Stock volatility may trigger the onset of acute coronary syndrome: A nationwide case-crossover analysis

Xinlei Zhu,1,12 Renjie Chen,1,12 Feng Liu,1,12 Yixuan Jiang,1 Zuomin Yin,4 Yuzeng Xue,6 Yali Hu,6 Yi He,6 Bin Wang,7 Xiang Tian,1 Yundai Chen,9,* Lixia Yang,10,* and Haidong Kan1,11,*

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GRAPHICAL ABSTRACT

PUBLIC SUMMARY

- Both stock rise and fall increase the risk of acute coronary syndrome onset.
- Effects occur on the concurrent day of stock volatility and last for three days.
- The increased risk is significantly higher for unstable angina and ST-segment-elevation myocardial infarction.
- Heart care and psychological support are vital during stock market fluctuations.
Stock volatility may trigger the onset of acute coronary syndrome: A nationwide case-crossover analysis

**Xinlei Zhu,1,10 Renjie Chen,1,10 Feng Liu,1,21 Yixuan Jiang,1 Zuomin Yin,1 Yuzeng Xue,1 Yali Hu,1 Yi He,1 Bin Wang,1 Xiang Tian,1 Yunbai Chen,1,9 Lixia Yang,1,2 and Haidong Kan1,4,5**

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INTRODUCTION

Acute coronary syndrome (ACS), the acute manifestation of ischemic heart disease, remains a major cause of morbidity and mortality worldwide and places a large burden on the health care system.1,2 Acute coronary syndrome (ACS) describes the range of myocardial ischemic states that includes unstable angina (UA), ST-segment-elevation myocardial infarction (STEMI) and non-ST-segment-elevation myocardial infarction (NSTEMI).3 Mounting evidence shows that emotional and psychosocial stressors could have negative impacts on cardiovascular health.4–6 Economic events could also serve as sociopsychological stressors, potentially increasing the risk of cardiovascular diseases.7–9 Accordingly, as the essential component of economic activities, fluctuations in stock market, may adversely affect cardiovascular health and have the potential of increasing the risk of acute cardiovascular events.

Few studies had examined the association between the fluctuations of stock market and adverse cardiovascular events. Several time-series studies have linked daily stock market changes with daily cardiovascular mortality or hospitalizations.10–12 However, these studies all adopted ecological time-series design and analyzed the data at the daily aggregate level, which could not control for individual-level confounders. Besides, all prior investigations evaluated daily counts of cardiovascular hospitalization or mortality, which would result in temporal misclassification of exposures from the symptom onset to hospital admission or death.13 Furthermore, the existing findings were also challenged by the relatively small sample size and restricted geographical areas (e.g., single centers).13 Accordingly, a large-scale multicenter study based on ample individual cases data on symptom onset would be very helpful to establish a stable association between stock volatility and ACS events.

China is a booming economy with the less mature stock market and higher proportion of individual investors than developed countries. Also, China faces the largest disease burden of ACS in the world.14 However, there has been no investigation quantifying the potential risk of ACS onset from the stock market fluctuation. Hence, taking advantage of a nationwide registry of individual ACS events in China, we conducted a case-crossover study to comprehensively explore the links between daily stock returns and the symptom onset of ACS and its subtypes. We also examined potential effect modifications by sex, age, and season.

METHODS

Study populations

This analysis was conducted based on the Chinese Cardiovascular Association (CCA) Database–Chest Pain Center, a nationwide registry established in 2015 that monitors the quality of medical care for patients who present to the emergency department with symptoms of acute chest pain or discomfort. This nationwide registry collects demographics information such as sex, age, as well as the treatment procedures, diagnosis, and time of symptom onset for each ACS case. We only included hospitals that had been accredited in the National Chest Pain Centers Program (NCPCP) by the end of 2021.15 Details of the database were published elsewhere.11,14

