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Long-Term Mortality Hazard Associated with Persistent Smoking in Survivors of Acute Coronary Syndromes

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STRUCTURED ABSTRACT

Objective:

We aim ascertain the relative risk of death in patients who persist with smoking and the benefit associated with smoking cessation after an acute coronary syndrome (ACS) in the era of percutaneous coronary intervention (PCI) and optimal secondary prevention pharmacotherapy.

Methods:

Consecutive patients with ACS as the indication for their index PCI from the Melbourne Interventional Group registry (2005-2013) who were alive at 30-days were included in our observational cohort study. Patients were divided into four categories based on their smoking status: non-smoker; ex-smoker (quit >1 month before ACS); recent quitter (smoker at presentation but quit by 30-days); and persistent smoker (smoker at presentation and at 30-days). The primary endpoint was long-term mortality through Australian National Death Index linkage.

Results:

Of the 9,375 patients included, 2,728 (29.1%) never smoked, 3,712 (39.6%) were ex-smokers, 1,612 (17.2%) were recent quitters and 1,323 (14.1%) were persistent smokers. Multivariate analysis revealed, compared to those who had never smoked, that persistent smoking (OR 1.78, 95% CI 1.36-2.32, p<0.001) was an independent predictor of long-term mortality (mean follow-up 3.9±2.2 years) while being a recent quitter (OR 1.27, 95% CI 0.96-1.68, p=0.10) or an ex-smoker (OR 1.03, 95% CI 0.87-1.22, p=0.72) was not.

Conclusions:

In a contemporary cohort of patients with ACS, those who continued to smoke had a nearly two-fold higher risk of death while those who quit had comparable survival to lifelong non-smokers. This underscores the importance of smoking cessation in secondary prevention despite the improvement in management of ACS with PCI and pharmacotherapy.

Keywords: smoking; secondary prevention; acute coronary syndromes; long-term mortality; percutaneous coronary intervention

ARTICLE SUMMARY

Article Focus

- This article examines the risk of death associated with ongoing smoking in patients who receive optimal management of their acute coronary syndrome.

Key Messages

- Smoking cessation rates post-acute coronary syndromes (ACS) remain suboptimal.
- Despite optimal contemporary ACS management, persistent smoking is associated with a near two-fold increase in all-cause mortality compared to non-smokers. Long-term survival in patients who quit smoking after ACS approaches the level of life-long non-smokers.

Strengths and limitations of this study

- The main strength of this study is the assessment of smoking cessation in a contemporary patient population receiving optimal medical therapy; something which has not been explored.
- Patients' smoking habits can change over time and thus our study is limited by the assessment of smoking status at only one time point.

BACKGROUND

Smoking is a well-recognized risk factor for coronary heart disease and accounts for 11% of cardiovascular deaths worldwide.[1] Smoking cessation has been consistently associated with a mortality benefit in both stable coronary artery disease and post acute coronary syndromes (ACS).[2-4] Consequently, smoking cessation is one of the cornerstones of secondary prevention.[5]

However, the mortality hazard of persistent smoking post ACS in contemporary cardiology has not been described. Systematic reviews and meta-analysis have predominantly included studies from the pre-percutaneous coronary intervention era. [2-4] More recent studies assessing the impact of smoking post ACS have focused primarily on younger (<35 years)[6] or older populations (>65 years),[7] have had low rates of revascularization,[6-9] had suboptimal medical management[10] or did not assess the impact of smoking cessation.[7 11 12]

Thus we aimed to assess the impact of persistent smoking or cessation at 30-days compared to non-smokers, on long-term mortality in patients treated with percutaneous coronary intervention (PCI) and optimal secondary prevention pharmacotherapy.

METHODS

The study cohort included consecutive patients enrolled in the Melbourne Interventional Group (MIG) registry who underwent their index PCI for management of ACS between January 2005 and November 2013.

The MIG registry is a multicentre PCI registry and has been previously described in detail.[13] Briefly, demographic, clinical, procedural and in-hospital outcome data are prospectively recorded on case-report forms using standardized definitions for all fields with follow up performed at 30 days and 12 months.[14]

The registry is coordinated by the Centre of Cardiovascular Research and Education in Therapeutics; an independent research body within the School of Public Health and Preventive Medicine at Monash University (Melbourne, Australia). An audit of a number of verifiable fields from 5% of randomly selected procedures at each institution is undertaken periodically.[15] In the most recent audit, 27 fields were assessed with data accuracy of 98%. This compares favorably to audits from other large registries.[16] The ethics committee in each participating hospital has approved the MIG registry, including the use of "opt-out" consent. This means that consent is presumed unless the patient "opts out" after giving each patient a "Patient Information Sheet". If a patient informs a staff member that they do not wish to participate, the patient's data are not collected.

Patients who underwent PCI for acute coronary syndrome (ACS) and survived to 30-days were included. ACS encompasses the spectrum of ST-elevation myocardial infarction (STEMI), non-ST-elevation myocardial infarction (NSTEMI) and unstable angina. STEMI was defined as ECG changes (new ST-segment elevation at the J-point or development of Q-waves in two or more contiguous leads) with confirmed myocardial necrosis (elevation in troponin T or I or CK-MB on at least one occasion within 24 hours from the index event). NSTEMI was defined as biomarker elevation consistent with myocardial necrosis and one of: either ST-segment depression or T-wave abnormality on ECG; or

ischaemic symptoms. Unstable angina is defined by clinical history suggestive of progressive, unstable ischaemic symptoms without cardiac biomarker elevation.

Acute management of all patients including interventional strategy, stent selection and antithrombotic therapy were left at the discretion of the operator in all procedures. Optimal secondary prevention pharmacotherapy was encouraged according to guidelines. No records were made of contraindications to medications or decisions regarding use/omission of particular guideline-directed therapies.

Patients were divided into four groups based on their smoking status at 30-days. Those who never smoked tobacco were included in the non-smoker group. Those who had quit smoking more than one month prior to ACS were classified as ex-smokers. Recent quitters were smokers at baseline but had quit by 30-days. Persistent smokers were smokers at baseline and were still smoking 30-days post ACS.

The primary outcome was long-term all-cause mortality. Long-term mortality data were obtained by linkage to the Australian National Death Index (NDI). The Australian NDI is a database housed at the Australian Institute of Health and Welfare, which contains records of all deaths occurring in Australia since 1980. Data are obtained from the registries of births, deaths, and marriages in each state and territory. The following variables for each deceased patient were identified: name, date of birth (or estimated year of birth), age at death, gender, date of death, state/territory of registration, and registration number. Successful matching of patients through this linkage process was achieved in 99.4% of patients in the MIG registry.

Secondary outcomes were 12-month mortality, myocardial infarction, stroke and major adverse cardiovascular events (MACCE). 12-month MACCE was defined as the combination of mortality, myocardial infarction (MI), stroke and target vessel revascularization. MI was defined as: an increase in creatine kinase or creatine kinase-MB ≥3 times the upper limit of normal; and/or a significant ST-

segment change, development of new Q waves in ≥2 contiguous electrocardiographic leads, or new left branch bundle block pattern in the context of new clinical symptoms.

Statistical Analysis

Continuous variables are expressed as mean ± standard deviation (SD), and categorical data are expressed as numbers/percentages. Continuous variables were compared using Kruskal-Wallis equality-of-populations rank test. Categorical variables were compared using Fisher's exact or Pearson's chi-square tests as appropriate. Variables were tested for linear trends across the years 2005-2013 using Stata's *nptrend* command. This is a nonparametric test for trend across ordered groups that is an extension of the Wilcoxon rank-sum test. A Cox-proportional hazards model was used to estimate the adjusted hazard ratio and 95% confidence interval (CI) for long-term mortality. Univariate variables with $p<0.10$ were included for stepwise removal for the final multivariate model.

All statistical analyses were performed using Stata 13.1, StataCorp LP, College Station, TX, USA. P-values < 0.05 were considered to be statistically significant.

Patient Involvement

The design of the study was inspired by patients' desire to quantify the benefit of the smoking cessation after ACS. Patients were not involved in the conduct of the study. Results will be disseminated through usual scientific channels but not directly to study participants.

RESULTS

Of the 9,375 survivors following PCI for ACS at 30 days, 2,728 (29.1%) had never smoked, 3,712 (39.6%) were ex-smokers, 1,612 (17.2%) were recent quitters (smokers at the time of ACS but quit by 30-days) and 1,323 (14.1%) were persistent smokers. The smoking cessation rate at 30-days post ACS was 54.9%. Of the patients alive at 12-months, 23% of quitters had relapsed and 71% of persistent smokers continued to smoke (Figure 1).

Trends in smoking status

Figure 2 depicts the trends in smoking status over the 9-year period from 2005 to 2013. The percentage of non-smokers presenting with ACS increased over the time period while the rate of ex-smokers has decreased (p-value for trend =0.02). There has been no significant change in the trend of smokers presenting with ACS.

Clinical characteristics

Baseline clinical characteristics stratified by smoking status at 30-days are shown in Table 1. It is evident smokers at the time of ACS (subsequent quitters and persistent smokers) were younger, had less co-morbidities but a higher rate of a family history of premature CAD. Compared to quitters, persistent smokers were more likely to have had previously documented CAD (high rates of previous MI/PCI/CABG), peripheral vascular disease and stroke.

ACS presentation type, angiographic characteristics and acute outcomes are shown in Table 2. Smokers at time of ACS were more likely to present with STEMI, have single vessel CAD and receive a bare-metal stent. They also had earlier discharge from hospital. The use of secondary prevention pharmacotherapy across all groups is depicted in Table 3.

Clinical Outcomes

Unadjusted long-term mortality at mean follow-up of 3.9±2.2 years showed quitters had lower death rates than persistent smokers, non-smokers or ex-

smokers (5.3% vs. 8.2% vs. 9.6% vs. 12.1%, respectively; p<0.001). The full details of 12-month clinical outcomes and long-term mortality are shown in Table 4. On multivariate analysis being an ex-smoker (HR 1.03, 95% CI 0.87-1.22) or a quitter (HR 1.27, 95% CI 0.96–1.67) was not associated with an increased mortality risk compared to non-smokers but being a persistent smoker was associated with increased mortality (HR 1.78, 95% CI 1.36 – 2.32) (Table 5 and Figure 3).

DISCUSSION

In a contemporary cohort of patients presenting with ACS and treated with PCI and optimal secondary prevention pharmacotherapy, only 54% of patients stopped smoking by 30-days. Persistent smokers at 30 days post PCI experienced an almost two-fold increase in long-term mortality. Patients who quit smoking had a survival rate at 4 years that was similar to that of a life-long non-smoker.

Cigarette smoking is a well-established cardiovascular risk factor and continues to be a major preventable cause of death. Ezzati *et al* estimated 11% (1.62 million) of all global cardiovascular deaths in 2000 were attributable to smoking.[1] Although the prevalence of smoking in the general population has decreased over the past 50 years in the United States, in our study the proportion of current smokers at time of ACS did not change significantly over 9 years.[17] This emphasizes the malignant pathophysiological effects of smoking, namely endothelial dysfunction, thrombogenicity and coronary vasoconstriction, which predispose patients to ACS events.[18] Indeed, the significant role of smoking in the pathogenesis of ACS is further highlighted by the fact smokers were younger and lower rates of diabetes, hypertension and hypercholesterolaemia.

