**The role of diabetes mellitus as an effect-modifier of the association between smoking cessation and its clinical prognoses: an observational cohort study**

Yang Wanga, MSc, Lap Ah Tseb, MD, PhD, Guangwei Lic, MD, Lu Yina, PhD, Tao Chend, PhD, Yanyan Zhaoa, MSc, Bo Xuc, MBBS, Ying Xiane, MD, PhD, Wei Lia, PhD

a Medical Research & Biometrics Center, National Center for Cardiovascular Diseases, Fu Wai Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

b JC School of Public Health and Primary Care, the Chinese University of Hong Kong, Hong Kong, China

c Fu Wai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

d Tropical Clinical Trials Unit, Department of Clinical Sciences, Liverpool School of Tropic Medicine, Liverpool, UK

e Duke Clinical Research Institute, Durham, North Carolina, USA

**Running title:**

Interaction between DM and smoking cessation

**Corresponding author:**

Prof. Wei Li

Medical Research & Biometrics Center, National Center for Cardiovascular Diseases, Room 101, Block A, Feng Cun Xi Li, Yongding Zhen, Mentougou District, Beijing, China, 102300

Telephone: +86 10 60866499; Fax: +86 10 60866513;

E-mail: liwei@mrbc-nccd.com

**Author contribution**

All authors contributed to: (1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, and, (3) final approval of the version to be published.

**Abstract**

The smoker’s paradox refers to an increased risk of adverse clinical outcomes after smoking cessation in patients with coronary artery disease. The mechanisms involved are controversial. The present study evaluated the effect of delay in smoking cessation on clinical outcomes among patients after percutaneous coronary intervention (PCI) stratified by diabetes mellitus (DM). Patients included in this study came from an established Fu Wai hospital PCI cohort. Smoking behavior was recorded; clinical endpoints included all-cause mortality and repeat revascularization. The analyses were based on 8,489 smokers who underwent PCI. Patients with and without DM were examined separately. Multivariable model analysis suggested that smoking cessation was associated with significant lower all-cause mortality both for non-DM and DM patients. The smoking paradox was observed for revascularization. However, the increased risk of repeat revascularization correlated with quitting time among non-DM patients only, especially if they stopped smoking late (>90 days) after their index procedure (adjusted HR, 3.40; 95% CI, 2.45-4.72). In conclusion, smoking cessation is associated with a lower mortality rate for PCI patients. However, the relative benefit on repeated revascularization was only observed among non-DM patients if they quit smoking early.

**Key words:** smoking cessation, diabetes mellitus, effect modifier, percutaneous coronary intervention

**Data Availability**

The individual level data used to support the findings of this study are restricted by the National Center for Cardiovascular Diseases (NCCD) and Fuwai hospital in order to protect patient privacy. Data are available [contact Prof. Wei Li, liwei@mrbc-nccd.com, +86 10 60866499] for researchers who meet the criteria for access to confidential data.

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**Introduction**

Smoking cessation is a modifiable lifestyle factor associated with better clinical outcomes in patients undergoing coronary revascularization.1-4 However, lower adverse outcomes among smokers after percutaneous coronary intervention (PCI), the “smoker’s paradox”, have also been reported.3,5,6,7 This phenomenon is more likely attributed to residual confounding.8,9 Further, the time point of quitting especially during the peri-procedure period (e.g. the delay on smoking cessation when the date of index procedure is fixed) may play an important role but relevant investigations are rare.

The patient internal environment changes with smoking cessation.10 Evidence showed that insulin resistance is elevated when smoking induced nicotine concentration increases.11 Peri-procedure smoking cessation overlaps with the endothelial repair process in the acute/sub-acute stage after PCI. The impacts maybe varied among patient with diabetes (DM) or not, because DM is an independent prognostic factor in secondary prevention of coronary artery disease (CAD).1,12,13 DM may be a modifier of the relationship between smoking cessation and clinical outcomes.

The aims of the present study were to examine the prognostic effect of smoking cessation according to DM status and to test the potential interaction between the time lag of quitting smoking and DM among patients who underwent PCI.

**Methods**

***Study Population***

The study was based on an observational cohort consisted of 22,743 consecutive PCI patients with or without DM. The study population was part of the Fu Wai Hospital coronary heart disease registry.3 After excluding nonsmokers and former smokers, 8,489 patients were included in the present analysis. Baseline information was collected from the standardized electronic data capture system included demographics, medical history, angiography characteristics and PCI-related variables. The requirement on minimum follow-up time was 1 year for this study and response rate was 90.4%. In order to collect detailed information regarding smoking behavior changes, a group of trained investigators contacted and interviewed each enrolled patient during the follow-up period. To assure the reliability of the data collection process, a study investigation brochure, case report form and step-by-step training material were used. The protocol was approved by the ethics committee and inform consent had been obtained from each participant.

