

## ORIGINAL ARTICLE

# Factor XI levels and the risk of cardiovascular events: a systematic review and meta-analysis of case-control and cohort studies

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**Abstract**

**Background:** The relationship between coagulation factor (F)XI and the risk of cardiovascular events has been investigated in several epidemiological studies, but the overall results remain inconclusive.

**Objectives:** The aim of this systematic review and meta-analysis of case-control and cohort studies was to evaluate the relationship between FXI and the risk of cardiovascular events. FXI levels in the general population and the risk of different cardiovascular events were the primary exposure and outcome, respectively.

**Methods:** Two independent reviewers (Li and Ma) screened all available literature to identify studies that met the inclusion criteria. A random or fixed-effects model was used, and heterogeneity was quantitatively tested by the  $I^2$  statistic.

**Results:** A total of 16 original studies were included in the quantitative meta-analysis. The meta-analysis results of both case-control and cohort studies showed a positive correlation between FXI levels and the risk of cardiovascular events (odds ratio [OR], 1.77; 95% CI, 1.17-2.68; hazard ratio [HR], 1.34; 95% CI, 1.09-1.64). Subgroup analysis revealed a positive correlation between FXI levels and the risk of myocardial infarction (OR, 1.63; 95% CI, 1.02-2.60; HR, 2.53; 95% CI, 1.15-5.60), while there was no significant correlation between FXI levels and acute coronary syndrome or ischemic stroke (OR, 1.78; 95% CI, 0.40-7.82; HR, 1.15; 95% CI, 0.93-1.41).

**Conclusion:** Our findings support a positive correlation between FXI levels and the risk of cardiovascular events.

**KEYWORDS**

acute coronary syndrome, factor XI, ischemic stroke, myocardial infarction, cardiovascular events

**Essentials**

- The purpose of this research was to investigate the relationship between coagulation factor levels and the risk of different cardiovascular events.
- For statistical analysis, case-control and cohort studies were employed.
- The results confirm that the risk of cardiovascular events is positively correlated with FXI levels.
- Coagulation variables and myocardial infarction risk are significantly positively correlated according to subgroup analysis.

## 1 | INTRODUCTION

The human F11 gene encodes the plasma serine protease coagulation factor (FXI), sometimes referred to as plasma thromboplastin antecedent. Through the contact reaction, it contributes to the synthesis of fibrin and thrombin and is mostly generated in the liver [1]. Multiple clinical trials have shown that anticoagulants targeting FXI have better anticoagulant effects and lower bleeding risks compared with existing anticoagulants [2,3]. They may also be more applicable when treating thromboembolic conditions (such as ischemic stroke, lower extremity vascular embolism, atrial fibrillation [AF], and stent implantation following acute myocardial infarction) [4–6]. Additionally, several studies have demonstrated that FXI is involved in physiological processes such as inflammatory responses, tumor growth, and hepatocyte expansion in addition to aiding in hemostasis and promoting coagulation [7]. This suggests that FXI may also regulate the course of heart failure (HF) by taking part in myocardial inflammatory responses. A considerable number of studies have identified HF as a prothrombotic condition, particularly when accompanied by AF [8]. Endothelial dysfunction, blood flow stasis, platelet activation, and their effects on the coagulation cascade collectively contribute to a high-risk environment for thrombogenesis, which increases the risk of both arterial and venous thromboembolic events [9,10].

In a case-control study by Doggen et al. [11], the risk of myocardial infarction rose as FXI activity increased in all participants with FXI activity >55%. However, a study by Alehagen et al. [12] discovered that among older adults (65–82 years old) with HF symptoms, a lower FXI level was linked to a higher risk of cardiovascular death. The cardiovascular death risk was 3.01 times greater (95% CI, 1.02–8.83) for patients with FXI levels < 0.60 IU/mL than for those with FXI > 0.60 IU/mL. This could be because the older study population had decreased liver function. Furthermore, Preis et al. [13] examined the Israeli national individual database with FXI level data and discovered that AF and HF were more common in people with lower FXI levels. According to Cao et al. [14], over-expressing FXI in mouse models of HF with preserved ejection fraction (HfpEF) and AF may alleviate HF and lessen diastolic dysfunction and fibrosis. Additionally, the scientists discovered that a decrease in the E/e' ratio (ie, enhanced diastolic function) was linked to an increase in plasma FXI levels in HfpEF patients. The same authors, however, found no discernible difference in plasma FXI levels between patients with and without HfpEF in a small-scale auxiliary clinical trial ( $n = 40$ ) [14].

In conclusion, the studies mentioned above collectively show that there is ongoing debate regarding the association between FXI and cardiovascular events and that further investigation is required to completely comprehend the advantages and disadvantages of FXI levels on cardiovascular events.

## 2 | METHODS

### 2.1 | Search strategy and study selection

Our findings reported the findings following the Meta-analysis of Observational Studies in Epidemiology standards [15] and adhere to the Preferred Reporting Items for Systematic reviews and Meta-Analyses 2020 review manual's methodological recommendations [16] for systematic reviews and meta-analyses. This study and the corresponding search protocol were registered in the Prospective Register of Systematic Reviews registry (<http://www.crd.ac.uk/PROSPERO>) with registration number CRD420251007265.

