in plasma fibrinogen level [51].

Fibrinogen levels were related with several established risk factors, for example, blood pressure and serum cholesterol levels. Panagiotakos et al. showed that in individuals with heterozygous familial hypercholesterolemia, fibrinogen levels are among the strong predictors of CHD [52]. These confounding factors probably have been measured with some error so substantial residual confounding may remain. Furthermore, an interesting study by Several limitations were presented in this study. Firstly, we only evaluated associations between plasma level and CHD risk among Chinese population, other populations should be considered. Secondly, there is large heterologous among studies in our analysis due to a small group of patients. Thirdly, fibrinogen levels may correlate with several other factors such as smoking, sex, serum lipid levels which should be considered. Fourthly, we did not investigate whether genetic and environmental factors modify each other in these associations.

Overall, our study found that plasma fibrinogen levels were higher in patients with CHD compared to normal subjects. These results proved that there is a significant relationship between fibrinogen levels and the progress of CHD. Further studies involving larger numbers of patients and relating with other risk factors may elucidate the clearly association between fibrinogen levels and the CHD severity.

Disclosure of conflict of interest

None.

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