Bidirectional association between tobacco use and depression risk in the SUN cohort study

Asociación bidireccional entre uso de tabaco y riesgo de depresión en el estudio de cohorte SUN

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Abstract

We assessed the association of tobacco use or smoking cessation with depression risk and determined if the presence of a depressive disorder was associated with smoking onset. We conducted a prospective cohort study (SUN Project) based on 16,519 Spanish university graduates without depression at baseline. Tobacco use was determined at baseline and after four years of follow-up. Incident cases of depression were ascertained according to a previously validated report of a clinical diagnosis of depression during follow-up. Multivariable Cox regression models were used to estimate hazard ratios (HR) of depression according to previous smoking status. We used logistic regression models as a secondary analysis to estimate Odds Ratios (OR) of smoking onset during the first four years of follow-up according to lifetime depression prevalence at baseline. The multivariable HR (95% CI) for current smokers was 1.24 (1.05-1.46) as compared to participants who had never smoked. Participants with the highest exposure to tobacco (≥ 20 packs-years) had a significant 38% relative increment in depression risk. Smoking cessation during the first four years of follow-up was inversely associated with depression (HR = 0.63; 95% CI = 0.40-0.99). Finally, a significant increment in the risk of smoking onset for participants with lifetime depression prevalence was observed (multivariable OR = 1.44; 95% CI = 1.13-1.83). A bidirectional association between tobacco use and depression in the SUN cohort was found. Therefore, tobacco control and health promotion campaigns for smoking cessation could be considered as effective strategies of public health for the prevention and management of depressive disorders.

Key words: Smoking; packs-year; cohort; depression risk; smoking cessation; smoking onset.

Resumen

Evaluamos la asociación del consumo de tabaco o su abandono con el riesgo de depresión y determinamos si presentar depresión se asoció al inicio de fumar. Diseño: estudio de cohortes prospectivo de 16.519 graduados universitarios españoles sin depresión al inicio del estudio. El consumo de tabaco se determinó al inicio y tras cuatro años de seguimiento. Los casos incidentes de depresión fueron autoinformados en los cuestionarios de seguimiento. Usamos modelos de regresión de Cox para estimar los Hazard Ratios (HR) de depresión según el nivel de tabaquismo inicial y sus cambios. Se estimaron los Odds Ratios (OR) para la asociación entre prevalencia de tabaquismo a lo largo de la vida y comienzo del hábito con modelos de regresión logística. Se observó un HR (IC 95%) para fumadores de 1,24 (1,05-1,46) en comparación con los que nunca habían fumado. Los participantes con la exposición más alta al tabaco (≥ 20 paquetes-año) tuvieron un incremento relativo del riesgo de depresión de 38%. Dejar de fumar durante los primeros cuatro años de seguimiento se asoció inversamente con la depresión (HR = 0,63; IC 95% = 0,40-0,99). Observamos un incremento significativo del riesgo de aparición de tabaquismo en los participantes con prevalencia de depresión a lo largo de la vida (OR multivariable = 1,44; IC 95% = 1,13-1,83). Encontramos una asociación bidireccional entre el consumo de tabaco y la depresión en la cohorte SUN. El control del tabaco y las campañas sanitarias de abstinencia deberían considerarse estrategias efectivas de salud pública para prevenir y manejar los trastornos depresivos.

Palabras clave: Fumar; paquetes-año; cohorte; riesgo de depresión; dejar de fumar; comienzo de fumar.

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Unipolar depression is considered an important global cause of disability-adjusted life years (DALYs) (Kyu et al., 2018) and this disease was the third cause of years lost due to disability (YLDs) in 2017 (James et al., 2018). In this context, preventing depression is an important aim from a public health perspective. Depression is a multifactorial disease. Several lifestyle factors have been analyzed as potentially modifiable determinants of depression development. Diet (Lassale et al., 2019; Opie et al., 2017), physical activity (Fernández-Montero et al., 2020), and toxic habits (Kedzior & Laeber, 2014) are clinically relevant modifiable determinants of depression risk; toxic habits refer to smoking, alcohol intake and use of illegal drugs. Regarding tobacco, a systematic review has suggested a bidirectional association between smoking and mental health measured as depression and anxiety, with smoking increasing the risk of mental diseases and mental diseases increasing the risk of smoking onset (Fluharty, Taylor, Grabski & Munafò, 2017). Moreover, another meta-analysis yielded significant reductions in depressive symptomatology after smoking cessation (Taylor et al., 2014). Some authors have also observed a tendency towards a linear association between the number of cigarettes/day consumed and severity of depression according to the Hamilton Depression Scale (HDRS), suggesting a relationship between severity of consumption and severity of depressive symptoms (Jiménez-Treviño et al., 2019). Finally, several studies have reported that individuals with mental illness tend to be more likely to adopt smoking habits and to smoke more heavily than the general population (Fluharty et al., 2017; Fluharty, Sallis & Munafò, 2018). In this context, there is a scarcity of longitudinal epidemiological studies that have analyzed all these aspects simultaneously. We consider that our study provides clarification in determining the association between smoking habit, including use, dose, smoking duration and smoking cessation, and the risk of developing depression, as well as analyzing whether having a depressive disorder represents a risk factor for smoking onset/relapse using a prospective epidemiological design. The use of this type of design allowed us to efficiently assess both the role of depression in smoking onset or relapse and the role of smoking use and duration on the risk of developing depression after several years of follow-up.