Up until December 15, 2024, a thorough English-language literature search was carried out in the Cochrane Library, PubMed, Embase, and Medline databases. Table 1 displays the search tactics. To find other references, we also looked through the reference lists of pertinent publications.

### 2.2 | Inclusion criteria and study selection

The following were the precise requirements for inclusion: (1) published in English; (2) using cohort studies or case-control study methods; (3) verifying the occurrence of cardiovascular events, including myocardial infarction, ischemic stroke, acute coronary syndrome, or HF; and (4) possessing markers of FXI concentration levels. The following studies were excluded: (1) studies with the largest sample size or the longest follow-up period, with multiple published articles in overlapping groups, and the same outcome indicators; (2) case reports, letters, reviews, conference abstracts, and animal model studies; and (3) studies published in languages other than English.

The entire text of a study was retrieved for additional analysis after 2 independent reviewers filtered the abstracts and titles based on the inclusion criteria. Lastly, 8 case-control studies (a total of 126,076 cases and 46,336 controls) that examined the relationship between FXI and the risk of cardiovascular events satisfied the inclusion requirements, as did 8 cohort studies (a total of 22,657 subjects, including 2452 patients). Acute coronary syndrome and myocardial infarction subgroups were examined in the case-control studies, whereas ischemic stroke and myocardial infarction subgroups were examined in the cohort studies.

### 2.3 | Data extraction and quality assessment

The study name, study design, age, country, number of participants, cardiovascular events, publication year, follow-up, and FXI monitoring method were all extracted by 2 separate reviewers (Li and Zhou). If there were any discrepancies, they were discussed until an agreement

**TABLE 1** Search formulas.

| Databases        | Search terms                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| PubMed           | ((Coagulation factor XI) OR FXI) AND ((ischemic stroke) OR [stroke] OR [myocardial infarction] OR [heart failure])                                                                                                                                                                                                                                                                                                                                                              |
| Embase           | ("coagulation factor xi"/exp OR "coagulation factor xi" OR ["coagulation"/exp OR coagulation] AND factor AND ["xi"/exp OR xi] OR fxi) AND ("ischemic stroke"/exp OR "ischemic stroke" OR [ischemic AND {"stroke"/exp OR stroke}]) OR "stroke"/exp OR stroke OR "myocardial infarction"/exp OR "myocardial infarction" OR (myocardial AND ["infarction"/exp OR infarction]) OR "heart failure"/exp OR "heart failure" OR [{"heart"/exp OR heart] AND ["failure"/exp OR failure]) |
| Medline          | (coagulation factor XI or FXI) AND (ischemic stroke or stroke or myocardial infarction or heart failure)                                                                                                                                                                                                                                                                                                                                                                        |
| Cochrane Library | ((Coagulation factor XI) OR FXI) AND ((ischemic stroke) OR [stroke] OR [myocardial infarction] OR [heart failure])                                                                                                                                                                                                                                                                                                                                                              |

FXI, factor XI.

was reached. The Newcastle–Ottawa Scale score (0–9 points) was used to assess the quality of the included studies; a higher score denoted higher quality. Two authors separately conducted the evaluation process.

## 2.4 | Statistical analysis

Stata 14.0 (StataCorp) and RevMan 5.4 software (The Cochrane Collaboration, The Nordic Cochrane Centre) were used for data analysis. The natural log-transformed odds ratio (OR), hazard ratio (HR), and 95% CI values of the highest and lowest categories of FXI levels were combined and compared using either fixed-effects or random-effects models. FXI was regarded as a risk factor for an event when its OR or HR in relation to event risk was  $>1$ . Only information from multivariable Cox regression models that were adjusted for potential confounders was included to exclude the impact of confounding variables such as age, sex, race, usage of antihypertensive drugs, and diabetes status. The degree of heterogeneity of each study was evaluated using the  $I^2$  statistic. The results were summarized using the fixed-effects model if there was no significant heterogeneity ( $I^2 < 50\%$  and  $P \geq .05$ ), and the random-effects model if there was substantial heterogeneity ( $I^2 \geq 50\%$  or  $P < .05$ ). Additionally, publication bias in the included studies was evaluated using Egger's test.

## 3 | RESULTS

### 3.1 | Study characteristics

Following a manual search and an initial search in the PubMed, Embase, Medline, and Cochrane Library databases, 1609 items were found after duplicates were eliminated (Figure 1). Based on the abstract and title information, 1574 articles were removed according to the exclusion requirements. As a result, 35 articles were used for additional assessment. Lastly, the quantitative comprehensive meta-analysis included 16 publications in total (Figure 1).

Tables 2 and 3 display the pertinent data for each study. Eight case-control studies and 8 cohort studies, totaling 195,069 people from various nations worldwide, were included in this meta-analysis: 6 from the United States, 5 from the Netherlands, 2 from Poland, 1 from Germany, 1 from China, and 1 from Europe. Prospective cohort studies had follow-up periods ranging from 3 to 18 years. Only 1 study was assessed as "low quality" ( $<4$  points), 7 studies were rated as "moderate" (4–6 points), and half of the studies were rated as "high quality" ( $\geq 7$  points).

