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Smoking cessation and depression after acute coronary syndrome☆

Kristina Krasieva [a], Carole Clair [a], Baris Gencer [b], David Carballo [b], Roland Klingenberg [c], Lorenz Räber [d], Stephan Windecker [d], Nicolas Rodondi [e,f], Christian M. Matter [c], Thomas F. Lüscher [g], François Mach [b], Olivier Muller [h], David Nanchen [a,*]

[a] Center for Primary Care and Public Health (Unisanté), University of Lausanne, Lausanne, Switzerland
[b] Division of Cardiology, Faculty of Medicine, Geneva University Hospitals, Geneva, Switzerland
[c] Department of Cardiology, University Heart Center, University Hospital Zurich and University of Zurich, Zurich, Switzerland
[d] Department of Cardiology, University Hospital Bern, Bern, Switzerland
[e] Institute of Primary Health Care (BIHAM), University of Bern, Switzerland
[f] Department of General Internal Medicine, Inselspital, Bern University Hospital, University of Bern, Switzerland
[g] Royal Brompton & Harefield Hospital Trust and Imperial College, London SW3 6NP, UK
[h] Service of Cardiology, Lausanne University Hospital, Lausanne, Switzerland

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ABSTRACT

Smoking and depression are risk factors for acute coronary syndrome (ACS) that often co-exist. We investigated the evolution of depression according to smoking cessation one-year after ACS. Data from 1822 ACS patients of the Swiss multicenter SPUM-ACS cohort study were analyzed over a one-year follow-up. Participants were classified in three groups based on smoking status one-year post-ACS – continuous smokers, smokers who quit within the year, and non-smokers. Depression status at baseline and one-year was assessed with the Center for Epidemiologic Studies Depression scale (CES-D) and antidepressant drug use. A CES-D score $\geq$ 16 defined depression. A multivariate-adjusted logistic regression model was used to calculate odds ratios (OR) between groups. The study sample mean age was 62.4 years and females represented 20.8%. At baseline, 22.6% were depressed, 40.9% were smokers, and 47.5% of these quit smoking over the year post-ACS. In comparison to depressed continuous smokers, depressed smokers who quit had an adjusted OR 2.59 (95% confidence interval (CI) 1.27–5.25) of going below a CES-D score of 16 or not using antidepressants. New depression at one-year was found in 24.4% of non-depressed smokers who quit, and in 27.1% of non-depressed continuous smokers, with an adjusted OR 0.85 (95% CI 0.55–1.29) of moving to a CES-D score of $\geq$16 or using antidepressants. In conclusion, smokers with depression at time of ACS who quit smoking improved their depression more frequently compared to continuous smokers. The incidence of new depression among smokers who quit after ACS was similar compared to continuous smokers.

1. Introduction

Acute coronary syndrome (ACS) is one of the manifestations of coronary heart disease, and is the first cause of morbidity and mortality worldwide (Nowbar et al., 2019). Among the modifiable risk factors for the development of coronary heart disease, depression and smoking share similar pathophysiological mechanisms, such as increased sympathetic activity and a pro-inflammatory state (Lichtman et al., 2014; Dalkou and Clair, 2017). A recent meta-analysis gathered that 28% of patients with myocardial infarction had depression (Feng et al., 2019). Prevalence of tobacco use in ACS patients reached 42% in Switzerland (Selby et al., 2015). These two risk factors are often simultaneously present, as smokers are more likely to be depressed (Luger et al., 2014) and people that are depressed are more likely to be smokers (Aubin et al., 2012). Depressed smokers usually also have other behavioral risk factors, such as physical inactivity, higher body mass index, and lower medication adherence (Whooley et al., 2008). Since one of the main symptoms of depression is lack of motivation, depressed ACS patients

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* Corresponding author at: Center for Primary Care and Public Health (Unisanté), University of Lausanne, Rue du Bugnon 44, CH-1011 Lausanne, Switzerland
E-mail address: david.nanchen@unisante.ch (D. Nanchen).