From this nationwide registry, we derived all patients diagnosed with ACS (including STEMI, NSTEMI and UA) between 1st January 2015 and 31st December 2021. All the ACS diagnoses were confirmed by cardiologists based on evidence from electrocardiograms and cardiac troponin quantitative analysis, according to standard clinical guidelines.14,15 We excluded those without specific symptom onset time recorded. The Institutional Review Board at the School of Public Health, Fudan University, approved the study protocol (IRB#2021-04-0889). All the dered data will be afore-reviewed by the Data Management Committee of the CCA Database with formal application process.
Dailystockreturns(%)ofindex =
Closing value of today - Closing value of previous day
Closing value of previous day

2,539,922 patients diagnosed with ACS between January 1, 2015 and December 31, 2021 were initially included

426,147 referred patients were excluded
2,113,775 patients that were sent to hospitals once ACS occured
47 without ACS onset time were excluded
2,113,728 patients finally included in analysis

The associations between stock volatility and ACS onset were analyzed using the time-stratified case-crossover design, which could autonomically control for the potential confounding from time-invariant or relative stable risk factors at the individual level. For each ACS patient, stock volatility levels during the case period were compared to those during control periods from the same individual when the event did not occur. The case-period was defined as the time (i.e., the lag hours mentioned thereafter) before the symptom onset, and the control-periods (3 or 4 per case) were identified using the time-stratified approach by matching the same hours of the same day of the week within the same calendar month and year. For example, if the first ACS symptom occurred at 10 AM on Tuesday, May 18, 2021, we would define 10 AM on Tuesday, May 18, 2021 as the case index hour and 10 AM on all other Tuesdays in May 2021 (May 4, 11, and 25) as the control index hours.

Exposure ascertainment

Daily stock information during the observational period (i.e., from 1st January 2015 to 31st December 2021) was obtained from the Wind Economic Database, including the opening index, and daily stock returns (%) of the Shanghai Stock Exchange Composite Index, Shenzhen Stock Exchange Composite Index and ChiNext Stock Index. Daily stock returns (%) of the three indexes were calculated by the formula followed:

Dailystockreturns(%) of index =
Closing value of today - Closing value of previous day
Closing value of previous day

We only included daily stock returns within 3 times standard deviation (SD) of the mean to reduce the statistical uncertainty in effect estimation at the extremes (Figure S1). We matched the daily stock returns with ACS events according to the time (hourly level) of symptom onset. Specifically, as Chinese stock markets open at 9:30 a.m. and close at 15:00, we matched stock returns at the current day (lag 0 d) to ACS events occurring during the 24-h interval from the current-day 9:30 a.m. to the next-day 9:30 a.m., and considered another two lag days (i.e., lag 1 d, lag 2 d) in a similar fashion. We did not explore more lag days as no previous studies have reported more prolonged effects of stock fluctuation.

Statistical analyses

We applied conditional logistic regression models to analyze the associations of the stock returns with ACS onset and its subtypes (i.e., UA, AMI, STEMI and NSTEMI) for Shanghai, Shenzhen and ChiNext indexes respectively. Based on the previous literature, we plotted their relationships in nonlinear models by adding a natural cubic spline with 3 degrees of freedom (df) for daily stock returns. All the models were adjusted for a natural cubic spline (3 df) of the opening index.

As previous studies generally found a U- or V-shaped relationship between daily stock returns and risk of cardiovascular disease, we quantified the ACS risk per unit rise and fall of daily stock index respectively. We hereby assumed a linear relationship from the minimum-risk point of daily returns to the maximum-risk point for each side of the exposure-response curves (i.e., rise-side and fall-side). Then, four steps were taken to compute the percent change of relative risk and its 95% confidence interval (CI) at the maximum-risk point compared to the minimum-risk point for the rise-side and fall-side of exposure-response curve respectively. The four steps were summarized as follows, and details were described in Online Methods (See Supplemental Materials, Online Methods).