### 3.2 | Meta-analysis of case-control and cohort studies

Eight case-control studies (Table 2) and 8 cohort studies (Table 3) were among the 16 papers chosen for analysis. Of the 8 case-control studies, 4 examined the relationship between FXI levels and myocardial infarction events, 2 examined the relationship between FXI levels and events of acute coronary syndrome, 1 examined the relationship between FXI levels and ischemic stroke events, and 1 examined the relationship between FXI levels and stroke or transient cerebral ischemia attacks. FXI levels and the risk of cardiovascular events were positively correlated according to the overall effect size (OR, 1.77; 95% CI, 1.17–2.68; heterogeneity  $I^2 = 70\%$ ; Figure 2A). Five of the 8 cohort studies examined the relationship between FXI levels and ischemic stroke events, 2 examined the relationship between FXI levels and myocardial infarction events, and 1 examined the relationship between FXI levels and HF events. FXI levels and the risk of cardiovascular events were positively correlated according to the total effect size (HR, 1.34; 95% CI, 1.09–1.64; heterogeneity  $I^2 = 86\%$ ; Figure 2).

### 3.3 | FXI levels and acute coronary syndrome

There was no significant link (OR, 1.78; 95% CI, 0.40–7.82; heterogeneity  $I^2 = 77\%$ ) between FXI levels and acute coronary syndrome occurrences according to subgroup analysis of 2 case-control studies [17,20] (Figure 3).

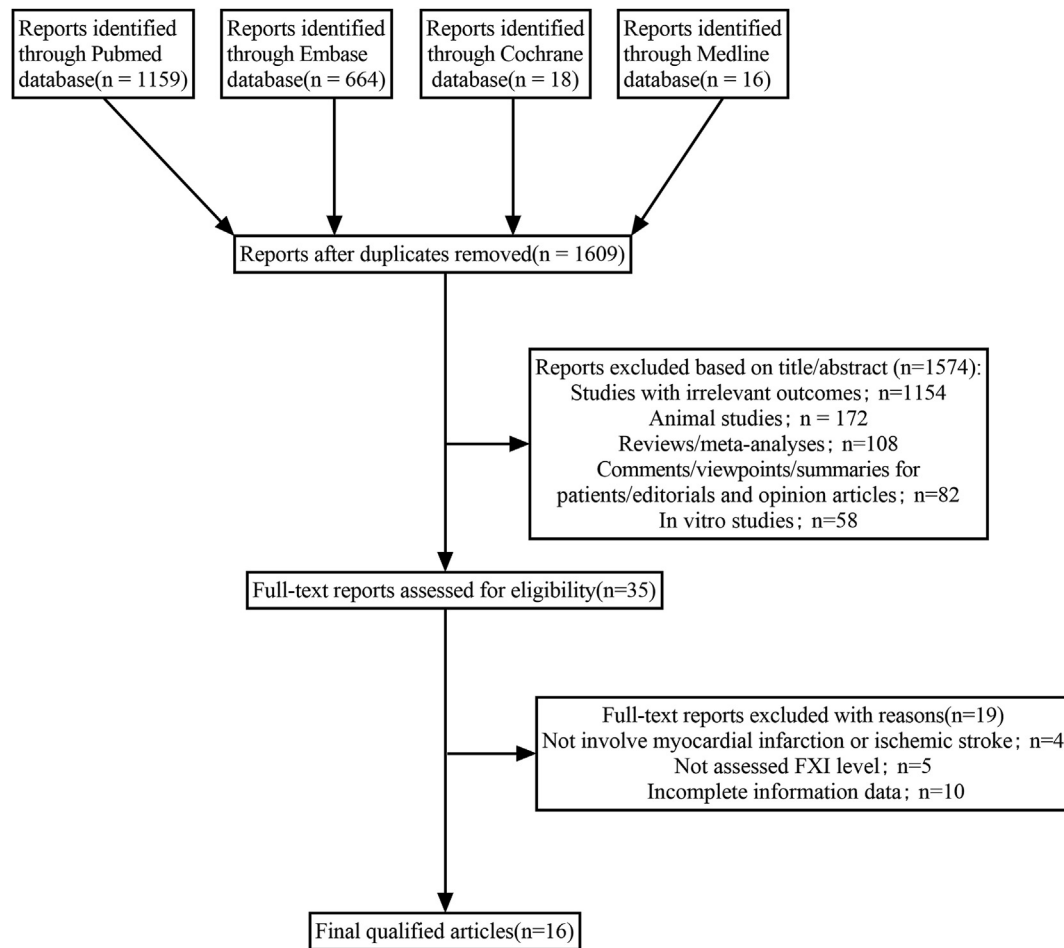


**FIGURE 1** Literature screening flowchart. FXI, factor XI.

### 3.4 | FXI levels and myocardial infarction

We gathered case-control study data (124,806 cases and 44,492 controls) [11,18,19,22] and used FXI levels to assess the likelihood of myocardial infarction occurrences (Figure 3). The case group's FXI level was 1.63 times higher than the control group, according to the

results (OR, 1.63; 95% CI, 1.02-2.60; heterogeneity  $I^2 = 64\%$ ). One hundred twenty-one myocardial infarction instances involving 696 individuals were examined in relation to prospective cohort studies (Figure 4). The findings demonstrated that when FXI levels rise, so does the prevalence of myocardial infarction in the population (HR, 2.53; 95% CI, 1.15-5.60; heterogeneity  $I^2 = 64\%$ ).

