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## Smoking was associated with lower in-hospital mortality among patients with acute myocardial infarction—Insights from China Acute Myocardial Infarction (CAMI) registry

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2019-030252
Article Type:	Research
Date Submitted by the Author:	10-Mar-2019
Complete List of Authors:	<p>Song, Chenxi Fu, Rui; Chinese Academy of Medical Sciences and Peking Union Medical College Fuwai Hospital, Cardiology Dou, Kefei; Chinese Academy of Medical Sciences and Peking Union Medical College Fuwai Hospital, Yang, Jingang; Fu Wai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, Coronary Heart Disease Center Xu, Haiyan; Fu Wai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, Coronary Heart Disease Center Gao, Xiaojin; Fu Wai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, Coronary Heart Disease Center Wang, Hao; Fu Wai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, Coronary Heart Disease Center Liu, Shuai; Fu Wai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, Coronary Heart Disease Center Fan, Xiaoxue; Fu Wai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, Coronary Heart Disease Center Yang, Yuejing; Fu Wai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, Coronary Heart Disease Center</p>
Keywords:	smoking, in-hospital mortality, acute myocardial infarction

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4 **Smoking was associated with lower in-hospital mortality**  
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6 **among patients with acute myocardial infarction—Insights**  
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8 **from China Acute Myocardial Infarction (CAMI) registry**  
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13 **Chenxi Song, MD<sup>1</sup>, Rui Fu, MD<sup>1</sup>, Kefei Dou, MD, PhD<sup>1</sup>, Jingang Yang, MD,**  
14 **PhD<sup>1</sup>, Haiyan Xu, MD, PhD<sup>1</sup>, Xiaojin Gao, MD, PhD<sup>1</sup>, Hao Wang, MD<sup>1</sup>, Shuai**  
15 **Liu, MD<sup>1</sup>, Xiaoxue Fan, PhD<sup>1</sup>, Yuejin Yang, MD, PhD<sup>1</sup>**  
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21 <sup>1</sup> Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese  
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23  
24 Academy of Medical Sciences and Peking Union Medical College  
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26

27  
28 The first two authors Chenxi Song and Rui Fu made equal contribution to this work.  
29  
30 Kefei Dou and Yuejin Yang contributed equally to the article and accept equal and  
31  
32 full responsibility for the work as correspondence authors.  
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36 **Contact information**  
37

38 Chenxi Song	1933769555@qq.com
39 Rui Fu	fwfurui@163.com
40 Kefei Dou	drdoukefei@126.com
41 Jingang Yang	yangjingang@mrbc-nccd.com
42 Haiyan Xu	xuhaiyan@fuwaihospital.org
43 Xiaojin Gao	sophie_gao@sina.com
44 Hao Wang	wanghao_fuwai@126.com
45 Shuai Liu	liushuai851213@163.com
46 Xiaoxue Fan	fanxiaoxue@mrbc-nccd.com
47 Yuejin Yang	yangyjfw@126.com

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## ***Abstract***

**Introduction:** Smoking is a well-established risk factor for cardiovascular disease. However, the impact of smoking on in-hospital mortality among patients with acute myocardial infarction (AMI) managed by contemporary treatment is still unclear.

**Methods:** A cohort study was conducted using data between 2013 and 2016 from China AMI (CAMI) Registry were extracted. Eligible patients were diagnosed with AMI in accordance with third Universal Definition of MI. Propensity score (PS) matching and multivariable logistic regression were used to control for confounders. Subgroup analysis was performed to examine whether the association between smoking and in-hospital mortality varies according to baseline characteristics.

**Results:** A total of 37614 patients were included. Smokers were younger, more often males with fewer comorbidities than non-smokers. After PS matching and multivariable log regression analysis was performed, difference in in-hospital mortality between current smokers vs. non-smokers reduced but was still statistical significant (5.1% vs.6.1%,  $p=0.0045$ ; adjusted odds ratio 0.78, 95% CI 0.69–0.88,  $P<0.001$ ). Among all subgroups, there was a trend toward lower in-hospital mortality in current smoker or ex-smoker group compared with non-smoker.

**Conclusions:** Smoking was associated with lower in-hospital mortality among AMI patients even after multiple analyses to control for potential confounders. “Smoker’s paradox” cannot be fully explained by confounding alone.

## **Keywords:**

smoking; in-hospital mortality; acute myocardial infarction

## **Strength:**

The study utilized data from a large-scale multicenter registry in contemporary era of PCI.

We used both propensity score matching and multivariable cox regression model to adjust confounders, which ensure the robustness of our conclusion.

### **Limitations:**

It is still possible that we didn't adjust for potential unmeasured confounders.

## **INTRODUCTION**

Smoking is a well-established risk factor of cardiovascular disease<sup>1,2</sup>. However, evidence regarding the impact of smoking on in-hospital mortality among patients with acute myocardial infarction (AMI), especially in the context of contemporary era of percutaneous coronary intervention (PCI), is still controversial. Some studies reported that the difference in in-hospital mortality was not significant between smokers and non-smokers after accounting for age and other baseline characteristics<sup>3-9</sup>. Other studies reported that smokers had lower in-hospital mortality rate as compared with non-smokers even after adjustment for potential confounders, which is called "smoker's paradox"<sup>10-14</sup>. Thus, the aim of our study is to assess how smoking impacts the in-hospital mortality of patients receiving contemporary management of AMI. We hypothesized that smokers have lower in-hospital mortality than non-smokers.

## **METHODS**

### **Data source**

A cohort study was conducted by using data from China AMI (CAMI) registry between January 1, 2013 and January 31, 2016. Detailed description of the registry design was published previously<sup>15</sup>. Briefly, CAMI registry was a prospective, multicenter observational registry. The project included Chinese patients with acute myocardial infarction and collected data on patients' characteristics, treatments and outcomes. A total of 108 hospitals covering a broad geographic region participated the project, which assured a good representation of all the AMI patients in China and reduced selection bias<sup>15</sup>. Our study was approved by the institutional review board central committee at Fuwai Hospital, NCCD of China. Written informed consent was obtained from each patient included in the study. If the patient could not be communicable, informed consent was obtained from his family member. The study

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4 protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki.

5 CAMI registry was registered on [www.clinicaltrials.gov](http://www.clinicaltrials.gov), and the registration number  
6 was NCT01874691.  
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### 8 9 **Study population**

10 We included study population from CAMI registry. Eligible patients were diagnosed  
11 with AMI and within 7 days of ischemia symptoms. Diagnostic criteria of AMI were  
12 in accordance with third Universal Definition of MI<sup>16</sup>. We excluded patients with age  
13 < 18 or > 100 years old, missing or invalid data on gender, admission diagnosis and  
14 detailed smoking status.  
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16 Data were extracted by trained researchers using standard definition to reduce  
17 measure and report bias. These data included age, sex, height, weight, clinical  
18 presentation (symptoms, ST-segment elevation, anterior wall MI, blood pressure,  
19 heart rate, heart failure, cardiac shock, fatal arrhythmia, cardiac arrest, Killip  
20 classification), comorbidities (hypertension, hyperlipidemia, diabetes, heart failure,  
21 peripheral vascular disease, stroke, chronic kidney disease, COPD), medical history  
22 (family history of premature CAD, prior angina or MI, prior coronary intervention,  
23 prior CABG) , initial reperfusion strategy (prime PCI, thrombolysis, conservative  
24 therapy), lab results (creatinine, Hb, LVEF) and in-hospital outcome.  
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### 39 **Patient and Public Involvement**

40 We did not involve patients or the public in our work  
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### 42 **Definition of variables**

43 All patients were divided into three groups according to smoking status. Current  
44 smokers were defined as those who have smoked within one month before registration.  
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46 Ex-smokers were defined as those who quit smoking for at least one month.  
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48 Non-smokers were defined as those who never smoked. Standard definition of the  
49 medical history and physical examination elements were well described in the  
50 ACC/AHA Task Force on clinical Data Standards and NCDR-ACTION-GWTG  
51 element dictionary<sup>17-19</sup>. ECG and echocardiogram were interpreted locally.  
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4 The primary endpoint was all-cause in-hospital mortality, which was defined as all  
5 cause death during hospitalization.  
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### 7 **Statistical analysis**

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10 Baseline continuous data were presented as mean $\pm$ SD or median(25th-75th  
11 percentiles) and were compared using 1-way ANOVA test. This was followed by  
12 Bonferroni t test with corrected P value 0.05/3. Categorical data were presented as  
13 counts and frequencies and were compared using  $X^2$  test. Propensity score matching  
14 was used to control for baseline differences and to make the two groups more  
15 comparable. We used a multivariable logistic regression model to estimate propensity  
16 scores, with smoking as dependent variable and the following factors as covariates:  
17 age, gender, BMI, systolic blood pressure, heart rate, admission diagnosis, cardiac  
18 arrest, chest pain, ST elevation, anterior wall MI, killip classification, risk factor  
19 (medical history of diabetes, hypertension, hyperlipidemia, premature family CAD  
20 history, heart failure ,renal failure, COPD), medical history (previous angina, PCI,  
21 CABG), creatinine level, hemoglobin level, grace risk score, primary PCI. These  
22 variables were chosen as covariates because the difference in these baseline  
23 characteristics reached statistical significance or these variables were previously  
24 reported to be associated with patients' outcome.  
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39 Matching was performed with the use of greedy nearest matching algorithm and a 1:1  
40 fashion. We performed PS between current smokers vs. non-smokers, and ex-smokers  
41 vs. non-smokers. The caliper width was equal to 0.01 of the SD of the score.  
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45 McNemar's and paired t-tests were used to compare continuous and categorical  
46 variables between the two groups after matching. For each variable in the PS model,  
47 we computed SD between the two groups with SD less than 0.1 indicating good  
48 balance.  
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53 Multivariable logistic regression analysis was used to compare in-hospital mortality  
54 between the two groups in order to adjust for potential confounders. Variables  
55 included in the model were: age, gender, BMI, systolic blood pressure, heart rate,  
56 admission diagnosis, cardiac arrest, chest pain, ST elevation, anterior wall MI, killip  
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4 classification, risk factor (medical history of diabetes, hypertension, hyperlipidemia,  
5 premature family CAD history, heart failure, renal failure, COPD), medical history  
6 (previous angina, PCI, CABG), creatinine level, hemoglobin level, grace risk score,  
7 primary PCI. To determine whether the association between smoking and in-hospital  
8 mortality varied according to baseline patient characteristics, we performed the same  
9 multivariable logistic analysis in subgroups stratified by age, sex, BMI, presence or  
10 absence of hypertension, diabetes, hyperlipidemia, heart failure, prior angina, MI or  
11 coronary intervention, admission diagnosis. For interaction test, a P value less than  
12 0.1 is considered significant. During statistical analysis phase, based on the type,  
13 pattern and amount of missing data, appropriated methods will be used to handle  
14 missing data.  
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## 28 **RESULTS**

### 29 **Baseline characteristics**

30 From January 1, 2013 to January 31, 2016, a total number of 41590 continuous  
31 patients were registered in CAMI registry. We excluded those age < 18 or > 100 years  
32 old (n=1178), with missing or invalid data on gender (n=18), admission diagnosis  
33 (n=1237) and detailed smoking status (n=1543). The final cohort included 37614  
34 patients (Figure 1).  
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41 Baseline characteristics before matching were shown in Table 1. A total of 16664  
42 (44.3%) patients were current smokers, 843 (2.2%) patients quit smoking less or equal  
43 to 1 year, 3410 (9.1%) patients quit smoking greater than 1 year, and 16697 (44.4%)  
44 patients were non-smokers. Compared with non-smokers, current smokers were  
45 younger ( $57.99 \pm 11.81$  vs.  $66.59 \pm 11.82$ ) and had higher BMI ( $24.39 \pm 2.87$  vs.  $23.98$   
46  $\pm 2.95$  kg/m<sup>2</sup>). The proportion of male (93.7% vs. 49.8%) and Killip I (80.5% vs.  
47 72.1%) was higher among current smokers. Compared with non-smokers, current  
48 smokers were less likely to have hypertension, diabetes, heart failure, stroke or  
49 chronic kidney disease, but more likely to have hyperlipidemia. Among ex-smokers,  
50 the proportion of male, hyperlipidemia, heart failure, PVD, stroke was higher than  
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4 those of current smokers. Ex-smokers also had a trend towards old age, low  
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6 proportion of hypertension, diabetes than current smokers, but the difference was less  
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8 significant compared with the difference between current and non-smokers.

### 9 10 **Propensity score matching**

11 Before PS, there were differences in almost all baseline variables among different  
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13 groups (Table 1). To control for potential confounding, we matched 8552 current  
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15 smokers with 8552 non-smokers (supplementary table 1), as well as 4142 ex-smokers  
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17 and 4142 non-smokers (supplementary table 1). The standardized differences were  
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19 less than 10.0% for all variables after matching, indicating a good match between the  
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21 two groups. After PS matching, current smokers still have lower in-hospital mortality  
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23 than non-smokers (5.1% vs. 6.1%,  $p=0.0045$ ), but difference in in-hospital mortality  
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25 was not significant between ex-smokers and non-smokers (7.0% vs. 7.4%,  $p=0.5198$ )  
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27 (Supplementary Table 2).

### 28 29 **In-hospital outcomes**

30 Overall, 2370 patients died before discharge. There were 614 deaths (3.7%) in current  
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32 smokers group, 306 deaths (7.2%) in ex-smoker group and 1450 (8.7%) in  
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34 non-smokers group. Unadjusted OR for in-hospital mortality was 0.4 (95% CI:  
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36 0.37-0.44,  $p < .0001$ ) in current smokers and was 0.82 (95% CI: 0.72-0.93,  $p=0.0018$ )  
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38 in ex-smokers relative to non-smokers (table 2). After adjustment for potential  
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40 confounders, current smoking status was associated with lower in-hospital mortality  
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42 relative to non-smokers (adjusted OR: 0.78, 95% CI 0.69–0.88,  $p < 0.001$ ) (table 2). No  
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44 difference in in-hospital mortality was detected between ex- and non-smokers (OR:  
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46 0.89, 95% CI: 0.77-1.04,  $p=0.1443$ ).

### 47 48 **Subgroup analysis**

49 Subgroup analysis indicated that a significant interaction between smoking status and  
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51 age ( $P_{\text{interaction}}: 0.0986$ ), sex ( $P_{\text{interaction}}: 0.0163$ ), LVEF ( $P_{\text{interaction}}: 0.0149$ ), previous MI  
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53 ( $P_{\text{interaction}}: 0.0557$ ), previous HF ( $P_{\text{interaction}}: 0.0086$ ) on in-hospital mortality (table 3).  
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55 However, compared with non-smoker group, there was a trend toward lower  
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57 in-hospital mortality in current smoker or ex-smoker group among all subgroups.  
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## DISCUSSION

Our major finding was that among patients with AMI, current-smokers had lower in-hospital mortality than non-smokers among both the whole population and almost all subgroups, after adjusting for potential confounders by using propensity score matching, multivariable logistic regression model in our analysis of CAMI registry, the largest contemporary registry of AMI patients in east Asia.

### Comparison with previous study

Most previous studies were conducted in “thrombolytic era” and we only identified 4 studies enrolling patients in current “primary PCI era”<sup>9,14,20,21</sup>. Of these 4 studies, three studies used multivariate regression analysis to control confounders. The results of our study were in consistent with another large-scale study<sup>14</sup>, which also demonstrated that among STEMI patients receiving primary PCI, smokers (including both current and ex-smoker) had lower adjusted in-hospital mortality risk than non-smokers. In our study, we further separated current and ex-smokers, and used PS matching to comprehensively control for potential confounders. Several mechanisms have been proposed to explain this paradox phenomenon.