The quitters were defined as participants who permanently quit smoking due to their index PCI and maintained abstinence after the procedure until the end of study. If the patients did not quit smoking or intermittently smoked during the follow-up period, they were categorized as smokers. If the patient quit smoke after an event during the follow-up, the changes on his/her smoking status were not counted (e.g. if a patient quit smoking due to re-occurrence of adverse cardiac event, this subject was categorized as persistent smoker).

According to our hypothesis, the quitters were divided into 5 subgroups according to the time point of their smoking cessation. Firstly, the time window (difference between quitting and index procedure) was calculated by: “date of permanently quitting smoking” minus “date of index PCI procedure”. Then, we specified the subgroups (based on the calculated time lag) as follows: -30 days to 0 day (no delay), 1 to 7 days (mild delay), 8 to 30 days (moderate delay), 31 to 90 days (severe delay) or >90 days (late). Each quitter was assigned to 1 of the 5 time intervals (subgroups), respectively. The persistent smokers were used as the reference group for all comparisons. The credibility of reported smoking behavior changes had been validated by an extra 5% random re-sampling process. The reliability of key exposure information was confirmed by the consistency comparison between 2 independent interviews (Kappa coefficient range 0.93 to 0.97).

***Study Endpoints***

The primary outcomes of the current study were all-cause mortality and any repeated revascularization separately. In order to avoid the competing risk induced by death (if the patient dies before restenosis or disease progression), the composite endpoint of all-cause mortality and repeated revascularization was also analyzed. The cause of death and type of repeat revascularization (target lesions or other segments) for each subject were adjudicated by a group of cardiologists according to available evidence. Patient self-reported clinical endpoints included the recurrence of angina, myocardial infarction, stent thrombosis and stroke were not included, because those adverse clinical events had a lack of supportive evidence and formal adjudication procedure.

***Statistical Analysis***

Data were presented as means ± standard deviation (SD) for continuous variables, and counts with proportions for categorical variables. To achieve the primary objective, we compared the baseline characteristics between different smoking status groups stratified by DM. The Student-t or Chi-square tests were used for continuous and categorical variables respectively during the between group comparisons. The incidence rates of all-cause mortality, revascularization and their composite were presented by number of events/1,000 patient-years. Multivariable Cox proportional hazard model was used to estimate adjusted hazard ratios (HRs) and corresponding 95% confidence intervals (CIs).

Covariates adjustment including age, gender, unstable angina, prior myocardial infarction, prior bypass surgery, hypertension, dyslipidemia, family history of coronary heart diseases, ejection fraction, reference vessel diameter, lesion length, stent length, stenosis diameter, lesion angulation, calcification, total occlusion of lesions, lesion thrombosis, TIMI (Thrombolysis in Myocardial Infarction) classification, access position, pre- and post-dilation. Missing data due to loss to follow up was set as censor in the COX model. A two-sided p<0.05 was considered significant.

Additional sensitivity analyses were conducted through a 5,000 times Monte-Carlo simulation.14 In each simulation, firstly we randomly selected a fixed proportion of death events (without replacement) from the persistent smokers and changed their group as quitters. After that, the Cox regression model using the new simulated dataset was built to obtain the estimated HR. The above process was repeated 5,000 times to generate the range of possible HRs. If the 97.5th percentile (and also the median value) of estimated HR was still lower than 1, then we increased the random sampling proportion in the first step and did a new 5,000 times simulation again. Until the “tipping point” is found (the threshold on proportion of death events shifting from persistent smokers to quitters would change the results (HR turns non-significant or <1)). All statistical analyses was carried out using SAS® 9.4 (SAS Institute Inc., Cary, NC, USA).

**Results**

Overall, 8,489 patients were included in the final analysis. Median follow-up time was 3.0 years. Compared with the non-DM participants (n=7,069), DM patients (n=1,420; 1,401 type 2 diabetes) were slightly older (55.2±9.4 *vs* 54.2±9.9 years; p<0.001), more likely to have hypertension (62.0 *vs* 43.0%; p<0.001) and dyslipidemia (49.9 *vs* 28.0%; p<0.001), having family history of coronary heart diseases (7.9 *vs* 4.1%; p<0.001) and prior coronary artery bypass graft (2.2 *vs* 1.4%; p=0.041). Their reference vessel diameters (3.1±0.4 *vs* 3.1±0.5 mm; p<0.001), lesion length (26.6±15.9 *vs* 25.7±15.1 mm; p=0.036), total stent length (32.4±17.7 *vs* 30.8±16.6 mm; p=0.0001) and pre-dilation prevalence (91.6 *vs* 89.4%; p=0.014) also reached statistical significant difference compared with the non-DM cohorts. Smoking quitters accounted for around 50% of both the DM (51.1%) and non-DM (52.6%) cohorts. Baseline characteristics comparison between quitters and persistent smokers stratified by DM status are shown in Table 1.