**TABLE 2** Research characteristics of case-control studies in this systematic review and meta-analysis.

| Study                      | Country         | Age (y) <sup>b</sup> | Controls, n (M/F) | Cardiovascular events                 | Cases, n (M/F) | FXI status            | Quality |
|----------------------------|-----------------|----------------------|-------------------|---------------------------------------|----------------|-----------------------|---------|
| Chen et al.,2021 [17]      | China           | 67 ± 7.6             | 549 (301/248)     | Acute coronary syndrome               | 549 (301/248)  | Q3 vs Q1 <sup>a</sup> | 7/9     |
| Doggen et al.,2006 [11]    | Netherlands     | ≤70                  | 646 (646/-)       | Myocardial infarction                 | 560 (560/-)    | Q5 vs Q1              | 8/9     |
| Gill et al.,2018 [18]      | Europe          | -                    | 123,504           | Myocardial infarction                 | 43,676         | Continuous            | 2/9     |
| Loeffen et al.,2014 [19]   | The Netherlands | 34-86                | 30 (21/9)         | Myocardial infarction                 | 56 (40/16)     | Continuous            | 6/9     |
| Loeffen et al.,2015 [20]   | The Netherlands | -                    | 42                | Acute coronary syndrome               | 1042           | Continuous            | 7/9     |
| Siegerink et al.,2014 [21] | The Netherlands | 18-50                | 639               | Ischemic stroke                       | 175            | Q4 vs Q1              | 6/9     |
| Tanis et al.,2006 [22]     | The Netherlands | 18-49                | 626 (-/626)       | Myocardial infarction                 | 200 (-/200)    | Q4 vs Q1              | 6/9     |
| Yang et al.,2006 [23]      | USA             | ≤55                  | 40 (15/25)        | Stroke or transient cerebral ischemia | 78 (35/43)     | Continuous            | 4/9     |

F, female; FXI, factor XI; M, male; Q, quartile.

<sup>a</sup>This study used concentration intervals to represent FXI. FXI levels were divided into 5 quartile intervals according to numerical ranges to characterize the characteristics of participants in different intervals and to examine the relationship between FXI and other parameters.

<sup>b</sup>The age of this study is represented by mean ± SD or range.

**TABLE 3** Research characteristics of cohort studies in this systematic review and meta-analysis.

| Study                    | Country | Age (y)    | Total population, n (M/F) | Cardiovascular events | Incident cases, n (M/F) | FXI status  | Follow-up (y) | Quality |
|--------------------------|---------|------------|---------------------------|-----------------------|-------------------------|-------------|---------------|---------|
| Appiah et al.,2017 [24]  | USA     | ≥65        | 3394 (1256/2138)          | Ischemic stroke       | 473                     | Q5 vs Q1    | 13            | 8/9     |
| Folsom et al.,2015 [25]  | USA     | 45-64      | 11,439                    | Ischemic stroke       | 631                     | Q5 vs Q1    | 18            | 8/9     |
| Ji et al.,2024 [26]      | USA     | 45-64      | 4158                      | Heart failure         | 580                     | Q4 vs Q1    | 11            | 8/9     |
| Olson et al.,2017 [27]   | USA     | ≥45        | 2185                      | Ischemic stroke       | 538                     | Q5 vs Q1    | 5.8           | 6/9     |
| Paszek et al.,2022 [28]  | Poland  | 57-70.3    | 120 (94/26)               | Myocardial infarction | 27 (19/8)               | Continuous  | 8.8           | 5/9     |
| Rohmann et al.,2020 [29] | Germany | ≥18        | 576 (351/225)             | Myocardial infarction | 94                      | Continuous  | 3             | 6/9     |
| Suri et al.,2010 [30]    | USA     | 45-64      | 501                       | Ischemic stroke       | 89                      | Q4 vs Q1    | 7.5           | 9/9     |
| Ząbczyk et al.,2022 [31] | Poland  | 63.3 ± 8.8 | 284 (150/134)             | Ischemic stroke       | 20                      | Categorical | 3.9           | 7/9     |

F, female; FXI, factor XI; M, male; Q, quartile.