Thus, the aims of this study were to (1) assess the association between tobacco (use, and dose and smoking duration measured through pack-years of cigarette smoking) and depression risk; (2) assess the role of smoking cessation in depression risk; (3) and finally to ascertain if the presence of a depressive disorder was associated with smoking onset in the SUN cohort study.

Method

Study population

The SUN Project is a prospective, dynamic cohort study, initiated in December 1999 in Spain. The sample is composed of Spanish university graduates who agree to participate. Its methods have been previously described (Carlos et al., 2018; Martínez-González, Sánchez-Villegas, De Irala, Marti & Martínez, 2002). Briefly, information about sociodemographic and lifestyle characteristics, anthropometric variables, and medical history or use of medication is gathered biennially by mail or by Web-based questionnaires sent to participants every two years. The overall retention in the cohort approaches 90%.

Up to July 2018, 22,791 participants had completed the baseline questionnaire of the SUN Project. Participants who were lost to follow-up, who had not completed at least one follow-up questionnaire, or who were outside of predefined limits for baseline total energy intake were excluded from the analyses. For analyses considering the incidence of depression as the outcome, we also excluded those participants who were users of antidepressant medication or had reported a present or previous history of clinical diagnosis of depression (lifetime depression) at baseline. Finally, 16,519 participants were included in the prospective analyses for the incidence of new-onset depression (Figure 1). In an ancillary analysis, we selected 11,246 participants of the cohort with at least four years of follow-up and being nonsmokers or former smokers at baseline to assess the role of lifetime-prevalence of depression in the relapse. (Figure 2).

The study was approved by the Institutional Review Board of the University of Navarra and registered at clinicaltrials.gov (NCT02669602). Written informed consent was not requested from the participants. Voluntary completion of the first questionnaire was considered to imply informed consent.

Exposure assessment

Tobacco use was ascertained at baseline and after four years of follow-up. A participant was considered as a current or former smoker if he/she responded positively to the question: "Have you smoked 100 or more cigarettes in your life?" in the baseline questionnaire (Q_0). Those participants who answered positively were additionally asked about the mean number of cigarettes consumed per day at some specific periods of their life. If a participant referred to be a former smoker he/she was inquired about how long ago he/she gave up smoking. Former smokers were then classified into two groups, former smokers who quit ten or more years ago and former smokers who quit less than 10 years ago. We chose this cut-off point because we consider that ten years is a relevant period to ascertain the overcoming of smoking habit and ensures that the state of the participant is really that of the former smoker.

The number of pack-years consumed by current and former smokers was also estimated. We used the pack-years definition according to the National Cancer Institute Dictionary of Cancer Terms; pack-years were calculated by multiplying the number of packs of cigarettes smoked per day by the number of years the person had smoked. For example, 1 pack-year is equal to smoking 1 pack per day for 1 year, or 2 packs per day for half a year, and so on (National Cancer Institute, 2019).

Participants updated their smoking status after four years of follow-up. Thus, the number of quitters and starters in smoking habit were ascertained.

Outcome assessment

Incident cases of depression were defined as participants who positively responded to the following question 'Have you ever been diagnosed with depression by a medical doctor?' in any of the biennial follow-up questionnaires from the second year of follow-up (Q_2–Q_16). A self-reported physician-provided diagnosis of depression has demonstrated acceptable validity in a subsample of our cohort using the Structured Clinical Interview for DSM-IV as 'gold standard' applied by experienced psychiatrists blinded to the answers of the questionnaires (Sánchez-Villegas et al., 2008a). The percentage of confirmed depression was 74.2% [95% Confidence Interval (CI) = 63.3-85.1]. The percentage of confirmed non-depression was 81.1% (95% CI = 69.1-92.9).

Other variables assessment

Information about socio-demographic (e.g., sex, age, marital status and employment status) and lifestyle-related variables (e.g., physical activity, dietary habits) were obtained from Q_0. Physical activity was assessed using a validated physical activity questionnaire with data about seventeen activities used in Spanish-speaking populations and previously adapted from US (Nurses' Health Study and Health Professionals' Follow-up Study) (Martínez-González, López-Fontana, Varo, Sánchez-Villegas & Martínez, 2005). The validation study consisted in calculating the non-