Firstly, we fitted the models and obtained the exposure-response curves. Secondly, for each side of the exposure-response curve, extreme high and extreme low values of daily stock returns were defined as the maximum risk points (point\(_{2}^{+}\)) (i.e., extreme high point for the rise-side and extreme low point for the fall-side). Thirdly, the minimum risk point (point\(_{2}^{-}\)) of each side of the curve would be defined under 3 scenarios. They include “point\(_{2}^{+}\)exactly the 0 value of daily stock return (briefed as scenario 1, point\(_{2}^{+}\)0), “point\(_{2}^{+}\)higher than the 0 value (scenario 2, point\(_{2}^{+}\)positive)” and “point\(_{2}^{+}\)lower than the 0 value (scenario 3, point\(_{2}^{+}\)negative).” Fourthly, as assumed the linear relationship for each side of the exposure-response curve, the slope was then calculated between the two selected points for each side of curve based on the below formula:

\[
\text{Slope of curves} = \frac{(\beta_{1} - \beta_{2}) \pm 1.96 \sqrt{se_{1}^{2} + se_{2}^{2}}}{point_{1}^{2} - point_{2}^{2}}
\]

Where \(\beta_{1}\) and \(\beta_{2}\) are the coefficients of the two points in the curve, \(se_{1}\) and \(se_{2}\) are the corresponding standard errors. There are varied values for point\(_{2}\) among three scenarios explained above.

To further examine the temporal pattern for the relationship between daily stock returns and ACS onset, we fitted the model with different lag days, i.e., from lag 0 d to lag 2 d. Additionally, in order to investigate potential effect modifications, we fitted separate models for ACS cases stratified by sex (male vs. female), age (< 65 vs. ≥ 65 years), season (warm: April-September...
The associations varied by subtypes of ACS (Figure 2). The effects of both stock rise and fall were stronger on UA than AMI, especially for stock rise (Table 2). The lag pattern for the effects of stock fall on UA was similar to that for AMI with the excess risk highest at the lag 0 day and lasting for 2 days approximately, whereas the effects of stock rise was significant only on UA and lasting for 3 days (Figure 3). For the specific subtypes of AMI (Figure 2 and Figure 3), STEMI onset was significantly associated with the falling of stock indexes with lag patterns similar to AMI. There were generally no significant associations for STEMI and stock rise and for NSTEMI and all stock volatility (Table 2).

In stratified analyses (Table 2), there were consistently stronger associations of daily stock returns with ACS and its subtypes among females with significant between-stratum differences for decrease for Shanghai index and Shenzhen index (p for difference <0.05). People aged less than 65 years generally showed slightly larger risk than those older than 65 years. The associations of daily stock volatility with ACS were generally more pronounced in the warm season than in the cold season, especially for stock fall of all the Indexes (p for difference <0.05).

**DISCUSSION**

This large-scale nationwide case-crossover study provides the novel and robust evidence that both stock rise and fall could trigger the symptom onset of ACS and its specific subtypes. The excess risks were strongest on the concurrent day, attenuated gradually and disappeared after 3 days. Our study further demonstrate that UA was most sensitive to stock volatility, followed by STEMI, while NSTEMI showed null associations. Additionally, we found stronger associations among females, patients younger than 65 years and in the warm season.

Our findings are consistent with previous studies linking daily stock market volatility and adverse cardiovascular outcomes.10,12,19 These findings have indicated U- or J- shaped relationships of stock market volatility with hospitalizations or mortality due to overall cardiovascular diseases or specific diseases such as coronary heart disease, AMI, stroke. However, existing evidence obtained the associations by fitting daily aggregate cases of hospital admissions or deaths through time-series analyses,20,21 which could result in serious concerns about the apparent ecological fallacy.27 In contrast, the present nationwide case-crossover study utilized ample individual-level information on symptom onset of ACS, which could reduce the ecological fallacy, provide more robust estimates on the relationship between stock volatility and ACS events, and more clearly illustrate the lag pattern for the excess risks.