First, some studies showed the suppression effect of clopidogrel on platelet was greater among smokers than non-smokers<sup>22-24</sup>. Potential explanation were that smoking can enhance in vivo bioactivation of clopidogrel via increasing induction of cytochrome P450 (CYP1A2 and CYP2B6) and increased active metabolite concentration of clopidogrel<sup>25,26</sup>. Thus, smokers may respond better to clopidogrel therapy and consequently had a lower in-hospital mortality rate than non-smokers.

Second, smoking was unexpectedly associated with lower risk of adverse LV remodeling post infarction LV remodeling. Rolf Symons et al performed cardiac MRI at 4 days and 4 months after MI. They found that smokers had improved LVEF, which was attributable to a decrease of end diastolic volume index but not an increase of systolic volume index<sup>27</sup>.

However, the results of our study were not consistent with two studies, which found the absence of “smoker paradox” after baseline risk adjustment<sup>9,21</sup>. This difference

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4 may be related to study population selection and sample size. For instance, one study  
5 enrolled patients with symptomatic CAD, including those presented with stable or  
6 unstable angina<sup>9</sup>, while we included patients with AMI. Patients with stable angina  
7 represented a relatively “lower risk” group, thus enrollment of this patient subset may  
8 have an impact on the association between smoking and mortality. The other study  
9 had a small sample size (N=382), which may not be powered to detect the difference  
10 in mortality between smokers and non-smokers.  
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### 13 **Interpretation of our results:**

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15 Our results should be interpreted with caution. First, even though our study had a  
16 large sample size and we adjusted many variables, we still can't assure the precision  
17 of our results. This is also the case in the interpretation of three analysis of the  
18 AFFIRM trial, in which digoxin use was associated with increase, no change or  
19 decrease in mortality risk<sup>28-30</sup>. In addition, it is also possible that we didn't adjust all  
20 potential confounders. Second, our results did not mean we encourage patients to  
21 smoke. Since it is well established that smoking is an independent risk factor for  
22 mortality, and recurrent myocardial infarction<sup>31</sup>, as well as subacute stent thrombosis  
23 <sup>32</sup> in the long-term, and patients with CHD can benefit from smoking cessation<sup>33</sup>, we  
24 still recommend patients to stop smoking. However, the phenomenon might give us  
25 clue about potential mechanisms underlying myocardial protection related to smoking  
26 and further exploring novel therapy. For instance, smoking might lead to chronic  
27 ischemic state (ischemic preconditioning)<sup>34</sup>, therefore smokers might have better  
28 tolerance for acute ischemic event like an heart attack. The phenomenon can give us  
29 clue to explore whether pre-conditioning therapy or brief period of reversible  
30 ischemia) can protect myocardium and improve outcome.  
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34 Our subgroup analysis results indicated a significant interaction between smoking  
35 status and age, gender, LVEF, previous MI, previous HF. However, currently we  
36 can't reach the conclusion that these baseline characteristics had a significant impact  
37 on the relationship between smoking and in-hospital mortality because there was a  
38 similar trend among all subgroups that current smokers and ex-smokers had lower  
39 in-hospital mortality risk compared with non-smokers. A significant P value may be  
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4 attributed to different OR value between subgroups of smokers and non-smokers, as  
5 well as a large sample size of some subgroups.  
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### 7 **Limitations**

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9 Some patients might die before reaching hospital, therefore early death might be  
10 underestimated. CAMI registry was a multicenter, large-scale study involving over  
11 100 hospitals. Although standardized data collection procedure was emphasized, the  
12 accuracy of data still depends greatly on the expertise of local investigators. Our  
13 results require further external validation in another independent cohort. We did not  
14 account for angiographic variables or other potential unknown confounders, which  
15 could also play a role in predicting patients' outcome. Smoking status might be  
16 modified after myocardial infarction onset. However, we asked the patients about  
17 their smoking status prior to AMI onset and all patients were enrolled within 7 days of  
18 symptom onset. Therefore, this might not have a significant impact on smoking status.  
19 We only assessed the association between smoking and short-term outcome, future  
20 studies are required to investigate this association in the long-term.  
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### 33 **Conclusions:**

34 We demonstrated that in-hospital mortality rate was lower among smokers compared  
35 with non-smokers in a large scale contemporary cohort representing AMI patients in  
36 China. Our findings indicated that future studies should be done to further explore the  
37 potential biological mechanisms that may explain this phenomenon.  
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### 45 **Declaration of interests:**

46 We confirm that there are no known conflicts of interest associated with this  
47 publication.  
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### 51 **Author contributions:**

52 Chenxi Song and Rui fu were major contributors in writing the manuscript. Kefei Dou  
53 and Yuejin Yang contributed substantially to the conception and design of the study.  
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4 important intellectual content. Wei Li, Yang Wang and Xiaoxue Fan made  
5  
6 contribution to analysis and interpretation of data.  
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10 **Funding statement:**

11 This work was supported by CAMS Innovation Fund for Medical  
12  
13 Sciences (CIFMS) (2016-I2M-1-009), the Twelfth Five-Year Planning Project of the  
14  
15 Scientific and Technological Department of China (2011BAI11B02), and 2014  
16  
17 Special fund for scientific research in the public interest by National Health and  
18  
19 Family Planning Commission of the People's Republic of China (No. 201402001).  
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23 **Acknowledgement:**

24 We are very grateful to the TIMI Study Group and the Duke Clinical Research  
25  
26 Institute for their contributions in the design, conduct, and data analyses of CAMI  
27  
28 registry. We also want to thank all the investigators and coordinators for their great  
29  
30 work and active participation.  
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34 **Data availability statement**

35 Data are available from corresponding author on reasonable request.  
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49 **Figure and table legends:**

50 Table 1 Baseline characteristics according to smoking status (Before matching)

51 Table 2 Association between Smoking and In-hospital Mortality

52 Table 3 Association between smoking and in-hospital mortality according to baseline  
53 characteristics  
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Supplementary Table 1 Baseline characteristics between current smokers vs. non-smokers (After matching)

Supplementary Table 2 Baseline characteristics between ex-smokers vs. non-smokers (After matching)

**Figure legend:** Figure 1 Study flow chart. From January, 2013 to January, 2016, 41590 continuous patients were registered in CAMI registry. Those with age < 18 or > 100 years old (n=1178), with missing or invalid data on gender (n=18), admission diagnosis (n=1237) and detailed smoking status (n=1543) were excluded. The final cohort included 37614 patients

**Table 1 Baseline characteristics according to smoking status (Before matching)**

Variable	Current Smokers (N=16664)	Ex-smokers (N=4253)	Non-smokers (N=16697)	p value
Age	57.99 ± 11.81	66.49 ± 11.50	66.59 ± 11.82	<0.0001
Male	93.7%	94.0%	49.8%	<0.0001
BMI (Kg/m <sup>2</sup> )	24.39 ± 2.87	23.95 ± 2.84	23.98 ± 2.95	<0.0001
ST-elevation on ECG	74.3%	65.7%	66.7%	0.1845
Heart failure on admission	11.1%	19.2%	18.1%	0.0856
Cardiac shock	3.1%	4.1%	3.9%	0.6058
Killip classification				<0.0001

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I	80.5%	68.5%	72.1%	
II	13.6%	18.8%	17.3%	
III	2.8%	7.6%	5.7%	
IV	3.0%	5.1%	4.9%	
<b>Comorbidities</b>				
Hypertension	43.7%	54.7%	56.5%	0.0387
Hyperlipidemia	8.0%	8.6%	6.1%	<0.0001
Diabetes	14.7%	21.7%	23.3%	0.0271
PVD	0.6%	1.2%	0.7%	0.0035
Heart failure	1.1%	4.7%	3.2%	<0.0001
Stroke	7.1%	13.4%	10.0%	<0.0001
COPD	1.7%	4.5%	1.7%	<0.0001
Chronic kidney disease	0.7%	2.4%	1.5%	<0.0001
Smoking duration (year)	30.38 ± 11.89	26.86 ± 11.99	NA	<0.0001
Number of cigarettes/ day	21.23 ± 11.10	19.13 ± 10.93	NA	<0.0001
<b>Drinking history</b>				<0.0001
Never drink	27.7%	26.9%	76.2%	
Occasionally	53.1%	60.5%	21.5%	
Frequently	19.2%	12.6%	2.2%	
Duration (years)	27.80 ± 11.72	28.75 ± 11.91	27.04 ± 13.07	0.2033
Frequency/per week	5.78 ± 2.53	6.02 ± 3.08	5.95 ± 2.75	0.2453
<b>Drinking preference</b>				0.2515
Liquor	88.3%	92.4%	88.3%	
Beer	4.6%	0.9%	3.9%	
Wine	0.2%	0.3%	0.8%	
Others	6.9%	6.4%	7.0%	
<b>Volume (ml)/per time</b>				0.2899
Liquor	172.91 ± 133.18	183.30 ± 158.05	183.60 ± 142.70	
Beer	722.21 ± 1033.0	308.50 ± 364.87	489.58 ± 527.71	
Wine	69.17 ± 227.54	75.00 ± 119.66	34.62 ± 74.68	
In-hospital mortality	3.7%	7.2%	8.7%	0.0015

Data are presented as mean ± SD or frequencies; BMI: body mass index; ECG: electrocardiogram; PVD: peripheral vascular disease; COPD: chronic obstructive pulmonary disease;

**Table 2 Association between Smoking and In-hospital Mortality**

Smoking status	OR (95% CI)			p value <sup>b</sup>
	Unadjusted	Adjusted <sup>a</sup>	PS matching	
Current smokers vs non-smokers	0.40 (0.37, 0.44)	0.78 (0.69, 0.88)	0.80 (0.69, 0.92)	<.0001
Ex- smokers vs non-smokers	0.82 (0.72, 0.93)	0.89 (0.77, 1.04)	1.03 (1.02, 1.04)	0.1443

a: adjusted for age, gender, BMI, systolic blood pressure, heart rate, admission diagnosis, cardiac arrest, chest pain, ST elevation, anterior wall MI, killip classification, risk factor (medical history of diabetes, hypertension, hyperlipidemia, premature family CAD history, heart failure ,renal

failure, COPD), medical history (previous angina, PCI, CABG), creatinine level, hemoglobin level, grace risk score, primary PCI.

b: adjusted p value

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**Table 3 Association between smoking and in-hospital mortality according to baseline characteristics**

Baseline characteristics	Current smoker	Ex-smoker	Non-smoker	P <sub>interaction</sub>
Age $\geq$ 55 years	0.78 (0.69, 0.89)	0.90 (0.77, 1.05)	reference	0.0986
Age < 55 years	0.72 (0.53, 0.99)	0.85 (0.48, 1.49)	reference	
Male	0.78 (0.68, 0.89)	0.94 (0.80, 1.10)	reference	0.0163
Female	0.75 (0.58, 0.98)	0.45 (0.26, 0.77)	reference	
BMI $\geq$ 24 kg/m <sup>2</sup>	0.80 (0.67, 0.94)	0.89 (0.71, 1.12)	reference	0.2063
BMI < 24 kg/m <sup>2</sup>	0.74 (0.63, 0.88)	0.89 (0.73, 1.10)	reference	

3	LVEF $\geq$ 50%	0.77 (0.67, 0.88)	0.98 (0.82, 1.16)	reference	0.0149
4	LVEF < 50%	0.87 (0.68, 1.11)	0.74 (0.54, 1.01)	reference	
6	Hypertension-Yes	0.85 (0.72, 1.00)	0.96 (0.78, 1.17)	reference	0.4556
7	Hypertension-No	0.70 (0.59, 0.83)	0.80 (0.64, 1.01)	reference	
8	Previous angina-Yes	0.84 (0.65, 1.07)	0.83 (0.62, 1.12)	reference	0.1833
9	Previous angina-No	0.76 (0.66, 0.87)	0.92 (0.78, 1.10)	reference	
11	Previous MI-Yes	0.67 (0.47, 0.97)	0.67 (0.45, 1.00)	reference	0.0557
12	Previous MI-No	0.77 (0.68, 0.87)	0.91 (0.78, 1.07)	reference	
13	Previous PCI-Yes	0.95 (0.44, 2.04)	1.23 (0.56, 2.72)	reference	0.7975
14	Previous PCI-No	0.78 (0.69, 0.88)	0.89 (0.76, 1.04)	reference	
15	Previous HF-Yes	0.96 (0.57, 1.60)	0.85 (0.53, 1.37)	reference	0.0086
16	Previous HF-No	0.77 (0.68, 0.87)	0.88 (0.76, 1.03)	reference	
19	Diabetes-Yes	0.78 (0.60, 1.02)	0.86 (0.63, 1.18)	reference	0.4065
20	Diabetes-No	0.77 (0.67, 0.88)	0.90 (0.76, 1.07)	reference	
21	Hyperlipidemia -Yes	0.75 (0.45, 1.24)	1.16 (0.66, 2.03)	reference	0.1239
22	Hyperlipidemia -No	0.77 (0.68, 0.87)	0.87 (0.74, 1.02)	reference	
23	Diagnosis of STEMI	0.81 (0.71, 0.93)	0.93 (0.78, 1.11)	reference	0.9700
24	Diagnosis of NSTEMI	0.61 (0.48, 0.78)	0.71 (0.54, 0.92)	reference	

adjusted for age, gender, BMI, systolic blood pressure, heart rate, admission diagnosis, cardiac arrest, chest pain, ST elevation, anterior wall MI, killip classification, risk factor (medical history of diabetes, hypertension, hyperlipidemia, premature family CAD history, heart failure, renal failure, COPD), medical history (previous angina, PCI, CABG), creatinine level, hemoglobin level, grace risk score, primary PCI.