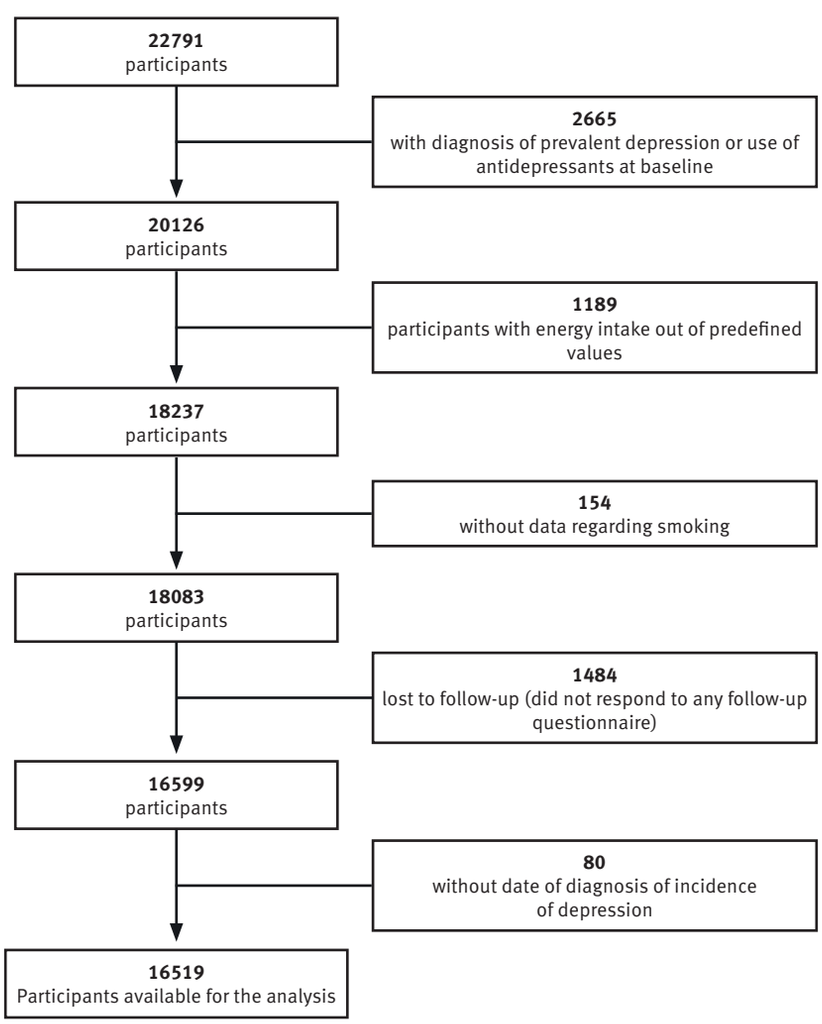

Figure 1. Flow chart for the selection of participants.

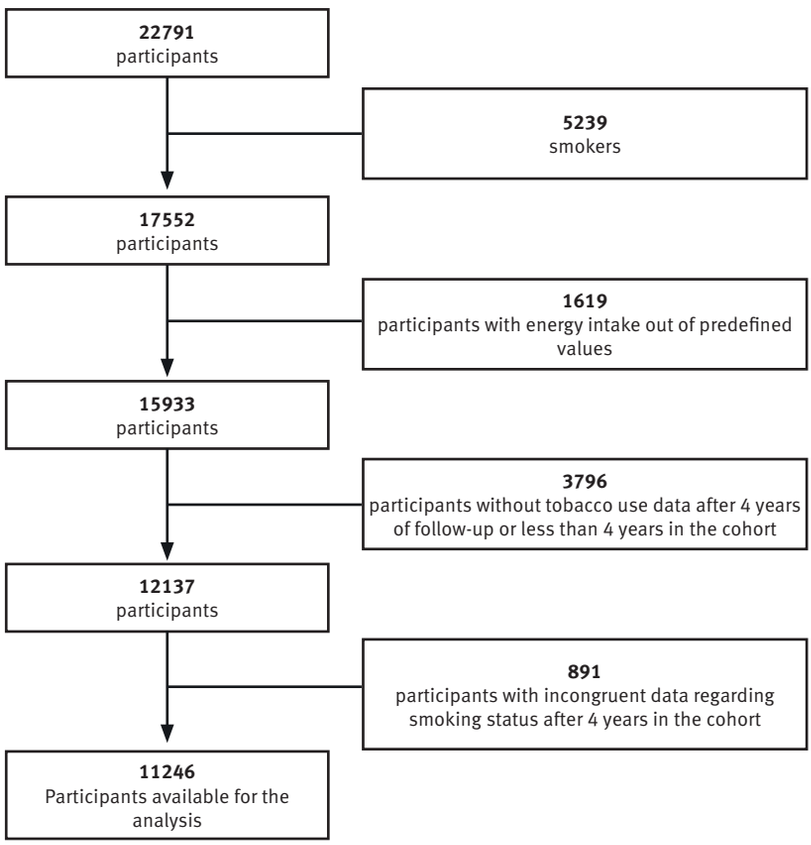

Figure 2. Flow chart for the selection of participants (secondary analysis).

parametric correlation coefficients between the level of physical activity and sedentary lifestyle collected by the self-administered questionnaire and the triaxial accelerometer measurements. Percentage of misclassification and kappa coefficients were also calculated. The study population consisted of a sample of 40 obese women who were participants of the SUN project. Physical activity during leisure time (estimated as MET-h week) derived from the self-administered questionnaire moderately correlated with kcal/day assessed through the accelerometer (Spearman's r = 0.507, 95% confidence interval (CI) 0.232-0.707). The Spearman correlation between the ratio of sedentary lifestyle to physical activity obtained through the questionnaire and the direct estimation (RT3) was –0.578 (95% CI –0.754, –0.325). The kappa index was 0.25 (P = .002) when assessing the cross-classification into quintiles and 0.41 for the dichotomous estimation of a sedentary lifestyle. Only 2.5% of participants were misclassified by the questionnaire more than two quintiles apart from the estimates of the RT3.