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may be less adherent to cardiac risk-reducing lifestyle changes, such as smoking cessation (Kronish et al., 2006; Lane et al., 2001). Additionally, clinicians may feel more reticent to offer smoking cessation counseling when they feel they could worsen patients' depressive symptoms (Prochaska, 2011).

A recent meta-analysis (Taylor et al., 2021) as well as other studies (Patten et al., 2017; Stepankova et al., 2017; Taylor et al., 2014; McClave et al., 2009) have shown that in the general population, smoking cessation does not worsen mental health and could even decrease depressive symptoms. However, this relationship has been poorly studied after ACS. There is evidence that smokers may be more vulnerable to developing significant depression post-ACS (Parker et al., 2008) and are more likely to be depressed 5 years following ACS (Bjerkeset et al., 2005), but these studies do not investigate smoking cessation. Other studies reported that the presence of depressive symptoms decreases the probability of smoking cessation in ACS patients (Kronish et al., 2006; Rocha et al., 2017). These studies also had small samples of smokers at baseline with short follow-up periods. Also, whether smoking cessation increases the risk of new depression remains unclear, particularly among ACS patients (Taylor et al., 2021). Further investigation of smoking cessation and depression is important because patients with ACS need to decrease their cardiovascular risk factor burden as much as possible for secondary prevention. Thus, among patients with ACS, we aimed to: 1) assess how smoking cessation impacts the evolution of depression over one year, and 2) assess the role of smoking and smoking cessation on the incidence of new depression one-year post-ACS.

2. Methods

2.1. Study population

We conducted our analysis in the SPUM-ACS (Special Programme University Medicine – Acute Coronary Syndromes) cohort study. The SPUM-ACS study is a large prospective multicenter cohort study of patients hospitalized with acute coronary syndrome (ACS) in four university centers in Switzerland that has been enrolling patients since 2009 (Nanchen et al., 2016). Patients included in the study population were enrolled from 2009 to 2015. Patients excluded were those that had no information about depression at one year post-ACS ($n = 4520$), those that started smoking during the year post-ACS ($n = 5$) and those that restarted smoking during the year post-ACS ($n = 12$). Therefore, 1822 (28.7%) study participants were included in this analysis. Appendix Fig. S1 shows the flow chart of participants. Appendix Table S1 compares the characteristics of included and excluded patients. Participants included were younger and had a higher educational status than the excluded participants.

2.2. Smoking status

The participants were classified in three groups based on evolution of smoking status during the year post-ACS. These groups were defined as continuous smokers (smoking both at the time of ACS and one year after ACS), smokers who quit smoking during the year following ACS, and continuous non-smokers (non-smokers both at the time of ACS and one year after ACS). The 5 patients who started smoking after ACS were excluded, as seen in Appendix Fig. S1. Smoking status at baseline was self-reported. Smoking status at one-year was self-reported or assessed by carbon monoxide (CO) breath analysis. 19 patients who were smokers at baseline and for whom there is no data on smoking status at one-year were considered as continuous smokers.

2.3. Evolution of depression

Depression at baseline and at one-year was defined as a Center for Epidemiologic Studies Depression scale (CES-D)(Radloff, 1977) score of more than or equal to 16, or use of antidepressant medication. The CES-D scale is a 20-item self-reported questionnaire designed to measure depressive symptomatology in the general population and to study associations between depression and other variables (Radloff, 1977). The cut-off score of $\geq$16 to define mild or moderate depression has been validated in psychiatric and general populations (Weissman et al., 1977; Vilagut et al., 2016) and has been previously used in coronary patients (Lucas et al., 2003; McManus et al., 2005; Ren et al., 2015). To take a clinical approach, we performed our analysis based on the dichotomized CES-D scale: no depression vs depression. To test our first hypothesis, we only studied patients who were depressed at baseline (CES-D $\geq$ 16 or on antidepressant medication) and assessed those who were no longer in the depression category at one-year (CES-D $<$ 16 at one-year or on antidepressant medication). To test our second hypothesis, we studied only patients who were not depressed at baseline (CES-D $<$ 16 nor antidepressant medication) and assessed those who moved into the depression category over the year post-ACS (CES-D $\geq$ 16 at one-year or on antidepressant medication) (Appendix Fig. S1).

