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Association Between Electronic Cigarette Use and Smoking Reduction in France

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Key Points:

- Question: Is electronic cigarette (EC) use associated with smoking reduction in the general population?
- Findings: Among daily smokers, regular (daily) EC use is associated with a significantly higher decrease in the number of cigarettes smoked/day as well as an increase in smoking cessation attempts. However, among former smokers, EC use is associated with an increase in the rate of smoking relapse.
- Meaning: Daily EC use appears helpful in initiating smoking cessation among persons who intend to quit tobacco, however in the general population its efficacy with regard to smoking abstinence in the long term is uncertain.

Abstract

IMPORTANCE The electronic cigarette (EC) has become popular among smokers who wish to reduce their tobacco use levels or quit smoking, but its effectiveness as a cessation aid is uncertain.

OBJECTIVE To examine the association of regular EC use with the number of cigarettes smoked per day, smoking cessation among current smokers, and smoking relapse among former smokers.

DESIGN, SETTING, AND PARTICIPANTS The CONSTANCES (Consultants des Centres d'Examens de Santé) cohort study, based in France, began recruiting participants January 6, 2012, and is currently ongoing. Participants were enrolled in CONSTANCES through 2015, and included 5400 smokers (mean [SD] follow-up of 23.4 [9.3] months) and 2025 former smokers (mean [SD] follow-up of 22.1 [8.6] months) at baseline who quit smoking in 2010, the year in which ECs were introduced in France, or afterward. Analyses were performed from February 8, 2017, to October 15, 2018.

MAIN OUTCOMES AND MEASURES The association between EC use and the number of cigarettes smoked during follow-up was studied using mixed regression models. The likelihood of smoking cessation was studied using Poisson regression models with robust sandwich variance estimators. The association between EC use and smoking relapse among former smokers was studied using Cox proportional hazards regression models. All statistical analyses were adjusted for sociodemographic characteristics, duration of follow-up, and smoking characteristics.

RESULTS Among the 5400 daily smokers (2906 women and 2494 men; mean [SD] age, 44.9 [12.4] years), regular EC use was associated with a significantly higher decrease in the number of cigarettes smoked per day compared with daily smokers who did not use ECs (−4.4 [95%CI, −4.8 to −3.9] vs −2.7 [95%CI, −3.1 to −2.4]), as well as a higher adjusted relative risk of smoking cessation (1.67; 95%CI, 1.51-1.84). At the same time, among the 2025 former smokers (1004 women and 1021 men; mean [SD] age, 43.6 [12.1] years), EC use was associated with an increase in the rate of smoking relapse among former smokers (adjusted hazard ratio, 1.70; 95%CI, 1.25-2.30).

CONCLUSIONS AND RELEVANCE This study's findings suggest that, among adult smokers, EC use appears to be associated with a decrease in smoking level and an increase in smoking cessation attempts but also with an increase in the level of smoking relapse in the general population after approximately 2 years of follow-up.

1. INTRODUCTION

Cigarette smoking has been identified as a cause of cancer incidence and mortality since the end of World War II¹ and remains a major public health problem today^{2,3}. Most smokers initiate tobacco use in adolescence⁴ and attempt to quit around age 30 (especially women) or after age 50⁵. Pharmacotherapy (nicotine replacement therapies (NRT), Bupropion, Varenicline), as well as behavioural therapies have been shown to be effective in helping smokers quit⁶⁻⁸. Yet, the appeal of smoking cessation aids is relatively low⁹ and most quit attempts are “cold turkey” (i.e. stopping nicotine consumption all at once), without professional assistance or treatment¹⁰⁻¹³. This may be because smoking cessation aids have a financial cost, or because persons lack knowledge about effectiveness and safety. Additionally other reasons such as the belief that quitting without help gives greater satisfaction and a feeling of self-control, strength and autonomy¹⁰ are also at play. However, studies show that smokers who use assistance for smoking cessation are more likely to remain abstinent¹⁴.

Electronic cigarettes (EC), sometimes also referred to as electronic nicotine delivery systems, have become popular in recent years. In the United States approximately 15.3% of adults have ever used ECs,¹⁵ 14.6% in Europe¹⁶ (41.7% in France)¹⁷. Approximately 3.2% of persons in the United States use ECs regularly¹⁵, 1.8% in Europe¹⁶ (3.8% in France)¹⁷. ECs are generally used by smokers who consider them as less harmful than conventional cigarettes^{18,19} and try to reduce or quit their cigarette consumption¹². In some countries, such as France, ECs have become the leading smoking cessation method (27% of smokers who try to quit use an EC), ahead of NRT (18%)¹². Yet, the effectiveness of EC as a smoking reduction and cessation aid is still a subject of controversy²⁰⁻²⁴. Randomized controlled trials have shown that ECs are as effective as²¹ or more effective than²⁵ NRT with regard to aid smoking reduction or cessation. On the other hand, there is also evidence that concurrent use of EC and NRT may hamper smoking

cessation²⁶. However, prior studies have been based on relatively small samples or conducted over short follow-up periods and have limited external validity.