Dietary intake was assessed at baseline with a 136-item, validated, semi-quantitative food frequency questionnaire (FFQ) (De La Fuente-Arrillaga, Vázquez-Ruiz, Bes-Rastrollo, Sampson & Martínez-González, 2010; Fernández-Ballart et al., 2010). Nutrient and energy intakes were calculated as frequency multiplied by the nutrient composition of specified portion size for each food item using an ad hoc computer program specifically developed for this aim. A trained dietician updated the nutrient database using the latest available information included in food composition tables for Spain (Mataix, 2003; Moreiras, Carbajal, Cabrera & Cuadrado, 2005). Adherence to the Mediterranean Diet was evaluated using the information included in the FFQ and calculating the MEDAS score (Schröder et al., 2011).

Information regarding personality traits (self-perceived level of competitiveness, psychological tension, and dependency) was also obtained with Q_0 using Likert scales. Participants were categorized into three different groups according to the declared answers in the Q_0: low level (1-4), moderate level (5-6), and high level (7-10).

Body mass index (BMI) was calculated as weight (kg) divided by the square of height (m^2) using data collected in Q_0. Validity of auto-referred weight and height has been assessed in the cohort (Bes-Rastrollo, Pérez-Valdivieso, Sánchez-Villegas, Alonso & Martínez-González, 2005).

The prevalence and history of cancer, cardiovascular disease, hypertension, and type 2 diabetes mellitus were determined at baseline. Cardiovascular disease included myocardial infarction, stroke, atrial fibrillation, paroxysmal tachycardia, coronary artery bypass grafting or other revascularization procedures, heart failure, aortic aneurism,

pulmonary embolism, or peripheral venous thrombosis. All the diagnoses were based on participants' self-reports. The validity of self-reported hypertension diagnosis has been assessed in a subsample of the cohort (Alonso, Beunza, Delgado-Rodríguez & Martínez-González, 2005).

Statistical methods

Baseline characteristics of participants adjusted for age and sex, using inverse probability weighting, were described according to their smoking habits using relative frequencies, means, and standard deviations.

For each participant, we computed person-years of follow-up from the date of returning the Q_0 to the date of depression diagnosis or the date of returning the last follow-up questionnaire, whichever came first.

Cox proportional-hazards regression models were fitted to assess the relationship between tobacco use and the incidence of depression during the follow-up. Hazard ratios (HR) and their 95 % CI were calculated considering nonsmokers as the reference category. To control for potential confounding factors, we conducted a multivariable-adjusted model adjusting for sex, age, BMI (kg/m^2, continuous), physical activity during leisure time (METs/h-w, continuous), total energy intake (kcal/d, continuous), adherence to the Mediterranean Diet (1-14, continuous), alcohol intake (abstainers; 0.1-9.9 g/d; 10-25 g/d; >25 g/d), living alone (yes, no, unknown), unemployment (yes/no), years of education (continuous) and personality traits (competitiveness, psychological tension, and dependence, three categories). Other confounding factors such as the presence of several diseases (cancer, cardiovascular disease, hypertension, and diabetes), or marital status were also explored but not included in the final models because their inclusion in the regression models did not substantially change the reported associations.

The role of tobacco cessation (during the first four years of follow-up) in depression risk was also evaluated through multivariable Cox proportional-hazards regression models considering no cessation in tobacco use as the reference value. We represented adjusted cumulative incidence of depression according to the smoking habit, using inverse probability weighting. We then estimated the number needed to treat (NNT) as the inverse of the risk difference, which was estimated using a pooled logistic model. The 95% CI was the 2.5^{th} and 97.5^{th} percentiles of the distribution obtained from a nonparametric bootstrap with 1000 samples.

Subgroup analyses were performed by sex, age, adherence to the Mediterranean diet, physical activity level, and personality traits as stratification variables. To assess possible interactions product terms were introduced in the different multivariable models. *P* values for the interaction were calculated using the likelihood ratio test.

In addition, several sensitivity analyses were conducted after (1) considering a maximum time of follow-up of 6 years (participants with a longer period of follow-up were censored to 6 years and depression cases occurred after the sixth year were considered non-depressed); (2) considering only depression cases diagnosed after 2 years of follow-up; (3) considering only depression cases diagnosed after 4 years of follow-up and (4) excluding participants with cancer, cardiovascular disease or type two diabetes at baseline.

Among former smokers, we also calculated the possible non-linear association between the number of years since tobacco cessation and depression risk with the same method. Tests for nonlinearity used the likelihood ratio test, comparing the model with only the linear term to the model with the cubic spline terms. The results were adjusted for the same potential confounding factors as the main Cox regression analysis.

Finally, to assess a possible bidirectional association tobacco-depression we analyzed the role of depression in tobacco initiation. In an ancillary analysis based on 11,246 participants of the cohort (with at least four years of follow-up and being nonsmokers or former smokers at baseline), we analyzed the association between lifetime prevalence of depression at baseline and the likelihood of tobacco onset/relapse after four years of follow-up in the cohort, by using multivariable-adjusted logistic regression models with smoking onset during the first 4 years of follow-up as the outcome. Analyses were repeated after separating never and former smokers in two different groups and analyzing the role of depression in smoking onset and smoking relapse individually.

All p values were two-tailed, and $p < .05$ was considered significant. Statistical analysis was performed using STATA version 12.0 (StataCorp).

Results

Table 1 shows the baseline characteristics of participants according to categories of smoking status. Current smokers were younger than former smokers, more likely to be single, and tended to have a lower physical activity level, higher alcohol intake, and lower adherence to the Mediterranean Diet. However, the prevalence of major chronic disease at baseline (including cancer, cardiovascular disease, diabetes or hypertension) was lower among these participants.