### 3.5 | FXI levels and ischemic stroke

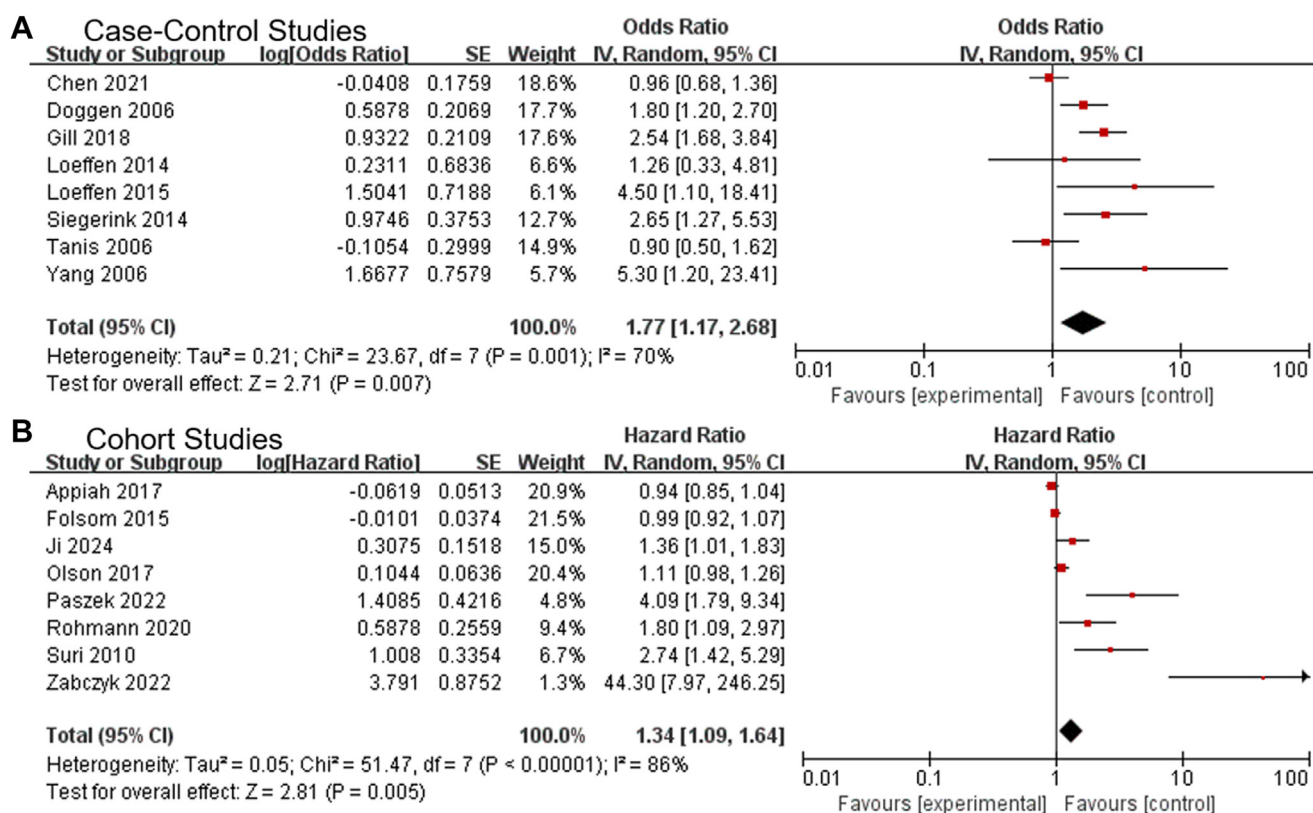
After conducting a subgroup analysis of 5 cohort studies [24,25,27,30,31], we found no significant connection between FXI levels and the risk of ischemic stroke (HR, 1.15; 95% CI, 0.93-1.41; heterogeneity  $I^2 = 87\%$ ; Figure 4).

### 3.6 | FXI levels and HF

The relationship between FXI levels and HF risk was studied in only 1 cohort study, which found a positive link between the 2 (HR, 1.36; 95% CI, 1.01-1.83; Figure 4).

### 3.7 | Publication bias

We used the trim-and-fill method for further analysis (Figure 5) to confirm the robustness of the results because the meta-analysis of case-control and cohort studies evaluating the correlation between FXI levels and cardiovascular events in all subjects showed no evidence of publication bias in the case-control studies ( $P = .309$ ), but a certain degree of publication bias in the cohort studies ( $P < .01$ ). The results of the Egger's test are shown in Table 4. Three estimated missing virtual studies were included after 4 iterations of the linear method. The reanalysis of the combined effect values revealed no significant correlation between FXI levels and the risk of cardiovascular events

**FIGURE 2** Correlation between coagulation factor XI levels and the risk of cardiovascular events. (A) Case-control studies and (B) cohort studies.