One of the major concerns regarding the consequences of EC use is that it might reduce smokers' motivation to quit²⁷ by providing a cue for smoking relapse²⁸. Thus, paradoxically, EC users might need a larger number of quit attempts to achieve successful smoking cessation. Because former smokers may relapse at different rates, some after only a few days, others after several months²⁹, it is necessary to follow the consequences of EC use over extended periods of time. To date, population-based evidence of long-term smoking trajectories following EC use is limited.

Moreover, most studies have focused on the link between EC use and smoking cessation among smokers who are trying to stop smoking^{21,22}, i.e. those most motivated to quit. However, in the general population, smokers use EC for various reasons – to reduce smoking level, to 'smoke' indoor, to reduce tobacco-related expenses, to reduce health risks, or simply out of curiosity^{30,31}. Recent studies have examined the impact of EC use in the general population^{23,32}, but they have mostly been cross-sectional or short-termed.

The aim of our study, based on the French CONSTANCES (CONSULTANTs des Centres d'Examens de Santé) cohort, was to investigate whether in a community sample with prospective follow-up, EC use is associated a) with changes in the number of cigarettes smoked, b) with smoking cessation rates among smokers, and c) with smoking relapse among former smokers.

2. METHODS AND MATERIALS

2.1 Study design, settings and participants

The CONSTANCES cohort was designed as a randomly selected sample of 200 000 adults drawn from France's compulsory health insurance scheme (Caisse nationale d'assurance maladie), which covers about 85% of persons living in France (excluding farmers and self-employed workers). Recruitment started January 6, 2012, and is currently ongoing, among persons 18 to 69 years of age who live throughout France; the sociodemographic and economic characteristics of participants' districts of residence are very similar to the French average. The sampling base at inclusion is composed of all persons meeting eligibility criteria; to obtain a sample comparable to the French population, an unequal probability sampling scheme over-representing men, younger participants and those belonging to socioeconomically disadvantaged groups, who generally tend to have low participation levels in epidemiological surveys, was implemented^{33,34}. Every year, participants are invited to complete a paper and pencil or web-based questionnaire and additionally undergo a medical examination every 4 years^{33,34}. Participants involved in the first wave of recruitment had more follow-up questionnaires than those recruited at later stages.

The CONSTANCES cohort received the approval of the French legal authorities (CNIL, Commission nationale de l'informatique et des libertés) that ensure ethical review, including an evaluation of participants' informed consent, data confidentiality and safety³³.

Our investigation is based on CONSTANCES cohort participants included in the study up to 2015 and who had at least one completed follow-up questionnaire (n = 40,311). 19,912 participants were non-smokers (49.4%), 6,423 (15.9%) were current smokers (at least 1 cigarette/day) and 13,976 (34.7%) were former smokers at the time of inclusion in CONSTANCES (**eFigure 1**).

We focused on current smokers and former smokers who reported having quit smoking from 2010 onwards (the year ECs were commercially introduced in France; n = 2,046). After excluding participants with no data on EC use (n=1023 and n =21 respectively), our final

analytical sample comprised 5,400 current smokers and 2,025 former smokers with at least one year of follow-up (mean of 2.6 [SD = 0.7] and 2.5 [0.6] years of follow-up respectively). First, among current smokers, we studied the association between EC use and a) the number of cigarettes smoked; b) smoking cessation. Second, among participants who quit smoking from 2010 onwards, we studied the association between EC use and smoking relapse.

2.2 Variables

2.2.1 Outcomes

The four study outcomes examined are: 1) the number of cigarettes smoked per day; 2) the difference between the number of cigarettes smoked per day at baseline and follow-up; 3) smoking cessation among smokers (i.e. 0 cigarettes/day in any year of follow-up; and 4) cigarette smoking relapse among former smokers (\geq one cigarette/day in any follow-up questionnaire).

2.2.2 Exposure: Electronic cigarette use

Participants reported current regular (daily) EC use (yes or no) (n=822, 15.2% of smokers; n=176, 8.7% of former smokers) and the date of initiation of regular EC use, which made it possible to calculate the duration of regular EC use. For each participant, we evaluated EC use prospectively irrespective of the type of device (rechargeable vs. disposable; data on device type was not usable because of missingness). As data on motives for using EC were not collected, EC use in our study is not restricted to only those who want to stop smoking. Among the 822 smokers who used an EC during the study, 194 (23.6%) had started EC use prior to study baseline.