BMI: body mass index; LVEF: left ventricular ejection fraction; MI: myocardial infarction; PCI: percutaneous coronary intervention; HF: heart failure;

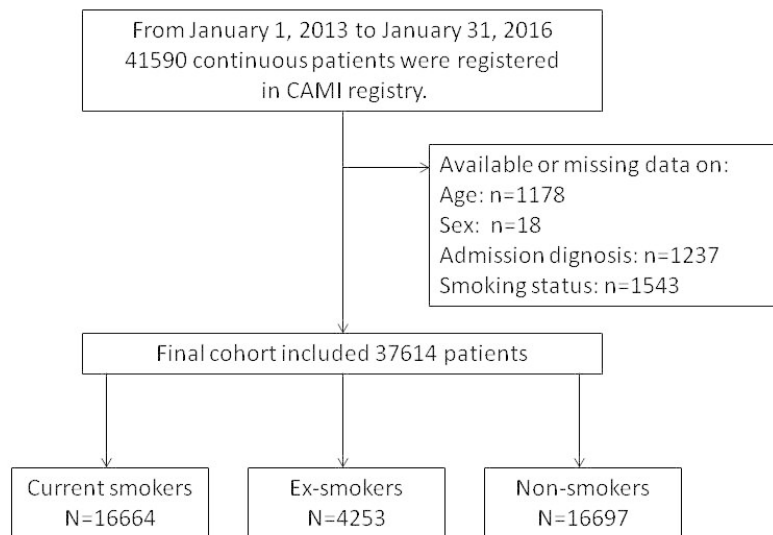


Figure 1 Study flow chart. From January, 2013 to January, 2016, 41590 continuous patients were registered in CAMI registry. Those with age < 18 or > 100 years old (n=1178), with missing or invalid data on gender (n=18), admission diagnosis (n=1237) and detailed smoking status (n=1543) were excluded. The final cohort included 37614 patients

254x190mm (96 x 96 DPI)

**Supplementary Table 1 Baseline characteristics between current smokers vs. non-smokers  
(After matching)**

Variable	Current Smokers (N=8552)	Non-smokers (N=8552)	p value	SD
Age	62.80 ± 11.53	62.84 ± 12.04	0.6983	0.0035
Male	87.7%	87.5%	0.0995	0.0067
BMI (Kg/m <sup>2</sup> )	24.18 ± 2.88	24.17 ± 2.79	0.7580	0.0047
ST-elevation on ECG	71.1%	71.5%	0.5830	0.0083
Heart failure on admission	14.1%	13.4%	0.1448	0.0217
Cardiac shock	3.5%	3.3%	0.6165	0.0077
Killip classification			0.6823	0.0080
I	76.8%	77.1%		
II	15.3%	15.2%		
III	4.0%	3.9%		
IV	3.9%	3.8%		
<b>Comorbidities</b>				
Hypertension	50.4%	49.8%	0.4066	0.0124
Hyperlipidemia	6.8%	6.4%	0.3293	0.0151
Diabetes	19.0%	18.4%	0.2747	0.0162
PVD	0.8%	0.5%	0.0376	0.0319
Heart failure	1.7%	1.7%	0.8570	0.0027
Stroke	8.9%	8.8%	0.7671	0.0045
COPD	1.8%	1.8%	1.0000	0.0000
Chronic kidney disease	1.1%	1.0%	0.8206	0.0034
In-hospital mortality	5.1%	6.1%	0.0045	

Data are presented as mean ± SD or frequencies; BMI: body mass index; ECG: electrocardiogram; PVD: peripheral vascular disease; COPD: chronic obstructive pulmonary disease;



**Supplementary Table 2 Baseline characteristics between ex-smokers vs. non-smokers (After matching)**

Variable	Ex-smokers (N=4142)	Non-smokers (N=4142)	p value	SD
<b>Age</b>	66.28 ± 11.49	66.02 ± 12.19	0.2242	0.0222
<b>Male</b>	93.8%	93.8%	0.3173	0.0010
<b>BMI (Kg/m<sup>2</sup>)</b>	23.96 ± 2.83	24.02 ± 2.79	0.2900	0.0226
<b>ST-elevation on ECG</b>	70.4%	71.2%	0.4054	0.0175
<b>Heart failure on admission</b>	18.4%	18.7%	0.7158	0.0075
<b>Cardiac shock</b>	4.1%	3.5%	0.1701	0.0302
<b>Killip classification</b>			0.4505	0.0157
<b>I</b>	69.2%	70.0%		
<b>II</b>	18.5%	18.4%		
<b>III</b>	7.3%	6.5%		
<b>IV</b>	5.0%	5.1%		
<b>Comorbidities</b>				
<b>Hypertension</b>	54.4%	53.7%	0.4668	0.0155
<b>Hyperlipidemia</b>	8.2%	7.5%	0.2057	0.0270
<b>Diabetes</b>	21.5%	21.3%	0.7664	0.0065
<b>PVD</b>	1.1%	0.6%	0.0050	0.0611
<b>Heart failure</b>	4.1%	3.5%	0.1466	0.0289
<b>Stroke</b>	12.8%	12.8%	1.0000	0.0000
<b>COPD</b>	3.5%	3.0%	0.1294	0.0260
<b>Chronic kidney disease</b>	2.2%	2.1%	0.8108	0.0050
<b>In-hospital mortality</b>	7.0%	7.4%	0.5198	

Data are presented as mean ± SD or frequencies; BMI: body mass index; ECG: electrocardiogram; PVD: peripheral vascular disease; COPD: chronic obstructive pulmonary disease;

STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation	Page No
<b>Title and abstract</b>	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	2
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
<b>Introduction</b>			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	2
Objectives	3	State specific objectives, including any prespecified hypotheses	3
<b>Methods</b>			
Study design	4	Present key elements of study design early in the paper	3
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	3, 4
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	4
		(b) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4-5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4-5
Bias	9	Describe any efforts to address potential sources of bias	3-4
Study size	10	Explain how the study size was arrived at	4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	5
		(b) Describe any methods used to examine subgroups and interactions	6
		(c) Explain how missing data were addressed	6
		(d) If applicable, explain how loss to follow-up was addressed	NA
		(e) Describe any sensitivity analyses	NA
<b>Results</b>			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	6
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6
		(b) Indicate number of participants with missing data for each variable of interest	6
		(c) Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	Report numbers of outcome events or summary measures over time	7

1	Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7
2			(b) Report category boundaries when continuous variables were categorized	NA
3			(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
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9	Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	6
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11	<b>Discussion</b>			
12				
13	Key results	18	Summarise key results with reference to study objectives	8
14	Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10
15				
16	Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9
17				
18				
19	Generalisability	21	Discuss the generalisability (external validity) of the study results	10
20				
21	<b>Other information</b>			
22	Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	11
23				
24				

\*Give information separately for exposed and unexposed groups.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at <http://www.strobe-statement.org>.

# BMJ Open

## Association between smoking and in-hospital mortality in patients with acute myocardial infarction: a prospective, multicenter, observational study

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2019-030252.R1
Article Type:	Research
Date Submitted by the Author:	31-May-2019
Complete List of Authors:	Song, Chenxi; Chinese Academy of Medical Sciences & Peking Union Medical College Fuwai Hospital, Cardiology Fu, Rui; Chinese Academy of Medical Sciences and Peking Union Medical College Fuwai Hospital, Cardiology Dou, Kefei; Chinese Academy of Medical Sciences and Peking Union Medical College Fuwai Hospital, Yang, Jingang; Fu Wai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, Coronary Heart Disease Center Xu, Haiyan; Fu Wai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, Coronary Heart Disease Center Gao, Xiaojin; Fu Wai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, Coronary Heart Disease Center Wang, Hao; Fu Wai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, Coronary Heart Disease Center Liu, Shuai; Fu Wai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, Coronary Heart Disease Center Fan, Xiaoxue; Fu Wai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, Coronary Heart Disease Center Yang, Yuejin; Fu Wai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, Coronary Heart Disease Center
<b>Primary Subject Heading</b>:	Cardiovascular medicine
Secondary Subject Heading:	Cardiovascular medicine
Keywords:	smoking, in-hospital mortality, acute myocardial infarction

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4 **Association between smoking and in-hospital mortality in**  
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6 **patients with acute myocardial infarction: a prospective,**  
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8 **multicenter, observational study**  
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11 **Chenxi Song, MD<sup>1</sup>, Rui Fu, MD<sup>1</sup>, Kefei Dou, MD, PhD<sup>1</sup>, Jingang Yang, MD,**  
12 **PhD<sup>1</sup>, Haiyan Xu, MD, PhD<sup>1</sup>, Xiaojin Gao, MD, PhD<sup>1</sup>, Hao Wang, MD<sup>1</sup>, Shuai**  
13 **Liu, MD<sup>1</sup>, Xiaoxue Fan, PhD<sup>1</sup>, Yuejin Yang, MD, PhD<sup>1</sup>**  
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19 <sup>1</sup> Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of  
20 Medical Sciences and Peking Union Medical College  
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25 The first two authors Chenxi Song and Rui Fu made equal contribution to this work.  
26  
27 Kefei Dou and Yuejin Yang contributed equally to the article and accept equal and  
28 full responsibility for the work as correspondence authors.  
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32  
33 **Contact information**  
34

35 Chenxi Song 1933769555@qq.com  
36  
37 Rui Fu [fwfurui@163.com](mailto:fwfurui@163.com)  
38  
39 Kefei Dou [drdoukefei@126.com](mailto:drdoukefei@126.com)  
40  
41 Jingang Yang [yangjingang@mrbc-nccd.com](mailto:yangjingang@mrbc-nccd.com)  
42  
43 Haiyan Xu [xuhaiyan@fuwaihospital.org](mailto:xuhaiyan@fuwaihospital.org)  
44  
45 Xiaojin Gao [sophie\\_gao@sina.com](mailto:sophie_gao@sina.com)  
46  
47 Hao Wang [wanghao\\_fuwai@126.com](mailto:wanghao_fuwai@126.com)  
48  
49 Shuai Liu [liushuai851213@163.com](mailto:liushuai851213@163.com)  
50  
51 Xiaoxue Fan [fanxiaoxue@mrbc-nccd.com](mailto:fanxiaoxue@mrbc-nccd.com)  
52  
53 Yuejin Yang [yangyjfw@126.com](mailto:yangyjfw@126.com)  
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56 Affiliation information: Chenxi Song, Fuwai Hospital, Department of Cardiology,  
57 Chinese Academy of Medical Sciences and Peking Union Medical College  
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## ***Abstract***

**Introduction:** Smoking is a well-established risk factor for cardiovascular disease. However, the effect of smoking on in-hospital mortality in patients with acute myocardial infarction (AMI) who are managed by contemporary treatment is still unclear.

**Methods:** A cohort study was conducted using data from the China AMI registry between 2013 and 2016. Eligible patients were diagnosed with AMI in accordance with the third Universal Definition of Myocardial Infarction. Propensity score matching and multivariable logistic regression were used to control for confounders. Subgroup analysis was performed to examine whether the association between smoking and in-hospital mortality varies according to baseline characteristics.

**Results:** A total of 37,614 patients were included. Smokers were younger and more frequently men with fewer comorbidities than non-smokers. After propensity score matching and multivariable log regression analysis was performed, the difference in in-hospital mortality between current smokers versus non-smokers was reduced, but it was still significant (5.1% vs.6.1%,  $p=0.0045$ ; adjusted odds ratio: 0.78; 95% confidence interval: 0.69–0.88,  $p<0.001$ ). Among all subgroups, there was a trend toward lower in-hospital mortality in current smokers or ex-smokers compared with non-smokers.

**Conclusions:** Smoking is associated with lower in-hospital mortality in patients with AMI, even after multiple analyses to control for potential confounders. This “smoker’s paradox” cannot be fully explained by confounding alone.

## **Keywords:**

smoking; in-hospital mortality; acute myocardial infarction

## **Strengths and limitations of the study**

This study used data from a large-scale multicenter registry in a contemporary era of PCI.

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4 We used propensity score matching and the multivariable logistic regression model to  
5 adjust for confounders, which ensured the robustness of our conclusion.

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7 The current study did not include data on patients who died before hospitalization,  
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9 which may have caused index event bias (type of selection bias).

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11 The current study did not adjust for unmeasured confounders.

## 12 13 **INTRODUCTION**

14  
15 Smoking is a well-established risk factor of cardiovascular disease<sup>1,2</sup>. However, some  
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17 previous studies have shown that smokers have a better outcome than do non-smokers  
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19 following AMI. This phenomenon is referred to as “smoker’s paradox”. This  
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21 phenomenon was first introduced in the 1970s, when Helmers found that smokers had  
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23 a lower risk of mortality than did nonsmokers<sup>3</sup>. Some subsequent studies also showed  
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25 smoker’s paradox in patients with acute coronary syndrome<sup>4</sup>. This paradox may be  
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27 explained by differences in baseline characteristics between smokers and  
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29 non-smokers<sup>5</sup>. Additionally, the anti-platelet response may differ according to  
30  
31 smoking status because of the effect of smoking on pharmacodynamics of clopidogrel  
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33 therapy<sup>6</sup>. Notably, most studies regarding smoker’s paradox were conducted in the era  
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35 of thrombolysis, while the association between smoking and in-hospital mortality in  
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37 patients who are treated with percutaneous intervention (PCI) remains controversial.  
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39 Some studies have reported that the difference in in-hospital mortality was not  
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41 significant between smokers and non-smokers after accounting for age and other  
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43 baseline characteristics<sup>7-13</sup>. Other studies reported that smokers had a lower  
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45 in-hospital mortality rate compared with non-smokers, even after adjustment for  
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47 potential confounders (smoker’s paradox)<sup>14-18</sup>.

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49 Examining the true effect of smoking on outcome among contemporary patients with  
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51 AMI is important. If smoker’s paradox is explained by confounding and smoking is  
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53 not associated with favorable outcomes, physicians should disseminate this message  
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55 to patients and help them quit smoking. However, if smoker’s paradox still exists in  
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57 the contemporary era of PCI, the biochemical basis for this phenomenon should be  
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investigated. This investigation may promote development of novel therapy for myocardial protection.

This study aimed to assess how smoking affects in-hospital mortality of patients receiving contemporary management of AMI. We hypothesized that smokers have lower in-hospital mortality than do non-smokers.

## METHODS

### Data source

A cohort study was conducted by using data from the China AMI (CAMI) registry between January 1, 2013 and January 31, 2016. A detailed description of the registry design was published previously<sup>19</sup>. Briefly, the CAMI registry was a prospective, multicenter, observational registry. The project included Chinese patients with AMI and data were collected on patients' characteristics, treatments, and outcomes. A total of 108 hospitals covering a broad geographic region participated in the project. This assured a good representation of all of the patients with AMI in China and reduced selection bias<sup>19</sup>. Our study was approved by the institutional review board central committee at Fuwai Hospital, NCCD of China (approval ID: 2012-431). Written informed consent was obtained from each patient who was included in the study. If the patient was not able to communicate, informed consent was obtained from a family member. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki. The CAMI registry was registered at [www.clinicaltrials.gov](http://www.clinicaltrials.gov) (registration number: NCT01874691).

### Study population

We included the study population from the CAMI registry. Eligible patients were diagnosed with AMI and within 7 days of ischemic symptoms. Diagnostic criteria of AMI were in accordance with the third Universal Definition of Myocardial Infarction<sup>20</sup>. We excluded patients who were aged <18 or >100 years, and those with missing or invalid data on sex, admission diagnosis, and smoking status.

Data were extracted by trained researchers using standard definitions to reduce measurement and reporting bias. These data included age, sex, height, weight, clinical

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4 presentation (symptoms, ST-segment elevation, anterior wall myocardial infarction  
5 [MI], blood pressure, heart rate, heart failure, cardiac shock, fatal arrhythmia, cardiac  
6 arrest, and Killip classification), risk factors (hypertension, hyperlipidemia, diabetes),  
7 comorbidities (heart failure, peripheral vascular disease, stroke, chronic kidney  
8 disease, and chronic obstructive pulmonary disease [COPD]), medical history (family  
9 history of premature coronary artery disease [CAD], prior angina or MI, prior  
10 coronary intervention, prior coronary artery bypass grafting [CABG]), initial  
11 reperfusion strategy (primary PCI, thrombolysis, and conservative therapy),  
12 laboratory results (creatinine, hemoglobin, and left ventricular ejection fraction  
13 [LVEF]) and in-hospital outcome.

### 23 **Patient and public involvement**

24 We did not involve patients or the public in our work

### 27 **Definition of variables**

28 All patients were divided into three groups according to smoking status. Current  
29 smokers were defined as those who smoked within 1 month before registration.

30 Ex-smokers were defined as those who quit smoking for at least 1 month.

31 Non-smokers were defined as those who never smoked. Standard definitions of the  
32 medical history and physical examination elements were well described in the  
33 ACC/AHA Task Force on clinical Data Standards and the NCDR-ACTION-GWTG  
34 element dictionary<sup>21-23</sup>. Electrocardiograms and echocardiograms were interpreted  
35 locally.

36 The primary endpoint was all-cause in-hospital mortality, which was defined as  
37 all-cause death during hospitalization.