The quitters had lower mortality rate but higher revascularization rate than persistent smokers. The results were similar when the overall population was divided into DM and non-DM cohorts. Smoking cessation due to PCI showed clear benefits in reducing all-cause mortality; the adjusted HR was 0.11 (95% CI: 0.05-0.22; p<0.001) and 0.14 (95% CI: 0.03-0.68; p=0.015) among non-DM and DM cohorts, respectively. However, smoking quitters were more likely to have additional revascularizations than persistent smokers both in the non-DM cohort (HR, 1.62; 95% CI: 1.37-1.91; p<0.001) and the DM cohort (HR, 1.59; 95% CI: 1.13-2.22; p=0.007). Regarding the composite endpoint of death and revascularization, both non-DM and DM quitters were at higher risk than persistent smokers (HR, 1.30; 95% CI: 1.11-1.52] and 1.39; 95% CI: 1.01-1.92, respectively). The detailed results are described in Table 2.

Compared with non-DM patients, there was no significant difference in all-cause mortality of DM patients (2.5 *vs* 3.1 per 1,000 patient-years; Log-Rank p=0.528), but DM patients had higher revascularization incidence than non-DM patients (32.1 *vs* 26.6 patient-years; Log-Rank p=0.028). 162 and 661 composite endpoints were observed in DM and non-DM patients, respectively. Composite endpoint incidence among DM and non-DM cohorts were 34.2 and 29.3 per 1,000 patient-years (p=0.059 for Log-Rank test).

The quitters were further divided into 5 groups according to their smoking cessation time window (Table 3). For patients who did not have DM, the risk of revascularization was tripled compared with the persistent smokers (HR, 3.40; 95% CI, 2.45-4.72) if they quit smoking too late (over 90 days after their index PCI procedures). However, the association between delayed smoking cessation (>90 days) and revascularizations was not observed among DM patients. The results were similar for composite endpoints. If we focused on the quitter subgroup and divided them by quitting at ≤90 or >90 days, non-DM late quitters (>90 days) showed significant higher risk compared with the early quitter (≤90 days) non-DM patients. The detail results are displayed in Figure 1.

With regard to the observed decreased risk of death and the opposing increased risk of revascularization related to smoking cessation, a further characteristics comparison has been undertaken focusing on the patients who experience clinical endpoints. Figure 2a and 2b show the risk factors distribution between quitters and persistent smokers among the fatal and revascularized cases, respectively. It indicated the fatal cases from the quitter’s cohort (compared with those who died from the persistent smoker’s cohort) had a significantly higher prevalence of hypertension, angina, history of CABG, calcification, thrombosis treatment and post-dilation. It suggested that smoking cessation could save lives unless the risk of patient was extremely high. However, the difference of risk factors was not seen between quitters and persistent smokers for patients who experienced a revascularization event. This may partly explain why the positive effect of smoking cessation was attenuated for the quitters.

Further, the sensitivity Monte-Carlo simulation analysis showed that only if 31.3% or greater fatal events shift from the persistent smoking cohort to the quitters, the benefit of smoking cessation on mortality will change to non-significance (the upper limit of 95% confidence interval of hazard ratio cross 1, quitters *vs* persistent smokers). Further, the tipping-point is 44.2% of the fatal events move from the persistent smokers to the quitters’ cohort. In that case, the point estimate of hazard ratio will increase to 1 or higher (the direction of HR is changed, quitters *vs* persistent smokers). The above scenarios supported the observed benefits of smoking cessation on mortality.

**Discussion**

In this retrospective cohort study, smoking cessation after successful PCI was significantly associated with the declined risk of all-cause mortality, but also related with an increased risk of additional revascularization both for DM and non-DM patients. However, non-DM patients who quit smoking within 90 days after their index PCI procedures were more likely to gain a relative ‘cardio-protective’ benefit than those who stop smoking late; DM patients failed to gain this relative benefit from early smoking cession. These findings suggested that DM may act as an effect-modifier for the association between smoking cessation and clinical outcome among the PCI population.