2.4. Covariates

Higher education was defined as having a high school education or higher. Moderate-intensity physical activity or higher was defined as >500 MET-min per week (metabolic equivalent of task). Baseline diabetes was defined based on self-report or taking anti-diabetic medication. Family history of cardiovascular disease was based on patient reports of a coronary event in a first-degree relative younger than 55 years old for men or younger than 60 years old for women.

2.5. Statistical analyses

Patients were stratified by smoking status over the year post-ACS: continued smoking, quit smoking, and continued no smoking. We used unadjusted and multivariable model logistic regression to calculate the odds ratio (OR) of depression improvement and new depression among the different groups over one year, in reference to continuous smokers. The baseline model was adjusted for age and sex. In Model 1, we adjusted for age, sex, body mass index, higher education, marital status, moderate-intensity or higher physical activity, diabetes, and history of cardiovascular disease. Model 2 consisted of the previous covariates, as well as attendance to cardiac rehabilitation and prescription of high-dose statins at discharge. Model 3 consisted of the previous covariates, as well as alcohol consumption, in units per week. These potential confounders were selected based on clinical and biological plausibility. 95% confidence intervals and *p*-values were calculated for each OR result. We conducted propensity-score matching (see Appendix 1 and Appendix Figs. S2 and S3). Stata16 software was used for all the statistical analyses.

2.6. Ethics statement

The SPUM-ACS study was approved by the Medical Ethics Committee of each center and all participants gave their written informed consent to participate.

3. Results

The characteristics of the study population at the time of the index ACS according to smoking behavior after ACS are summarized in Table 1. Mean age was 62.4 years and 59.1% were continuous non-smokers. Smokers who quit were less frequently living alone, and had fewer cardiovascular risk factors, including hypertension, diabetes, obesity, and pre-existing cardiovascular disease, than smokers who continued to smoke over the year post ACS. The prevalence of depression (CES-D score $\geq$ 16 or antidepressant drug use) at the time of ACS was 411/1822 (22.6%), 29.3% among smokers who continued to

Table 1
Characteristics of study participants at the time of acute coronary syndrome (ACS), by smoking behavior over one year post ACS ($n = 1822$).

	Continued smoking ($n = 392$)	Quit smoking ($n = 354$)	Continued no smoking ($n = 1076$)	Total ($n = 1822$)
Demographics				
Age, years*	57.0 (10.1)	54.9 (10.3)	66.8 (11.3)	62.4 (12.1)
Female	88 (22.5)	64 (18.1)	226 (21.0)	378 (20.8)
Higher education*,[1] ($n = 1789$)	131 (33.6)	134 (38.4)	431 (40.9)	696 (38.9)
Married* (n = 1822)	210 (53.6)	232 (65.5)	696 (64.7)	1138 (62.5)
Living alone* ($n = 1819$)	132 (33.9)	68 (19.2)	264 (24.6)	464 (25.5)
Habits				
Alcohol consumption, units/week (n = 1787)	10.7 (15.1)	11.8 (16.0)	9.1 (12.1)	10.0 (13.6)
At risk alcohol use*,[2] ($n = 1787$)	96 (25.2)	87 (25.3)	209 (19.7)	392 (21.9)
Moderate-intensity or higher physical activity[3] ($n = 1727$)	304 (82.2)	278 (85.5)	890 (86.2)	1472 (85.2)
Comorbidities				
Depression*,[4] (n = 1822)	115 (29.3)	88 (24.9)	208 (19.3)	411 (22.6)
Depression[5] CES-D score* ($n = 1353$)	91 (31.8)	77 (28.0)	171 (21.6)	339 (25.1)
Depression AD drugs* (n = 1822)	43 (11.0)	17 (4.8)	55 (5.1)	115 (6.3)
Hypertension* (n = 1822)	173 (44.1)	138 (39.0)	638 (59.3)	949 (52.1)
Diabetes mellitus* (n = 1822)	66 (16.8)	43 (12.2)	193 (17.9)	302 (16.6)
Pre-existing CVD* ($n = 1821$)	101 (21.8)	41 (11.6)	300 (27.9)	442 (24.3)
Obesity[6] (n = 1822)	82 (20.9)	62 (17.5)	229 (21.3)	373 (20.5)
Medication use at admission				
Lipid-lowering drugs* (n = 1822)	107 (27.3)	75 (21.2)	354 (32.9)	536 (29.4)
Aspirin* (n = 1822)	100 (25.5)	48 (13.6)	336 (31.2)	484 (26.6)