### 48 **Statistical analysis**

49 Baseline continuous data are presented as mean±SD or median (25th–75th percentiles)  
50 and were compared using one-way ANOVA. This was followed by the Bonferroni t  
51 test with a corrected p value of 0.05/3. Categorical data are presented as counts and  
52 frequencies and were compared using the  $\chi^2$  test. Propensity score (PS) matching was  
53 used to control for baseline differences. We performed PS matching between current  
54 smokers and non-smokers, and between ex-smokers and non-smokers. We used a  
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4 multivariable logistic regression model to estimate propensity scores, with smoking as  
5 the dependent variable and the following factors as covariates: age, sex, body mass  
6 index (BMI), systolic blood pressure, heart rate, admission diagnosis, cardiac arrest,  
7 chest pain, ST elevation, anterior wall MI, Killip classification, risk factor (medical  
8 history of diabetes, hypertension, hyperlipidemia, premature family CAD history,  
9 heart failure, renal failure, and COPD), medical history (previous angina, PCI, and  
10 CABG), creatinine levels, hemoglobin levels, Global Registry of Acute Coronary  
11 Events (GRACE) risk score, and primary PCI. These variables were chosen as  
12 covariates because the difference in these baseline characteristics reached statistical  
13 significance or these variables were previously reported to be associated with patients'  
14 outcome.

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16 Matching was performed using the greedy nearest matching algorithm and a 1:1  
17 fashion. The caliper width was equal to 0.01 of the standardized difference of the  
18 score. McNemar's and paired t-tests were used to compare continuous and categorical  
19 variables between the two groups after matching. For each variable in the PS model,  
20 we computed the standardized difference between the two groups, with a standardized  
21 difference less than 0.1 indicating good balance.

22  
23 The stepwise selection method was used to compare in-hospital mortality across the  
24 different groups. Baseline characteristics that significantly differed across the groups  
25 and those of clinical importance were included in the model. These variables were the  
26 same as those used for propensity matching. A p value  $<0.1$  was used as the entry  
27 criterion and a p value  $<0.05$  was used as the removal criterion. To determine whether  
28 the association between smoking and in-hospital mortality varied according to  
29 baseline patients' characteristics, we performed the same multivariable logistic  
30 analysis in subgroups that were stratified by age, sex, BMI, presence or absence of  
31 hypertension, diabetes, hyperlipidemia, heart failure, prior angina, MI or coronary  
32 intervention, and admission diagnosis. A two-sided p value  $<0.05$  was considered  
33 significant. For the interaction test, a p value  $<0.1$  was considered significant. For all  
34 variables included in our study, less than 2% of the data were missing. We used  
35 complete case analysis to deal with missing data<sup>24</sup>. Patients with missing data were  
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4 excluded from analysis. We presented data as “counts/total numbers available  
5 (frequencies)” for categorical variables.  
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## 10 11 **RESULTS**

### 12 13 **Baseline characteristics**

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16 From January 1, 2013 to January 31, 2016, a total of 41,590 continuous patients were  
17 registered in the CAMI registry. We excluded 118 patients aged <18 or >100 years,  
18 and those with missing or invalid data on sex (n=18), admission diagnosis (n=1237),  
19 and detailed smoking status (n=1543). The final cohort included 37,614 patients  
20 (Figure 1).  
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26 Baseline characteristics before matching are shown in Table 1. A total of 16,664  
27 (44.3%) patients were current smokers, 843 (2.2%) quit smoking before or at 1 year,  
28 3410 (9.1%) quit smoking after 1 year, and 16,697 (44.4%) were non-smokers.  
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30 Current smokers were younger ( $57.99 \pm 11.81$  vs.  $66.59 \pm 11.82$  years) and had a higher  
31 BMI ( $24.39 \pm 2.87$  vs.  $23.98 \pm 2.95$  kg/m<sup>2</sup>) compared with non-smokers. The proportion  
32 of men (93.7% vs. 49.8%) and Killip class I (80.5% vs. 72.1%) was higher in current  
33 smokers compared with non-smokers. Compared with non-smokers, current smokers  
34 were less likely to have hypertension, diabetes, heart failure, stroke, or chronic kidney  
35 disease, but more likely to have hyperlipidemia. Among ex-smokers, the proportions  
36 of male sex, hyperlipidemia, heart failure, peripheral vascular disease (PVD), and  
37 stroke were higher than those of current smokers. Ex-smokers also showed a trend  
38 towards old age and a low proportion of hypertension and diabetes than did current  
39 smokers, but these differences were less significant compared with the differences  
40 between current and non-smokers.  
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### 53 **In-hospital outcomes**

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55 Overall, 2370 patients died before discharge. There were 614 (3.7%) deaths in the  
56 current smoker group, 306 (7.2%) deaths in the ex-smoker group, and 1450 (8.7%)  
57 deaths in the non-smoker group. Causes of mortality are shown in supplementary  
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4 table 1. The unadjusted odds ratio (OR) for in-hospital mortality was 0.4 (95%  
5 confidence interval [CI]: 0.37–0.44,  $p < 0.0001$ ) in current smokers and 0.82 (95% CI:  
6 0.72–0.93,  $p = 0.0018$ ) in ex-smokers relative to non-smokers (Table 2). After  
7 adjustment for potential confounders, current smoking status was significantly  
8 associated with lower in-hospital mortality relative to non-smokers (adjusted OR:  
9 0.78, 95% CI: 0.69–0.88,  $p < 0.001$ ) (Table 2). No difference in in-hospital mortality  
10 was detected between ex- and non-smokers (OR: 0.89, 95% CI: 0.77–1.04,  
11  $p = 0.1443$ ).

### 12 **Propensity score matching**

13 Before PS matching, there were differences in almost all baseline variables among the  
14 different groups (Table 1). To control for potential confounding, we matched 8552  
15 current smokers with 8552 non-smokers, as well as 4142 ex-smokers and 4142  
16 non-smokers (Supplementary Table 2). The standardized differences were less than  
17 10.0% for all variables after matching, which indicated a good match between two  
18 groups. After PS matching, current smokers still had lower in-hospital mortality than  
19 did non-smokers (5.1% vs. 6.1%,  $p = 0.0045$ ), but the difference in in-hospital  
20 mortality was not significant between ex-smokers and non-smokers (7.0% vs. 7.4%,  
21  $p = 0.5198$ ) (Supplementary Table 3).

### 22 **Subgroup analysis**

23 Subgroup analysis indicated significant interactions between smoking status and age  
24 ( $p_{\text{interaction}}: 0.0986$ ), sex ( $p_{\text{interaction}}: 0.0163$ ), LVEF ( $p_{\text{interaction}}: 0.0149$ ), previous MI  
25 ( $p_{\text{interaction}}: 0.0557$ ), and previous heart failure ( $p_{\text{interaction}}: 0.0086$ ) for in-hospital  
26 mortality (Table 3). However, there was a trend toward lower in-hospital mortality in  
27 the current smoker or ex-smoker group compared with the non-smoker group.

## 28 **DISCUSSION**

29 Our study used data from the CAMI registry, which is the largest contemporary  
30 registry of patients with AMI in East Asia. Our major finding was that in patients with  
31 AMI, current-smokers had lower in-hospital mortality than did non-smokers in the  
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4 whole population and in almost all subgroups, after adjusting for potential  
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6 confounders by using PS matching.

### 7 **Comparison with previous studies**

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9 Most previous studies were conducted in the thrombolytic era and we only identified  
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11 four studies that enrolled patients in the current primary PCI era<sup>13,18,25,26</sup>. Of these four  
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13 studies, three studies used multivariate regression analysis to control for confounders.  
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15 Our study results are consistent with those from another large-scale study<sup>18</sup>. This  
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17 previous study also showed that among patients with ST elevation myocardial  
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19 infarction (STEMI) who received primary PCI, smokers (including current and  
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21 ex-smokers) had a lower adjusted in-hospital mortality risk than did non-smokers. In  
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23 our study, we further separated current and ex-smokers, and used PS matching to  
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25 comprehensively control for potential confounders. Several mechanisms have been  
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27 proposed to explain this paradox phenomenon.

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29 First, some studies showed that a suppressive effect of clopidogrel on platelets was  
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31 greater in smokers than in non-smokers<sup>27-29</sup>. A potential explanation for this finding is  
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33 that smoking can enhance *in vivo* bioactivation of clopidogrel via increasing induction  
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35 of cytochrome P450 (CYP1A2 and CYP2B6) and increased active metabolite  
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37 concentrations of clopidogrel<sup>30,31</sup>. Therefore, smokers may respond better to  
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39 clopidogrel therapy and consequently have a lower in-hospital mortality rate than  
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41 non-smokers. Second, smoking was unexpectedly associated with a lower risk of  
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43 adverse left ventricular remodeling post-infarction. Rolf Symons et al performed  
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45 cardiac magnetic resonance imaging at 4 days and 4 months after MI. They found that  
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47 smokers had an improved LVEF, which was attributable to a decrease in the  
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49 end-diastolic volume index, but not an increase in the systolic volume index<sup>32</sup>.  
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51 However, our results are not consistent with two studies, which found an absence of  
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53 the smoker paradox after baseline risk adjustment<sup>13,26</sup>. This difference may be related  
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55 to selection of the study population and sample size. One previous study enrolled  
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57 patients with symptomatic CAD, including those who presented with stable or  
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59 unstable angina<sup>9</sup>, while we included patients with AMI. Patients with stable angina  
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represent a relatively lower risk group. Therefore, enrollment of this patient subset

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4 may affect the association between smoking and mortality. The other study had a  
5 small sample size (n=382), and it may not have had sufficient statistical power to  
6 detect a difference in mortality between smokers and non-smokers.  
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### 9 **Interpretation of our results**

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11 Our results should be interpreted with caution. Although we adjusted for many  
12 common confounders, our study was still subject to selection bias as discussed below  
13 in the Limitations subsection. Our results should not be interpreted as encouraging  
14 patients to smoke. Smoking is well established as an independent risk factor for  
15 mortality and recurrent MI<sup>33</sup>, as well as for subacute stent thrombosis<sup>34</sup> in the  
16 long-term, and patients with coronary heart disease can benefit from cessation of  
17 smoking<sup>35</sup>. Therefore, we still recommend that patients stop smoking. Our results  
18 indicated potential mechanisms underlying the protective effect of smoking. Future  
19 studies should investigate novel therapies to protect the myocardium by targeting the  
20 relevant pathways. Smoking might lead to a chronic ischemic state (ischemic  
21 preconditioning)<sup>36</sup>; therefore, smokers might have better tolerance for an acute  
22 ischemic event, such as a heart attack. The phenomenon could be investigated by  
23 examining whether pre-conditioning therapy or a brief period of reversible ischemia  
24 can protect the myocardium and improve outcome.  
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28 Our subgroup analysis showed a significant interaction between smoking status and  
29 age, sex, LVEF, previous MI, and previous heart failure. However, currently, we  
30 cannot reach the conclusion that these baseline characteristics had a significant effect  
31 on the relationship between smoking and in-hospital mortality. This is because there  
32 was a similar trend among all subgroups that current smokers and ex-smokers had a  
33 lower in-hospital mortality risk compared with non-smokers. A significant p value  
34 may be attributed to a different OR value between subgroups of smokers and  
35 non-smokers, as well as a large sample size of some of the subgroups.  
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### 38 **Limitations**

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40 Our study may have been subject to selection bias. The CAMI registry did not collect  
41 data on patients who died before hospitalization. Failing to account for pre-hospital  
42 deaths may have led to selection bias. The distribution of risk factors was significantly  
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4 different between smokers and non-smokers. Although we adjusted for known and  
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6 measured variables, there are likely to be other unmeasured variables leading to  
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8 selection bias. The CAMI registry was a multicenter, large-scale study that involved  
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10 more than 100 hospitals. Although a standardized data collection procedure was  
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12 emphasized, the accuracy of data still greatly depends on the expertise of local  
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14 investigators. The CAMI registry did not collect detailed data regarding smoking  
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16 status. Smoking status might be modified after onset of MI. However, we asked the  
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18 patients about their smoking status before onset of AMI and all patients were enrolled  
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20 within 7 days of symptom onset. We only assessed the association between smoking  
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22 and short-term outcome. Future studies are required to investigate this association in  
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24 the long-term.

### 25 **Conclusions:**

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27 Our study showed that the in-hospital mortality rate was lower in smokers compared  
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29 with non-smokers in a large-scale, contemporary cohort representing patients with  
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31 AMI in China. Our findings indicate that future studies should be performed to further  
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33 explore the potential biological mechanisms that may explain this phenomenon.  
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### 36 **Declaration of interests:**

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38 We confirm that there are no known conflicts of interest associated with this  
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40 publication.  
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### 43 **Author contributions:**

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45 Chenxi Song and Rui fu were major contributors in writing the manuscript. Kefei Dou  
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47 and Yuejin Yang contributed substantially to the conception and design of the study.  
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49 Jingang Yang, Haiyan Xu, Xiaojin Gao, Hao Wang, Shuai Liu revised it critically for  
50  
51 important intellectual content. Xiaoxue Fan made contribution to analysis and  
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53 interpretation of data.  
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### 56 **Funding statement:**



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4 This work was supported by CAMS Innovation Fund for Medical  
5 Sciences (CIFMS) (2016-I2M-1-009), the Twelfth Five-Year Planning Project of the  
6 Scientific and Technological Department of China (2011BAI11B02), and 2014  
7 Special fund for scientific research in the public interest by National Health and  
8 Family Planning Commission of the People's Republic of China (No. 201402001).  
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### 15 **Acknowledgement:**

16  
17 We are very grateful to the TIMI Study Group and the Duke Clinical Research  
18 Institute for their contributions in the design, conduct, and data analyses of CAMI  
19 registry. We also want to thank all the investigators and coordinators for their great  
20 work and active participation. We thank Ellen Knapp, PhD, from Liwen Bianji, Edanz  
21 Group China (www.liwenbianji.cn/ac), for editing the English text of a draft of this  
22 manuscript. We thank Yang Wang and Wei Li for statistical analysis.  
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### 31 **Data availability statement**

32 Data are available from corresponding author on reasonable request.  
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19 **Figure and table legends:**

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21 Table 1 Baseline characteristics according to smoking status (Before matching)

22 Table 2 Association between Smoking and In-hospital Mortality

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24 Table 3 Association between smoking and in-hospital mortality according to baseline  
25 characteristics

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27 Figure legend: Figure 1 Study flow chart. From January, 2013 to January, 2016,  
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29 41590 continuous patients were registered in CAMI registry. Those with age < 18 or  
30 > 100 years old (n=1178), with missing or invalid data on gender (n=18), admission  
31 diagnosis (n=1237) and detailed smoking status (n=1543) were excluded. The final  
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33 cohort included 37614 patients  
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Table 1 Baseline characteristics according to smoking status (Before matching)