The length of EC use has been shown to influence smoking cessation³⁵, and in secondary analyses we studied the influence of the duration of EC use (< vs. ≥one year) on smoking patterns.

2.2.3 Covariates

Our statistical analyses controlled for covariates previously shown to be associated either with tobacco cessation or EC use: sex, age³³, marital status (single vs. cohabiting/married), educational level³⁷ (≤ high school vs. higher education), employment status (employed, unemployed or retired), citizenship (non-French vs. French), household income³⁷ (< 1500, 1500-2799 or ≥ 2800 euros/month), financial difficulties (yes vs. no), alcohol abuse (AUDIT score), the number of cigarettes smoked per day at the time of inclusion³⁶, pack-years of smoking (lifetime tobacco exposure - a pack year is defined as twenty cigarettes smoked every day for one year), depressive symptoms measured by the Center for Epidemiologic Studies-Depression scale (CES-D), lifetime history of depression (yes vs. no), respiratory problems in the preceding 12 months (yes vs. no), lifetime history of cardiovascular disease (yes vs. no) and lifetime history of cancer (yes vs. no). Additionally, we controlled for participants' year of inclusion in the CONSTANCES cohort, the duration of follow-up, and prior lifetime episodes of smoking cessation³⁶ (none, < one year, ≥ one year).

2.3 Statistical methods

To identify covariates related both to the study exposure and outcomes, we conducted univariate logistic and linear regression analyses.

2.3.1 Is EC use associated with smoking reduction or quitting?

Among daily smokers, the association between EC use with a) the number of cigarettes smoked per day and b) the difference in the number of cigarettes smoked per day between baseline and follow-up was estimated using mixed linear models adjusted for socio-demographic characteristics such as sex, age, marital status, educational level and income, substance use including alcohol abuse, the number of cigarettes smoked per day, pack-years of smoking, and health characteristics such as depressive symptoms and respiratory problems. Variables included in the final model were selected using the ‘least absolute shrinkage and selection operator’ (Lasso) method³⁸.

To predict the likelihood of smoking cessation associated with EC use, we used Poisson regression models with robust sandwich variance estimators³⁹, adjusted for socio-demographic characteristics, duration of follow-up and previous smoking cessation attempts. This method was preferred to logistic regression, for which the adjusted odds ratios would have overstated the participants’ relative risk⁴⁰ of quitting smoking (28 % of smokers reported quitting in any year of follow-up). Because associations between EC use and cigarette smoking can vary with individuals’ sex, age, duration of previous smoking cessation attempts, and educational level, we additionally carried out analyses stratified on these characteristics.

2.3.2 Is EC use associated with smoking relapse in former smokers?

To test whether EC use is associated with later smoking relapse, we focused on former smokers who quit tobacco in or after 2010, and used Cox proportional hazard regression models adjusted for socio-demographic characteristics including sex, age, marital status, educational level and income, alcohol and cigarette use as well as health conditions such as depressive symptoms and respiratory problems. To estimate the time to event (relapse/regular smoking), we calculated the number of months between the inclusion in the CONSTANCES cohort and the follow-up questionnaire in which the participant reported regular smoking. Among former smokers who

did not relapse, data were censored at the last follow-up questionnaire available. We verified the proportional hazard assumption both graphically and statistically.

Because the level of EC use increased and the devices used evolved over time, we carried out supplementary analyses stratifying our sample on the year of smoking cessation.

2.3.3 Missing data and Multiple Imputations

Overall, less than 2% of data were missing, except for data on number of pack-years of smoking, which were unavailable for 718 of 7425 participants (9.7%). Missing data on all covariates were imputed using multiple imputations (10 imputations per missing value) with fully conditional specification (FCS MI)⁴¹.

All data analyses were conducted using SAS version 9.4.

3. RESULTS

3.1 Study population characteristics

In our study, smokers (N = 5,400) were followed for a mean period of 23.4 months (SD = 9.3 months) during which 822 (15.2%) reported regularly (daily) using an EC. As shown in **Table 1**, univariate analyses show that compared to non-users, EC users were more likely to be male (51.5% vs. 45.2%), older (mean age: 45.9 vs. 44.7 years), in a civil partnership /married (49.0% vs. 46.8%) and were followed for a longer period (mean 26.2 vs. 22.9 months). EC users were heavier smokers (mean [SD], 12.9 [6.8] vs. 10.0 [6.6] cigarettes per /day; 17.5 [14.1] vs. 12.6 [12.1] pack-years of smoking) and were more likely to have previously made an attempt to quit smoking (72.3% vs. 68.7%). EC users were also more likely to have depressive symptoms (mean [SD] Center for Epidemiologic Studies Depression scale score, 14.1 [10.3] vs. 12.2 [9.5]), a history of depression (24.2% vs. 19.9%) or respiratory problems (78.6% vs. 68.1%).