As this is a dynamic cohort, the time of follow-up is not equal for all the participants included in the analysis. The maximum time of follow-up was 13.5 years approximately, however, the median follow-up in this analysis was 11.1 years.

For the main analysis, during a total of 174,754 person-years of follow-up, we found 889 incident cases of depression. The association between tobacco use and depression is shown in table 2. The results indicate a direct

Table 1. *Baseline characteristics of the participants of the SUN Cohort study according to tobacco use adjusted for age and sex with the inverse probability weighting.*

	Never smoker (n = 8022)	**Former smoker >10y*** (n = 1854)	**Former smoker <10y*** (n = 2674)	**Current smoker** (n = 3510)
Body Mass Index (kg/m^2)	23.5 (3.6)	24.5 (3.6)	23.9 (3.6)	23.5 (3.5)
Physical activity (MET-h/w)	24.2 (23.1)	23.9 (23.7)	22.3 (21.4)	20.3 (19.6)
Energy intake (kcal/day)	2345 (625)	2308 (617)	2320 (611)	2347 (629)
Mediterranean Diet (1-14)	6.0 (2.0)	6.3 (1.9)	5.9 (1.9)	5.7 (1.8)
Alcohol intake (g/day)	4.9 (7.5)	8.7 (12.2)	8.2 (11.6)	8.9 (12.2)
Competitiveness level (0-10)	7.0 (1.7)	6.9 (1.8)	6.9 (1.7)	6.9 (1.8)
Psychological tension (0-10)	5.8 (2.3)	6.0 (2.1)	6.0 (2.2)	5.8 (2.3)
Dependence level (0-10)	3.5 (2.8)	3.5 (3.0)	3.7 (2.9)	3.6 (2.9)
Years of university education	5.1 (1.6)	5.3 (1.6)	5.0 (1.4)	5.0 (1.4)
Living alone (%)	7.0	4.1	7.5	6.9
Unemployment (%)	3.9	2.4	3.5	4.5
Married (%)	48.8	77.4	57.0	48.2
Prevalence of diseases (%)				
Cancer	3.5	5.1	3.3	3.0
Cardiovascular disease	1.7	1.9	2.2	1.1
Diabetes	2.2	2.3	2.1	1.5
Hypertension	21.8	26.7	18.8	18.4

Data represent means and standard deviations or percentages.
*Date of tobacco cessation was not available in 134 participants.

and significant association between smoking and depression risk. The multivariable HR (95% CI) for depression in current smokers was 1.24 (1.05-1.46) as compared to never smokers. We did not find any significant association for former smokers regardless of the years since they quitted compared with never smokers. However, compared to current smokers, being a former smoker was associated with a lower incidence of depression: 0.85 (0.70-1.02). This

Table 2. *Association (HR and 95% CI) between tobacco use and risk of depression in the SUN Cohort study.*

	Cases	**Person-years**	**Model 1**	**Model 2**
Never smoker	407	85610	1 (ref.)	1 (ref.)
Former smoker	252	50757	1.08 (0.92-1.27)	1.05 (0.89-1.25)
Current smoker	230	38386	**1.27 (1.08-1.49)**	**1.24 (1.05-1.46)**
Never smoker	407	85610	1 (ref.)	1 (ref.)
Former smoker > 10y*	86	20317	0.93 (0.72-1.19)	0.92 (0.71-1.19)
Former smoker < 10y*	161	29150	1.17 (0.97-1.41)	1.14 (0.94-1.37)
Current smoker	230	38386	**1.27 (1.08-1.49)**	**1.24 (1.05-1.47)**
Number of packs-year**				
0	407	85610	1 (ref.)	1 (ref.)
<10	215	40741	1.07 (0.91-1.27)	1.08 (0.91-1.28)
10 -< 20	95	18453	1.15 (0.91-1.44)	1.11 (0.88-1.40)
20 +	90	15056	**1.50 (1.16-1.93)**	**1.38 (1.07-1.79)**
For +10 packs-year			**1.11 (1.03-1.19)**	**1.08 (1.01-1.06)**
Quitting smoking (0 to 4-y)***				
No	64	17018	1 (ref.)	1 (ref.)
Yes	27	10653	0.65 (0.41-1.02)	**0.63 (0.40-0.99)**

*Date of tobacco cessation was not available in 134 participants.
** Data regarding packs-years was not available in 1423 participants.
***Including only baseline smokers with 4-y follow-up data and without incident depression in the 4 first years of follow-up (n = 2193).
HR: Hazard Ratio; CI: Confidence Interval.
Model 1: HR and 95% CI adjusted for age and sex.
Model 2: Model 1 additionally adjusted for years of education (y, continuous), living alone (yes, no, unknown), unemployment (yes/no), body mass index (Kg/m2, continuous), physical activity (METs-h/w, continuous), total energy intake (kcal/d, continuous), alcohol consumption (four categories), adherence to the Mediterranean diet (MEDAS questionnaire unit, continuous) and personality traits (competitiveness, psychological tension and dependency: low, medium, high, unknown).

association was especially relevant for smokers who quit more than 10 years before baseline: 0.74 (0.57-0.97).