Variable	Current Smokers (N=16664)	Ex-smokers (N=4253)	Non-smokers (N=16697)	p value
Age	57.99 ± 11.81	66.49 ± 11.50	66.59 ± 11.82	<0.0001
Male	15616/16664 (93.7%)	3997/4253 (94.0%)	8317/16697 (49.8%)	<0.0001
BMI (Kg/m <sup>2</sup> )	24.39 ± 2.87	23.95 ± 2.84	23.98 ± 2.95	<0.0001
ST-elevation on ECG	12044/16330 (74.3%)	2725/4185 (65.7%)	10822/16374 (66.7%)	0.2338
SBP (mmHg)	127.82 ± 24.69	129.71 ± 25.17	130.58 ± 25.97	<0.0001
Heart rate (bpm)	76.74 ± 17.40	79.85 ± 19.82	79.47 ± 18.89	<0.0001
Heart failure on admission	1851/16608 (11.1%)	817 /4227 (19.2%)	3016/16620 (18.1%)	0.0781
Cardiac shock	512/16597 (3.1%)	175/4227 (4.1%)	658/16614 (3.9%)	0.5962
Killip classification				<0.0001
I	13332/16577 (80.4%)	2877 /4215 (68.3%)	11906 /16568 (71.9%)	
II	2272 /16577 (13.7%)	799/4215 (19.0%)	2892 /16568 (17.5%)	
III	472/16577 (2.8%)	324 /4215 (7.7%)	951/16568 (5.7%)	
IV	501/16577 (3.0%)	215 /4215 (5.1%)	819 /16568 (4.9%)	
<b>Comorbidities</b>				
Hypertension	7288/16653 (43.8%)	2328/4251 (54.8%)	9434/16693 (56.5%)	0.0401
Hyperlipidemia	1329/16640 (8.0%)	367 /4247 (8.6%)	1020 /16679 (6.1%)	<0.0001
Diabetes	2451/ 16635 (14.7%)	924 /4242 (21.8%)	3893 /16672 (23.4%)	0.0295
PVD	100 /16611 (0.6%)	49 / 4234 (1.2%)	115 /16642 (0.7%)	0.0035
Heart failure	177 /16628 (1.1%)	199 /4235 (4.7%)	528 /16638 (3.2%)	<0.0001
Stroke	1176 /16616 (7.1%)	570 /4237 (13.5%)	1666 /16648 (10.0%)	<0.0001
COPD	277 /16664 (1.7%)	191 /4253 (4.5%)	277/16697 (1.7%)	<0.0001
Chronic kidney disease	121 /16588 (0.7%)	103 /4222 (2.4%)	257 /16612 (1.5%)	0.0001
Smoking duration (year)	30.38 ± 11.89	26.86 ± 11.99	NA	<0.0001

Number of cigarettes/ day	21.23 ±11.10	19.13 ±10.93	NA	<0.0001
Hb (g/L)	142.15 ±17.42	135.38 ±19.39	130.18 ±19.43	<0.0001
Creatinine (mg/L)	37.40 ±0.69	37.40 ±0.46	37.42 ±2.04	0.1842
Primary PCI	8499/16544 (51.4%)	1566/4224 (37.1%)	6369/16579 (38.4%)	0.1084
P2Y12 inhibitors	16086/16458 (97.7%)	4030/4186 (96.3%)	15837/16446 (96.3%)	0.9423
GRACE risk score	151.43 ±33.02	171.34 ±35.63	169.61 ±35.89	<0.0001
<b>In-hospital mortality</b>	614/16664 (3.7%)	306/4325 (7.2%)	1450/16679 (8.7%)	0.0015

Data are presented as mean±SD or frequencies; BMI: body mass index; ECG: electrocardiogram; SBP: systolic blood pressure; PVD: peripheral vascular disease; COPD: chronic obstructive pulmonary disease; Hb: hemoglobin; GRACE: the global registry of acute coronary events

Table 2 Association between Smoking and In-hospital Mortality

Smoking status	OR (95% CI)			<i>p</i> value <sup>b</sup>
	Unadjusted	Adjusted <sup>a</sup>	PS matching	
Current smokers vs non-smokers	0.40 (0.37, 0.44)	0.78 (0.69, 0.88)	0.80 (0.69, 0.92)	<.0001
Ex-smokers vs non-smokers	0.82 (0.72, 0.93)	0.89 (0.77, 1.04)	1.03 (1.02, 1.04)	0.1443

a: adjusted for age, gender, BMI, systolic blood pressure, heart rate, admission diagnosis, cardiac arrest, chest pain, ST elevation, anterior wall MI, killip classification, risk factor (medical history of diabetes, hypertension, hyperlipidemia, premature family CAD history, heart failure, renal failure, COPD), medical history (previous angina, PCI, CABG), creatinine level, hemoglobin level, grace risk score, primary PCI. The number of patients included in the adjusted model was 37614.

b: adjusted *p* value

Table 3 Association between smoking and in-hospital mortality according to baseline characteristics

Baseline characteristics	Current smoker	Ex-smoker	Non-smoker	P <sub>interaction</sub>
Age ≥ 55 years	0.78 (0.69, 0.89)	0.90 (0.77, 1.05)	reference	0.0986
Age < 55 years	0.72 (0.53, 0.99)	0.85 (0.48, 1.49)	reference	
Male	0.78 (0.68, 0.89)	0.94 (0.80, 1.10)	reference	0.0163
Female	0.75 (0.58, 0.98)	0.45 (0.26, 0.77)	reference	
BMI ≥ 24 kg/m <sup>2</sup>	0.80 (0.67, 0.94)	0.89 (0.71, 1.12)	reference	0.2063
BMI < 24 kg/m <sup>2</sup>	0.74 (0.63, 0.88)	0.89 (0.73, 1.10)	reference	
LVEF ≥ 50%	0.77 (0.67, 0.88)	0.98 (0.82, 1.16)	reference	0.0149
LVEF < 50%	0.87 (0.68, 1.11)	0.74 (0.54, 1.01)	reference	
Hypertension-Yes	0.85 (0.72, 1.00)	0.96 (0.78, 1.17)	reference	0.4556
Hypertension-No	0.70 (0.59, 0.83)	0.80 (0.64, 1.01)	reference	
Previous angina-Yes	0.84 (0.65, 1.07)	0.83 (0.62, 1.12)	reference	0.1833
Previous angina-No	0.76 (0.66, 0.87)	0.92 (0.78, 1.10)	reference	
Previous MI-Yes	0.67 (0.47, 0.97)	0.67 (0.45, 1.00)	reference	0.0557
Previous MI-No	0.77 (0.68, 0.87)	0.91 (0.78, 1.07)	reference	
Previous PCI-Yes	0.95 (0.44, 2.04)	1.23 (0.56, 2.72)	reference	0.7975
Previous PCI-No	0.78 (0.69, 0.88)	0.89 (0.76, 1.04)	reference	
Previous HF-Yes	0.96 (0.57, 1.60)	0.85 (0.53, 1.37)	reference	0.0086
Previous HF-No	0.77 (0.68, 0.87)	0.88 (0.76, 1.03)	reference	
Diabetes-Yes	0.78 (0.60, 1.02)	0.86 (0.63, 1.18)	reference	0.4065
Diabetes-No	0.77 (0.67, 0.88)	0.90 (0.76, 1.07)	reference	
Hyperlipidemia -Yes	0.75 (0.45, 1.24)	1.16 (0.66, 2.03)	reference	0.1239
Hyperlipidemia -No	0.77 (0.68, 0.87)	0.87 (0.74, 1.02)	reference	
Diagnosis of STEMI	0.81 (0.71, 0.93)	0.93 (0.78, 1.11)	reference	0.9700
Diagnosis of NSTEMI	0.61 (0.48, 0.78)	0.71 (0.54, 0.92)	reference	

adjusted for age, gender, BMI, systolic blood pressure, heart rate, admission diagnosis, cardiac arrest, chest pain, ST elevation, anterior wall MI, killip classification, risk factor (medical history of diabetes, hypertension, hyperlipidemia, premature family CAD history, heart failure, renal failure, COPD), medical history (previous angina, PCI, CABG), creatinine level, hemoglobin level, grace risk score, primary PCI. BMI: body mass index; LVEF: left ventricular ejection fraction; MI: myocardial infarction; PCI: percutaneous coronary intervention; HF: heart failure;

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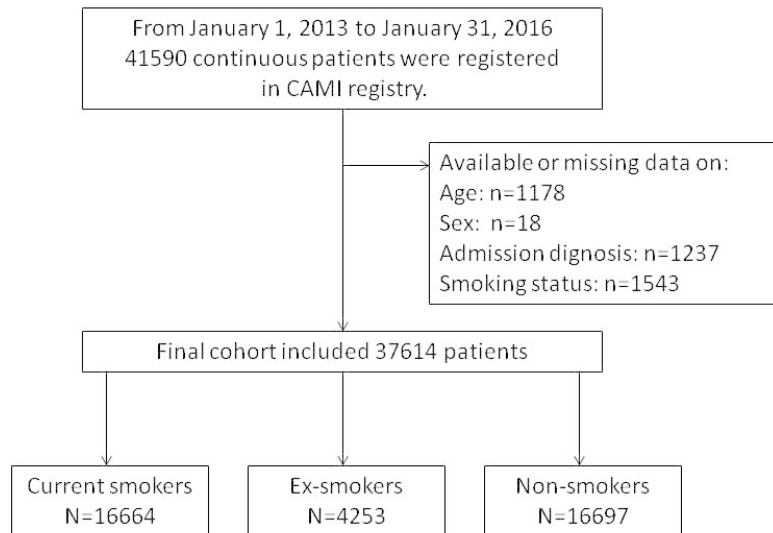


Figure 1 Study flow chart. From January, 2013 to January, 2016, 41590 continuous patients were registered in CAMI registry. Those with age <18 or >100 years old (n=1178), with missing or invalid data on gender (n=18), admission diagnosis (n=1237) and detailed smoking status (n=1543) were excluded. The final cohort included 37614 patients

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Supplementary Table 1 Causes of mortality according to smoking status

Variable	Current Smokers (N=16664)	Ex-smokers (N=4253)	Non-smokers (N=16697)	p value
Sudden cardiac death	202/16664 (1.2%)	107/4253 (2.5%)	519/16697 (3.1%)	0.0387
Cardiac shock	157/16664 (0.9%)	85/4253 (2.0%)	375/16697 (2.2%)	0.3203
Heart failure	121/16664 (0.7%)	65/4253 (1.5%)	291/16697 (1.7%)	0.3277
Intracerebral hemorrhage	4/16664 (0.0%)	1/4253 (0%)	3/16697 (0%)	0.8199
Lung infection	15/16664 (0.1%)	10/4253 (0.2%)	26/16697 (0.2%)	0.2833
Ischemic stroke	3/16664 (0.0%)	2/4253 (0%)	7/16697 (0.0%)	0.8873
Major bleeding	3/16664 (0.0%)	0/4253 (0%)	6/16697 (0.0%)	0.0989
Others	25/16664 (0.2%)	9/4253 (0.2%)	47/16697 (0.3%)	0.4176

**Supplementary Table 2 Baseline characteristics between current smokers vs. non-smokers  
(After matching)**

Variable	Current Smokers (N=8552)	Non-smokers (N=8552)	p value	Standardized difference
<b>Age</b>	62.80 ± 11.53	62.84 ± 12.04	0.6983	0.0035
<b>Male</b>	1048/8552 (87.7%)	7485/8552 (87.5%)	0.0995	0.0067
<b>BMI (Kg/m<sup>2</sup>)</b>	24.18 ± 2.88	24.17 ± 2.79	0.7580	0.0047
<b>ST-elevation on ECG</b>	71.1%	71.5%	0.5830	0.0083
SBP(mmHg)	129.01 ± 25.75	128.90 ± 24.68	0.7767	0.0043
Heart rate(bpm)	77.88 ± 18.55	77.61 ± 17.40	0.3279	0.0147
<b>Heart failure on admission</b>	1208 ( 14.1%)	1144 (13.4%)	0.1448	0.0217
<b>Cardiac shock</b>	297 (3.5%)	285 (3.3%)	0.6165	0.0077
<b>Killip classification</b>			0.6823	0.0080
<b>I</b>	6564/8552 (76.8%)	6593/8552 (77.1%)		
<b>II</b>	1312/8552 (15.3%)	1301 /8552 (15.2%)		
<b>III</b>	341 /8552 (4.0%)	330/8552 (3.9%)		
<b>IV</b>	335 /8552 (3.9%)	328 /8552 (3.8%)		
<b>Comorbidities</b>				
<b>Hypertension</b>	4309/8552 (50.4%)	4256 /8552 (49.8%)	0.4066	0.0124
<b>Hyperlipidemia</b>	582/8552 (6.8%)	550 /8552 (6.4%)	0.3293	0.0151
<b>Diabetes</b>	1629 /8552 (19.0%)	1575/8552 (18.4%)	0.2747	0.0162
<b>PVD</b>	67 /8552 (0.8%)	45/8552 (0.5%)	0.0376	0.0319
<b>Heart failure</b>	146 /8552 (1.7%)	143 //8552 (1.7%)	0.8570	0.0027
<b>Stroke</b>	762/8552 (8.9%)	751 /8552 (8.8%)	0.7671	0.0045
<b>COPD</b>	150/8552 (1.8%)	150 /8552 (1.8%)	1.0000	0.0000
<b>Chronic kidney disease</b>	92 /8552 (1.1%)	89/8552 (1.0%)	0.8206	0.0034
Hb (g/L)	137.32 ± 18.04	137.46 ± 18.20	0.5606	0.0076
Creatinine (mg/L)	37.40 ± 0.59	37.40 ± 1.13	0.9837	0.0003
Primary PCI	3778 /8552 (44.2%)	3858/8552 (42.3%)	0.1966	0.0188
P2Y12 inhibitors	7880/8552 (92.1%)	7912/8552 (92.5%)	0.3576	0.0141
GRACE risk score	161.33 ± 34.18	161.31 ± 34.22	0.9460	0.0008
<b>In-hospital mortality</b>	438/8552 (5.1%)	522/8552 (6.1%)	0.0045	

Data are presented as mean ± SD or frequencies; BMI: body mass index; ECG: electrocardiogram; SBP: systolic blood pressure; PVD: peripheral vascular disease; COPD: chronic obstructive pulmonary disease; Hb: hemoglobin; GRACE: the global registry of acute coronary events  
PVD: peripheral vascular disease; COPD: chronic obstructive pulmonary disease;



**Supplementary Table 3 Baseline characteristics between ex-smokers vs. non-smokers (After matching)**

Variable	Ex-smokers (N=4142)	Non-smokers (N=4142)	p value	Standardized difference
<b>Age</b>	66.28 ± 11.49	66.02 ± 12.19	0.2242	0.0222
<b>Male</b>	3887/4142 (93.8%)	3886 /4142(93.8%)	0.3173	0.0010
<b>BMI (Kg/m<sup>2</sup>)</b>	23.96 ± 2.83	24.02 ± 2.79	0.2900	0.0226
<b>ST-elevation on ECG</b>	2740 /4142 (66.2%)	2753 /4142 (66.5%)	0.4054	0.0175
SBP(mmHg)	129.62 ± 25.19	129.58 ± 25.12	0.9422	0.0016
HR (bpm)	79.66 ± 19.73	79.65 ± 18.75	0.9679	0.0009
<b>Heart failure on admission</b>	763 /4142 (18.4%)	775 /4142 (18.7%)	0.7158	0.0075
<b>Cardiac shock</b>	171/4142 (4.1%)	147/4142 (3.5%)	0.1701	0.0302
<b>Killip classification</b>			0.4505	0.0157
<b>I</b>	2868/4142 (69.2%)	2898/4142 (70.0%)		
<b>II</b>	767/4142(18.5%)	764 /4142(18.4%)		
<b>III</b>	301/4142(7.3%)	270/4142(6.5%)		
<b>IV</b>	206/4142(5.0%)	210 /4142(5.1%)		
<b>Comorbidities</b>				
<b>Hypertension</b>	2255/4142 (54.4%)	2223/4142 (53.7%)	0.4668	0.0155
<b>Hyperlipidemia</b>	339 /4142(8.2%)	309/4142 (7.5%)	0.2057	0.0270
<b>Diabetes</b>	892/4142 (21.5%)	881/4142 (21.3%)	0.7664	0.0065
<b>PVD</b>	46 /4142 (1.1%)	23/4142 (0.6%)	0.0050	0.0611
<b>Heart failure</b>	170 /4142 (4.1%)	147/4142 (3.5%)	0.1466	0.0289
<b>Stroke</b>	532 /4142 (12.8%)	532/4142 (12.8%)	1.0000	0.0000
<b>COPD</b>	143/4142 (3.5%)	124 /4142 (3.0%)	0.1294	0.0260
<b>Chronic kidney disease</b>	92 /4142 (2.2%)	89/4142 (2.1%)	0.8108	0.0050
Hb (g/L)	135.50 ± 19.39	135.48 ± 19.08	0.9618	0.0010
Creatinine (mg/L)	37.40 ± 0.47	37.40 ± 1.14	0.8868	0.0031
Primary PCI	1541/4142 (37.2%)	1575/4142 (38.0%)	0.4060	0.0169
P2Y12 inhibitors	3813/4142 (92.1%)	3842/4142 (92.8%)	0.2345	0.0264
GRACE risk score	170.68 ± 35.39	169.90 ± 36.56	0.2587	0.0215
<b>In-hospital mortality</b>	292/4142 (7.0%)	307 /4142 (7.4%)	0.5198	