Data are given as mean (standard deviation) or number (percentage), unless indicated.
Abbreviations: CVD, cardiovascular disease; MET, metabolic equivalent; CES-D scale, Center for Epidemiological Studies Depression scale.
* Variables that showed a significant difference ($p < 0.05$) between the three smoker groups.
[1] Defined as a high school or university graduation or higher.
[2] Defined as self-reported >14 drinks per week.
[3] Defined as >500 MET-min per week.
[4] Defined as a CES-D score greater than or equal to 16 or antidepressant drug use.
[5] Defined as a CES-D score greater than or equal to 16.
[6] Defined as a body mass index of greater than or equal to 30 kg/m^2.

smoke, 24.9% among smokers who will quit and 19.3% among patients who remained non-smokers.

The characteristics of the 411 patients with depression at the time of the index ACS are summarized in Appendix Table S2. Out of these 411 patients, 153 (37%) passed into the non-depression category at one-year post ACS (Table 2). Compared to smokers who continued to smoke, those who stopped smoking were more likely to be in the CES-D score non-depression category or to not be on antidepressants one year after

Table 2
One-year improvement of depression[1] among patients with depression at the time of acute coronary syndrome (ACS), with respect to smoking behavior over the year post ACS ($n = 411$).

	Continued smoking ($n = 115$)	Quit smoking ($n = 88$)	Continued no smoking ($n = 208$)
Number of patients who moved into the non-depression category (CES-D score or antidepressant use)	24 (20.9)	38 (43.2)	91 (43.8)
Unadjusted OR (95% CI) (n = 411) R^2=0.036	1.00 (ref)	2.88 (1.56–5.34) $p = 0.001$	2.95 (1.74–4.99) $p = 0.000$
Age sex-adjusted OR (95% CI) (n = 411) R^2=0.052	1.00 (ref)	2.81 (1.50–5.23) p = 0.001	2.53 (1.42–4.49) $p = 0.002$
Model 1-adjusted OR (95% CI)[2] ($n = 362$) R^2=0.063	1.00 (ref)	2.47 (1.23–4.98) $p = 0.011$	2.70 (1.43–5.09) p = 0.002
Model 2-adjusted OR (95% CI)[3] ($n = 359$) R^2= 0.070	1.00 (ref)	2.47 (1.22–4.99) $p = 0.012$	2.76 (1.46–5.23) p = 0.002
Model 3-adjusted OR (95% CI)[4] ($n = 356$) R^2=0.079	1.00 (ref)	2.59 (1.27–5.25) $p = 0.009$	2.95 (1.54–5.64) p = 0.001

Abbreviations: OR, odds ratio; CI, confidence interval; R^2, McFadden Pseudo R^2.
[1] Depression at one-year post-ACS defined as a CES-D score of ≥16 or antidepressant use.
[2] Adjusted for age, sex, body mass index, higher education, marital status, moderate-intensity or higher physical activity, diabetes, and family history of cardiovascular disease.
[3] Adjusted for model 1 and attendance to cardiac rehabilitation and high-dose statin at discharge.
[4] Adjusted for model 2 and alcohol consumption (units/week).