Smoking cessation is difficult, even after life-threatening events such as acute coronary syndromes. Systematic reviews have reported smoking cessation rates averaging around 50% in patients with coronary heart disease; this is consistent with the rates observed in our study.[2-4] In addition we found 23% of those who quit smoking at 30-days had relapsed at 12-months highlighting the difficulty of long-term abstinence. The severity of presentation may be a strong trigger to quit as a smoking cessation rate of 74% was reported in one study with STEMI patients alone.[10] We also observed this in our study as patients presenting with STEMI were more likely to quit compared to those presenting with NSTEMI or unstable angina. Implementation of smoking cessation strategies is crucial and the index hospitalization provides a perfect opportunity for this. Indeed a

Cochrane review showed that smoking cessation rates were higher if counseling and pharmacotherapy were initiated during hospital admission.[19]

The "smoker's paradox" in patients with acute coronary syndromes suggests there could be potential survival benefit seen in smokers.[20] In our study, smokers had lower unadjusted mortality rates at 12-months and long-term. However, when accounting for baseline differences in age and co-morbidities, smoking status was no longer associated with improved survival, thus suggesting debunking of the "smoker's paradox". This is supported by a systematic review showing only studies in the pre-thrombolytic and thrombolytic era supporting the paradox, while none of the contemporary studies do.[20]

The cardiovascular risk associated with smoking appears to dissipate within 3 years of cessation.[21 22] Systematic reviews have shown smoking cessation to be associated with a 35% relative risk reduction in patients with coronary heart disease and up to 46% in those with a myocardial infarction.[2-4] A limitation of these reviews is the inclusion of a significant proportion of patients from an era preceding percutaneous coronary intervention and optimal secondary prevention pharmacotherapy. More recent studies assessing the impact of smoking status following ACS have had suboptimal rates of revascularization or medical management.[6-10] Other studies did not assess the hazard of persistent smoking.[7 11 12] In our study, persistent smoking after ACS was associated with an increased relative mortality risk of 78% at 4 years. The mortality hazard in our study was lower than the one described in a study of STEMI patients by Kinjo et al (HR 1.78 vs. 2.27). Although their revascularization rate was high (>85%), only 30% of patients received statin therapy. Thus, it could be hypothesized that our higher rate of statin therapy may be responsible for our lower long-term mortality risk. What is unquestionable, as observed in our study, is that a substantial residual mortality risk remains in patients who persist with smoking despite optimal contemporary management with PCI and optimal secondary prevention pharmacotherapy. This increased risk is of similar magnitude to those seen from earlier cardiology eras.[2-4]

Encouragingly, smoking cessation is beneficial and by 4 years our cohort of quitters had a mortality hazard approaching that of life-long non-smokers. This is theoretically plausible as the deleterious hazards of smoking appear to be reversed within this time frame and cardiac risk has been shown to return to baseline.[18 21 22] Although complete smoking abstinence is difficult, as previously discussed, Gerber *et al* showed that even a five cigarette a day reduction is associated with an 18% decline in mortality.[8] Again this highlights the importance of smoking cessation or even smoking reduction in secondary prevention.

Our study has a number of limitations. Firstly, inherent to all studies assessing the impact of persistent smoking and cessation, the associations described in our study could be attributed, at least partly, to unaccounted or unmeasured variables. In particular, we did not account for the participation in cardiac rehabilitation programs or for smoking cessation strategies utilized. Secondly, we have measured smoking status at one time point and even at 12-months there were a significant number of patients who changed their smoking habits and thus were initially misclassified. We chose smoking cessation at 30-days to assess the impact of the admission with ACS and early medical intervention. Thirdly, we ascertained smoking status by self-report. Although it has been shown to correlate with biochemical assessment in a meta-analysis, there is always a potential for misclassification.[23] Lastly, we do not collect a detailed smoking history and thus we could not quantify the mortality hazard based on the quantity of cigarettes smoked over a lifetime, nor could we quantify the benefit of cessation based on the time since the last cigarette was smoked.

CONCLUSION

Patients who continued to smoke after an ACS had a nearly two-fold mortality hazard while those who quit had comparable survival to a non-smoker. This underscores the importance of smoking cessation in secondary prevention, despite the improvement in management of ACS with percutaneous coronary intervention and optimal medical therapy.

Figure 1. Smokers at Baseline, 30-days and 12-months

* Includes only those patients alive at 12 months.
Recent quitters were smokers at baseline but had quit by 30 days. Persistent smokers were smokers at baseline and were still smoking 30 days and 12 months post ACS. Relapsed smokers were smoking at 12 months although they temporarily quit at 30 days.

Figure 2. Trends in Smoking Status in ACS Survivors at 30-days

Figure 3. Cox Proportional Hazard Regression Survival Curve

Table 1. Baseline clinical characteristics N(%) stratified by smoking status at 30-days

	Non-Smoker (N=2,728)	Ex-Smoker (N=3,712)	Recent Quitter (N=1,612)	Persistent Smoker (N=1,323)	P
Age (mean±SD years)	67.0±12.3	67.0±11.5	56.1±10.2	56.7±10.6	<0.001
Age >75 years	857 (31.4)	1,093 (29.5)	74 (4.6)	82 (6.2)	<0.001
Male	1,753 (64.3)	3,038 (81.8)	1,310 (81.3)	1,028 (77.7)	<0.001
BMI (mean±SD kg/m^2)	28.0±5.3	28.4±5.1	28.4±5.3	28.2±5.6	0.004
Hypertension	1,738 (63.7)	2,628 (70.8)	752 (46.7)	701 (53.0)	<0.001
Hypercholesterolaemia	1,665 (61.1)	2,627 (70.8)	895 (55.6)	806 (61.1)	<0.001
Diabetes Mellitus	630 (23.1)	1,014 (27.3)	216 (13.4)	244 (18.4)	<0.001
Family History of CAD	964 (35.5)	1,412 (38.3)	704 (44.1)	554 (42.2)	<0.001
Previous MI	444 (16.3)	1,043 (28.1)	183 (11.4)	249 (18.8)	<0.001
Previous PCI	445 (16.3)	884 (23.8)	168 (10.4)	222 (16.8)	<0.001
Previous CABG	159 (5.8)	378 (10.2)	29 (1.8)	43 (3.3)	<0.001
Congestive Heart Failure	83 (3.0)	167 (4.5)	12 (0.8)	30 (2.3)	<0.001
PVD	92 (3.4)	313 (8.4)	55 (3.4)	83 (6.3)	<0.001
Stroke	157 (5.8)	293 (7.9)	46 (2.9)	61 (4.6)	<0.001
Chronic Lung Disease	166 (6.1)	516 (13.9)	118 (7.3)	170 (12.9)	<0.001
eGFR ≥ 60ml/min/1.73m^2	1,970 (74.3)	2,726 (74.9)	1,384 (89.4)	1,135 (88.9)	<0.001
Ejection Fraction >45%	1,791 (72.2)	2,311 (70.5)	1,077 (71.9)	846 (70.6)	0.61

SD = standard deviation. BMI = body mass index. CAD = coronary artery disease. MI = myocardial infarction. PCI = percutaneous coronary intervention. CABG = coronary artery bypass graft surgery. PVD = peripheral vascular disease. eGFR = estimated glomerular filtration rate.

Table 2. ACS presentation, angiographic characteristics and acute outcomes N(%) by smoking status at 30-days

	Non-Smoker (N=2,728)	Ex-Smoker (N=3,712)	Recent Quitter (N=1,612)	Persistent Smoker (N=1,323)	P
STEMI	1243 (45.6)	1430 (38.5)	971 (60.2)	615 (46.5)	
NSTEMI	1100 (40.3)	1591 (42.9)	547 (33.9)	559 (42.3)	
Unstable Angina	385(14.1)	691 (18.6)	94 (5.8)	149 (11.3)	<0.001
Multivessel CAD	1507 (55.3)	2291 (61.8)	806 (50.2)	655 (49.7)	<0.001
Left main disease	21 (0.8)	55 (1.5)	3 (0.2)	4 (0.3)	<0.001
Balloon angioplasty only	162 (5.9)	236 (6.4)	66 (4.1)	50 (3.8)	<0.001
Bare Metal Stent	1356 (49.7)	1949 (52.5)	918 (57.0)	781 (59.0)	
Drug Eluting Stent	1210 (44.4)	1527 (41.1)	628 (39.0)	492 (37.2)	<0.001
Number of stents inserted (mean±SD)	1.2±0.6	1.2±0.6	1.2±0.6	1.2±0.6	0.44
Successful PCI	2728 (100)	3711 (100)	1612 (100)	1322 (99.9)	0.42
New Renal impairment	34 (1.3)	35 (0.9)	10 (0.6)	4 (0.3)	0.01
New Heart Failure	130 (4.8)	151 (4.1)	53 (3.3)	26 (2.0)	<0.001
Length of stay (mean±SD days)	5.2±5.2	5.2±5.5	4.5±4.1	4.1±3.4	<0.001

STEMI = ST-segment elevation myocardial infarction. NSTEMI = non- ST-segment elevation myocardial infarction. CAD = coronary artery disease. SD = standard deviation. PCI = percutaneous coronary intervention.

Table 3. Cardiovascular pharmacotherapy N(%) at 30-days by smoking status at 30-days

	Non-Smoker (N=2,728)	Ex-Smoker (N=3,712)	Recent Quitter (N=1,612)	Persistent Smoker (N=1,323)	P
Aspirin	2665 (97.7)	3620 (97.5)	1593 (98.8)	1299 (98.2)	0.02
P2Y12 inhibitor	2409 (88.3)	3301 (88.9)	1423 (88.3)	1204 (91.0)	0.06
Statin	2610 (95.7)	3523 (94.9)	1583 (98.2)	1279 (96.7)	<0.001
Beta-blocker	2328 (85.3)	3019 (81.3)	1380 (85.6)	1120 (84.7)	<0.001
ACE-I/ARB	2313 (84.8)	3105 (83.7)	1381 (85.7)	1070 (80.9)	0.002
Warfarin	259 (9.5)	295 (8.0)	111 (6.9)	84 (6.4)	0.001
Spironolactone	66 (2.4)	96 (2.6)	11 (0.7)	29 (2.2)	<0.001
Eplerenone	60 (2.2)	67 (1.8)	38 (2.4)	30 (2.3)	0.49
Ezetimibe	82 (3.0)	219 (5.9)	34 (2.1)	32 (2.4)	<0.001
Fibrate	27 (1.0)	62 (1.7)	16 (1.0)	20 (1.5)	0.06

ACE-I = Angiotensin converting enzyme inhibitor. ARB = angiotensin receptor blocker.