When the analysis was repeated separating never and former smokers, the association between the presence of depression at baseline and the risk of smoking onset or relapse was no longer significant. The multivariable OR for the association between lifetime depression prevalence and smoking onset among never smokers was 1.13 (0.71-1.82); whereas OR for smoking relapse among former smokers was 1.26 (0.89-1.78).

Tobacco dose and smoking duration were also directly associated with depression risk. Participants with higher exposure to tobacco products or prolonged smoking duration (20 or more packs-years) had a 38% significant increment in the relative risk of developing depression during follow-up (95% CI = 1.07-1.79). On the other hand, smoking cessation during the first four years of follow-up was inversely associated with depression risk (HR = 0.63; 95% CI = 0.40-0.99) compared to current smokers. As shown in figure 3, the risk of participants who quit smoking reaches the rates of never smokers after around 8-10 years. These results seem consistent with the results found for baseline exposure. For every 47 participants who quit smoking, 1 incident case could be avoided during the following 10 years: NNT (95% CI): 47 (22-276). (Figure 3).

We did not find any significant interaction between tobacco use and several baseline characteristics of participants (sex, age, physical activity, adherence to the Mediterranean Diet, or personality traits) (Table 3). Nevertheless, the results suggested that smoking could be especially detrimental among younger participants with poorer dietary habits and those with several personality characteristics (less competitive and more relaxed persons).

The main results did not change after carrying out several sensitivity analyses (Table 4).

Finally, to assess the role of depression in smoke initiation, never and former smokers were evaluated after 4 years of follow-up with the presence of depression at baseline. Among 11,246 participants with four years of follow-up and who were never or former smokers at baseline, we observed a significant increment in the risk of smoking onset associated with the presence of depression at baseline (multivariable OR = 1.44; 95% CI = 1.13-1.83). When the analysis was repeated separating never and former smokers, the association between the presence of depression at baseline and the risk of smoking onset or relapse was no longer significant. Multivariable OR for smoking onset among never smokers: 1.13 (0.71-1.82), OR for smoking relapse among former smokers: 1.26 (0.89-1.78).

Discussion

In these analyses conducted within the framework of the SUN cohort, we found that current smoking was prospectively associated with a higher risk of depression. Additionally, participants with elevated tobacco dose and smoking duration (measured as at least 20 pack-years of cigarette smoking) had a significant increment in the risk of developing depression during follow-up. Moreover, smoking cessation was inversely associated with depression incidence.

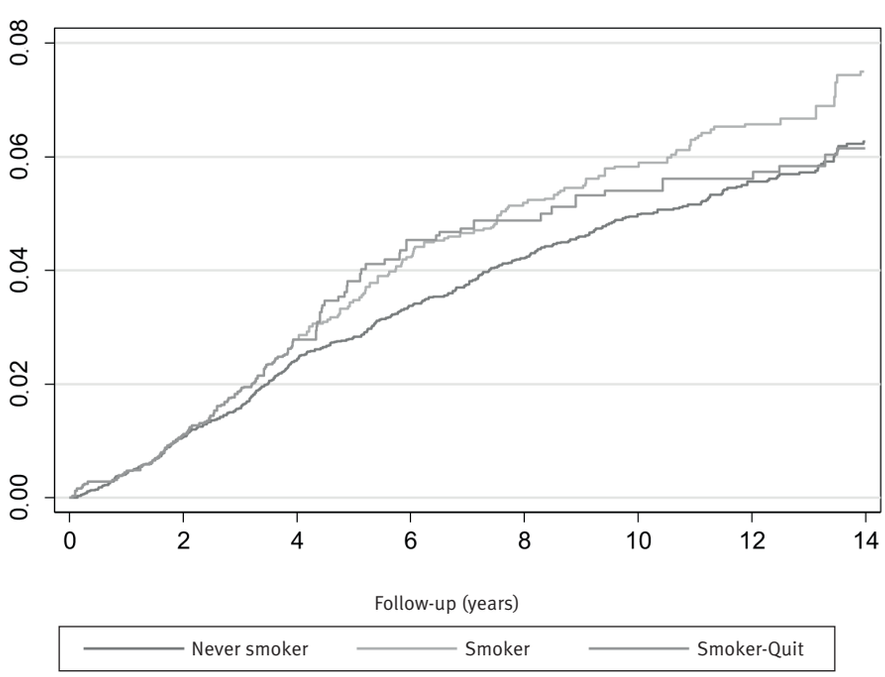

Figure 3. Cumulative incidence of depression according to tobacco use: The SUN Cohort study 1999-2018.

Table 3. *Association (HR and 95% CI) between tobacco use and risk of depression in the SUN Cohort study according to several characteristics of the participants.*