ACS, with an unadjusted OR of 2.88 (95% confidence interval (CI) 1.56–5.34, $p = 0.001$). Further adjustment for age, sex, body mass index, higher education, physical activity, family history of cardiovascular disease, diabetes, attendance to cardiac rehabilitation, high-dose statin at discharge and alcohol consumption did not change this association significantly, with an OR of 2.59 (95% CI 1.27–5.25, $p = 0.009$).

The characteristics of the 1411 patients without depression at the time of the index ACS are summarized in Appendix Table S3. We report the one-year new depression among ACS patients in Table 3. Out of these 1411 patients, 284 (20.1%) developed a new depression at one-year post ACS. There was no difference between smokers who continued to smoke and those who stopped smoking regarding the risk of moving into the CES-D depression category or to be on antidepressants one year after ACS, with an unadjusted OR of 0.87, 95% CI 0.59–1.28, $p = 0.482$. Further multivariable adjustments did not significantly change this association, with the fully-adjusted model giving an OR of 0.85 (95% CI 0.55–1.29, $p = 0.436$). Continuous non-smokers had a significantly lower likelihood of being in the CES-D depression category or to be on antidepressants at one-year post-ACS, compared to smokers who continued to smoke (unadjusted OR 0.54, 95% CI 0.39–0.74, $p = 0.000$).

When using propensity-score matching instead of multivariate adjustment, the two methods of statistical analysis gave very similar odds ratios (cf. Appendix Fig. S2 and S3).

4. Discussion

In this multicenter cohort study of patients hospitalized for ACS and well characterized for depressive symptoms with repeated self-reported questionnaires, we found that smokers with depression who quit smoking over one year post-ACS were more likely to move into the CES-D non-depression category or to not be on antidepressants as compared to continuous smokers. In addition, we found that smokers without

Table 3
One-year new depression[1] among patients without depression at the time of acute coronary syndrome (ACS), with respect to smoking behavior over the year post ACS ($n = 1411$).

	Continued smoking ($n = 277$)	Quit smoking ($n = 266$)	Continued no smoking ($n = 868$)
Number of patients who moved into the depression category (CES-D score or antidepressant use)	75 (27.1)	65 (24.4)	144 (16.6)
Unadjusted OR (95% CI) (n = 1411) R^2=0.013	1.00 (ref)	0.87 (0.59–1.28) p = 0.482	0.54 (0.39–0.74) p = 0.000
Age sex-adjusted OR (95% CI) (n = 1411) R^2=0.015	1.00 (ref)	0.86 (0.59–1.27) p = 0.461	0.56 (0.40–0.79) p = 0.001
Model 1-adjusted OR (95% CI)[2] ($n = 1319$) R^2=0.024	1.00 (ref)	0.90 (0.60–1.35) p = 0.613	0.61 (0.42–0.87) p = 0.006
Model 2-adjusted OR (95% CI)[3] ($n = 1280$) R^2=0.027	1.00 (ref)	0.91 (0.60–1.37) p = 0.639	0.60 (0.42–0.87) p = 0.007
Model 3-adjusted OR (95% CI)[4] ($n = 1257$) R^2=0.029	1.00 (ref)	0.85 (0.55–1.29) p = 0.436	0.56 (0.39–0.82) p = 0.003

Abbreviations: OR, odds ratio; CI, confidence interval; R^2, McFadden Pseudo R^2.

[1] Depression at one-year post-ACS defined as a CES-D score of ≥16 or antidepressant use.

[2] Adjusted for age, sex, body mass index, higher education, marital status, moderate-intensity or higher physical activity, diabetes, and family history of cardiovascular disease.

[3] Adjusted for model 1 and attendance to cardiac rehabilitation and high-dose statin at discharge.