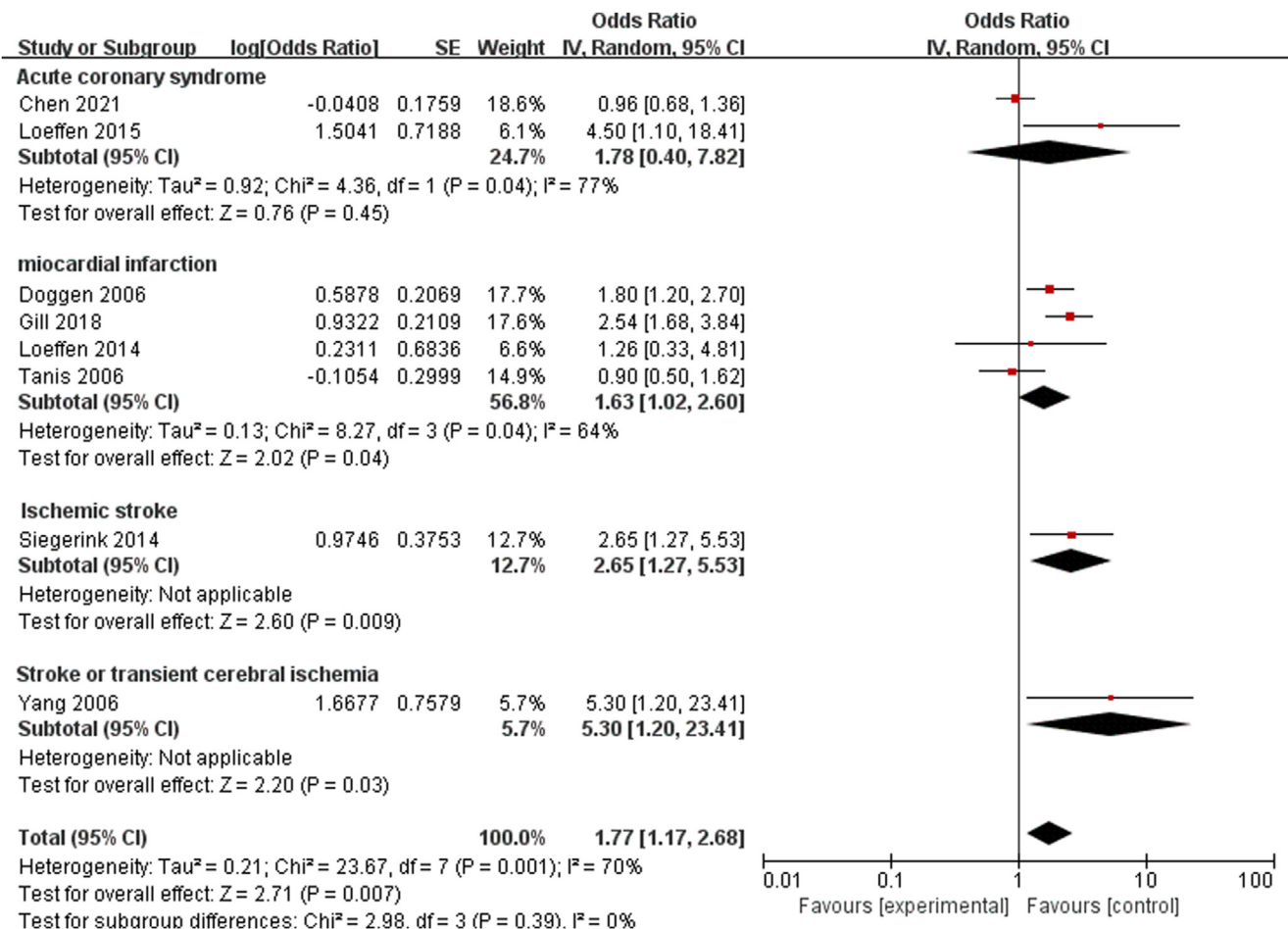


**FIGURE 3** Forest plot of subgroup analysis of the case-control studies.

(HR, 1.129; 95% CI, 0.89-1.43), which is in contrast to the earlier findings.

## 4 | DISCUSSION

We examined the relationship between FXI levels and several cardiovascular events in case-control studies. The risk of cardiovascular events had a positive correlation with FXI (OR, 1.77; 95% CI, 1.17-2.68). Cohort studies also revealed a comparable association (HR, 1.34; 95% CI, 1.09-1.64). Stratified subgroup analysis revealed that myocardial infarction (OR, 1.63; 95% CI, 1.02-2.60; HR, 2.53; 95% CI, 1.15-5.60), rather than ischemic stroke (HR, 1.15; 95% CI, 0.93-1.41) or acute coronary syndrome (OR, 1.78; 95% CI, 0.40-7.82), may be the cause of the association between FXI and cardiovascular events.

When examining the cohort studies, it is important to keep in mind that there was some publication bias and that the trim-and-fill method produced varied results. The following are some potential causes for this discrepancy: this study excluded some gray literature that was not indexed in mainstream databases, such as conference papers and internal reports, which may have led to publication bias. Positive result studies were overincluded in the meta-analysis because

studies with statistically significant positive results are frequently more likely to be published.

A sequential method is used to activate the serine protease FXI. By triggering the catalytic domain, the activation causes a conformational shift that reveals several exosites on the apple domain. Platelets, thrombin, FIX, heparin, glycoprotein Ib, and other substances can all be bound by these exosites [32,33]. Through the so-called tissue factor pathway, tissue factor interacts with activated FVII to initiate hemostasis. FX is transformed into activated FX, its active form, as a result of this interaction. Subsequently, activated FX starts a chain of events that eventually trigger FII, causing fibrin to develop and hemostatic clots to form [7]. Actually, FXI plays a very small part in hemostasis. Thrombin primarily activates FXI into FXIa, and activating FIX solidifies the hemostatic clot.

FXI has a significant function in pathological thrombosis, in contrast to its minor role in hemostasis [34]. The tissue factor pathway and the contact pathway are the 2 primary pathways that can cause pathological thrombosis. Either way, the first step involves the production of thrombin, followed by the activation of FXI. During the amplification process, FXI then promotes thrombus formation and spread [35]. Research has demonstrated that in animal models, FXI inhibition or deficiency lowers the risk of thrombosis [36].