	n	Cases	Never smoker	Former smoker >10y*	Former smoker <10y*	Current smoker	*p* interaction
Sex							0,319
Men	6723	260	1 (ref.)	1.09 (0.72-1.64)	0.97 (0.67-1.41)	1.35 (0.98-1.84)	
Woman	9662	624	1 (ref.)	0.79 (0.56-1.11)	1.22 (0.98-1.52)	1.21 (0.99-1.47)	
Age							0.717
< 50 y	13477	749	1 (ref.)	1.03 (0.76-1.41)	1.19 (0.97-1.45)	**1.27 (1.07-1.52)**	
≥50 y	2908	135	1 (ref.)	0.80 (0.52-1.24)	0.96 (0.56-1.64)	1.01 (0.61-1.68)	
Mediterranean diet							0.745
Low (< 6 puntos)	7135	444	1 (ref.)	1.05 (0.71-1.55)	1.09 (0.83-1.43)	**1.29 (1.03-1.63)**	
High (≥ 6 puntos)	9250	440	1 (ref.)	0.83 (0.59-1.16)	1.18 (0.91-1.52)	1.19 (0.93-1.52)	
Physical activity							0.636
Low (< P50)	8185	484	1 (ref.)	0.97 (0.67-1.40)	1.26 (0.98-1.62)	1.24 (0.99-1.54)	
High (≥P50)	8200	400	1 (ref.)	0.86 (0.61-1.23)	1.00 (0.75-1.33)	1.23 (0.95-1.59)	
Competitiveness**							0.510
Low (< P50)	9245	490	1 (ref.)	0.94 (0.66-1.34)	1.13 (0.88-1.46)	**1.39 (1.12-1.73)**	
High (≥ P50)	7283	399	1 (ref.)	0.90 (0.62-1.29)	1.14 (0.87-1.50)	1.06 (0.82-1.38)	
Tension**							0.272
Low (< P50)	9133	383	1 (ref.)	0.91 (0.60-1.39)	**1.41 (1.06-1.87)**	**1.42 (1.11-1.81)**	
High (≥P50)	7403	509	1 (ref.)	0.89 (0.65-1.23)	0.97 (0.76-1.24)	1.13 (0.90-1.41)	
Dependency**							0.408
Low (< P50)	10147	503	1 (ref.)	0.96 (0.69-1.34)	1.29 (1.01-1.65)	1.24 (0.99-1.55)	
High (≥P50)	6469	391	1 (ref.)	0.84 (0.56-1.26)	0.95 (0.71-1.26)	1.22 (0.95-1.56)	

*Date of tobacco cessation was not available in 134 participants.
**Several missing values for competitiveness, tension and dependency.
HR: Hazard Ratio; CI: Confidence Interval; P50: Percentile 50.

Table 4. *Association (HR and 95% CI) between tobacco use and risk of depression in the SUN Cohort study. Sensitivity analysis.*

	cases/N	Former smoker >10y*	Former smoker <10y*	Current smoker
Overall sample	884/16385	0.92 (0.71-1.19)	1.14 (0.94-1.37)	**1.24 (1.05-1.47)**
Analysis from baseline to the first 6 years of follow-up	545/16385	0.78 (0.56-1.09)	1.09 (0.86-1.39)	**1.30 (1.05-1.60)**
Considering only cases diagnosed after the first 2 years of follow-up	716/16138	1.01 (0.76-1.34)	1.18 (0.96-1.45)	**1.27 (1.05-1.53)**
Considering only cases diagnosed after the first 4 years of follow-up	488/14900	1.03(0.73-1.46)	1.15 (0.89-1.48)	**1.29 (1.04-1.62)**
Excluding participants with cardiovascular disease, diabetes or cancer at baseline	827/15423	1.02 (0.78-1.32)	1.11 (0.92-1.35)	**1.25 (1.05-1.49)**

*Date of tobacco cessation was not available in 134 participants.
Adjusted for sex, age, years of education (y, continuous), living alone (yes, no, unknown), unemployment (yes/no), body mass index (Kg/m2, continuous), physical activity (METs-h/w, continuous), total energy intake (kcal/d, continuous), alcohol consumption (four categories), adherence to the Mediterranean diet (MEDAS questionnaire unit, continuous) and personality traits (competitiveness, psychological tension and dependence: low, medium, high, unknown).
HR: Hazard Ratio; CI: Confidence Interval; Q_2: questionnaire 2; 2-y of follow-up; Q_4: questionnaire 4; 4-y of follow-up.

These results confirm the results obtained in our cohort more than 10 years ago with less time of follow-up and a smaller sample size. In that analysis, being a smoker was associated with a 39% relative increment in the risk of depression. Moreover, smoking duration and the number of cigarettes smoked per day were also associated with the depression risk (Sánchez-Villegas, Serrano-Martínez, Alonso, Tortosa & Martínez-González, 2008b).

The presence of depression at baseline doesn't seem to be associated with smoking onset in our cohort. However, although the association was not statistically significant for smoking relapse among former smokers, the magnitude of the association could be considered moderate, with an increment in the risk of smoking relapse of 26%. Probably the small number of participants in this analysis did not allow us to detect statistically significant associations.

A detrimental role of smoking in depression have been reported by some longitudinal studies (Clyde, Smith, Gariépy & Schmitz, 2015; Flensborg-Madsen et al., 2011; Raffetti, Donato, Forsell & Galanti, 2019; Zhang, Woud, Becker & Margraf, 2018) although the results are not fully consistent (Bruin, Comijs, Kok, Van der Mast & Van den Berg, 2018; Furihata et al., 2018).

Several mechanisms could explain the deleterious role of tobacco in depression. Exposure to nicotine and other additives of tobacco cigarettes could predispose to

depression through several physiological mechanisms related to central nervous system function. For example, smokers show an important reduction in monoamine oxidase B levels (Fowler et al., 1996). This enzyme is involved in brain and peripheral oxidative catabolism of neurotransmitters including dopamine. Dopamine system dysregulation has been recently associated with several core symptoms in depression such as the presence of anhedonia (Belujon & Grace, 2017). Moreover, animal models and human studies have suggested that long-term exposure to nicotine might act as a stressor leading to a dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis (Furihata et al, 2018) with cortisol, adrenocorticotrophic hormone, and corticotropin-releasing hormone simultaneously elevated. This dysregulation would be implicated in a reduced volume of the hippocampus, reduced rates of neurogenesis, and increased levels of pro-inflammatory cytokines and oxidative stress markers. Both low-grade systemic inflammation and oxidative stress are implicated in several pathophysiologic mechanisms related to depression.