Data are presented as mean ± SD or frequencies; BMI: body mass index; ECG: electrocardiogram; SBP: systolic blood pressure; PVD: peripheral vascular disease; COPD: chronic obstructive pulmonary disease; Hb: hemoglobin; GRACE: the global registry of acute coronary events  
PVD: peripheral vascular disease; COPD: chronic obstructive pulmonary disease;

STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation	Page No
<b>Title and abstract</b>	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	2
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
<b>Introduction</b>			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	2
Objectives	3	State specific objectives, including any prespecified hypotheses	3
<b>Methods</b>			
Study design	4	Present key elements of study design early in the paper	3
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	3, 4
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	4
		(b) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4-5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4-5
Bias	9	Describe any efforts to address potential sources of bias	3-4
Study size	10	Explain how the study size was arrived at	4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	5
		(b) Describe any methods used to examine subgroups and interactions	6
		(c) Explain how missing data were addressed	6
		(d) If applicable, explain how loss to follow-up was addressed	NA
		(e) Describe any sensitivity analyses	NA
<b>Results</b>			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	6
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6
		(b) Indicate number of participants with missing data for each variable of interest	6
		(c) Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	Report numbers of outcome events or summary measures over time	7

1	Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7
2			(b) Report category boundaries when continuous variables were categorized	NA
3			(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
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9	Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	6
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11	<b>Discussion</b>			
12				
13	Key results	18	Summarise key results with reference to study objectives	8
14	Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10
15				
16	Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9
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18				
19	Generalisability	21	Discuss the generalisability (external validity) of the study results	10
20				
21	<b>Other information</b>			
22	Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	11
23				
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\*Give information separately for exposed and unexposed groups.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at <http://www.strobe-statement.org>.

# BMJ Open

## Association between smoking and in-hospital mortality in patients with acute myocardial infarction: results from a prospective, multicenter, observational study in China

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2019-030252.R2
Article Type:	Research
Date Submitted by the Author:	29-Jul-2019
Complete List of Authors:	Song, Chenxi; Chinese Academy of Medical Sciences & Peking Union Medical College Fuwai Hospital, Cardiology Fu, Rui; Chinese Academy of Medical Sciences and Peking Union Medical College Fuwai Hospital, Cardiology Dou, Kefei; Chinese Academy of Medical Sciences and Peking Union Medical College Fuwai Hospital, Yang, Jingang; Fu Wai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, Coronary Heart Disease Center Xu, Haiyan; Fu Wai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, Coronary Heart Disease Center Gao, Xiaojin; Fu Wai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, Coronary Heart Disease Center Wang, Hao; Fu Wai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, Coronary Heart Disease Center Liu, Shuai; Fu Wai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, Coronary Heart Disease Center Fan, Xiaoxue; Fu Wai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, Coronary Heart Disease Center Yang, Yuejin; Fu Wai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, Coronary Heart Disease Center
<b>Primary Subject Heading</b>:	Cardiovascular medicine
Secondary Subject Heading:	Cardiovascular medicine
Keywords:	smoking, in-hospital mortality, acute myocardial infarction

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4 **Association between smoking and in-hospital mortality in**  
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8 **prospective, multicenter, observational study in China**  
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11 **Chenxi Song, MD<sup>1</sup>, Rui Fu, MD<sup>1</sup>, Kefei Dou, MD, PhD<sup>1</sup>, Jingang Yang, MD,**  
12 **PhD<sup>1</sup>, Haiyan Xu, MD, PhD<sup>1</sup>, Xiaojin Gao, MD, PhD<sup>1</sup>, Hao Wang, MD<sup>1</sup>, Shuai**  
13 **Liu, MD<sup>1</sup>, Xiaoxue Fan, PhD<sup>1</sup>, Yuejin Yang, MD, PhD<sup>1</sup>**  
14  
15  
16

17  
18  
19 <sup>1</sup> Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of  
20 Medical Sciences and Peking Union Medical College  
21  
22

23  
24  
25 The first two authors Chenxi Song and Rui Fu made equal contribution to this work.  
26  
27 Kefei Dou and Yuejin Yang contributed equally to the article and accept equal and  
28 full responsibility for the work as correspondence authors.  
29  
30  
31

32  
33 **Contact information**  
34

35 Chenxi Song 1933769555@qq.com  
36  
37 Rui Fu [fwfurui@163.com](mailto:fwfurui@163.com)  
38  
39 Kefei Dou [drdoukefei@126.com](mailto:drdoukefei@126.com)  
40  
41 Jingang Yang [yangjingang@mrbc-nccd.com](mailto:yangjingang@mrbc-nccd.com)  
42  
43 Haiyan Xu [xuhaiyan@fuwaihospital.org](mailto:xuhaiyan@fuwaihospital.org)  
44  
45 Xiaojin Gao [sophie\\_gao@sina.com](mailto:sophie_gao@sina.com)  
46  
47 Hao Wang [wanghao\\_fuwai@126.com](mailto:wanghao_fuwai@126.com)  
48  
49 Shuai Liu [liushuai851213@163.com](mailto:liushuai851213@163.com)  
50  
51 Xiaoxue Fan [fanxiaoxue@mrbc-nccd.com](mailto:fanxiaoxue@mrbc-nccd.com)  
52  
53 Yuejin Yang [yangyjfw@126.com](mailto:yangyjfw@126.com)  
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56 Affiliation information: Chenxi Song, Fuwai Hospital, Department of Cardiology,  
57 Chinese Academy of Medical Sciences and Peking Union Medical College  
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## ***Abstract***

**Introduction:** Smoking is a well-established risk factor for cardiovascular disease. However, the effect of smoking on in-hospital mortality in patients with acute myocardial infarction (AMI) who are managed by contemporary treatment is still unclear.

**Methods:** A cohort study was conducted using data from the China AMI registry between 2013 and 2016. Eligible patients were diagnosed with AMI in accordance with the third Universal Definition of Myocardial Infarction. Propensity score matching and multivariable logistic regression were used to control for confounders. Subgroup analysis was performed to examine whether the association between smoking and in-hospital mortality varies according to baseline characteristics.

**Results:** A total of 37,614 patients were included. Smokers were younger and more frequently men with fewer comorbidities than non-smokers. After propensity score matching and multivariable log regression analysis was performed, the difference in in-hospital mortality between current smokers versus non-smokers was reduced, but it was still significant (5.1% vs.6.1%,  $p=0.0045$ ; adjusted odds ratio: 0.78; 95% confidence interval: 0.69–0.88,  $p<0.001$ ). Among all subgroups, there was a trend toward lower in-hospital mortality in current smokers or ex-smokers compared with non-smokers.

**Conclusions:** Smoking is associated with lower in-hospital mortality in patients with AMI, even after multiple analyses to control for potential confounders. This “smoker’s paradox” cannot be fully explained by confounding alone.

## **Keywords:**

smoking; in-hospital mortality; acute myocardial infarction

## **Strengths and limitations of the study**

This study used data from a large-scale multicenter registry in a contemporary era of PCI.

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4 We used propensity score matching and the multivariable logistic regression model to  
5 adjust for confounders, which ensured the robustness of our conclusion.  
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7 The current study did not include data on patients who died before hospitalization,  
8 which may have caused index event bias (type of selection bias).  
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10 The current study did not adjust for unmeasured confounders.  
11

## 12 **INTRODUCTION**

13  
14 Smoking is a well-established risk factor of cardiovascular disease<sup>1,2</sup>. However, some  
15 previous studies have shown that smokers have a better outcome than do non-smokers  
16 following AMI. This phenomenon is referred to as “smoker’s paradox”. This  
17 phenomenon was first introduced in the 1970s, when Helmers found that smokers had  
18 a lower risk of mortality than did nonsmokers<sup>3</sup>. Some subsequent studies also showed  
19 smoker’s paradox in patients with acute coronary syndrome<sup>4</sup>. This paradox may be  
20 explained by differences in baseline characteristics between smokers and  
21 non-smokers<sup>5</sup>. Additionally, the anti-platelet response may differ according to  
22 smoking status because of the effect of smoking on pharmacodynamics of clopidogrel  
23 therapy<sup>6</sup>. Notably, most studies regarding smoker’s paradox were conducted in the era  
24 of thrombolysis, while the association between smoking and in-hospital mortality in  
25 patients who are treated with percutaneous intervention (PCI) remains controversial.  
26 Some studies have reported that the difference in in-hospital mortality was not  
27 significant between smokers and non-smokers after accounting for age and other  
28 baseline characteristics<sup>7-13</sup>. Other studies reported that smokers had a lower  
29 in-hospital mortality rate compared with non-smokers, even after adjustment for  
30 potential confounders (smoker’s paradox)<sup>14-18</sup>.  
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33 Examining the true effect of smoking on outcome among contemporary patients with  
34 AMI is important. On the one hand, the phenomenon of “smoking paradox” has a  
35 negative effect on quitting smoking in a public health perspective. On the other hand,  
36 if smoker’s paradox still exists in the contemporary era of PCI, the biochemical basis  
37 for this phenomenon should be investigated. This investigation may promote  
38 development of novel therapy for myocardial protection.  
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4 This study aimed to assess how smoking affects in-hospital mortality of patients  
5 receiving contemporary management of AMI.  
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## 9 10 **METHODS**

### 11 **Data source**

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13 A cohort study was conducted by using data from the China AMI (CAMI) registry  
14 between January 1, 2013 and January 31, 2016. A detailed description of the registry  
15 design was published previously<sup>19</sup>. Briefly, the CAMI registry was a prospective,  
16 multicenter, observational registry. The project included Chinese patients with AMI  
17 and data were collected on patients' characteristics, treatments, and outcomes. A total  
18 of 108 hospitals covering a broad geographic region participated in the project. This  
19 assured a good representation of all of the patients with AMI in China and reduced  
20 selection bias<sup>19</sup>. Our study was approved by the institutional review board central  
21 committee at Fuwai Hospital, NCCD of China (approval ID: 2012-431). Written  
22 informed consent was obtained from each patient who was included in the study. If  
23 the patient was not able to communicate, informed consent was obtained from a  
24 family member. The study protocol conforms to the ethical guidelines of the 1975  
25 Declaration of Helsinki. The CAMI registry was registered at [www.clinicaltrials.gov](http://www.clinicaltrials.gov)  
26 (registration number: NCT01874691).  
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### 41 **Study population**

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43 We included the study population from the CAMI registry. Eligible patients were  
44 diagnosed with AMI and within 7 days of ischemic symptoms. Diagnostic criteria of  
45 AMI were in accordance with the third Universal Definition of Myocardial  
46 Infarction<sup>20</sup>. We excluded patients who were aged <18 or >100 years, and those with  
47 missing or invalid data on sex, admission diagnosis, and smoking status.  
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53 Data were extracted by trained researchers using standard definitions to reduce  
54 measurement and reporting bias. These data included age, sex, height, weight, clinical  
55 presentation (symptoms, ST-segment elevation, anterior wall myocardial infarction  
56 [MI], blood pressure, heart rate, heart failure, cardiac shock, fatal arrhythmia, cardiac  
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4 arrest, and Killip classification), risk factors (hypertension, hyperlipidemia, diabetes),  
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6 comorbidities (heart failure, peripheral vascular disease, stroke, chronic kidney  
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8 disease, and chronic obstructive pulmonary disease [COPD]), medical history (family  
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10 history of premature coronary artery disease [CAD], prior angina or MI, prior  
11  
12 coronary intervention, prior coronary artery bypass grafting [CABG]), initial  
13  
14 reperfusion strategy (primary PCI, thrombolysis, and conservative therapy),  
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16 laboratory results (creatinine, hemoglobin, and left ventricular ejection fraction  
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18 [LVEF]) and in-hospital outcome.

### 19 **Patient and public involvement**

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21 We did not involve patients or the public in our work

### 22 **Definition of variables**

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24 All patients were divided into three groups according to smoking status. Current  
25  
26 smokers were defined as those who smoked within 1 month before registration.

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28 Ex-smokers were defined as those who quit smoking for at least 1 month.

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30 Non-smokers were defined as those who never smoked. Standard definitions of the  
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32 medical history and physical examination elements were well described in the  
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34 ACC/AHA Task Force on clinical Data Standards and the NCDR-ACTION-GWTG  
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36 element dictionary<sup>21-23</sup>. Electrocardiograms and echocardiograms were interpreted  
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38 locally.

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40 The primary endpoint was all-cause in-hospital mortality, which was defined as  
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42 all-cause death during hospitalization.

### 43 **Statistical analysis**

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45 Baseline continuous data are presented as mean±SD or median (25th–75th percentiles)  
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47 and were compared using one-way ANOVA. This was followed by the Bonferroni t  
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49 test with a corrected p value of 0.05/3. Categorical data are presented as counts and  
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51 frequencies and were compared using the  $\chi^2$  test. Propensity score (PS) matching was  
52  
53 used to control for baseline differences. We performed PS matching between current  
54  
55 smokers and non-smokers, and between ex-smokers and non-smokers. We used a  
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57 multivariable logistic regression model to estimate propensity scores, with smoking as  
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59 the dependent variable and the following factors as covariates: age, sex, body mass  
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4 index (BMI), systolic blood pressure, heart rate, admission diagnosis, cardiac arrest,  
5 chest pain, ST elevation, anterior wall MI, Killip classification, risk factor (medical  
6 history of diabetes, hypertension, hyperlipidemia, premature family CAD history,  
7 heart failure, renal failure, and COPD), medical history (previous angina, PCI, and  
8 CABG), creatinine levels, hemoglobin levels, Global Registry of Acute Coronary  
9 Events (GRACE) risk score, and primary PCI. These variables were chosen as  
10 covariates because the difference in these baseline characteristics reached statistical  
11 significance or these variables were previously reported to be associated with patients'  
12 outcome.

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21 Matching was performed using the greedy nearest matching algorithm and a 1:1  
22 fashion. The caliper width was equal to 0.01 of the standardized difference of the  
23 score. McNemar's and paired t-tests were used to compare continuous and categorical  
24 variables between the two groups after matching. For each variable in the PS model,  
25 we computed the standardized difference between the two groups, with a standardized  
26 difference less than 0.1 indicating good balance.

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33 The stepwise selection method was used to compare in-hospital mortality across the  
34 different groups. Baseline characteristics that significantly differed across the groups  
35 and those of clinical importance were included in the model. These variables were the  
36 same as those used for propensity matching. A p value <0.1 was used as the entry  
37 criterion and a p value <0.05 was used as the removal criterion. To determine whether  
38 the association between smoking and in-hospital mortality varied according to  
39 baseline patients' characteristics, we performed the same multivariable logistic  
40 analysis in subgroups that were stratified by age, sex, BMI, presence or absence of  
41 hypertension, diabetes, hyperlipidemia, heart failure, prior angina, MI or coronary  
42 intervention, and admission diagnosis. A two-sided p value <0.05 was considered  
43 significant. For the interaction test, a p value <0.1 was considered significant. For all  
44 variables included in our study, less than 2% of the data were missing. We used  
45 complete case analysis to deal with missing data<sup>24</sup>. Patients with missing data were  
46 excluded from analysis. We presented data as "counts/total numbers available  
47 (frequencies)" for categorical variables.