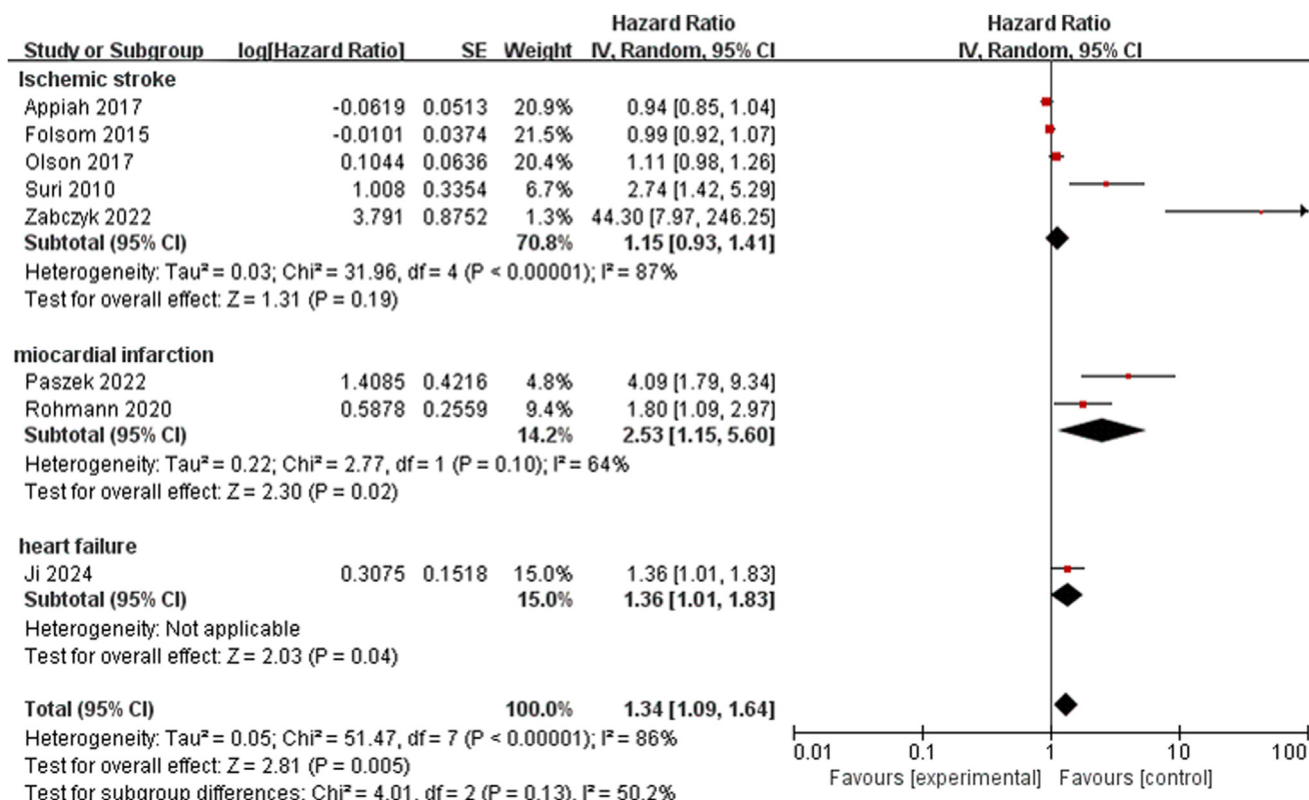


**FIGURE 4** Forest plot of subgroup analysis of cohort studies.

Furthermore, compared with the general population, people with FXI deficiency have a reduced incidence of deep vein thrombosis [37], while those with higher FXI levels are at a higher risk of venous thromboembolism [1].

Cao et al. [14] demonstrated in mice that the precursor of bone morphogenetic protein 7 (BMP 7) in the myocardium is cleaved by liver-derived FXI. In mice with HfpEF, this then triggers the BMP7-small mothers against decapentaplegic 1 (SMAD1)-SMAD5 pathway, which in turn reduces cardiac inflammation, fibrosis, and diastolic dysfunction. This is a previously undiscovered facet of the liver-heart relationship. Gailani et al. [38] found that the proteolytic activity of FXI remains crucial for its cardioprotective effect, but it targets different substrates through BMP 7. Although BMP 7 is expressed in a variety of tissues, it seems to be more abundant in cardiomyocytes, which could explain why FXI has a particular effect on the heart. Other systemic metabolic benefits, such as reduced weight gain and improved lipid profile, are also seen in mice with overexpressed FXI, suggesting that FXI has functions outside of the heart [39]. It is yet unknown if the BMP7-SMAD1-SMAD5 pathway mediates these further effects.

One of the primary causes of myocardial infarction is coronary atherosclerosis, which is linked to prethrombotic alterations such as increased fibrinogen, FVIII, and impaired fibrinolysis [40]. Tissue factor, which is exposed by plaque erosion or rupture, combines with FVIIa to activate plasma FIX and FX, causing the production of thrombin and the formation of fibrin clots [41]. According to reports,

atherosclerotic plaques contain FXI [42]. Apolipoprotein E/FXI double-gene knockout mice have a 25% to 49% smaller atherosclerotic plaque size and less macrophage infiltration than apolipoprotein E gene knockout control mice [43]. Persistent FXIa production may, therefore, exacerbate atherosclerosis, raising the risk of thrombosis during myocardial infarction.

Previous studies have found inconsistent evidence of the association between FXI levels and ischemic stroke events. The inconsistent results could be due to a variety of factors, including reverse causality, inadequate sample numbers, poor control of confounding variables, differences in study design and measuring procedures, or chance. FXI levels and the risk of ischemic stroke were consistently positively correlated in previous case-control studies after adjusting for a small number of covariates [17,21,23]. However, some prospective studies [24,25,27], including ours, have not observed a correlation between FXI and ischemic stroke. Case-control studies may be vulnerable to survival bias, and FXI levels are measured after a case event occurs, which increases the likelihood of a reverse causal relationship, in which the impact of the disease is mistaken for the cause of the disease.