Former smokers (N = 2,025) were followed for a mean period of 22.1 months (SD = 8.6 months) during which 8.7% (n= 176) reported regular EC use (**Table 1**). EC users were more likely to be male (63.1% vs. 49.2%), have higher levels of tobacco smoking (mean [SD], 16.9 [12.6] vs. 12.9 [13.7] pack-years) and lower levels of alcohol-related problems (mean [SD] Alcohol Use Disorders Identification Test score, 16.9 [12.6] vs. 12.9 [13.7]), as well as higher levels of depressive symptoms (mean [SD] Center for Epidemiologic Studies–Depression scale score, 12.6 [9.8] vs. 10.9 [8.6]).

3.2 EC use and longitudinal changes in cigarette smoking

In a univariate mixed linear model (**Table 2**), EC users smoked significantly more cigarettes per day than non-users (11.2 [10.8 - 11.7] vs. 9.8 [9.6 - 10.0]). However, after controlling for demographic, socioeconomic, substance use-related and health characteristics, the estimated number of cigarettes smoked per day was significantly lower among EC users than among non-users (11.2 [10.5 - 11.8] vs. 12.2 [11.6 - 12.8]). Adjusting for all covariates, EC users decreased their smoking level significantly more over the course of follow-up than non-users (respectively -4.4 [-4.8 - -3.9] vs. -2.7 [-3.1 - -2.4] cigarettes/day).

3.3 EC use and cigarette smoking cessation

In both univariate and multivariate models, EC users were more likely to quit smoking during follow-up compared to non-users (**Table 2**) with a relative risk (RR) of 1.59 [95% CI: 1.45-1.76] and 1.67 [95% CI: 1.51-1.84] respectively. In additional analyses, this association was stronger among participants who used an EC for more than one year (adjusted RR: 2.03 [95% CI: 1.82-2.27]) rather than less than one year (adjusted RR: 1.33 [95% CI: 1.15-1.54]) (**eTable 1**).

We found no statistical interaction between EC use and sex, age group, duration of prior smoking cessation, or educational level (**eTable 2**).

3.4 Smoking relapse in former smokers

Overall, compared to former smokers who did not use an EC, those who did were more likely to relapse to smoking (adjusted HR= 1.70 [95% CI: 1.25-2.30]) (**Figure 1**). This hazard ratio decreased with time from 1.70 among persons who quit as of 2010 (n=2025) to 0.94 [95% CI: 0.57-1.52] among persons who quit as of 2013 (n=601) (**Table 3**).

4. DISCUSSION

Main findings

Studying longitudinal associations between electronic cigarette (EC) use and tobacco smoking patterns in a large population-based cohort study, we found that EC use was associated with a reduction in smoking level as well as an increased probability of smoking cessation. However, we also observed that over time EC users who quit tobacco tended to relapse to smoking more frequently than non-users. Thus, while EC use can help persons reduce their smoking levels in the short term, there is no evidence that it is an efficacious smoking cessation aid in the long-term.

Limitations

Our investigation has weaknesses which need to be acknowledged. First, our study was not designed to test whether e-cigarettes are efficacious with regard to tobacco smoking reduction. We had no information on the motives underlying EC use nor the extent to which participants intended to quit smoking. Previous studies have shown that the main reason for EC use among adults is the intention to reduce or quit smoking³⁰ and it is the most used aid for smoking cessation in France (no aid (52%); EC (27%); NRT (18%))¹². Moreover, we controlled for previous smoking cessation attempts and our results are consistent with those of other

researchers who suggest that EC use is related to an increase in the reduction of tobacco consumption over time³². Therefore, it is likely that among regular smokers, electronic cigarettes primarily serve to help decrease tobacco use levels. Second, participants' nicotine dependence was not measured, but our analyses controlled for the number of cigarettes smoked per day and pack-years of smoking, which can be considered as valid proxies⁴². Similarly, smoking was self-reported, which could induce bias, but such measures are generally considered valid⁴³. Fagerström test for nicotine dependence were also not available. Third, the duration of follow-up was on 23 months on average, which is longer than in most previous studies, but it could be argued that it should be even longer as smokers often need several quit attempts before achieving successful long-term smoking cessation⁴⁴. Fourth, participants reported current EC use and date of initiation from which we derived the duration of EC use. However, the daily frequency of EC use (e.g. number of puffs) was not documented. Previous studies showed that smoking cessation is primarily related to extensive EC use^{20,45}. Similarly, we were not able to evaluate EC users' nicotine intake and examine whether it predicts smoking behaviour. Most participants reported using ECs with nicotine, but the information regarding the dosage in nicotine of the e-liquid was often missing. In future studies it will be important to assess the frequency of EC use and associated nicotine levels via questionnaires or other direct means of data collection.