[4] Adjusted for model 2 and alcohol consumption (units/week).

depression who quit over the year post-ACS had similar incidence rates of new depression compared to continuous smokers.

The link between smoking cessation and depression is intricate. To disentangle this issue, previous studies investigated the impact of depression on smoking cessation, in both ACS patients (Kronish et al., 2006; Rocha et al., 2017; Bauer et al., 2012; Dawood et al., 2008; Perez et al., 2008; Thorndike et al., 2008; Thorndike and Rigotti, 2009) and non-ACS patients (Stepankova et al., 2017; Huffman et al., 2018; Morozova et al., 2015). Overall, these studies found that depression renders smoking cessation more difficult, and that those who are depressed are less likely to quit. Some possible explanations for this outcome are the stronger nicotine withdrawal symptoms reported by depressed patients (Thorndike et al., 2008) and the lack of motivation, an integral part of depression, which positively predicts relapse (Perez et al., 2008). The prevalence of depression at baseline in our study sample was 23%, which is consistent with previous studies, that reported that around 28% of ACS patients were depressed (Feng et al., 2019).

In our study, however, we looked at the inverse relationship – the impact of smoking cessation on depression. In this regard, many studies in the general population showed that smoking cessation does not exacerbate mental health and decreases depressive symptoms (Taylor et al., 2021; Patten et al., 2017; Stepankova et al., 2017; Taylor et al., 2014; McClave et al., 2009). This trend is true even in populations that are socioeconomically disadvantaged and have mental illnesses (Hammett et al., 2019). It is difficult to distinguish whether these patterns are not also partially due to the idea that smoking cessation is seen as a positive achievement in society. However, most of the studies cited above did not specifically include ACS populations, who are in a different medical and psychological context.

It could be hypothesized that the association between decrease in depressive symptoms and smoking cessation is concurrent. To our knowledge, we are the first to report specifically on the evolution of depression according to smoking status one-year after ACS. The results of our study, which had a one-year follow-up period and a large study sample, reinforce the safety and benefice of smoking cessation in depressed patients after ACS.

Depression after ACS is associated with poorer cardiovascular outcomes (Parker et al., 2008; Kim et al., 2020). As a consequence, the American Heart Association has defined depression specifically as a risk factor for worse prognosis in ACS patients (Lichtman et al., 2014). It is not only preexisting depression that needs to be screened, but also new onset depression which develops post-ACS, as it has shown to have poorer cardiac outcomes (Parker et al., 2008; Goodman et al., 2008). To our knowledge, there are few studies showing the association between smoking cessation after ACS and incidence of new depression, which we investigate in our study. One study looked at the risk factors of incident depression among post-ACS patients and did not find smoking to be a significant risk factor (Ossola et al., 2015), but in the general population, smoking is considered one of the main predictors of incident depression (Almeida et al., 2013). Interestingly, our results also show that only 13.9% of continuous non-smokers moved into the depression CES-D category or were on antidepressants at one-year, as compared to 24.6% of continuous smokers. Again, it seems as if smokers may be more vulnerable to depressive symptoms, whereas non-smokers are less likely to develop them; hence, we found it necessary to investigate whether smoking cessation decreases the risk of developing depressive symptoms post-ACS. Our results suggest that smoking cessation may decrease the odds of developing a new depression post-ACS and may therefore have a "double-positive" impact on cardiovascular outcome.