Butenas et al. [44] observed that the levels of activated FXI in patients with coronary artery disease were higher than those in healthy controls, but this study only adjusted for age. Studies have shown that when other traditional coronary artery disease risk factors are considered, the positive correlation in the demographically adjusted model is eliminated [17,24]. The current study data suggest

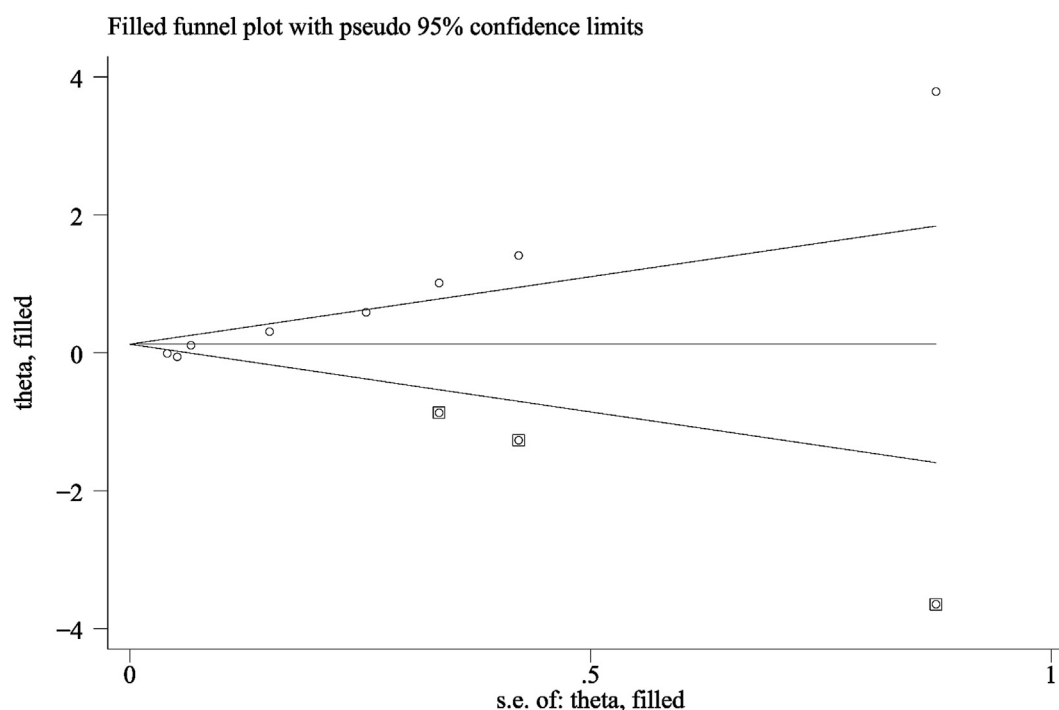


**FIGURE 5** Filled funnel plot with pseudo 95% confidence limits.

that in some previous studies [20,27], the positive correlation between FXI and the risk of acute coronary disease may reflect insufficient control of the related confounding factors.

There are several limitations to our study. First, since our study includes many types of studies from different geographical locations and periods, the  $I^2$  value indicates a high degree of heterogeneity among the studies. To address this issue, we conducted subgroup analyses to identify the sources of heterogeneity. It is worth noting that after subgroup analysis by disease, the statistical heterogeneity was still large, indicating that the heterogeneity may be derived from differences in FXI level measurement methods, age of the statistical population, sex, and the time points of measuring FXI levels. Second, certain stratified categories (such as HF) may have limited sample sizes, which limit the extent to which the impacts of these factors may be modified, even if we discovered that the risk of myocardial infarction with high FXI levels was more evident in some subgroups. Third, even though we have taken into account several confounding variables, including age, race, blood pressure, total cholesterol, diabetes, inflammation, acute condition, and smoking status, some studies have only used data from one sex, and others have not counted inflammation in their patients. Thus, uncontrolled

confounding factors continue to exist. Finally, owing to the lack of data, some cardiovascular events, such as arterial dissection and hemorrhagic stroke, were not included in this study. Therefore, it is impossible to explore their correlation with FXI levels.

## 5 | CONCLUSION

In this large-scale systematic review and meta-analysis of case-control and cohort studies, we observed that higher FXI levels were associated with the risk of various cardiovascular events, especially in myocardial infarction events. Many studies have demonstrated the prothrombotic role of FXI in thrombosis, but its role in normal hemostasis is not fully understood. Therefore, FXI inhibitors are expected to be the target of future anticoagulant drug development, with a potential lower bleeding risk. Further research should clarify the potential mechanisms and progress of FXI inhibitors.

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## AUTHOR CONTRIBUTIONS

W.L.: literature search, study selection, data extraction, bias assessment, review writing, and statistical analysis. Q.M.: literature search, study selection, review writing, data extraction, and bias assessment. W.Z.: data extraction, literature search, and study selection.

**TABLE 4** Egger’s test results.

| Study design       | Egger’s test |               |      |
|--------------------|--------------|---------------|------|
|                    | Intercept    | 95% CI        | P    |
| Case-control study | 1.11         | −1.87 to 4.98 | .309 |
| Cohort study       | 8.54         | 2.62 to 4.73  | <.01 |

F.Z.: resolve disagreement and critical appraisal. All authors read and approved the final manuscript.

## RELATIONSHIP DISCLOSURE

There are no competing interests to disclose.

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