Strengths

Despite these limitations, our study has important strengths. We assessed the association between EC use and smoking among smokers and former smokers prospectively in a large population sample, over approximately two years of follow-up on average. We were able to take into consideration the length of EC use, which seems to play a role with regard to smoking cessation. But our main contribution to the existing literature is the finding of an elevated rate of of smoking relapse among former smokers who use an EC.

Our results are in line with those of other studies showing that e-cigarette use can help reduce tobacco smoking^{32,46,47} and encourage smoking cessation^{23,25}. The decrease in tobacco consumption in smokers irrespective of EC use, observed in national surveys¹⁷, suggests that recent policies, such as the ban on smoking in public places, the reimbursement of nicotine replacement therapy and the increase in the price of tobacco products are bearing fruits. We found that smokers who used ECs decreased their smoking significantly more than non EC users and that they had a significantly higher probability of quitting smoking during follow-up. A recent randomized controlled trial showed that among smokers trying to quit smoking, compared to NRT, EC use was associated with a higher level of 1-year abstinence (Relative Risk of 1.83, 95% confidence interval, 1.30 to 2.58; $p < 0.001$)²⁵. Unfortunately, we had no information on reasons for EC use but previous studies indicates that in France, 82% of smokers and 89% of former smokers who use ECs consider they are an aid to quit smoking or prevent a relapse⁴⁸. It would be interesting to further explore whether this smoking reduction or cessation is observed mainly in smokers who use ECs as a cessation tool or also among those who use it for other reasons. In additional analyses we found that smoking cessation was related to duration of EC use, which is consistent with previous studies³⁵.

Although EC users in our study were more likely to be male, there were no gender differences in the relationship between EC use and smoking cessation. Previous research showed no gender differences⁴⁹ or higher levels of cessation among men⁵⁰, but these studies were conducted prior to the introduction of electronic cigarettes. In particular, women are more likely than men to quit smoking before the age of 50 years, while the opposite is true after 50 years of age⁴⁹. Since men and women have different patterns of use and expectancies regarding electronic cigarettes⁵¹, future research should focus on possible gender differences with regard to long-term patterns of smoking cessation.

While EC use in smokers is associated with an increased probability of attempts to quit smoking, its use by former smokers, on the other hand, is linked to a higher likelihood of smoking relapse. This may be due to higher nicotine dependency among EC users or the fact that EC use may contribute to maintaining individuals' levels of nicotine addiction over time. In particular, in case of technical problems with an EC (e.g. low battery, lack of e-liquid) or if an EC does not give the same pleasure as conventional cigarettes⁵²⁻⁵⁴, individuals may revert to smoking.

However, it is important to note that levels of smoking relapse were not increased among former smokers who quit in recent years. Measures of plasma nicotine levels have showed that compared to older models of ECs, the new generation delivers higher levels of nicotine to the bloodstream^{55,56}. This may be an explanation as to why smokers who recently quit smoking and switched to an EC are less likely to relapse than those who quit earlier. Though we found a higher probability of relapse among former smokers who use ECs than those who do not, the question of whether this difference could be related to a shorter period of follow-up, technical improvements in ECs over time, or a change in the profile of EC users, will need to be evaluated in future studies.

5. CONCLUSION

Among current smokers, e-cigarette use is associated with a decrease in the number of cigarettes smoked and with an increase in cessation attempts, especially if it lasts over one year. However, among former smokers, EC use predicts a higher likelihood of relapse to smoking. While electronic cigarettes use may help individuals decrease smoking levels and initiate smoking cessation, it is not clear whether it leads to complete long-term cessation.

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- The authors whose names are listed above certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers’ bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-

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Tables and Figures

Table 1: Characteristics of smokers (n = 5400) and former smokers (n = 2025) according to electronic cigarette (EC) use status, CONSTANCES cohort study, 2012-2017.