## RESULTS

### Baseline characteristics

From January 1, 2013 to January 31, 2016, a total of 41,590 continuous patients were registered in the CAMI registry. We excluded 118 patients aged <18 or >100 years, and those with missing or invalid data on sex (n=18), admission diagnosis (n=1237), and detailed smoking status (n=1543). The final cohort included 37,614 patients (Figure 1).

Baseline characteristics before matching are shown in Table 1. A total of 16,664 (44.3%) patients were current smokers, 843 (2.2%) quit smoking before or at 1 year, 3410 (9.1%) quit smoking after 1 year, and 16,697 (44.4%) were non-smokers. Current smokers were younger ( $57.99 \pm 11.81$  vs.  $66.59 \pm 11.82$  years) and had a higher BMI ( $24.39 \pm 2.87$  vs.  $23.98 \pm 2.95$  kg/m<sup>2</sup>) compared with non-smokers. The proportion of men (93.7% vs. 49.8%) and Killip class I (80.5% vs. 72.1%) was higher in current smokers compared with non-smokers. Compared with non-smokers, current smokers were less likely to have hypertension, diabetes, heart failure, stroke, or chronic kidney disease, but more likely to have hyperlipidemia. Among ex-smokers, the proportions of male sex, hyperlipidemia, heart failure, peripheral vascular disease (PVD), and stroke were higher than those of current smokers. Ex-smokers also showed a trend towards old age and a low proportion of hypertension and diabetes than did current smokers, but these differences were less significant compared with the differences between current and non-smokers.

### In-hospital outcomes

Overall, 2370 patients died before discharge. There were 614 (3.7%) deaths in the current smoker group, 306 (7.2%) deaths in the ex-smoker group, and 1450 (8.7%) deaths in the non-smoker group. Causes of mortality are shown in supplementary table 1. The unadjusted odds ratio (OR) for in-hospital mortality was 0.4 (95% confidence interval [CI]: 0.37–0.44,  $p < 0.0001$ ) in current smokers and 0.82 (95% CI:

0.72–0.93,  $p=0.0018$ ) in ex-smokers relative to non-smokers (Table 2). After adjustment for potential confounders, current smoking status was significantly associated with lower in-hospital mortality relative to non-smokers (adjusted OR: 0.78, 95% CI: 0.69–0.88,  $p<0.001$ ) (Table 2). No difference in in-hospital mortality was detected between ex- and non-smokers (OR: 0.89, 95% CI: 0.77–1.04,  $p=0.1443$ ).

### **Propensity score matching**

Before PS matching, there were differences in almost all baseline variables among the different groups (Table 1). To control for potential confounding, we matched 8552 current smokers with 8552 non-smokers, as well as 4142 ex-smokers and 4142 non-smokers (Supplementary Table 2). The standardized differences were less than 10.0% for all variables after matching, which indicated a good match between two groups. After PS matching, current smokers still had lower in-hospital mortality than did non-smokers (5.1% vs. 6.1%,  $p=0.0045$ ), but the difference in in-hospital mortality was not significant between ex-smokers and non-smokers (7.0% vs. 7.4%,  $p=0.5198$ ) (Supplementary Table 3).

### **Subgroup analysis**

Subgroup analysis indicated significant interactions between smoking status and age ( $p_{\text{interaction}}: 0.0986$ ), sex ( $p_{\text{interaction}}: 0.0163$ ), LVEF ( $p_{\text{interaction}}: 0.0149$ ), previous MI ( $p_{\text{interaction}}: 0.0557$ ), and previous heart failure ( $p_{\text{interaction}}: 0.0086$ ) for in-hospital mortality (Table 3). However, there was a trend toward lower in-hospital mortality in the current smoker or ex-smoker group compared with the non-smoker group.

## **DISCUSSION**

Our study used data from the CAMI registry, which is the largest contemporary registry of patients with AMI in East Asia. Our major finding was that in patients with AMI, current-smokers had lower in-hospital mortality than did non-smokers in the whole population and in almost all subgroups, after adjusting for potential confounders by using PS matching.

### **Comparison with previous studies**

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4 Most previous studies were conducted in the thrombolytic era and we only identified  
5 four studies that enrolled patients in the current primary PCI era<sup>13,18,25,26</sup>. Of these four  
6 studies, three studies used multivariate regression analysis to control for confounders.  
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8 Our study results are consistent with those from another large-scale study<sup>18</sup>. This  
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10 previous study also showed that among patients with ST elevation myocardial  
11 infarction (STEMI) who received primary PCI, smokers (including current and  
12 ex-smokers) had a lower adjusted in-hospital mortality risk than did non-smokers. In  
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14 our study, we further separated current and ex-smokers, and used PS matching to  
15 comprehensively control for potential confounders. Several mechanisms have been  
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17 proposed to explain this paradox phenomenon.  
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21 First, some studies showed that a suppressive effect of clopidogrel on platelets was  
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23 greater in smokers than in non-smokers<sup>27-29</sup>. A potential explanation for this finding is  
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25 that smoking can enhance *in vivo* bioactivation of clopidogrel via increasing induction  
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27 of cytochrome P450 (CYP1A2 and CYP2B6) and increased active metabolite  
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29 concentrations of clopidogrel<sup>30,31</sup>. Therefore, smokers may respond better to  
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31 clopidogrel therapy and consequently have a lower in-hospital mortality rate than  
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33 non-smokers. Second, smoking was unexpectedly associated with a lower risk of  
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35 adverse left ventricular remodeling post-infarction. Rolf Symons et al performed  
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37 cardiac magnetic resonance imaging at 4 days and 4 months after MI. They found that  
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39 smokers had an improved LVEF, which was attributable to a decrease in the  
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41 end-diastolic volume index, but not an increase in the systolic volume index<sup>32</sup>.

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43 However, our results are not consistent with two studies, which found an absence of  
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45 the smoker paradox after baseline risk adjustment<sup>13,26</sup>. This difference may be related  
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47 to selection of the study population and sample size. One previous study enrolled  
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49 patients with symptomatic CAD, including those who presented with stable or  
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51 unstable angina<sup>9</sup>, while we included patients with AMI. Patients with stable angina  
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53 represent a relatively lower risk group. Therefore, enrollment of this patient subset  
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55 may affect the association between smoking and mortality. The other study had a  
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57 small sample size (n=382), and it may not have had sufficient statistical power to  
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59 detect a difference in mortality between smokers and non-smokers.  
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## Interpretation of our results

Our results should be interpreted with caution. Although we adjusted for many common confounders, our study was still subject to selection bias as discussed below in the Limitations subsection. Our results should not be interpreted as encouraging patients to smoke. Smoking is well established as an independent risk factor for mortality and recurrent MI<sup>33</sup>, as well as for subacute stent thrombosis<sup>34</sup> in the long-term, and patients with coronary heart disease can benefit from cessation of smoking<sup>35</sup>. Therefore, we still recommend that patients stop smoking. Our results indicated potential mechanisms underlying the protective effect of smoking. Future studies should investigate novel therapies to protect the myocardium by targeting the relevant pathways. Smoking might lead to a chronic ischemic state (ischemic preconditioning)<sup>36</sup>; therefore, smokers might have better tolerance for an acute ischemic event, such as a heart attack. The phenomenon could be investigated by examining whether pre-conditioning therapy or a brief period of reversible ischemia can protect the myocardium and improve outcome.

Our subgroup analysis showed a significant interaction between smoking status and age, sex, LVEF, previous MI, and previous heart failure. However, currently, we cannot reach the conclusion that these baseline characteristics had a significant effect on the relationship between smoking and in-hospital mortality. This is because there was a similar trend among all subgroups that current smokers and ex-smokers had a lower in-hospital mortality risk compared with non-smokers. A significant p value may be attributed to a different OR value between subgroups of smokers and non-smokers, as well as a large sample size of some of the subgroups.

## Limitations

Our study may have been subject to selection bias. The CAMI registry did not collect data on patients who died before hospitalization. Failing to account for pre-hospital deaths may have led to selection bias. The distribution of risk factors was significantly different between smokers and non-smokers. Although we adjusted for known and measured variables, there are likely to be other unmeasured variables leading to selection bias. The CAMI registry was a multicenter, large-scale study that involved

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4 more than 100 hospitals. Although a standardized data collection procedure was  
5 emphasized, the accuracy of data still greatly depends on the expertise of local  
6 investigators. The CAMI registry did not collect detailed data regarding smoking  
7 status. Smoking status might be modified after onset of MI. However, we asked the  
8 patients about their smoking status before onset of AMI and all patients were enrolled  
9 within 7 days of symptom onset. We only assessed the association between smoking  
10 and short-term outcome. Future studies are required to investigate this association in  
11 the long-term.  
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19 **Conclusions:**

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21 Our study showed that the in-hospital mortality rate was lower in smokers compared  
22 with non-smokers in a large-scale, contemporary cohort representing patients with  
23 AMI in China. Our findings indicate that future studies should be performed to further  
24 explore the potential biological mechanisms that may explain this phenomenon.  
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31 **Declaration of interests:**

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33 We confirm that there are no known conflicts of interest associated with this  
34 publication.  
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39 **Author contributions:**

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41 Chenxi Song and Rui fu were major contributors in writing the manuscript. Kefei Dou  
42 and Yuejin Yang contributed substantially to the conception and design of the study.  
43 Jingang Yang, Haiyan Xu, Xiaojin Gao, Hao Wang, Shuai Liu revised it critically for  
44 important intellectual content. Xiaoxue Fan made contribution to analysis and  
45 interpretation of data.  
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52 **Funding statement:**

53  
54 This work was supported by CAMS Innovation Fund for Medical  
55 Sciences (CIFMS) (2016-I2M-1-009), the Twelfth Five-Year Planning Project of the  
56 Scientific and Technological Department of China (2011BAI11B02), and 2014  
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4 Special fund for scientific research in the public interest by National Health and  
5 Family Planning Commission of the People's Republic of China (No. 201402001).  
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9  
10 **Acknowledgement:**

11 We are very grateful to the TIMI Study Group and the Duke Clinical Research  
12 Institute for their contributions in the design, conduct, and data analyses of CAMI  
13 registry. We also want to thank all the investigators and coordinators for their great  
14 work and active participation. We thank Ellen Knapp, PhD, from Liwen Bianji, Edanz  
15 Group China (www.liwenbianji.cn/ac), for editing the English text of a draft of this  
16 manuscript. We thank Yang Wang and Wei Li for statistical analysis.  
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25 **Data availability statement**

26 Data are available from corresponding author on reasonable request.  
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8 **Figure and table legends:**

9 Table 1 Baseline characteristics according to smoking status (Before matching)

10 Table 2 Association between Smoking and In-hospital Mortality

11 Table 3 Association between smoking and in-hospital mortality according to baseline  
12 characteristics

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15 Figure legend: Figure 1 Study flow chart. From January, 2013 to January, 2016,  
16 41590 continuous patients were registered in CAMI registry. Those with age <18 or  
17 >100 years old (n=1178), with missing or invalid data on gender (n=18) , admission  
18 diagnosis (n=1237) and detailed smoking status (n=1543) were excluded. The final  
19 cohort included 37614 patients  
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**Table 1 Baseline characteristics according to smoking status (Before matching)**

Variable	Current Smokers (N=16664)	Ex-smokers (N=4253)	Non-smokers (N=16697)	p value
Age	57.99±11.81	66.49±11.50	66.59 ±11.82	<0.0001
Male	15616/16664 (93.7%)	3997/4253 (94.0%)	8317/16697 (49.8%)	<0.0001
BMI (Kg/m <sup>2</sup> )	24.39±2.87	23.95±2.84	23.98±2.95	<0.0001
ST-elevation on ECG	12044/16330 (74.3%)	2725/4185 (65.7%)	10822/16374 (66.7%)	0.2338
SBP(mmHg)	127.82 ±24.69	129.71 ±25.17	130.58 ±25.97	<0.0001
Heart rate (bpm)	76.74 ±17.40	79.85 ±19.82	79.47 ±18.89	<0.0001
Heart failure on admission	1851/16608 (11.1%)	817 /4227 (19.2%)	3016/16620 (18.1%)	0.0781
Cardiac shock	512/16597 (3.1%)	175/4227 (4.1%)	658/16614 (3.9%)	0.5962
Killip classification				<0.0001
I	13332/16577 (80.4%)	2877 /4215 (68.3%)	11906 /16568 (71.9%)	
II	2272 /16577 (13.7%)	799/4215 (19.0%)	2892 /16568 (17.5%)	
III	472/16577 (2.8%)	324 /4215 (7.7%)	951/16568 (5.7%)	
IV	501/16577 (3.0%)	215 /4215 (5.1%)	819 /16568 (4.9%)	
Comorbidities				
Hypertension	7288/16653 (43.8%)	2328/4251(54.8%)	9434/16693 (56.5%)	0.0401
Hyperlipidemia	1329/16640 (8.0%)	367 /4247 (8.6%)	1020 /16679 (6.1%)	<0.0001

<b>Diabetes</b>	2451/ 16635 (14.7%)	924 /4242 (21.8%)	3893 /16672 (23.4%)	0.0295
<b>PVD</b>	100 /16611 (0.6%)	49 / 4234 (1.2%)	115 /16642 (0.7%)	0.0035
<b>Heart failure</b>	177 /16628 (1.1%)	199 /4235 (4.7%)	528 /16638 (3.2%)	<0.0001
<b>Stroke</b>	1176 /16616 (7.1%)	570 /4237 (13.5%)	1666 /16648 (10.0%)	<0.0001
<b>COPD</b>	277 /16664 (1.7%)	191 /4253 (4.5%)	277/16697 (1.7%)	<0.0001
<b>Chronic kidney disease</b>	121 /16588 (0.7%)	103 /4222 (2.4%)	257 /16612 (1.5%)	0.0001
<b>Smoking duration (year)</b>	30.38±11.89	26.86 ±11.99	NA	<0.0001
<b>Number of cigarettes/day</b>	21.23 ±11.10	19.13 ±10.93	NA	<0.0001
<b>Hb (g/L)</b>	142.15 ±17.42	135.38 ±19.39	130.18 ±19.43	<0.0001
<b>Creatinine (mg/L)</b>	37.40 ±0.69	37.40 ±0.46	37.42 ±2.04	0.1842
<b>Primary PCI</b>	8499/16544 (51.4%)	1566/4224 (37.1%)	6369/16579 (38.4%)	0.1084
<b>P2Y12 inhibitors</b>	16086/16458 (97.7%)	4030/4186 (96.3%)	15837/16446 (96.3%)	0.9423
<b>GRACE risk score</b>	151.43 ±33.02	171.34 ±35.63	169.61 ±35.89	<0.0001
<b>In-hospital mortality</b>	614/16664 (3.7%)	306/4325 (7.2%)	1450/16679 (8.7%)	0.0015

Data are presented as mean±SD or frequencies; BMI: body mass index; ECG: electrocardiogram; SBP: systolic blood pressure; PVD: peripheral vascular disease; COPD: chronic obstructive pulmonary disease; Hb: hemoglobin; GRACE: the global registry of acute coronary events

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**Table 2 Association between Smoking and In-hospital Mortality**