The specific mechanisms by which stock market fluctuations affect cardiovascular health are not yet fully understood. The stock market’s fluctuations, whether rising or falling, may induce significant emotional, psychological, and physical stress.28,29 The association between psychological stress and cardiovascular diseases has been extensively documented.30 For example, randomized trials of controlled human exposures and in vivo experiments provide support that short-term mental stress can activate endothelial cells through the local release of norepinephrine, resulting in an increased influx of inflammatory leukocytes into tissues, including atherosclerotic plaques.31 A prospectively assessed study also found that the risk of STEMI among soccer spectators increased transiently during key games.32 Besides, the present study found that stock volatility was associated with STEMI but not NSTEMI, which may be because that patients with STEMI had increased plaque vulnerability (i.e., more plaque rupture and microvessels) and distinct layered phenotype at the culprit and nonculprit lesions.33

The stratified analyses revealed stronger effects of stock volatility on ACS onset among younger patients. It may be due to the greater volume of investment and more active investment activity among young people than the elders. However, some earlier studies concluded that the stock volatility had larger effects on elderly population.34,35 This difference may be due to the different population characteristics and relatively small sample size in prior investigations. Similar to a recent study conducted in China,36 our study indicated larger effect estimates among females, which might be partly explained by reduced fibrin clot lysisability of coronary plaques for women compared with men.37 Also, we found the associations were stronger in warm season than the cold season, which is probably due to that the stock market is more

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**Table 1. Baseline characteristics of study population.**

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>Number of subjects or proportion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case days</td>
<td>2,113,728</td>
</tr>
<tr>
<td>Control days</td>
<td>7,196,661</td>
</tr>
<tr>
<td>Disease type</td>
<td></td>
</tr>
<tr>
<td>AMI</td>
<td>1,207,625 (57.1)</td>
</tr>
<tr>
<td>STEMI</td>
<td>758,464 (35.9)</td>
</tr>
<tr>
<td>NSTEMI</td>
<td>449,161 (21.2)</td>
</tr>
<tr>
<td>UA</td>
<td>906,103 (42.9)</td>
</tr>
<tr>
<td>Ages at onset</td>
<td></td>
</tr>
<tr>
<td>&lt;65</td>
<td>1,057,510 (50.0)</td>
</tr>
<tr>
<td>≥65</td>
<td>1,055,834 (50.0)</td>
</tr>
<tr>
<td>Missing</td>
<td>384 (0.0)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1,431,036 (67.7)</td>
</tr>
<tr>
<td>Female</td>
<td>682,564 (32.3)</td>
</tr>
<tr>
<td>Missing</td>
<td>128 (0.0)</td>
</tr>
<tr>
<td>Season</td>
<td></td>
</tr>
<tr>
<td>Warm</td>
<td>1,038,028 (49.1)</td>
</tr>
<tr>
<td>Cold</td>
<td>1,075,700 (50.9)</td>
</tr>
</tbody>
</table>

Abbreviations: ACS, acute coronary syndrome; STEMI, ST-segment-elevation myocardial infarction; NSTEMI, non-ST-segment-elevation myocardial infarction; UA, unstable angina.

vs. cold: October-March). We assessed the statistical significance for the effect differences between the strata using two-sample z-tests.7

All the analyses were performed in R (Version 3.6.3, R Project for Statistical Computing) with the “survival” package for fitting conditional logistic regression models. The results were presented as percent changes of relative risk of ACS onset associated with 1%-point change of daily stock returns. All statistical tests were two-sided and a p-value < 0.05 was considered statistically significant.

**RESULTS**

**Descriptive results**

A total of 2,539,922 ACS cases were derived from the CCA Database-Chest Pain Center between January 1, 2015 and December 31, 2021. There were 2,113,728 patients finally included in this study according to the exclusion criteria (Figure 1), including 1,207,625 AMI, 758,464 STEMI, 449,161 NSTEMI and 906,103 UA. As shown in Figure S2, they were reported from 2,096 hospitals distributed across China (Figure S2). One half of these patients were aged over 65 and 67.7% were males (Table 1). As shown in Figure S3, the Shanghai, Shenzhen and ChiNext index have experienced significant and similar volatility during the study period.