Overall, our results underline the extent to which smoking cessation is important during the post-ACS period in decreasing the odds of depression, whether it be in patients who are already depressed or not. When a patient is hospitalized for an acute cardiac event such as ACS, it is considered to be a unique opportunity to quit smoking. With depressed patients, physicians are often reticent to offer smoking cessation counseling as patients report that smoking calms them down and physicians worry that their depressive symptoms will exacerbate if they quit (Prochaska, 2011). Our results add to the argument that on the contrary, smoking cessation is beneficial for improving depression and avoiding the incidence of new depression in post-ACS patients. Hence, physicians potentially need not be reticent to strongly suggest quitting smoking in all ACS patients, independently of their depression status. Our results suggest that it is possible to create and perpetuate a positive cycle of healthy behaviors - smoking cessation helps in decreasing depressive symptoms, which improves adherence to other healthy behaviors, such as taking medication, doing exercise, and sticking to a healthy diet (Bauer et al., 2012). Although this was not the focus of our study, our results support the argument for using medication that targets smoking cessation and depression, which can be an effective method for treating the two risk factors at once (Busch et al., 2012).

Our study has limitations. First, the observational nature of this study means that we need to interpret the results with caution with respect to causality as well as with respect to therapeutic recommendations. Second, patients who have suffered from an acute coronary syndrome may change several health behaviors including smoking cessation that improve their depressive symptoms. Therefore, although we adjusted our results for several confounding variables, the evolution of depression may also be explained by a general and holistic attitude towards better health after an acute coronary syndrome. Third, there is a risk of misclassification of the determinant: for example, smokers who quit and then started smoking again could have had an increase in depressive symptoms after their relapse and would have been classified as continuous smokers at one-year with depression, even though they had made an attempt to quit. Moreover, tobacco use at one-year was in some cases assessed with a CO breath test, but at baseline was based on patients' reports, which, if imprecise, could have also misclassified them in the smoker status classification or excluded them from the study. Fourth, the CES-D scale is not specific to ACS patients, although there are studies

that have used it in this context (Notara et al., 2016; Swardfager et al., 2009). Lastly, there are other confounding factors that were not collected or not taken into account, such as history of depression, which may increase two-fold the risk of depression after ACS (Murphy et al., 2020) or undergoing nicotine replacement therapy. One of the strengths of this study was the large study sample of well-characterized patients from real world clinical practice. Due to this, we could adjust our results on a clinical basis to different types of variables (determinants of socio-economic status, those that evaluate the management or the risk of recurrence of cardiovascular disease), which are strongly linked to depression.

5. Conclusions

In this large multicenter observational study, we found that smoking cessation was associated with improvement of depression in patients with ACS, but not with a lower incidence of new depression. Smoking cessation may be the first step in breaking the vicious cycle composed of smoking, depression, and cardiovascular disease.

Perspectives

More studies are needed on this topic, and it would be useful to have a closer and more subtle evaluation of depression, through more numerous follow-ups. It could also be interesting to investigate whether certain medication could be effective at targeting both risk factors simultaneously and investigate via a randomized study whether medication or close follow-ups or both are more effective at decreasing depressive symptoms and motivating smoking abstinence.

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Authors' contributions

R.K., C.M., N.R., L.R., S.W., B.G., F.M., acquired the data. K.K. and D. N. performed statistical analysis, interpreted the results, and drafted the manuscript. All authors revised the manuscript and gave final approval.

Declaration of Competing Interest

Prof Lüscher reports receiving research grants to the institution from Abbott, Biosensors, Biotronik, Boston Scientific, Daichi Sankyo, Eli Lilly and Medtronic, and consultant payments from AstraZeneca, Boehringer Ingelheim, Bayer, Merck, and Pfizer, MSD, Roche and Servier. Prof Matter reports receiving grants from MSD, Eli Lilly, AstraZeneca, Roche and Bayer; expert testimony from MSD; payment for lectures from MSD, AstraZeneca, and Roche; and having patents from Mabimmune, CH. Prof Windecker reports receiving research contracts to the institution from Abbott, Biotronik, Boston Scientific, Biosensors, Cordis, Medtronic, St. Jude Medical. Prof Mach has received honoraria for advisory boards and conferences on dyslipidaemia from Amgen, AstraZeneca, BMS, Eli Lilly, MSD, Sanofi, and Pfizer. All other authors report no conflicts of interest.

Data availability

Data will be made available on request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ypmed.2022.107177.

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