Smoking status	OR (95% CI)			<i>p</i> value <sup>b</sup>
	Unadjusted	Adjusted <sup>a</sup>	PS matching	
<b>Current smokers vs non-smokers</b>	0.40 (0.37, 0.44)	0.78 (0.69, 0.88)	0.80 (0.69, 0.92)	<.0001
<b>Ex- smokers vs non-smokers</b>	0.82 (0.72, 0.93)	0.89 (0.77, 1.04)	1.03 (1.02, 1.04)	0.1443

a: adjusted for age, gender, BMI, systolic blood pressure, heart rate, admission diagnosis, cardiac arrest, chest pain, ST elevation, anterior wall MI, killip classification, risk factor (medical history of diabetes, hypertension, hyperlipidemia, premature family CAD history, heart failure, renal failure, COPD), medical history (previous angina, PCI, CABG), creatinine level, hemoglobin level, grace risk score, primary PCI. The number of patients included in the adjusted model was 37614.

b: adjusted *p* value

**Table 3 Association between smoking and in-hospital mortality according to baseline characteristics**

<b>Baseline characteristics</b>	<b>Current smoker</b>	<b>Ex-smoker</b>	<b>Non-smoker</b>	<b>P<sub>interaction</sub></b>
Age $\geq$ 55 years	0.78 (0.69, 0.89)	0.90 (0.77, 1.05)	reference	0.0986
Age $<$ 55 years	0.72 (0.53, 0.99)	0.85 (0.48, 1.49)	reference	
Male	0.78 (0.68, 0.89)	0.94 (0.80, 1.10)	reference	0.0163
Female	0.75 (0.58, 0.98)	0.45 (0.26, 0.77)	reference	
BMI $\geq$ 24 kg/m <sup>2</sup>	0.80 (0.67, 0.94)	0.89 (0.71, 1.12)	reference	0.2063
BMI $<$ 24 kg/m <sup>2</sup>	0.74 (0.63, 0.88)	0.89 (0.73, 1.10)	reference	
LVEF $\geq$ 50%	0.77 (0.67, 0.88)	0.98 (0.82, 1.16)	reference	0.0149
LVEF $<$ 50%	0.87 (0.68, 1.11)	0.74 (0.54, 1.01)	reference	
Hypertension-Yes	0.85 (0.72, 1.00)	0.96 (0.78, 1.17)	reference	0.4556

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4	Hypertension-No	0.70 (0.59, 0.83)	0.80 (0.64, 1.01)	reference	
5	Previous angina-Yes	0.84 (0.65, 1.07)	0.83 (0.62, 1.12)	reference	0.1833
6	Previous angina-No	0.76 (0.66, 0.87)	0.92 (0.78, 1.10)	reference	
7	Previous MI-Yes	0.67 (0.47, 0.97)	0.67 (0.45, 1.00)	reference	0.0557
8	Previous MI-No	0.77 (0.68, 0.87)	0.91 (0.78, 1.07)	reference	
9	Previous PCI-Yes	0.95 (0.44, 2.04)	1.23 (0.56, 2.72)	reference	0.7975
10	Previous PCI-No	0.78 (0.69, 0.88)	0.89 (0.76, 1.04)	reference	
11	Previous HF-Yes	0.96 (0.57, 1.60)	0.85 (0.53, 1.37)	reference	0.0086
12	Previous HF-No	0.77 (0.68, 0.87)	0.88 (0.76, 1.03)	reference	
13	Diabetes-Yes	0.78 (0.60, 1.02)	0.86 (0.63, 1.18)	reference	0.4065
14	Diabetes-No	0.77 (0.67, 0.88)	0.90 (0.76, 1.07)	reference	
15	Hyperlipidemia -Yes	0.75 (0.45, 1.24)	1.16 (0.66, 2.03)	reference	0.1239
16	Hyperlipidemia -No	0.77 (0.68, 0.87)	0.87 (0.74, 1.02)	reference	
17	Diagnosis of STEMI	0.81 (0.71, 0.93)	0.93 (0.78, 1.11)	reference	0.9700
18	Diagnosis of NSTEMI	0.61 (0.48, 0.78)	0.71 (0.54, 0.92)	reference	

adjusted for age, gender, BMI, systolic blood pressure, heart rate, admission diagnosis, cardiac arrest, chest pain, ST elevation, anterior wall MI, killip classification, risk factor (medical history of diabetes, hypertension, hyperlipidemia, premature family CAD history, heart failure ,renal failure, COPD), medical history (previous angina, PCI, CABG), creatinine level, hemoglobin level, grace risk score, primary PCI. BMI: body mass index; LVEF: left ventricular ejection fraction; MI: myocardial infarction; PCI: percutaneous coronary intervention; HF: heart failure;

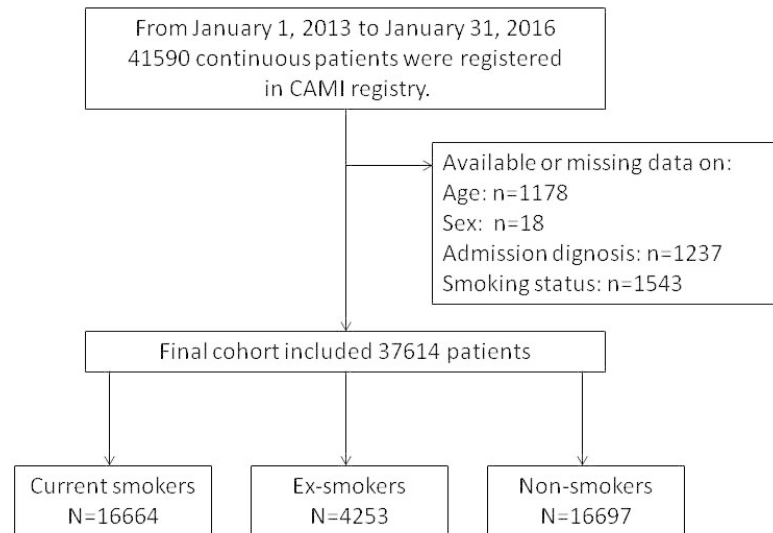


Figure 1 Study flow chart. From January, 2013 to January, 2016, 41590 continuous patients were registered in CAMI registry. Those with age <18 or >100 years old (n=1178), with missing or invalid data on gender (n=18), admission diagnosis (n=1237) and detailed smoking status (n=1543) were excluded. The final cohort included 37614 patients

254x190mm (96 x 96 DPI)

Supplementary Table 1 Causes of mortality according to smoking status

Variable	Current Smokers (N=16664)	Ex-smokers (N=4253)	Non-smokers (N=16697)	p value
Sudden cardiac death	202/16664 (1.2%)	107/4253 (2.5%)	519/16697 (3.1%)	0.0387
Cardiac shock	157/16664 (0.9%)	85/4253 (2.0%)	375/16697 (2.2%)	0.3203
Heart failure	121/16664 (0.7%)	65/4253 (1.5%)	291/16697 (1.7%)	0.3277
Intracerebral hemorrhage	4/16664 (0.0%)	1/4253 (0%)	3/16697 (0%)	0.8199
Lung infection	15/16664 (0.1%)	10/4253 (0.2%)	26/16697 (0.2%)	0.2833
Ischemic stroke	3/16664 (0.0%)	2/4253 (0%)	7/16697 (0.0%)	0.8873
Major bleeding	3/16664 (0.0%)	0/4253 (0%)	6/16697 (0.0%)	0.0989
Others	25/16664 (0.2%)	9/4253 (0.2%)	47/16697 (0.3%)	0.4176



**Supplementary Table 2 Baseline characteristics between current smokers vs. non-smokers  
(After matching)**

Variable	Current Smokers (N=8552)	Non-smokers (N=8552)	p value	Standardized difference
<b>Age</b>	62.80 ± 11.53	62.84 ± 12.04	0.6983	0.0035
<b>Male</b>	1048/8552 (87.7%)	7485/8552 (87.5%)	0.0995	0.0067
<b>BMI (Kg/m<sup>2</sup>)</b>	24.18 ± 2.88	24.17 ± 2.79	0.7580	0.0047
<b>ST-elevation on ECG</b>	71.1%	71.5%	0.5830	0.0083
SBP(mmHg)	129.01 ± 25.75	128.90 ± 24.68	0.7767	0.0043
Heart rate(bpm)	77.88 ± 18.55	77.61 ± 17.40	0.3279	0.0147
<b>Heart failure on admission</b>	1208 ( 14.1%)	1144 (13.4%)	0.1448	0.0217
<b>Cardiac shock</b>	297 (3.5%)	285 (3.3%)	0.6165	0.0077
<b>Killip classification</b>			0.6823	0.0080
<b>I</b>	6564/8552 (76.8%)	6593/8552 (77.1%)		
<b>II</b>	1312/8552 (15.3%)	1301 /8552 (15.2%)		
<b>III</b>	341 /8552 (4.0%)	330/8552 (3.9%)		
<b>IV</b>	335 /8552 (3.9%)	328 /8552 (3.8%)		
<b>Comorbidities</b>				
<b>Hypertension</b>	4309/8552 (50.4%)	4256 /8552 (49.8%)	0.4066	0.0124
<b>Hyperlipidemia</b>	582/8552 (6.8%)	550 /8552 (6.4%)	0.3293	0.0151
<b>Diabetes</b>	1629 /8552 (19.0%)	1575/8552 (18.4%)	0.2747	0.0162
<b>PVD</b>	67 /8552 (0.8%)	45/8552 (0.5%)	0.0376	0.0319
<b>Heart failure</b>	146 /8552 (1.7%)	143 //8552 (1.7%)	0.8570	0.0027
<b>Stroke</b>	762/8552 (8.9%)	751 /8552 (8.8%)	0.7671	0.0045
<b>COPD</b>	150/8552 (1.8%)	150 /8552 (1.8%)	1.0000	0.0000
<b>Chronic kidney disease</b>	92 /8552 (1.1%)	89/8552 (1.0%)	0.8206	0.0034
Hb (g/L)	137.32 ± 18.04	137.46 ± 18.20	0.5606	0.0076
Creatinine (mg/L)	37.40 ± 0.59	37.40 ± 1.13	0.9837	0.0003
Primary PCI	3778 /8552 (44.2%)	3858/8552 (42.3%)	0.1966	0.0188
P2Y12 inhibitors	7880/8552 (92.1%)	7912/8552 (92.5%)	0.3576	0.0141
GRACE risk score	161.33 ± 34.18	161.31 ± 34.22	0.9460	0.0008
<b>In-hospital mortality</b>	438/8552 (5.1%)	522/8552 (6.1%)	0.0045	

Data are presented as mean ± SD or frequencies; BMI: body mass index; ECG: electrocardiogram; SBP: systolic blood pressure; PVD: peripheral vascular disease; COPD: chronic obstructive pulmonary disease; Hb: hemoglobin; GRACE: the global registry of acute coronary events  
PVD: peripheral vascular disease; COPD: chronic obstructive pulmonary disease;

**Supplementary Table 3 Baseline characteristics between ex-smokers vs. non-smokers (After matching)**

Variable	Ex-smokers (N=4142)	Non-smokers (N=4142)	p value	Standardized difference
<b>Age</b>	66.28 ± 11.49	66.02 ± 12.19	0.2242	0.0222
<b>Male</b>	3887/4142 (93.8%)	3886 /4142(93.8%)	0.3173	0.0010
<b>BMI (Kg/m<sup>2</sup>)</b>	23.96 ± 2.83	24.02 ± 2.79	0.2900	0.0226
<b>ST-elevation on ECG</b>	2740 /4142 (66.2%)	2753 /4142 (66.5%)	0.4054	0.0175
SBP(mmHg)	129.62 ± 25.19	129.58 ± 25.12	0.9422	0.0016
HR (bpm)	79.66 ± 19.73	79.65 ± 18.75	0.9679	0.0009
<b>Heart failure on admission</b>	763 /4142 (18.4%)	775 /4142 (18.7%)	0.7158	0.0075
<b>Cardiac shock</b>	171/4142 (4.1%)	147/4142 (3.5%)	0.1701	0.0302
<b>Killip classification</b>			0.4505	0.0157
<b>I</b>	2868/4142 (69.2%)	2898/4142 (70.0%)		
<b>II</b>	767/4142(18.5%)	764 /4142(18.4%)		
<b>III</b>	301/4142(7.3%)	270/4142(6.5%)		
<b>IV</b>	206/4142(5.0%)	210 /4142(5.1%)		
<b>Comorbidities</b>				
<b>Hypertension</b>	2255/4142 (54.4%)	2223/4142 (53.7%)	0.4668	0.0155
<b>Hyperlipidemia</b>	339 /4142(8.2%)	309/4142 (7.5%)	0.2057	0.0270
<b>Diabetes</b>	892/4142 (21.5%)	881/4142 (21.3%)	0.7664	0.0065
<b>PVD</b>	46 /4142 (1.1%)	23/4142 (0.6%)	0.0050	0.0611
<b>Heart failure</b>	170 /4142 (4.1%)	147/4142 (3.5%)	0.1466	0.0289
<b>Stroke</b>	532 /4142 (12.8%)	532/4142 (12.8%)	1.0000	0.0000
<b>COPD</b>	143/4142 (3.5%)	124 /4142 (3.0%)	0.1294	0.0260
<b>Chronic kidney disease</b>	92 /4142 (2.2%)	89/4142 (2.1%)	0.8108	0.0050
Hb (g/L)	135.50 ± 19.39	135.48 ± 19.08	0.9618	0.0010
Creatinine (mg/L)	37.40 ± 0.47	37.40 ± 1.14	0.8868	0.0031
Primary PCI	1541/4142 (37.2%)	1575/4142 (38.0%)	0.4060	0.0169
P2Y12 inhibitors	3813/4142 (92.1%)	3842/4142 (92.8%)	0.2345	0.0264
GRACE risk score	170.68 ± 35.39	169.90 ± 36.56	0.2587	0.0215
<b>In-hospital mortality</b>	292/4142 (7.0%)	307 /4142 (7.4%)	0.5198	

Data are presented as mean ± SD or frequencies; BMI: body mass index; ECG: electrocardiogram; SBP: systolic blood pressure; PVD: peripheral vascular disease; COPD: chronic obstructive pulmonary disease; Hb: hemoglobin; GRACE: the global registry of acute coronary events  
PVD: peripheral vascular disease; COPD: chronic obstructive pulmonary disease;

STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation	Page No
<b>Title and abstract</b>	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	2 2
<b>Introduction</b>			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	2
Objectives	3	State specific objectives, including any prespecified hypotheses	3
<b>Methods</b>			
Study design	4	Present key elements of study design early in the paper	3
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	3, 4
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (b) For matched studies, give matching criteria and number of exposed and unexposed	4 NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4-5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4-5
Bias	9	Describe any efforts to address potential sources of bias	3-4
Study size	10	Explain how the study size was arrived at	4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) If applicable, explain how loss to follow-up was addressed (e) Describe any sensitivity analyses	5 6 6 NA NA
<b>Results</b>			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	6 NA 6
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	6 6 NA
Outcome data	15*	Report numbers of outcome events or summary measures over time	7

1	Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7
2			(b) Report category boundaries when continuous variables were categorized	NA
3			(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
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9	Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	6
10				
11	<b>Discussion</b>			
12				
13	Key results	18	Summarise key results with reference to study objectives	8
14	Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10
15				
16	Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9
17				
18				
19	Generalisability	21	Discuss the generalisability (external validity) of the study results	10
20				
21	<b>Other information</b>			
22	Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	11
23				
24				

\*Give information separately for exposed and unexposed groups.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at <http://www.strobe-statement.org>.