Table 4. Clinical outcomes N(%) by smoking status at 30-days

	Non-Smoker (N=2,728)	Ex-Smoker (N=3,712)	Recent Quitter (N=1,612)	Persistent Smoker (N=1,323)	P
Long-term Mortality	262 (9.6)	450 (12.1)	86 (5.3)	108 (8.2)	<0.001
12-month Mortality	50 (1.9)	100 (2.8)	13 (0.9)	18 (1.4)	<0.001
12-month MI	122 (4.7)	222 (6.2)	51 (3.3)	56 (4.5)	<0.001
12-month Stroke	28 (1.1)	37 (1.0)	9 (0.6)	9 (0.7)	0.3
12-month TVR	182 (7.0)	272 (7.6)	118 (7.7)	65 (5.2)	0.03
12-month MACCE	309 (11.9)	488 (13.7)	157 (10.2)	117 (9.3)	<0.001

MI = myocardial infarction. TVR = target-vessel revascularization. MACCE = major adverse cardiovascular events.

Table 5. Estimates of hazard ratio and 95% confidence interval of predictors of long-term mortality using Cox-proportional hazards analysis

	Hazard Ratio	95% Confidence Interval	p-value
Unadjusted			
Non-smoker	Reference	-	-
Ex-smoker	1.21	1.03 – 1.40	0.02
Recent Quitter	0.51	0.40 – 0.65	<0.001
Persistent Smoker	0.82	0.65 – 1.03	0.08
Multivariate analysis			
Non-smoker	Reference	-	-
Ex-smoker	1.03	0.87 – 1.22	0.72
Quitter	1.27	0.96 – 1.68	0.10
Persistent Smoker	1.78	1.36 – 2.32	<0.001
Age (per year)	1.07	1.06 – 1.08	<0.001
Multivessel CAD	1.43	1.21 – 1.69	<0.001
Drug-eluting stent	0.78	0.67- 0.92	0.002
eGFR ≥60ml/min/1.73m²	Reference	-	-
eGFR 30-59ml/min/1.73m²	1.47	1.24 – 1.73	<0.001
eGFR <30 ml/min/1.73m²	3.83	2.96 – 4.94	<0.001
EF > 45%	Reference	-	-
EF 30-45%	1.55	1.33 – 1.80	<0.001
EF <30%	1.60	1.12 – 2.29	0.010
Diabetes Mellitus	1.51	1.29 – 1.77	<0.001
Peri-procedural MI	1.33	1.13 – 1.56	<0.001
Peripheral vascular disease	1.65	1.35 – 2.02	<0.001
Chronic lung disease	1.73	1.44 – 2.08	<0.001

CAD = coronary artery disease. eGFR = estimated glomerular filtration rate. EF = ejection fraction. MI = myocardial infarction.

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Transparency Declaration: The lead author, Associate Professor David Clark, affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract – **Evident in Methods section of Abstract (Page 2)**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found – **Evident in Abstract (Page 2)**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported – **Evident in Background (Page 4)**
Objectives	3	State specific objectives, including any prespecified hypotheses **- Evident in Background (Page 4)**
Methods		
Study design	4	Present key elements of study design early in the paper – **Evident in Methods (Page 5-7)**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **- Evident in Methods (Page 5)**
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up **- Evident in Methods (Page 5-7)** *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls – **N/A** *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants – **N/A**
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed – **N/A** *Case-control study*—For matched studies, give matching criteria and the number of controls per case – **N/A**
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **- Evident in Methods (Page 5-7)**
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 – **Evident in Methods (Page 5-7)**
Bias	9	Describe any efforts to address potential sources of bias – **Evident in Methods (Page 5-7) including details of multivariate analysis**
Study size	10	Explain how the study size was arrived at – **it was based on a study period, not a particular sample size as described in Methods (Page 5-7)**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why – **Described in Methods (Page 6)**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding **– Described in Methods (Page 7)**
		(*b*) Describe any methods used to examine subgroups and interactions - **N/A**
		(*c*) Explain how missing data were addressed – **N/A (consecutive patients included)**
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed –

linkage to the Australian National Death Index allowed complete follow-up of patients. Described in Methods (Page 6)

Case-control study—If applicable, explain how matching of cases and controls was addressed – **N/A**

Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy – **N/A**

(*e*) Describe any sensitivity analyses – **N/A**

Continued on next page

Results		
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 – **All consecutive patients alive at 30-days were included. They were linked to the Australian National Death Index**
		(b) Give reasons for non-participation at each stage – **N/A**
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders – **Evident in Tables 1, 2 and 3.Table 3 (Pages 17-19)**
		(b) Indicate number of participants with missing data for each variable of interest – **Evident in Tables 1, 2 and 3.Table 3 (Pages 17-19)**
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount) – **Evident in Results (Page 8)**
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time – **Evident in Tables 4 (Pages 20)**
		Case-control study—Report numbers in each exposure category, or summary measures of exposure – **N/A**
		Cross-sectional study—Report numbers of outcome events or summary measures
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. **Evident in Tables 4 and 5 (Pages 20-21)**
		(*b*) Report category boundaries when continuous variables were categorized **- DONE**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives – **Evident in Discussion (Page 9)**
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 **- Evident in Discussion (Page 12)**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **- Evident in Conclusion (Page 13)**
Generalisability	21	Discuss the generalisability (external validity) of the study results – **Evident throughout Discussion section (Pages 10-12)**
Other information		
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 – **There was no funding for the study.**

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

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 www.strobe-statement.org.

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The Prognostic Significance of Smoking Cessation After Acute Coronary Syndromes: An Observational, Multicentre Study from the Melbourne Interventional Group Registry

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The Prognostic Significance of Smoking Cessation After Acute Coronary Syndromes: An Observational, Multicentre Study from the Melbourne Interventional Group Registry

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Keywords: smoking; secondary prevention; acute coronary syndromes; long-term mortality; percutaneous coronary intervention

STRUCTURED ABSTRACT

Objective:

We aim to ascertain the prognostic significance of persistent smoking and smoking cessation after an acute coronary syndrome (ACS) in the era of percutaneous coronary intervention (PCI) and optimal secondary prevention pharmacotherapy.

Methods:

Consecutive patients from the Melbourne Interventional Group registry (2005-2013) who were alive at 30-days post-ACS presentation were included in our observational cohort study. Patients were divided into four categories based on their smoking status: non-smoker; ex-smoker (quit >1 month before ACS); recent quitter (smoker at presentation but quit by 30-days); and persistent smoker (smoker at presentation and at 30-days). The primary endpoint was survival ascertained through the Australian National Death Index linkage. A Cox-proportional hazards model was used to estimate the adjusted hazard ratio and 95% confidence interval (CI) for survival.

Results:

Of the 9,375 patients included, 2,728 (29.1%) never smoked, 3,712 (39.6%) were ex-smokers, 1,612 (17.2%) were recent quitters and 1,323 (14.1%) were persistent smokers. Cox-proportional hazard modelling revealed, compared to those who had never smoked, that persistent smoking (HR 1.78, 95% CI 1.36-2.32, p<0.001) was an independent predictor of increased hazard (mean follow-up 3.9±2.2 years) while being a recent quitter (HR 1.27, 95% CI 0.96-1.68, p=0.10) or an ex-smoker (HR 1.03, 95% CI 0.87-1.22, p=0.72) were not.

Conclusions:

In a contemporary cohort of patients with ACS, those who continued to smoke had an 80% risk of lower survival while those who quit had comparable survival to lifelong non-smokers. This underscores the importance of smoking cessation in secondary prevention despite the improvement in management of ACS with PCI and pharmacotherapy.

Strengths and Limitations

- The main strength of this study is the assessment of smoking cessation in a large contemporary population who were treated with PCI and optimal medical therapy; something which has not been explored.
- Patients' smoking habits can change over time and thus our study is limited by the assessment of smoking status at only one time point.

BACKGROUND

Smoking is a well-recognized risk factor for coronary heart disease and accounts for 11% of cardiovascular deaths worldwide.[1] Smoking cessation has been consistently associated with a mortality benefit in both stable coronary artery disease and post acute coronary syndromes (ACS).[2-4] Consequently, smoking cessation is one of the cornerstones of secondary prevention.[5]

However, the hazard of persistent smoking post ACS in contemporary cardiology has not been described. Systematic reviews and meta-analysis have predominantly included studies from the pre-percutaneous coronary intervention era. [2-4] More recent studies assessing the impact of smoking post ACS have focused primarily on younger (<35 years)[6] or older populations (>65 years),[7] have had low rates of revascularization,[6-9] had suboptimal medical management[10] or did not assess the impact of smoking cessation.[7 11 12]

Thus we aimed to assess the impact of persistent smoking or cessation at 30-days compared to non-smokers, on survival in patients treated with percutaneous coronary intervention (PCI) and optimal secondary prevention pharmacotherapy.

METHODS

The study cohort included consecutive patients enrolled in the Melbourne Interventional Group (MIG) registry who underwent their index PCI for management of ACS between January 2005 and November 2013.

The MIG registry is a multicentre PCI registry and has been previously described in detail.[13] Briefly, demographic, clinical, procedural and in-hospital outcome data are prospectively recorded on case-report forms using standardized definitions for all fields with follow up performed at 30 days and 12 months.[14]

The registry is coordinated by the Centre of Cardiovascular Research and Education in Therapeutics; an independent research body within the School of Public Health and Preventive Medicine at Monash University (Melbourne, Australia). An audit of a number of verifiable fields from 5% of randomly selected procedures at each institution is undertaken periodically.[15] In the most recent audit, 27 fields were assessed with data accuracy of 98%. This compares favorably to audits from other large registries.[16] The ethics committee in each participating hospital has approved the MIG registry, including the use of "opt-out" consent. This means that consent is presumed unless the patient "opts out" after giving each patient a "Patient Information Sheet". If a patient informs a staff member that they do not wish to participate, the patient's data are not collected.

Patients who underwent PCI for acute coronary syndrome (ACS) and survived to 30-days were included. ACS encompasses the spectrum of ST-elevation myocardial infarction (STEMI), non-ST-elevation myocardial infarction (NSTEMI) and unstable angina. STEMI was defined as ECG changes (new ST-segment elevation at the J-point or development of Q-waves in two or more contiguous leads) with confirmed myocardial necrosis (elevation in troponin T or I or CK-MB on at least one occasion within 24 hours from the index event). NSTEMI was defined as biomarker elevation consistent with myocardial necrosis and one of: either ST-segment depression or T-wave abnormality on ECG; or

ischaemic symptoms. Unstable angina is defined by clinical history suggestive of progressive, unstable ischaemic symptoms without cardiac biomarker elevation.

Acute management of all patients including interventional strategy, stent selection and antithrombotic therapy were left at the discretion of the operator in all procedures. Optimal secondary prevention pharmacotherapy was encouraged according to guidelines. No records were made of contraindications to medications or decisions regarding use/omission of particular guideline-directed therapies.

Patients were divided into four groups based on their smoking status at 30-days. Those who never smoked tobacco were included in the non-smoker group. Those who had quit smoking more than one month prior to ACS were classified as ex-smokers. Recent quitters were smokers at baseline but had quit by 30-days. Persistent smokers were smokers at baseline and were still smoking 30-days post ACS.

The primary outcome was subsequent survival in those patients who were alive at 30 days post ACS. Survival status was obtained by linkage to the Australian National Death Index (NDI). The Australian NDI is a database housed at the Australian Institute of Health and Welfare, which contains records of all deaths occurring in Australia since 1980. Data are obtained from the registries of births, deaths, and marriages in each state and territory. The following variables for each deceased patient were identified: name, date of birth (or estimated year of birth), age at death, gender, date of death, state/territory of registration, and registration number. Successful matching of patients through this linkage process was achieved in 99.4% of patients in the MIG registry.