**Regression results**

We observed U- shaped relationships between daily returns of all stock indexes and ACS onset with both rising and falling of the stock indexes increasing the risk ACS onset (Figure 2). Each 1%-point decrease of Shanghai, Shenzhen and ChiNext indexes was associated with increments of 0.96% (95%CI: 0.40,1.51), 0.65% (95%CI: 0.27,1.03) and 0.87% (95%CI: 0.52,1.21) of ACS risk on the present day (lag 0 d), respectively. Similarly, the corresponding increments were 1.06% (95%CI: 0.61,1.52), 0.45% (95%CI: 0.11,0.80) and 0.17% (95%CI: -0.08,0.41) for a 1%-point increase of indexes (Table 2). The associations attenuated at lag 1 d and mostly tended to be insignificant at lag 2 d (Figure 3).
actively traded during the warm season, while it is more stable during the cool season. For example, in our dataset, the mean of daily stock returns for Shanghai, Shenzhen and ChiNext index was 0.836%, 1.113% and 1.394% in warm seasons and 0.707%, 0.947% and 1.173% in cold seasons, respectively. Our study indicated that women and younger people are more susceptible, so they should keep vigilance, reduce unnecessary stock involvement, especially when stock market fluctuates drastically.

Up to our knowledge, this is the first study to quantify the risk of ACS onset from stock market fluctuation. Our results have important implications for ACS prevention. Firstly, it provides the first-hand evidence that stock volatility may trigger the symptom onset of ACS. Accordingly, mitigating the influence of stock market fluctuation and communicating its possible health risks is helpful to reduce ACS disease burden and should be added to ACS control programs in clinical practice. Coping with stock volatility should be introduced into the management of behavioral risk factors and early prevention of cardiovascular diseases. Secondly, we identified the critical exposure time windows for the hazardous effects of stock volatility on ACS onset. Specifically, a lag of 3 days should be considered for the establishment of early-warning system for cardiovascular events in relation to stock volatility. Thirdly, we identified some subgroups who are vulnerable to the stress related to stock volatility, and effective intervention measures should be adopted, including the reduction of stock involvement, promotion of knowledge on investment-related risks and sufficient medical preparedness. Finally, community education is vitally needed to increase awareness of the public about ACS risk associated with stock volatility and promote rational investment behaviors.

There were several notable strengths of this study. Firstly, we utilized a large-scale, nationwide registry of ACS events, ensuring the geographical

Figure 2. Cumulative exposure-response curves for the associations of ACS onset with the stock returns of Shanghai, Shenzhen and ChiNext index over lag 0 d. The black solid lines are the mean estimates for the relative risks of ACS onset and the gray areas are the 95% confidence intervals. Abbreviations: ACS, acute coronary syndrome; STEMI, ST-segment-elevation myocardial infarction; NSTEMI, non-ST-segment-elevation myocardial infarction; UA, unstable angina.
Table 2. Percent change (%) and 95% confidence intervals in the risk of ACS onset associated with 1%-point change of daily stock returns of Shanghai, Shenzhen and ChiNext index over lag 0 d, stratified by disease type, sex, age, season, and region.

<table>
<thead>
<tr>
<th>Group</th>
<th>Sample Size</th>
<th>Decrease of index</th>
<th>Increase of index</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>shanghai Index</td>
<td>Shenzhen Index</td>
<td>ChiNext Index</td>
</tr>
<tr>
<td>ACS</td>
<td>2,113,728</td>
<td>0.96 (0.40, 1.51)</td>
<td>0.65 (0.27, 1.03)</td>
</tr>
<tr>
<td>Disease type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UA</td>
<td>906,103</td>
<td>1.20 (0.28, 2.12)</td>
<td>0.79 (0.12, 1.17)</td>
</tr>
<tr>
<td>AMI</td>
<td>1,207,625</td>
<td>0.76 (0.12, 1.40)</td>
<td>0.60 (0.14, 1.06)</td>
</tr>
<tr>
<td>STEMI</td>
<td>758,464</td>
<td>1.38 (0.47, 2.29)</td>
<td>1.29 (0.64, 1.93)</td>
</tr>
<tr>
<td>NSTEMI</td>
<td>449,161</td>
<td>-0.04 (-1.04, 0.96)</td>
<td>-0.34 (-1.09, 0.42)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1,431,036</td>
<td>0.44 (-0.23, 1.10)*</td>
<td>0.32 (-0.11, 0.75)*</td>
</tr>
<tr>
<td>Female</td>
<td>682,564</td>
<td>2.06 (1.07, 3.07)*</td>
<td>1.35 (0.66, 2.04)*</td>
</tr>
<tr>
<td>Ages at onset</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65</td>
<td>1,057,510</td>
<td>1.01 (0.26, 1.78)</td>
<td>0.83 (0.28, 1.37)</td>
</tr>
<tr>
<td>≥65</td>
<td>1,055,834</td>
<td>0.91 (0.10, 1.72)</td>
<td>0.47 (-0.04, 0.99)</td>
</tr>
<tr>
<td>Season</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warm</td>
<td>1,038,028</td>
<td>1.88 (1.20, 2.58)*</td>
<td>1.32 (0.75, 1.90)*</td>
</tr>
<tr>
<td>Cold</td>
<td>1,075,700</td>
<td>-0.37 (-1.07, 0.34)</td>
<td>0.00 (-0.51, 0.52)*</td>
</tr>
</tbody>
</table>