The role of smoking in depression risk could be mediated through the incidence of several diseases consequence of tobacco use such as cardiovascular disease that has been associated with depression in our cohort (Molero et al., 2017).

Another possible explanation of the association between tobacco use and depression is the presence of several confounding factors associated independently with both variables such as lifestyle or personality characteristics. However, this explanation is unlikely since we have adjusted the models for several lifestyle variables (e.g., physical activity, alcohol intake, or dietary habits) and personality traits such as tension, competitiveness, or dependence level. Finally, participants with subclinical depression but without a depression diagnosis at baseline could have initiated the smoking habit to alleviate their initial symptoms of an undiagnosed depression at baseline and the obtained results could have been a consequence of a reverse causation bias. These undiagnosed cases potentially responsible for a reverse causation bias are more likely to be reported after the first 2-4 years of follow-up. However, when we repeated the analyses after excluding early cases (in the first 2 o 4 years of follow-up) the results did not change.

The presence of depression at baseline was also prospectively associated with a higher likelihood of smoking onset in our cohort suggesting a bidirectional association between tobacco use and depression. Some other studies have reported results in the same line of thought. A representative sample of 44,921 adolescents found that among non-smoker, the lifetime prevalence of depression was approximately 50% lower than among smokers (Cohn, 2018). Other studies have found that among smokers with mental diseases smoking cessation rates remain consistently lower than for smokers without depressive symptoms (Huffman, Bromberg & Augustson, 2018; Secades-Villa, Weidberg, González-Roz, Reed & Fernández-Hermida, 2018). One of the most accepted explanations is that based on the self-medication hypothesis (as it has already been mentioned) that postulates that individuals turn to smoke to alleviate their symptoms but worsening them over time (Fluharty et al., 2017). Another possible explanation of this bidirectional association is shared vulnerability for both smoking addiction and depression occurrence, though that would not support a reduction of risk of depression associated with smoking cessation in this and other studies (Khaled et al., 2012; Zarghami, Taghizadeh, Sharifpour & Alipour, 2018).

Strengths of this study deserve to be mentioned and include its prospective longitudinal design, the use of previously validated methods, the large sample size, and the extensive control for confounding, including dietary factors. Participants were highly educated, which increases the quality of self-reported information and reduces the potential for misclassification bias. In addition, the restriction to a fairly homogenous subgroup of participants concerning educational level minimizes the potential for residual confounding and is an excellent technique to improve the internal validity of our results.

However, some possible limitations have to be also addressed. A limitation of this study is that the diagnosis of depression was self-reported, although the validity of the approach adopted to adjudicate incident cases of depression during follow-up was validated in a sub-sample of this cohort (Sánchez-Villegas et al., 2008a). In addition to a cohort, design mitigates this to some extent. We restricted our cohort to highly educated participants to obtain a better quality of self-reported information. In this context, misclassification is more likely to be non-differential and therefore would bias the results towards the null.

Although all results were adjusted for a variety of major potential confounders, we cannot exclude the possibility of some unknown or unmeasured factors that could partly explain the reported results. This possibility will fit well in the hypothesis of shared vulnerability and we admit that this limitation is inherent to the observational design of our study. However, it would be unlikely that such an unknown factor leading to "shared vulnerability" might not be correlated with the many potential confounders controlled for in our study. Finally, our sample was not representative of the general population. However, lack of representativeness does not prevent establishing associations that can be generalized to other groups, as long as no biological mechanism suggests that the association no longer holds for other populations. The selection of study groups that maintain homogeneity concerning important confounders such as educational level, has been recommended to maximize the cohort

validity, rather than aiming for a "representative sample" of a natural population (Rothman, Greenland & Lash, 2008), especially in the study of highly complex behaviors such as the ones that mediate depressive disorder and tobacco use.

In conclusion, a bidirectional association between tobacco use and depression was found in the SUN cohort study, reinforcing the conclusions of previous studies. The novelty brought by our study lays in the use of a design that is prospective longitudinal and the simultaneous analysis of the use, dose, and smoking duration. Moreover, we also assessed the role of smoking cessation in depression risk and we found that smoking cessation was inversely associated with depression incidence. On the other hand, the presence of a depressive disorder was prospectively associated with smoking onset, suggesting a bidirectional association between tobacco use and depression. Therefore, tobacco control and health promotion campaigns for smoking cessation could be considered as effective strategies of public health for the prevention and management of depressive disorders.

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Conflict of interests

Without relevance to this work, PM reports being supported by Clínica Universidad de Navarra and having received research grants from the Ministry of Education (Spain), the Government of Navarra (Spain), the Spanish Foundation of Psychiatry and Mental Health and AstraZeneca; he is a clinical consultant for MedAvanteProPhase and has received lecture honoraria from or has been a consultant for AB-Biotics, Janssen, Novumed, Roland Berger, and Scienta. The other authors declare no conflict of interests.

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