	Active smokers at study baseline			Former smokers since 2010		
Characteristics	EC users (N = 822)	Non-users (N = 4,578)		EC users (N = 176)	Non-users (N = 1,849)	
	^a N (%) or ^b Means (<u>SD</u>) or ^c Medians (IQR)		<i>p value</i>	^a N (%) or ^b Means (<u>SD</u>) or ^c Medians (IQR)		<i>p value</i>
Socio-demographic characteristics						
Gender: Male ^a	423 (51.5)	2071 (45.2)	0.001	111 (63.1)	910 (49.2)	<0.001
Age at inclusion period (years) ^b	45.9 (<u>11.6</u>)	44.7 (<u>12.5</u>)	0.01	44.6 (<u>10.6</u>)	43.5 (<u>12.2</u>)	0.23
Duration of follow-up (months) ^b	26.2 (<u>9.5</u>)	22.9 (<u>9.1</u>)	<0.001	21.9 (<u>8.9</u>)	22.2 (<u>8.6</u>)	0.65
Marital Status: in a civil partnership /married ^a	403 (49.0)	2142 (46.8)	0.02	94 (53.4)	1018 (55.1)	0.79
Educational level: No tertiary education ^a	377 (45.9)	2092 (45.7)	0.93	63 (35.8)	682 (36.9)	0.77
Citizenship: Non-French ^a	14 (1.7)	117 (2.6)	0.29	2 (1.2)	38 (2.1)	0.26
Monthly household income: < 1500 euros ^a	132 (16.1)	752 (16.4)	0.85	14 (8.0)	177 (9.6)	0.52
Financial difficulties ^a	269 (32.7)	1277 (27.9)	0.05	61 (34.7)	534 (28.9)	0.17
Alcohol and Tobacco use						
Alcohol abuse (AUDIT) ^a	134 (16.4)	621 (13.6)	0.09	24 (13.6)	136 (7.4)	0.05
Number of cigarettes smoked at baseline ^c	11.0 (<u>9.0</u>)	10.0 (<u>10.0</u>)	<0.001	0	0	
Cigarette pack-years* ^c	15.0 (<u>7-25</u>)	9.0 (<u>4-18</u>)	<0.001	15.5 (<u>8-23</u>)	8.3 (<u>4-18</u>)	<0.001
Made previous attempt to quit smoking ^a	594 (72.3)	3147 (68.7)	0.04	N/A	N/A	
Stopped smoking during follow-up ^a	339 (41.2)	1180 (25.8)	<0.001	N/A	N/A	
Relapsed to smoking during follow-up ^a	N/A	N/A		55 (31.3)	297 (16.1)	<0.001
Health characteristics						
Depressive symptoms (CES-D) ^c	12.0 (<u>7-19</u>)	10.0 (<u>5-17</u>)	<0.001	10.0 (<u>5-17</u>)	9.0 (<u>5-15</u>)	0.01
History of depression ^a	199 (24.2)	911 (19.9)	0.005	34 (19.4)	316 (17.3)	0.47
Respiratory problems ^a	646 (78.6)	3116 (68.1)	<0.001	103 (58.5)	1035 (56.0)	0.52
History of cardiovascular problems ^a	137 (16.7)	655 (14.3)	0.07	23 (13.1)	272 (14.8)	0.55
History of cancer ^a	28 (3.4)	157 (3.4)	0.97	6 (3.4)	79 (4.3)	0.57

*Lifetime tobacco exposure - a pack year is defined as twenty cigarettes smoked every day for one year.

Table 2: Longitudinal changes in cigarette smoking as a function of electronic cigarette (EC) use (univariate and multivariate mixed linear and Poisson regression models with robust variance): CONSTANCES cohort study, 2012-2017, N = 5,400 (β or Relative Risk, 95% CI).

<i>Univariate analyses</i>	EC users (n = 822)			Non-users (n = 4,578)			
Outcomes	Estimate	95% CI		Estimate	95% CI		<i>p</i>
Number of cigarettes smoked per day (β)	11.2	10.8	11.7	9.8	9.6	10.0	<0.001
Difference in the number of cigarettes per day between baseline and follow-up (β)	-4.0	-5.1	-2.8	-1.8	-2.9	-0.7	<0.001
Smoking cessation (RR)	1.59	1.45	1.76	reference			<0.001
<i>Adjusted analyses*</i>	EC users			Non-users			
Outcomes	Estimate	95% CI		Estimate	95% CI		<i>p</i>
Number of cigarettes smoked per day (β)	11.2	10.5	11.8	12.2	11.6	12.8	<0.001
Difference in number of cigarettes per day between baseline and follow-up (β)	-4.4	-4.8	-3.9	-2.7	-3.1	-2.4	<0.001
Smoking cessation (RR)	1.67	1.51	1.84	reference			<0.001

* Adjusted on: age, sex, educational level, income, financial difficulties, marital status, number of cigarettes smoked at baseline, pack-years of smoking, duration of previous quit attempts, history of depression and depression at baseline, respiratory problems.