* Means significant between-subgroup difference.

Abbreviations: ACS, acute coronary syndrome; STEMI, ST-segment-elevation myocardial infarction; NSTEMI, non-ST-segment-elevation myocardial infarction; UA, unstable angina.

Figure 3. Percent change (%) and 95% confidence intervals in the risk of ACS onset associated with 1%-point change of daily stock returns of Shanghai, Shenzhen and ChiNext index over different lag days [(A): Decrease of index; (B): Increase of index]. Abbreviations: ACS, acute coronary syndrome; STEMI, ST-segment-elevation myocardial infarction; NSTEMI, non-ST-segment-elevation myocardial infarction; UA, unstable angina.
representativeness and statistical power of our findings. Secondly, by virtue of ample information on the onset of each ACS event and the time-stratified case-crossover design, our study could have stronger ability of causal inference compared with previous ecological time-series studies. Thirdly, we utilized the hourly information on symptom onset of ACS, which has the advantage of accurately capturing the time course from stock volatility to ACS onset and ensuring the reasonable chronological disorder compared with previous studies of hospitalizations and mortality. Fourthly, we investigated the associations of fluctuations in different stock market with ACS and its multiple subtypes, reducing the possibility of publication bias.

Nevertheless, the present study still has several limitations. Firstly, we did not exactly know whether an ACS patient had been involved in the stock market directly or indirectly, so exposure misclassification is inevitable; however, as people who don’t invest in stock or stock-related investment would not be impacted by stock volatility, their inclusion would only downward bias our estimates in such a crossover analysis based on individual cases. Secondly, despite this is a nationwide registry of ACS, not all ACS cases in patients could be reported into this database, limited by the nature of chest-pain centers and their coverage. Thirdly, the use of a time-stratified case-crossover design may introduce overlap bias due to the potential positive correlation between exposure levels in case and controls periods. Nevertheless, we employed the conditional logistic regression to match controls for each case individually, which may mitigate this kind of bias. Lastly, this study was conducted in Chinese Mainland, therefore, the generalizability of our findings to other countries with different financial system and demographic characteristics is unclear.

CONCLUSION

In summary, this nationwide case-crossover study in China provides novel and robust evidence that both stock rise and fall may immediately trigger the onset of ACS and its multiple subtypes. These findings emphasize the significance of public health education and psychological support for vulnerable populations during periods of drastic stock fluctuations.

REFERENCES

Dr. Chen, Dr. Yang and Dr. Kan contributed equally, had full access to all the data in the study, and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Dr. Chen, Dr. Yang and Dr. Kan.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Ms. Zhu, Dr. Chen, and Dr. Liu.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Ms. Zhu, Dr. Chen, and Dr. Liu.
Administrative, technical, or material support: All authors.
Study supervision: Dr. Chen, Dr. Yang and Dr. Kan.

DECLARATION OF INTERESTS
The authors declare no competing interests.

SUPPLEMENTAL INFORMATION
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