Secondary outcomes were 12-month mortality, myocardial infarction, stroke and major adverse cardiovascular events (MACCE). 12-month MACCE was defined as the combination of mortality, myocardial infarction (MI), stroke and target vessel revascularization. MI was defined as: an increase in creatine kinase or creatine kinase-MB ≥3 times the upper limit of normal; and/or a significant ST-

segment change, development of new Q waves in ≥2 contiguous electrocardiographic leads, or new left branch bundle block pattern in the context of new clinical symptoms.

Statistical Analysis

Continuous variables are expressed as mean ± standard deviation (SD), and categorical data are expressed as numbers/percentages. Continuous variables were compared using Kruskal-Wallis equality-of-populations rank test. Categorical variables were compared using Fisher's exact or Pearson's chi-square tests as appropriate. Variables were tested for linear trends across the years 2005-2013 using Stata's *nptrend* command. This is a nonparametric test for trend across ordered groups that is an extension of the Wilcoxon rank-sum test. Cumulative incidence of mortality was estimated by the Kaplan-Meier method and the log-rank test was used to evaluate differences between groups. Cox-proportional hazards regression was used to estimate the adjusted hazard ratio and 95% confidence interval (CI) for survival. Univariate variables with $p<0.10$ were included for stepwise removal for the final multivariate model. The variables considered were: smoking status, age, sex, eGFR, hypertension, diabetes, hypercholesterolaemia, family history of coronary disease, previous MI, previous PCI, previous CABG, heart failure, peripheral vascular disease, cerebrovascular disease, left ventricular ejection fraction, multi-vessel CAD, angina type, chronic lung disease, cardiogenic shock, glycoprotein IIb/IIIa use, drug-eluting stent use and treated left main lesion.

All statistical analyses were performed using Stata 13.1, StataCorp LP, College Station, TX, USA. P-values < 0.05 were considered to be statistically significant.

RESULTS

Of the 9,375 survivors following PCI for ACS at 30 days, 2,728 (29.1%) had never smoked, 3,712 (39.6%) were ex-smokers, 1,612 (17.2%) were recent quitters (smokers at the time of ACS but quit by 30-days) and 1,323 (14.1%) were persistent smokers. The smoking cessation rate at 30-days post ACS was 54.9%. Of the patients alive at 12-months, 23% of quitters had relapsed and 71% of persistent smokers continued to smoke (Figure 1).

Trends in smoking status

Figure 2 depicts the trends in smoking status over the 9-year period from 2005 to 2013. The percentage of non-smokers presenting with ACS increased over the time period while the rate of ex-smokers has decreased (p-value for trend =0.02). There has been no significant change in the trend of smokers presenting with ACS.

Clinical characteristics

Baseline clinical characteristics stratified by smoking status at 30-days are shown in Table 1. It is evident smokers at the time of ACS (subsequent quitters and persistent smokers) were younger, had less co-morbidities but a higher rate of a family history of premature CAD. Compared to quitters, persistent smokers were more likely to have had previously documented CAD (high rates of previous MI/PCI/CABG), peripheral vascular disease and stroke.

ACS presentation type, angiographic characteristics and acute outcomes are shown in Table 2. Smokers at time of ACS were more likely to present with STEMI, have single vessel CAD and receive a bare-metal stent. They also had earlier discharge from hospital. The use of secondary prevention pharmacotherapy across all groups is depicted in Table 3.

Clinical Outcomes

Unadjusted survival at mean follow-up of 3.9±2.2 years showed quitters had lower death rates than persistent smokers, non-smokers or ex-smokers (5.3%

vs. 8.2% vs. 9.6% vs. 12.1%, respectively; p<0.001). The full details of 12-month clinical outcomes and survival are shown in Table 4. On multivariate analysis being an ex-smoker (HR 1.03, 95% CI 0.87-1.22) or a quitter (HR 1.27, 95% CI 0.96–1.67) was not associated with an increased hazard compared to non-smokers but being a persistent smoker was associated with increased hazard (HR 1.78, 95% CI 1.36 – 2.32) (Table 5 and Figure 3). There was no evidence of any violation of the proportional hazards assumption as based on Schoenfeld residuals with a global test of chi2=8.34 with 14 degrees of freedom, p=0.784.

DISCUSSION

In a contemporary cohort of patients presenting with ACS and treated with PCI and optimal secondary prevention pharmacotherapy, only 54% of patients stopped smoking by 30-days. Persistent smokers at 30 days post PCI experienced an almost two-fold increase in long-term mortality. Patients who quit smoking had a survival rate at 4 years that was similar to that of a life-long non-smoker.

Cigarette smoking is a well-established cardiovascular risk factor and continues to be a major preventable cause of death. Ezzati *et al* estimated 11% (1.62 million) of all global cardiovascular deaths in 2000 were attributable to smoking.[1] Although the prevalence of smoking in the general population has decreased over the past 50 years in the United States, in our study the proportion of current smokers at time of ACS did not change significantly over 9 years.[17] This emphasizes the malignant pathophysiological effects of smoking, namely endothelial dysfunction, thrombogenicity and coronary vasoconstriction, which predispose patients to ACS events.[18] Indeed, the significant role of smoking in the pathogenesis of ACS is further highlighted by the fact smokers were younger and lower rates of diabetes, hypertension and hypercholesterolaemia.

Smoking cessation is difficult, even after life-threatening events such as acute coronary syndromes. Systematic reviews have reported smoking cessation rates averaging around 50% in patients with coronary heart disease; this is consistent with the rates observed in our study.[2-4] In addition we found 23% of those who quit smoking at 30-days had relapsed at 12-months highlighting the difficulty of long-term abstinence. The severity of presentation may be a strong trigger to quit as a smoking cessation rate of 74% was reported in one study with STEMI patients alone.[10] We also observed this in our study as patients presenting with STEMI were more likely to quit compared to those presenting with NSTEMI or unstable angina. Implementation of smoking cessation strategies is crucial and the index hospitalization provides a perfect opportunity for this. Indeed a

Cochrane review showed that smoking cessation rates were higher if counseling and pharmacotherapy were initiated during hospital admission.[19]

The "smoker's paradox" in patients with acute coronary syndromes suggests there could be potential survival benefit seen in smokers.[20] In our study, smokers had lower unadjusted mortality rates at 12-months and long-term. However, when accounting for baseline differences in age and co-morbidities, smoking status was no longer associated with improved survival, thus suggesting debunking of the "smoker's paradox". This is supported by a systematic review showing only studies in the pre-thrombolytic and thrombolytic era supporting the paradox, while none of the contemporary studies do.[20]

The cardiovascular risk associated with smoking appears to dissipate within 3 years of cessation.[21 22] Systematic reviews have shown smoking cessation to be associated with a 35% relative risk reduction in patients with coronary heart disease and up to 46% in those with a myocardial infarction.[2-4] A limitation of these reviews is the inclusion of a significant proportion of patients from an era preceding percutaneous coronary intervention and optimal secondary prevention pharmacotherapy. More recent studies assessing the impact of smoking status following ACS have had suboptimal rates of revascularization or medical management.[6-10] Other studies did not assess the hazard of persistent smoking.[7 11 12] In our study, persistent smoking after ACS was associated with an increased relative mortality risk of 78% at 4 years. The mortality hazard in our study was lower than the one described in a study of STEMI patients by Kinjo et al (HR 1.78 vs. 2.27). Although their revascularization rate was high (>85%), only 30% of patients received statin therapy. Thus, it could be hypothesized that our higher rate of statin therapy may be responsible for our lower long-term mortality risk. What is unquestionable, as observed in our study, is that a substantial residual mortality risk remains in patients who persist with smoking despite optimal contemporary management with PCI and optimal secondary prevention pharmacotherapy. This increased risk is of similar magnitude to those seen from earlier cardiology eras.[2-4]

Encouragingly, smoking cessation is beneficial and by 4 years our cohort of quitters had a mortality hazard approaching that of life-long non-smokers. This is theoretically plausible as the deleterious hazards of smoking appear to be reversed within this time frame and cardiac risk has been shown to return to baseline.[18 21 22] Although complete smoking abstinence is difficult, as previously discussed, Gerber *et al* showed that even a five cigarette a day reduction is associated with an 18% decline in mortality.[8] Again this highlights the importance of smoking cessation or even smoking reduction in secondary prevention.

Our study has a number of limitations. Firstly, inherent to all studies assessing the impact of persistent smoking and cessation, the associations described in our study could be attributed, at least partly, to unaccounted or unmeasured variables. In particular, we did not account for the participation in cardiac rehabilitation programs or for smoking cessation strategies utilized. Secondly, we have measured smoking status at one time point and even at 12-months there were a significant number of patients who changed their smoking habits and thus were initially misclassified. We chose smoking cessation at 30-days to assess the impact of the admission with ACS and early medical intervention. Thirdly, we ascertained smoking status by self-report. Although it has been shown to correlate with biochemical assessment in a meta-analysis, there is always a potential for misclassification.[23] Lastly, we do not collect a detailed smoking history and thus we could not quantify the mortality hazard based on the quantity of cigarettes smoked over a lifetime, nor could we quantify the benefit of cessation based on the time since the last cigarette was smoked.

CONCLUSION

Patients who continued to smoke after an ACS had a nearly two-fold mortality hazard while those who quit had comparable survival to a non-smoker. This underscores the importance of smoking cessation in secondary prevention, despite the improvement in management of ACS with percutaneous coronary intervention and optimal medical therapy.

Figure 1. Smokers at Baseline, 30-days and 12-months

* Includes only those patients alive at 12 months.
Recent quitters were smokers at baseline but had quit by 30 days. Persistent smokers were smokers at baseline and were still smoking 30 days and 12 months post ACS. Relapsed smokers were smoking at 12 months although they temporarily quit at 30 days.