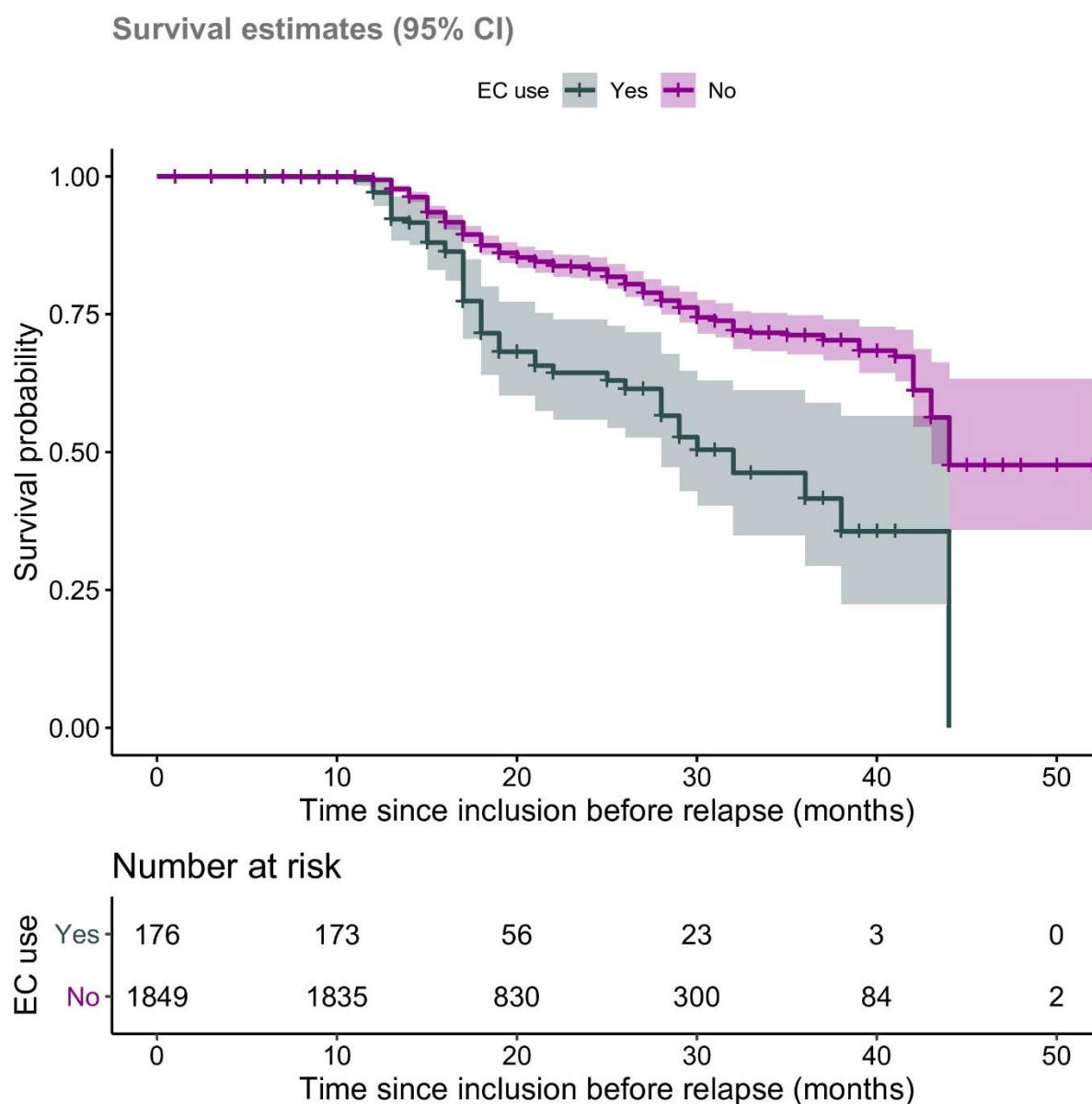
Table 3: Smoking relapse as a function of electronic cigarette (EC) use among former smokers who stopped smoking from 2010 (N =2,025), Cox regression: CONSTANCES cohort study, 2012-2017, Hazard Ratio, 95% CI.

Smoking relapse : EC user vs. non-user	Year ^a	N former smokers	N (%) EC users	Hazard Ratio	95% CI	<i>p</i>
Univariate model	2010	2,025	176 (8.7)	2.34	1.75 - 3.12	<0.001
	2011	1,636	166 (10.1)	1.96	1.45-2.64	<0.001
	2012	1,176	149 (12.7)	1.39	1.00-1.95	0.05
	2013	601	97 (16.1)	0.84	0.53-1.33	0.46
Adjusted model	2010	2,025	176 (8.7)	1.70	1.25 - 2,30	<0.001
	2011	1,636	166 (10.1)	1.57	1.15 - 2.16	0.005
	2012	1,176	149 (12.7)	1.21	0.85 -1.72	0.29
	2013	601	97 (16.1)	0.94	0.57 - 1.52	0.79