The benefit from smoking cessation in mortality for patients with coronary heart diseases had been reported in several studies.15-17 Quitting of smoke associated with a substantial reduction in risk of all-cause mortality and the degree of benefit seemed consistent between studies.18 On the other hand, quitters might have a higher risk of repeated revascularization. Similar results had been reported by Cohen and Hasdai.5,19 One possible reason revealed in our analyses was that smoking cessation seemed to reduce the incidence of fatal events, so the survivors suffered increased chances to experience a non-fatal event (e.g. repeat revascularization) during their extended life time. But the absolute difference in the number of deaths between quitters and persistent smokers appears too small to fully explain the excess risk for revascularization. The possibility of residual confounding arising from a higher risk profile among the quitters should also be considered. However, all participants in current study were smokers at the time of their index PCI and smoking cessation was not differentially related to other vascular risk factors in quitters and continuing smokers.20 Another contributing reason may be that the persistent smokers are more reluctant to seek medical services, in contrast to quitters.21-24

More importantly, our results suggested that non-DM patients should quit smoking as early as possible after PCI. It is well recognized that the process of endothelial recovery and arterial healing after stenting is complex.25 The early stage of endothelial function recovery is important and even drug-eluting stent implantation may delay that progress up to 6 months.26-28 In the early stage, PCI induced impairment (inflammation and the damage to microvascular function) may become worse if the patient is a smoker.10 During this critical period, if nicotine exposure can be prevented by stopping smoking, nicotine induced insulin resistance may decrease and the endovascular environment will improve.11,29 This may explain why the non-diabetic patients had significant increased risk of repeat revascularization if they quit smoking too late after PCI procedures (i.e. >90 days). However, revascularization incidence did not decrease along with the early smoking cession time among DM patients. The underlying reason may be that DM patients already have a higher sympathetic activity level, which may reduce the sensitivity for responds to postoperative behavioral changes.5,30 Furthermore, metformin use in combination with stent implantation among DM patients may delay endothelial recovery.31 Therefore, our study suggests that non-DM subjects may be more sensitive than DM patients to smoking cessation, especially for early smoking quitters. The interaction between smoke cessation time and endocrine factors may be involved in development of re-occurrence of ischemic heart diseases; this possibility should be explored in further studies.

Our study has several limitations. Firstly, the findings from single center may not be generalized to a broader population although Fu Wai hospital is a high volume national center (over 10,000 PCI procedures/year) for cardiovascular diseases. Secondly, smoking cessation was not confirmed by the biochemical test or breath CO monitoring which is a substantial limitation of our study. It may induce the patient misclassification, although our sensitivity analysis supported the reliability and validity of the key findings. Thirdly, the baseline heterogeneity across each cohort may affect the results, although multivariable adjustments were used to minimize this bias, but the results should still be interpreted with caution because unobserved confounding factors (e.g. concomitant medication for DM) cannot be fully adjusted. Fourthly, the sample size of the DM cohort was relatively small, especially when the DM cohort was further divided into different groups according to smoking cessation time. This may attenuate the potential association between quitting delay and repeat revascularization among that population. Finally, the findings (difference between DM *vs* non-DM patients) of our study should be treated as hypothesis generating only. The results need to be validated. Further studies are warranted.

**Conclusion**

Our study shows smoking cessation associate with lower all-cause mortality rate for both DM and non-DM patients who underwent PCI. Quitting smoking late was associated with an increased risk of repeat revascularization only among non-DM patients. Thus, DM may act as an effect modifier even under the situation of smoker’s paradox. Our data suggests that personalized smoking cessation strategies may need and become part of the secondary prevention strategy for PCI patients.

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**Declaration of Conflict of Interest**

The authors declare that there is no conflict of interest.

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**Figure legends**

**Figure 1. Subgroup analysis for late quitters *vs* early quitters stratified by DM/non-DM patients**

Left panel (a) shows the composite endpoint among the quitters. Right panel (b) shows the revascularization results in the quitter subgroup. Subjects were grouped by their smoking cessation time (≤90 *vs* >90 days). The results of crude event rate and adjusted hazard ratios (HR) were stratified by diabetes mellitus. The dark line and grey line in figure represent non-DM and DM patients, respectively.

**Figure 2. Comparison of baseline characteristics between quitters and persistent smokers for patients who died or had a revascularization event.**

Figure 2a shows the baseline characteristics (by smoking status) of patients who died. The relative proportion of dark/light grey bar represents the distribution of risk factors among quitters and persistent smokers, respectively.

Abbreviations: CABG, coronary artery bypass graft; RVD, reference vessel diameter; DS, diameter stenosis; MI, prior myocardial infarction; TIMI, Thrombolysis in Myocardial Infarction classification; LVEF, left ventricular ejection fraction; CHD, Coronary heart disease.

The information in Figure 2b was similar (dark/light grey bar represents the distribution of risk factors among quitters and persistent smokers, respectively), but for the patients who had repeat revascularization during the follow-up period.

Abbreviations: CABG, coronary artery bypass graft; RVD, reference vessel diameter; DS, diameter stenosis; MI, prior myocardial infarction; TIMI, Thrombolysis in Myocardial Infarction classification; LVEF, left ventricular ejection fraction; CHD, Coronary heart disease.