Figure 2. Trends in Smoking Status in ACS Survivors at 30-days

Figure 3. Cox Proportional Hazard Regression Survival Curve

Table 1. Baseline clinical characteristics N(%) stratified by smoking status at 30-days

	Non-Smoker (N=2,728)	Ex-Smoker (N=3,712)	Recent Quitter (N=1,612)	Persistent Smoker (N=1,323)	P
Age (mean±SD years)	67.0±12.3	67.0±11.5	56.1±10.2	56.7±10.6	<0.001
Age >75 years	857 (31.4)	1,093 (29.5)	74 (4.6)	82 (6.2)	<0.001
Male	1,753 (64.3)	3,038 (81.8)	1,310 (81.3)	1,028 (77.7)	<0.001
BMI (mean±SD kg/m^2)	28.0±5.3	28.4±5.1	28.4±5.3	28.2±5.6	0.004
Hypertension	1,738 (63.7)	2,628 (70.8)	752 (46.7)	701 (53.0)	<0.001
Hypercholesterolaemia	1,665 (61.1)	2,627 (70.8)	895 (55.6)	806 (61.1)	<0.001
Diabetes Mellitus	630 (23.1)	1,014 (27.3)	216 (13.4)	244 (18.4)	<0.001
Family History of CAD	964 (35.5)	1,412 (38.3)	704 (44.1)	554 (42.2)	<0.001
Previous MI	444 (16.3)	1,043 (28.1)	183 (11.4)	249 (18.8)	<0.001
Previous PCI	445 (16.3)	884 (23.8)	168 (10.4)	222 (16.8)	<0.001
Previous CABG	159 (5.8)	378 (10.2)	29 (1.8)	43 (3.3)	<0.001
Congestive Heart Failure	83 (3.0)	167 (4.5)	12 (0.8)	30 (2.3)	<0.001
PVD	92 (3.4)	313 (8.4)	55 (3.4)	83 (6.3)	<0.001
Stroke	157 (5.8)	293 (7.9)	46 (2.9)	61 (4.6)	<0.001
Chronic Lung Disease	166 (6.1)	516 (13.9)	118 (7.3)	170 (12.9)	<0.001
eGFR ≥ 60ml/min/1.73m^2	1,970 (74.3)	2,726 (74.9)	1,384 (89.4)	1,135 (88.9)	<0.001
Ejection Fraction >45%	1,791 (72.2)	2,311 (70.5)	1,077 (71.9)	846 (70.6)	0.61

SD = standard deviation. BMI = body mass index. CAD = coronary artery disease. MI = myocardial infarction. PCI = percutaneous coronary intervention. CABG = coronary artery bypass graft surgery. PVD = peripheral vascular disease. eGFR = estimated glomerular filtration rate.

Table 2. ACS presentation, angiographic characteristics and acute outcomes N(%) by smoking status at 30-days

	Non-Smoker (N=2,728)	Ex-Smoker (N=3,712)	Recent Quitter (N=1,612)	Persistent Smoker (N=1,323)	P
STEMI	1243 (45.6)	1430 (38.5)	971 (60.2)	615 (46.5)	
NSTEMI	1100 (40.3)	1591 (42.9)	547 (33.9)	559 (42.3)	
Unstable Angina	385(14.1)	691 (18.6)	94 (5.8)	149 (11.3)	<0.001
Multivessel CAD	1507 (55.3)	2291 (61.8)	806 (50.2)	655 (49.7)	<0.001
Left main disease	21 (0.8)	55 (1.5)	3 (0.2)	4 (0.3)	<0.001
Balloon angioplasty only	162 (5.9)	236 (6.4)	66 (4.1)	50 (3.8)	<0.001
Bare Metal Stent	1356 (49.7)	1949 (52.5)	918 (57.0)	781 (59.0)	
Drug Eluting Stent	1210 (44.4)	1527 (41.1)	628 (39.0)	492 (37.2)	<0.001
Number of stents inserted (mean±SD)	1.2±0.6	1.2±0.6	1.2±0.6	1.2±0.6	0.44
Successful PCI	2728 (100)	3711 (100)	1612 (100)	1322 (99.9)	0.42
New Renal impairment	34 (1.3)	35 (0.9)	10 (0.6)	4 (0.3)	0.01
New Heart Failure	130 (4.8)	151 (4.1)	53 (3.3)	26 (2.0)	<0.001
Length of stay (mean±SD days)	5.2±5.2	5.2±5.5	4.5±4.1	4.1±3.4	<0.001

STEMI = ST-segment elevation myocardial infarction. NSTEMI = non- ST-segment elevation myocardial infarction. CAD = coronary artery disease. SD = standard deviation. PCI = percutaneous coronary intervention.

Table 3. Cardiovascular pharmacotherapy N(%) at 30-days by smoking status at 30-days

	Non-Smoker (N=2,728)	Ex-Smoker (N=3,712)	Recent Quitter (N=1,612)	Persistent Smoker (N=1,323)	P
Aspirin	2665 (97.7)	3620 (97.5)	1593 (98.8)	1299 (98.2)	0.02
P2Y12 inhibitor	2409 (88.3)	3301 (88.9)	1423 (88.3)	1204 (91.0)	0.06
Statin	2610 (95.7)	3523 (94.9)	1583 (98.2)	1279 (96.7)	<0.001
Beta-blocker	2328 (85.3)	3019 (81.3)	1380 (85.6)	1120 (84.7)	<0.001
ACE-I/ARB	2313 (84.8)	3105 (83.7)	1381 (85.7)	1070 (80.9)	0.002
Warfarin	259 (9.5)	295 (8.0)	111 (6.9)	84 (6.4)	0.001
Spironolactone	66 (2.4)	96 (2.6)	11 (0.7)	29 (2.2)	<0.001
Eplerenone	60 (2.2)	67 (1.8)	38 (2.4)	30 (2.3)	0.49
Ezetimibe	82 (3.0)	219 (5.9)	34 (2.1)	32 (2.4)	<0.001
Fibrate	27 (1.0)	62 (1.7)	16 (1.0)	20 (1.5)	0.06

ACE-I = Angiotensin converting enzyme inhibitor. ARB = angiotensin receptor blocker.

Table 4. Clinical outcomes N(%) by smoking status at 30-days

	Non-Smoker (N=2,728)	Ex-Smoker (N=3,712)	Recent Quitter (N=1,612)	Persistent Smoker (N=1,323)	P
Long-term Mortality	262 (9.6)	450 (12.1)	86 (5.3)	108 (8.2)	<0.001
12-month Mortality	50 (1.9)	100 (2.8)	13 (0.9)	18 (1.4)	<0.001
12-month MI	122 (4.7)	222 (6.2)	51 (3.3)	56 (4.5)	<0.001
12-month Stroke	28 (1.1)	37 (1.0)	9 (0.6)	9 (0.7)	0.3
12-month TVR	182 (7.0)	272 (7.6)	118 (7.7)	65 (5.2)	0.03
12-month MACCE	309 (11.9)	488 (13.7)	157 (10.2)	117 (9.3)	<0.001

MI = myocardial infarction. TVR = target-vessel revascularization. MACCE = major adverse cardiovascular events.

Table 5. Estimates of hazard ratio and 95% confidence interval of predictors of long-term mortality using Cox-proportional hazards analysis

	Hazard Ratio	95% Confidence Interval	p-value
Unadjusted			
Non-smoker	Reference	-	-
Ex-smoker	1.21	1.03 – 1.40	0.02
Recent Quitter	0.51	0.40 – 0.65	<0.001
Persistent Smoker	0.82	0.65 – 1.03	0.08
Multivariate analysis			
Non-smoker	Reference	-	-
Ex-smoker	1.03	0.87 – 1.22	0.72
Quitter	1.27	0.96 – 1.68	0.10
Persistent Smoker	1.78	1.36 – 2.32	<0.001
Age (per year)	1.07	1.06 – 1.08	<0.001
Multivessel CAD	1.43	1.21 – 1.69	<0.001
Drug-eluting stent	0.78	0.67- 0.92	0.002
eGFR ≥60ml/min/1.73m²	Reference	-	-
eGFR 30-59ml/min/1.73m²	1.47	1.24 – 1.73	<0.001
eGFR <30 ml/min/1.73m²	3.83	2.96 – 4.94	<0.001
EF > 45%	Reference	-	-
EF 30-45%	1.55	1.33 – 1.80	<0.001
EF <30%	1.60	1.12 – 2.29	0.010
Diabetes Mellitus	1.51	1.29 – 1.77	<0.001
Peri-procedural MI	1.33	1.13 – 1.56	<0.001
Peripheral vascular disease	1.65	1.35 – 2.02	<0.001
Chronic lung disease	1.73	1.44 – 2.08	<0.001

CAD = coronary artery disease. eGFR = estimated glomerular filtration rate. EF = ejection fraction. MI = myocardial infarction.

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Contributorship Statement: MY, OF, DC developed the project concept and research hypothesis. MY, DC drafted the manuscript. NA, AB, CR provided statistical support. OF, AA, KK, JL, CH, EO, SD critically revised the manuscript for intellectual content. All authors read and approved the final document.

Transparency Declaration: The lead author, Associate Professor David Clark, affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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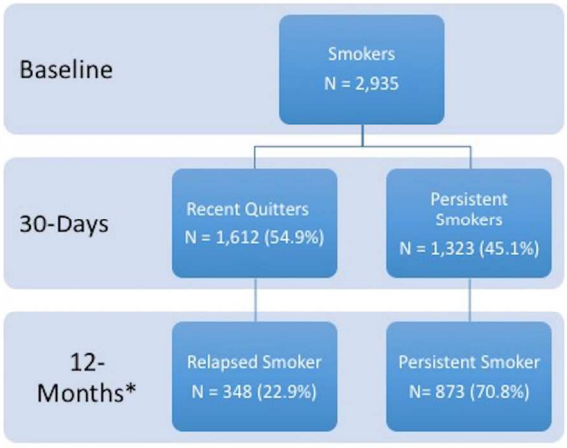

Figure 1. Smokers at Baseline, 30-days and 12-months

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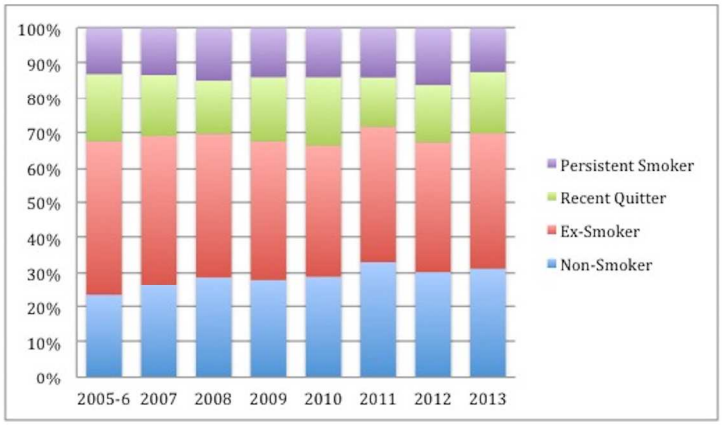

Figure 2. Trends in Smoking Status in ACS Survivors at 30-days

254x142mm (300 x 300 DPI)

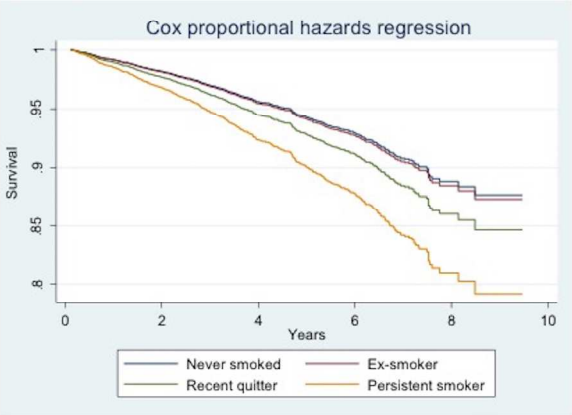

Figure 3. Cox Proportional Hazard Regression Survival Curve

254x142mm (300 x 300 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract – **Evident in the title (page 1, line 2)**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found – **Evident in Abstract (Page 2)**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported – **Evident in Background (Page 4, line 6-26)**
Objectives	3	State specific objectives, including any prespecified hypotheses **- Evident in Background (Page 4, line 30-35)**
Methods		
Study design	4	Present key elements of study design early in the paper **– Evident in Methods (Page 5, line 6-10)**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **- Evident in Methods (Page 5, line 22-27)**
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up **- Evident in Methods (Page 5, line 42-56)** *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls **– N/A** *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants **– N/A**
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed **– N/A** *Case-control study*—For matched studies, give matching criteria and the number of controls per case **– N/A**
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **- Evident in Methods (Page 6, line 32-40)**
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 **– Evident in Methods (Page 7, line 11-29)**
Bias	9	Describe any efforts to address potential sources of bias **– Evident in Methods (Page 7, line 24-29) including details of multivariate analysis**
Study size	10	Explain how the study size was arrived at **– it was based on a study period, not a particular sample size as described in Methods (Page 5, line 6-10)**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **– Described in Methods (Page 7, line 11-18)**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding **– Described in Methods (Page 7, line 12-29)**
		(*b*) Describe any methods used to examine subgroups and interactions **- N/A**
		(*c*) Explain how missing data were addressed – **N/A (consecutive patients**

	included)
	(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed – **linkage to the Australian National Death Index allowed complete follow-up of patients. Described in Methods (Page 6, line 32-48)** *Case-control study*—If applicable, explain how matching of cases and controls was addressed – **N/A** *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy – **N/A**
	(*e*) Describe any sensitivity analyses – **N/A**