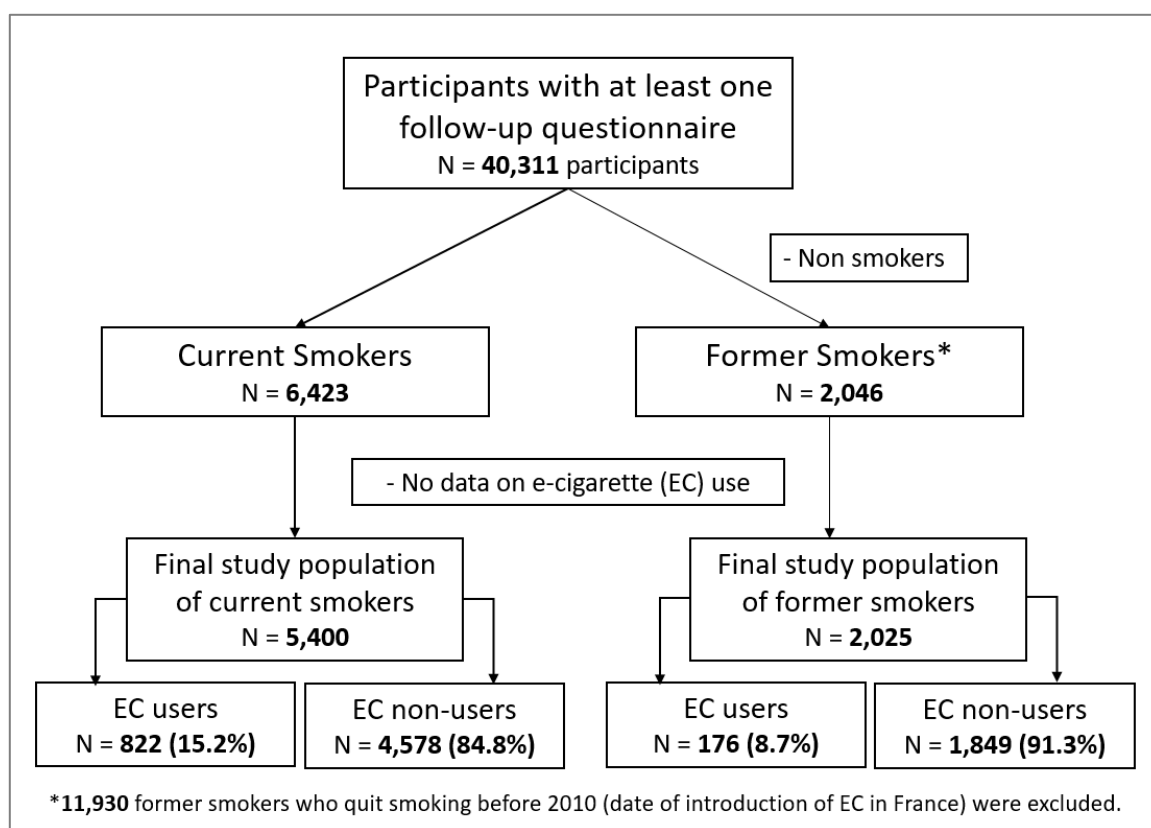
^a: year when participants quit smoking, e.g. 2012 corresponds to former smokers who stopped smoking in 2012 or later (exclusion of those who stopped before 2012).

Adjusted on: age, sex, education level, income, financial difficulties, marital status, AUDIT score, cigarettes pack-years, number of cigarettes smoked before cessation, and year of smoking cessation.

Figure 1: Survival estimates (time to smoking relapse) and 95% Confidence Intervals (shaded area) according to current regular electronic cigarette (EC) use among former smokers (N = 2,025), CONSTANCES cohort study, 2012-2017.



Supplementary Figure 1: Flow chart of CONSTANCES's cohort study participants included in the analysis (2012-2017).



Supplementary Table 1: Smoking cessation attempts among smokers as a function of EC duration of use, Poisson regression with robust variance: CONSTANCES cohort study, 2012-2017, N = 5,400 (Relative Risk, 95% CI).

EC use duration	<i>Non-users</i>	<i>EC use < one year</i>		<i>EC use >= one year</i>	
RR of smoking cessation		RR	95% CI	RR	95% CI
<i>Univariate analysis</i>	reference	1.28***	1.10 - 1.48	1.94***	1.74 - 2.17
<i>Multivariate analysis</i>	reference	1.33***	1.15 - 1.54	2.03***	1.82 - 2.27

***: $p < 0.001$

Adjusted on: age, sex, education level, income, financial difficulties, marital status, cigarettes packet years, number of cigarettes smoked at inclusion, cigarette pack-years, duration of previous quit attempts, history of depression and depression at baseline, and respiratory problems.