Continued on next page

Results		
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 – **(page 8, line 7-8) All consecutive patients alive at 30-days were included. They were linked to the Australian National Death Index**
		(b) Give reasons for non-participation at each stage – **N/A**
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders – **Evident in Tables 1, 2 and 3. (Pages 17-19)**
		(b) Indicate number of participants with missing data for each variable of interest – **Evident in Tables 1, 2 and 3. (Pages 17-19)**
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount) – **Evident in Results (Page 8, line 56-57)**
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time – **Evident in Tables 4 (Pages 20)**
		Case-control study—Report numbers in each exposure category, or summary measures of exposure – **N/A**
		Cross-sectional study—Report numbers of outcome events or summary measures
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. **Evident in Methods (page 7, line 15-20). Tables 4 and 5 (Pages 20-21)**
		(*b*) Report category boundaries when continuous variables were categorized – **Evident in Tables 1-3**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives – **Evident in Discussion (Page 10, line 6-16)**
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 - **Evident in Discussion (Page 12, line 22-44)**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence - **Evident in Conclusion (Page 13, line 7-14)**
Generalisability	21	Discuss the generalisability (external validity) of the study results – **Evident throughout Discussion section (Pages 10-12)**
Other information		
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 – **There was no funding for the study.**

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

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 www.strobe-statement.org.

BMJ Open

The Prognostic Significance of Smoking Cessation After Acute Coronary Syndromes: An Observational, Multicentre Study from the Melbourne Interventional Group Registry

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Keywords:	smoking, secondary prevention, acute coronary syndromes, long-term mortality, percutaneous coronary intervention

The Prognostic Significance of Smoking Cessation After Acute Coronary Syndromes: An Observational, Multicentre Study from the Melbourne Interventional Group Registry

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Keywords: smoking; secondary prevention; acute coronary syndromes; long-term mortality; percutaneous coronary intervention

STRUCTURED ABSTRACT

Objective:

We aim to ascertain the prognostic significance of persistent smoking and smoking cessation after an acute coronary syndrome (ACS) in the era of percutaneous coronary intervention (PCI) and optimal secondary prevention pharmacotherapy.

Methods:

Consecutive patients from the Melbourne Interventional Group registry (2005-2013) who were alive at 30-days post-ACS presentation were included in our observational cohort study. Patients were divided into four categories based on their smoking status: non-smoker; ex-smoker (quit >1 month before ACS); recent quitter (smoker at presentation but quit by 30-days); and persistent smoker (smoker at presentation and at 30-days). The primary endpoint was survival ascertained through the Australian National Death Index linkage. A Cox-proportional hazards model was used to estimate the adjusted hazard ratio and 95% confidence interval (CI) for survival.

Results:

Of the 9,375 patients included, 2,728 (29.1%) never smoked, 3,712 (39.6%) were ex-smokers, 1,612 (17.2%) were recent quitters and 1,323 (14.1%) were persistent smokers. Cox-proportional hazard modelling revealed, compared to those who had never smoked, that persistent smoking (HR 1.78, 95% CI 1.36-2.32, p<0.001) was an independent predictor of increased hazard (mean follow-up 3.9±2.2 years) while being a recent quitter (HR 1.27, 95% CI 0.96-1.68, p=0.10) or an ex-smoker (HR 1.03, 95% CI 0.87-1.22, p=0.72) were not.

Conclusions:

In a contemporary cohort of patients with ACS, those who continued to smoke had an 80% risk of lower survival while those who quit had comparable survival to lifelong non-smokers. This underscores the importance of smoking cessation in secondary prevention despite the improvement in management of ACS with PCI and pharmacotherapy.

Strengths and Limitations

- The main strength of this study is the assessment of smoking cessation in a large contemporary population who were treated with PCI and optimal medical therapy; something which has not been explored.
- Patients' smoking habits can change over time and thus our study is limited by the assessment of smoking status at only one time point.

BACKGROUND

Smoking is a well-recognized risk factor for coronary heart disease and accounts for 11% of cardiovascular deaths worldwide.[1] Smoking cessation has been consistently associated with a mortality benefit in both stable coronary artery disease and post acute coronary syndromes (ACS).[2-4] Consequently, smoking cessation is one of the cornerstones of secondary prevention.[5]

However, the hazard of persistent smoking post ACS in contemporary cardiology has not been described. Systematic reviews and meta-analysis have predominantly included studies from the pre-percutaneous coronary intervention era. [2-4] More recent studies assessing the impact of smoking post ACS have focused primarily on younger (<35 years)[6] or older populations (>65 years),[7] have had low rates of revascularization,[6-9] had suboptimal medical management[10] or did not assess the impact of smoking cessation.[7 11 12]

Thus we aimed to assess the impact of persistent smoking or cessation at 30-days compared to non-smokers, on survival in patients treated with percutaneous coronary intervention (PCI) and optimal secondary prevention pharmacotherapy.

METHODS

The study cohort included consecutive patients enrolled in the Melbourne Interventional Group (MIG) registry who underwent their index PCI for management of ACS between January 2005 and November 2013.

The MIG registry is a multicentre PCI registry and has been previously described in detail.[13] Briefly, demographic, clinical, procedural and in-hospital outcome data are prospectively recorded on case-report forms using standardized definitions for all fields with follow up performed at 30 days and 12 months.[14]

The registry is coordinated by the Centre of Cardiovascular Research and Education in Therapeutics; an independent research body within the School of Public Health and Preventive Medicine at Monash University (Melbourne, Australia). An audit of a number of verifiable fields from 5% of randomly selected procedures at each institution is undertaken periodically.[15] In the most recent audit, 27 fields were assessed with data accuracy of 98%. This compares favorably to audits from other large registries.[16] The ethics committee in each participating hospital has approved the MIG registry, including the use of "opt-out" consent. This means that consent is presumed unless the patient "opts out" after giving each patient a "Patient Information Sheet". If a patient informs a staff member that they do not wish to participate, the patient's data are not collected.

Patients who underwent PCI for acute coronary syndrome (ACS) and survived to 30-days were included. ACS encompasses the spectrum of ST-elevation myocardial infarction (STEMI), non-ST-elevation myocardial infarction (NSTEMI) and unstable angina. STEMI was defined as ECG changes (new ST-segment elevation at the J-point or development of Q-waves in two or more contiguous leads) with confirmed myocardial necrosis (elevation in troponin T or I or CK-MB on at least one occasion within 24 hours from the index event). NSTEMI was defined as biomarker elevation consistent with myocardial necrosis and one of: either ST-segment depression or T-wave abnormality on ECG; or

ischaemic symptoms. Unstable angina is defined by clinical history suggestive of progressive, unstable ischaemic symptoms without cardiac biomarker elevation.

Acute management of all patients including interventional strategy, stent selection and antithrombotic therapy were left at the discretion of the operator in all procedures. Optimal secondary prevention pharmacotherapy was encouraged according to guidelines. No records were made of contraindications to medications or decisions regarding use/omission of particular guideline-directed therapies.

Patients were divided into four groups based on their smoking status at 30-days. Those who never smoked tobacco were included in the non-smoker group. Those who had quit smoking more than one month prior to ACS were classified as ex-smokers. Recent quitters were smokers at baseline but had quit by 30-days. Persistent smokers were smokers at baseline and were still smoking 30-days post ACS.

The primary outcome was subsequent survival in those patients who were alive at 30 days post ACS. Survival status was obtained by linkage to the Australian National Death Index (NDI). The Australian NDI is a database housed at the Australian Institute of Health and Welfare, which contains records of all deaths occurring in Australia since 1980. Data are obtained from the registries of births, deaths, and marriages in each state and territory. The following variables for each deceased patient were identified: name, date of birth (or estimated year of birth), age at death, gender, date of death, state/territory of registration, and registration number. Successful matching of patients through this linkage process was achieved in 99.4% of patients in the MIG registry.

Secondary outcomes were 12-month mortality, myocardial infarction, stroke and major adverse cardiovascular events (MACCE). 12-month MACCE was defined as the combination of mortality, myocardial infarction (MI), stroke and target vessel revascularization. MI was defined as: an increase in creatine kinase or creatine kinase-MB ≥3 times the upper limit of normal; and/or a significant ST-

segment change, development of new Q waves in ≥2 contiguous electrocardiographic leads, or new left branch bundle block pattern in the context of new clinical symptoms.

Statistical Analysis

Continuous variables are expressed as mean ± standard deviation (SD), and categorical data are expressed as numbers/percentages. Continuous variables were compared using Kruskal-Wallis equality-of-populations rank test. Categorical variables were compared using Fisher's exact or Pearson's chi-square tests as appropriate. Variables were tested for linear trends across the years 2005-2013 using Stata's *nptrend* command. This is a nonparametric test for trend across ordered groups that is an extension of the Wilcoxon rank-sum test. Cumulative incidence of mortality was estimated by the Kaplan-Meier method and the log-rank test was used to evaluate differences between groups. Cox-proportional hazards regression was used to estimate the adjusted hazard ratio and 95% confidence interval (CI) for survival. Univariate variables with $p<0.10$ were included for stepwise removal for the final multivariate model. The variables considered were: smoking status, age, sex, eGFR, hypertension, diabetes, hypercholesterolaemia, family history of coronary disease, previous MI, previous PCI, previous CABG, heart failure, peripheral vascular disease, cerebrovascular disease, left ventricular ejection fraction, multi-vessel CAD, angina type, chronic lung disease, cardiogenic shock, glycoprotein IIb/IIIa use, drug-eluting stent use and treated left main lesion.

All statistical analyses were performed using Stata 13.1, StataCorp LP, College Station, TX, USA. P-values < 0.05 were considered to be statistically significant.

RESULTS

Of the 9,375 survivors following PCI for ACS at 30 days, 2,728 (29.1%) had never smoked, 3,712 (39.6%) were ex-smokers, 1,612 (17.2%) were recent quitters (smokers at the time of ACS but quit by 30-days) and 1,323 (14.1%) were persistent smokers. The smoking cessation rate at 30-days post ACS was 54.9%. Of the patients alive at 12-months, 23% of quitters had relapsed and 71% of persistent smokers continued to smoke (Figure 1).

Trends in smoking status

Figure 2 depicts the trends in smoking status over the 9-year period from 2005 to 2013. The percentage of non-smokers presenting with ACS increased over the time period while the rate of ex-smokers has decreased (p-value for trend =0.02). There has been no significant change in the trend of smokers presenting with ACS.

Clinical characteristics

Baseline clinical characteristics stratified by smoking status at 30-days are shown in Table 1. It is evident smokers at the time of ACS (subsequent quitters and persistent smokers) were younger, had less co-morbidities but a higher rate of a family history of premature CAD. Compared to quitters, persistent smokers were more likely to have had previously documented CAD (high rates of previous MI/PCI/CABG), peripheral vascular disease and stroke.

ACS presentation type, angiographic characteristics and acute outcomes are shown in Table 2. Smokers at time of ACS were more likely to present with STEMI, have single vessel CAD and receive a bare-metal stent. They also had earlier discharge from hospital. The use of secondary prevention pharmacotherapy across all groups is depicted in Table 3.

Clinical Outcomes

Unadjusted survival at mean follow-up of 3.9±2.2 years showed quitters had lower death rates than persistent smokers, non-smokers or ex-smokers (5.3%

vs. 8.2% vs. 9.6% vs. 12.1%, respectively; p<0.001). The full details of 12-month clinical outcomes and survival are shown in Table 4. On multivariate analysis being an ex-smoker (HR 1.03, 95% CI 0.87-1.22) or a quitter (HR 1.27, 95% CI 0.96–1.67) was not associated with an increased hazard compared to non-smokers but being a persistent smoker was associated with increased hazard (HR 1.78, 95% CI 1.36 – 2.32) (Table 5 and Figure 3). There was no evidence of any violation of the proportional hazards assumption as based on Schoenfeld residuals with a global test of chi2=8.34 with 14 degrees of freedom, p=0.784.

DISCUSSION

In a contemporary cohort of patients presenting with ACS and treated with PCI and optimal secondary prevention pharmacotherapy, only 54% of patients stopped smoking by 30-days. Persistent smokers at 30 days post PCI experienced an almost two-fold increase in long-term mortality. Patients who quit smoking had a survival rate at 4 years that was similar to that of a life-long non-smoker.

Cigarette smoking is a well-established cardiovascular risk factor and continues to be a major preventable cause of death. Ezzati *et al* estimated 11% (1.62 million) of all global cardiovascular deaths in 2000 were attributable to smoking.[1] Although the prevalence of smoking in the general population has decreased over the past 50 years in the United States, in our study the proportion of current smokers at time of ACS did not change significantly over 9 years.[17] This emphasizes the malignant pathophysiological effects of smoking, namely endothelial dysfunction, thrombogenicity and coronary vasoconstriction, which predispose patients to ACS events.[18] Indeed, the significant role of smoking in the pathogenesis of ACS is further highlighted by the fact smokers were younger and lower rates of diabetes, hypertension and hypercholesterolaemia.

Smoking cessation is difficult, even after life-threatening events such as acute coronary syndromes. Systematic reviews have reported smoking cessation rates averaging around 50% in patients with coronary heart disease; this is consistent with the rates observed in our study.[2-4] In addition we found 23% of those who quit smoking at 30-days had relapsed at 12-months highlighting the difficulty of long-term abstinence. The severity of presentation may be a strong trigger to quit as a smoking cessation rate of 74% was reported in one study with STEMI patients alone.[10] We also observed this in our study as patients presenting with STEMI were more likely to quit compared to those presenting with NSTEMI or unstable angina. Implementation of smoking cessation strategies is crucial and the index hospitalization provides a perfect opportunity for this. Indeed a

Cochrane review showed that smoking cessation rates were higher if counseling and pharmacotherapy were initiated during hospital admission.[19]

The "smoker's paradox" in patients with acute coronary syndromes suggests there could be potential survival benefit seen in smokers.[20] In our study, smokers had lower unadjusted mortality rates at 12-months and long-term. However, when accounting for baseline differences in age and co-morbidities, smoking status was no longer associated with improved survival, thus suggesting debunking of the "smoker's paradox". This is supported by a systematic review showing only studies in the pre-thrombolytic and thrombolytic era supporting the paradox, while none of the contemporary studies do.[20]

The cardiovascular risk associated with smoking appears to dissipate within 3 years of cessation.[21 22] Systematic reviews have shown smoking cessation to be associated with a 35% relative risk reduction in patients with coronary heart disease and up to 46% in those with a myocardial infarction.[2-4] A limitation of these reviews is the inclusion of a significant proportion of patients from an era preceding percutaneous coronary intervention and optimal secondary prevention pharmacotherapy. More recent studies assessing the impact of smoking status following ACS have had suboptimal rates of revascularization or medical management.[6-10] Other studies did not assess the hazard of persistent smoking.[7 11 12] In our study, persistent smoking after ACS was associated with an increased relative mortality risk of 78% at 4 years. The mortality hazard in our study was lower than the one described in a study of STEMI patients by Kinjo et al (HR 1.78 vs. 2.27). Although their revascularization rate was high (>85%), only 30% of patients received statin therapy. Thus, it could be hypothesized that our higher rate of statin therapy may be responsible for our lower long-term mortality risk. What is unquestionable, as observed in our study, is that a substantial residual mortality risk remains in patients who persist with smoking despite optimal contemporary management with PCI and optimal secondary prevention pharmacotherapy. This increased risk is of similar magnitude to those seen from earlier cardiology eras.[2-4]

Encouragingly, smoking cessation is beneficial and by 4 years our cohort of quitters had a mortality hazard approaching that of life-long non-smokers. This is theoretically plausible as the deleterious hazards of smoking appear to be reversed within this time frame and cardiac risk has been shown to return to baseline.[18 21 22] Although complete smoking abstinence is difficult, as previously discussed, Gerber *et al* showed that even a five cigarette a day reduction is associated with an 18% decline in mortality.[8] Again this highlights the importance of smoking cessation or even smoking reduction in secondary prevention.

Our study has a number of limitations. First, inherent to all studies assessing the impact of persistent smoking and cessation, the associations described in our study could be attributed, at least partly, to unaccounted or unmeasured variables. In particular, we did not account for the participation in cardiac rehabilitation programs or for smoking cessation strategies utilized. Second, we have measured smoking status at one time point and even at 12-months there were a significant number of patients who changed their smoking habits and thus were initially misclassified. We chose smoking cessation at 30-days to assess the impact of the admission with ACS and early medical intervention. Third, we ascertained smoking status by self-report. Although it has been shown to correlate with biochemical assessment in a meta-analysis, there is always a potential for misclassification.[23] Fourth, we have only included ACS patients treated with PCI which limits the generalizability of our results to this patient population. Fifth, we included repeated admissions as separate cases which raises the possibility of multiple counting. Lastly, we do not collect a detailed smoking history and thus we could not quantify the mortality hazard based on the quantity of cigarettes smoked over a lifetime, nor could we quantify the benefit of cessation based on the time since the last cigarette was smoked. Future research should focus on collecting and analyzing this data to more accurately quantify the effect of smoking post ACS.

CONCLUSION

Patients who continued to smoke after an ACS had a nearly two-fold mortality hazard while those who quit had comparable survival to a non-smoker. This underscores the importance of smoking cessation in secondary prevention, despite the improvement in management of ACS with percutaneous coronary intervention and optimal medical therapy.

Figure 1. Smokers at Baseline, 30-days and 12-months

* Includes only those patients alive at 12 months.
Recent quitters were smokers at baseline but had quit by 30 days. Persistent smokers were smokers at baseline and were still smoking 30 days and 12 months post ACS. Relapsed smokers were smoking at 12 months although they temporarily quit at 30 days.

Figure 2. Trends in Smoking Status in ACS Survivors at 30-days

Figure 3. Cox Proportional Hazard Regression Survival Curve

Table 1. Baseline clinical characteristics N(%) stratified by smoking status at 30-days

	Non-Smoker (N=2,728)	Ex-Smoker (N=3,712)	Recent Quitter (N=1,612)	Persistent Smoker (N=1,323)	P
Age (mean±SD years)	67.0±12.3	67.0±11.5	56.1±10.2	56.7±10.6	<0.001
Age >75 years	857 (31.4)	1,093 (29.5)	74 (4.6)	82 (6.2)	<0.001
Male	1,753 (64.3)	3,038 (81.8)	1,310 (81.3)	1,028 (77.7)	<0.001
BMI (mean±SD kg/m^2)	28.0±5.3	28.4±5.1	28.4±5.3	28.2±5.6	0.004
Hypertension	1,738 (63.7)	2,628 (70.8)	752 (46.7)	701 (53.0)	<0.001
Hypercholesterolaemia	1,665 (61.1)	2,627 (70.8)	895 (55.6)	806 (61.1)	<0.001
Diabetes Mellitus	630 (23.1)	1,014 (27.3)	216 (13.4)	244 (18.4)	<0.001
Family History of CAD	964 (35.5)	1,412 (38.3)	704 (44.1)	554 (42.2)	<0.001
Previous MI	444 (16.3)	1,043 (28.1)	183 (11.4)	249 (18.8)	<0.001
Previous PCI	445 (16.3)	884 (23.8)	168 (10.4)	222 (16.8)	<0.001
Previous CABG	159 (5.8)	378 (10.2)	29 (1.8)	43 (3.3)	<0.001
Congestive Heart Failure	83 (3.0)	167 (4.5)	12 (0.8)	30 (2.3)	<0.001
PVD	92 (3.4)	313 (8.4)	55 (3.4)	83 (6.3)	<0.001
Stroke	157 (5.8)	293 (7.9)	46 (2.9)	61 (4.6)	<0.001
Chronic Lung Disease	166 (6.1)	516 (13.9)	118 (7.3)	170 (12.9)	<0.001
eGFR ≥ 60ml/min/1.73m^2	1,970 (74.3)	2,726 (74.9)	1,384 (89.4)	1,135 (88.9)	<0.001
Ejection Fraction >45%	1,791 (72.2)	2,311 (70.5)	1,077 (71.9)	846 (70.6)	0.61

SD = standard deviation. BMI = body mass index. CAD = coronary artery disease. MI = myocardial infarction. PCI = percutaneous coronary intervention. CABG = coronary artery bypass graft surgery. PVD = peripheral vascular disease. eGFR = estimated glomerular filtration rate.

Table 2. ACS presentation, angiographic characteristics and acute outcomes N(%) by smoking status at 30-days

	Non-Smoker (N=2,728)	Ex-Smoker (N=3,712)	Recent Quitter (N=1,612)	Persistent Smoker (N=1,323)	P
STEMI	1243 (45.6)	1430 (38.5)	971 (60.2)	615 (46.5)	
NSTEMI	1100 (40.3)	1591 (42.9)	547 (33.9)	559 (42.3)	
Unstable Angina	385(14.1)	691 (18.6)	94 (5.8)	149 (11.3)	<0.001
Multivessel CAD	1507 (55.3)	2291 (61.8)	806 (50.2)	655 (49.7)	<0.001
Left main disease	21 (0.8)	55 (1.5)	3 (0.2)	4 (0.3)	<0.001
Balloon angioplasty only	162 (5.9)	236 (6.4)	66 (4.1)	50 (3.8)	<0.001
Bare Metal Stent	1356 (49.7)	1949 (52.5)	918 (57.0)	781 (59.0)	
Drug Eluting Stent	1210 (44.4)	1527 (41.1)	628 (39.0)	492 (37.2)	<0.001
Number of stents inserted (mean±SD)	1.2±0.6	1.2±0.6	1.2±0.6	1.2±0.6	0.44
Successful PCI	2728 (100)	3711 (100)	1612 (100)	1322 (99.9)	0.42
New Renal impairment	34 (1.3)	35 (0.9)	10 (0.6)	4 (0.3)	0.01
New Heart Failure	130 (4.8)	151 (4.1)	53 (3.3)	26 (2.0)	<0.001
Length of stay (mean±SD days)	5.2±5.2	5.2±5.5	4.5±4.1	4.1±3.4	<0.001

STEMI = ST-segment elevation myocardial infarction. NSTEMI = non- ST-segment elevation myocardial infarction. CAD = coronary artery disease. SD = standard deviation. PCI = percutaneous coronary intervention.

Table 3. Cardiovascular pharmacotherapy N(%) at 30-days by smoking status at 30-days

	Non-Smoker (N=2,728)	Ex-Smoker (N=3,712)	Recent Quitter (N=1,612)	Persistent Smoker (N=1,323)	P
Aspirin	2665 (97.7)	3620 (97.5)	1593 (98.8)	1299 (98.2)	0.02
P2Y12 inhibitor	2409 (88.3)	3301 (88.9)	1423 (88.3)	1204 (91.0)	0.06
Statin	2610 (95.7)	3523 (94.9)	1583 (98.2)	1279 (96.7)	<0.001
Beta-blocker	2328 (85.3)	3019 (81.3)	1380 (85.6)	1120 (84.7)	<0.001
ACE-I/ARB	2313 (84.8)	3105 (83.7)	1381 (85.7)	1070 (80.9)	0.002
Warfarin	259 (9.5)	295 (8.0)	111 (6.9)	84 (6.4)	0.001
Spironolactone	66 (2.4)	96 (2.6)	11 (0.7)	29 (2.2)	<0.001
Eplerenone	60 (2.2)	67 (1.8)	38 (2.4)	30 (2.3)	0.49
Ezetimibe	82 (3.0)	219 (5.9)	34 (2.1)	32 (2.4)	<0.001
Fibrate	27 (1.0)	62 (1.7)	16 (1.0)	20 (1.5)	0.06

ACE-I = Angiotensin converting enzyme inhibitor. ARB = angiotensin receptor blocker.

Table 4. Clinical outcomes N(%) by smoking status at 30-days

	Non-Smoker (N=2,728)	Ex-Smoker (N=3,712)	Recent Quitter (N=1,612)	Persistent Smoker (N=1,323)	P
Long-term Mortality	262 (9.6)	450 (12.1)	86 (5.3)	108 (8.2)	<0.001
12-month Mortality	50 (1.9)	100 (2.8)	13 (0.9)	18 (1.4)	<0.001
12-month MI	122 (4.7)	222 (6.2)	51 (3.3)	56 (4.5)	<0.001
12-month Stroke	28 (1.1)	37 (1.0)	9 (0.6)	9 (0.7)	0.3
12-month TVR	182 (7.0)	272 (7.6)	118 (7.7)	65 (5.2)	0.03
12-month MACCE	309 (11.9)	488 (13.7)	157 (10.2)	117 (9.3)	<0.001

MI = myocardial infarction. TVR = target-vessel revascularization. MACCE = major adverse cardiovascular events.

Table 5. Estimates of hazard ratio and 95% confidence interval of predictors of long-term mortality using Cox-proportional hazards analysis

	Hazard Ratio	95% Confidence Interval	p-value
Unadjusted			
Non-smoker	Reference	-	-
Ex-smoker	1.21	1.03 – 1.40	0.02
Recent Quitter	0.51	0.40 – 0.65	<0.001
Persistent Smoker	0.82	0.65 – 1.03	0.08
Multivariate analysis			
Non-smoker	Reference	-	-
Ex-smoker	1.03	0.87 – 1.22	0.72
Quitter	1.27	0.96 – 1.68	0.10
Persistent Smoker	1.78	1.36 – 2.32	<0.001
Age (per year)	1.07	1.06 – 1.08	<0.001
Multivessel CAD	1.43	1.21 – 1.69	<0.001
Drug-eluting stent	0.78	0.67- 0.92	0.002
eGFR ≥60ml/min/1.73m²	Reference	-	-
eGFR 30-59ml/min/1.73m²	1.47	1.24 – 1.73	<0.001
eGFR <30 ml/min/1.73m²	3.83	2.96 – 4.94	<0.001
EF > 45%	Reference	-	-
EF 30-45%	1.55	1.33 – 1.80	<0.001
EF <30%	1.60	1.12 – 2.29	0.010
Diabetes Mellitus	1.51	1.29 – 1.77	<0.001
Peri-procedural MI	1.33	1.13 – 1.56	<0.001
Peripheral vascular disease	1.65	1.35 – 2.02	<0.001
Chronic lung disease	1.73	1.44 – 2.08	<0.001

CAD = coronary artery disease. eGFR = estimated glomerular filtration rate. EF = ejection fraction. MI = myocardial infarction.

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Transparency Declaration: The lead author, Associate Professor David Clark, affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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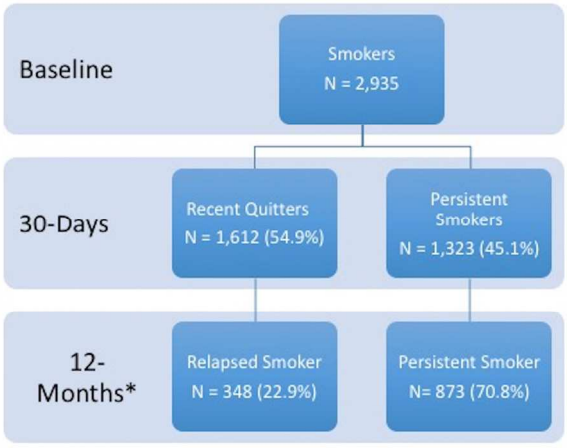

Figure 1. Smokers at Baseline, 30-days and 12-months

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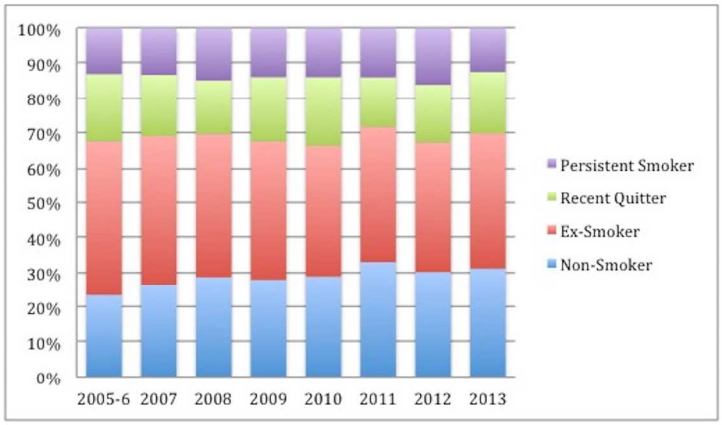

Figure 2. Trends in Smoking Status in ACS Survivors at 30-days

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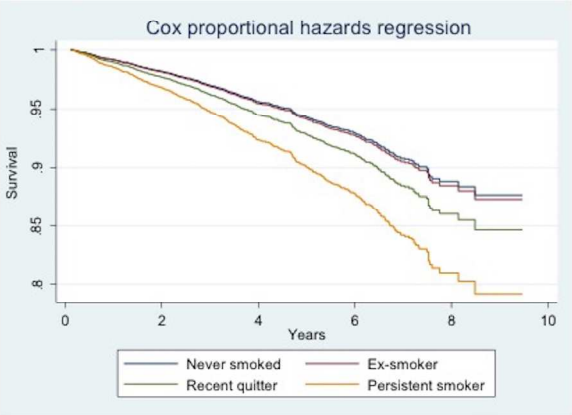

Figure 3. Cox Proportional Hazard Regression Survival Curve

254x142mm (300 x 300 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract – **Evident in the title (page 1, line 2)**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found – **Evident in Abstract (Page 2)**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported – **Evident in Background (Page 4, line 6-26)**
Objectives	3	State specific objectives, including any prespecified hypotheses **- Evident in Background (Page 4, line 30-35)**
Methods		
Study design	4	Present key elements of study design early in the paper **– Evident in Methods (Page 5, line 6-10)**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **- Evident in Methods (Page 5, line 22-27)**
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up **- Evident in Methods (Page 5, line 42-56)** *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls **– N/A** *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants **– N/A**
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed **– N/A** *Case-control study*—For matched studies, give matching criteria and the number of controls per case **– N/A**
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **- Evident in Methods (Page 6, line 32-40)**
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 **– Evident in Methods (Page 7, line 11-29)**
Bias	9	Describe any efforts to address potential sources of bias **– Evident in Methods (Page 7, line 24-29) including details of multivariate analysis**
Study size	10	Explain how the study size was arrived at **– it was based on a study period, not a particular sample size as described in Methods (Page 5, line 6-10)**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **– Described in Methods (Page 7, line 11-18)**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding **– Described in Methods (Page 7, line 12-29)**
		(*b*) Describe any methods used to examine subgroups and interactions **- N/A**
		(*c*) Explain how missing data were addressed – **N/A (consecutive patients**

included)
(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed – **linkage to the Australian National Death Index allowed complete follow-up of patients. Described in Methods (Page 6, line 32-48)** *Case-control study*—If applicable, explain how matching of cases and controls was addressed – **N/A** *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy – **N/A**
(*e*) Describe any sensitivity analyses – **N/A**

Continued on next page

Results		
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 – **(page 8, line 7-8) All consecutive patients alive at 30-days were included. They were linked to the Australian National Death Index**
		(b) Give reasons for non-participation at each stage – **N/A**
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders – **Evident in Tables 1, 2 and 3. (Pages 17-19)**
		(b) Indicate number of participants with missing data for each variable of interest – **Evident in Tables 1, 2 and 3. (Pages 17-19)**
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount) – **Evident in Results (Page 8, line 56-57)**
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time **– Evident in Tables 4 (Pages 20)**
		Case-control study—Report numbers in each exposure category, or summary measures of exposure – **N/A**
		Cross-sectional study—Report numbers of outcome events or summary measures
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. **Evident in Methods (page 7, line 15-20). Tables 4 and 5 (Pages 20-21)**
		(*b*) Report category boundaries when continuous variables were categorized **– Evident in Tables 1-3**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives **– Evident in Discussion (Page 10, line 6-16)**
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 **- Evident in Discussion (Page 12, line 22-44)**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **- Evident in Conclusion (Page 13, line 7-14)**
Generalisability	21	Discuss the generalisability (external validity) of the study results **– Evident in Limitations section (Pages 12)**
Other information		
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 **– There was no funding for the study.**

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

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 www.strobe-statement.org.