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Electronic cigarette use is associated with depressive symptoms among smokers and former smokers: Cross-sectional and longitudinal findings from the Constances cohort

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HIGHLIGHTS

- Depressive symptoms were positively associated with electronic cigarette use.
- For smokers at baseline, they were associated with co-use of tobacco at follow-up.
- For former smokers, a link was found with tobacco only or electronic cigarette only.
- Nicotine concentration and depressive symptoms were also positively associated.

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ABSTRACT

Aims: To examine the cross-sectional and longitudinal associations between depressive symptoms and electronic cigarette (e-cig) use in a large population-based sample while taking into account smoking status and socio-demographic confounders.

Methods: Participants from the French Constances cohort were included from February 2012 to December 2016. Smoking status, e-cig use (never/ever/current) and nicotine concentration were self-reported. Depressive symptoms were measured with the Center for Epidemiologic Studies Depression (CES-D) scale. Logistic regressions were used to provide odds ratios (ORs) and 95% confidence intervals (95%CI) of e-cig use according to depressive symptoms, adjusting for age, sex and education.

Results: In cross-sectional analyses (n = 35,337), depressive symptoms (i.e. a CES-D score ≥ 19) were associated with both ever (OR [95%CI]: 1.67 [1.53–1.82]) and current (1.73 [1.53–1.96]) e-cig use with a dose-dependent relationship (p-trend < 0.001). In longitudinal analyses (n = 30,818), depressive symptoms at baseline were associated with current e-cig use at follow-up (2.02 [1.72–2.37]) with a similar dose-dependent relationship. These associations were mainly significant among smokers or former smokers at baseline. Furthermore, among smokers at baseline, depressive symptoms were associated with dual consumption at follow-up (1.58 [1.41–1.77]), whereas among former smokers, they were associated with either smoking only (1.52 [1.34–1.73]) or e-cig use only (2.02 [1.64–2.49]), but not with dual consumption (1.11 [0.73–1.68]) at follow-up. Finally, depressive symptoms were positively associated with nicotine concentration among e-cig users at baseline.

Conclusions: Depressive symptoms were positively associated with e-cig use in both cross-sectional and longitudinal analyses with a dose-dependent relationship. In addition, nicotine concentration and depressive symptoms were positively associated.

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1. Introduction

Tobacco consumption is one of the main causes of premature death worldwide (GBD 2015, 2017) and is strongly associated with depression, which is the most disabling condition worldwide (Fluharty, Taylor, Grabski, & Munafò, 2017; Vulser et al., 2015). In addition, depressed smokers have a reduced likelihood to successfully quit as well as a greater tobacco dependence (Fluharty et al., 2017; Weinberger et al., 2017). Electronic nicotine delivery systems, the most common of which are electronic cigarettes (e-cig), have been commercialized since about 2010 and their use has increased in recent years, with an ongoing debate regarding their influence on tobacco consumption. On one hand, as e-cig delivers nicotine, its use might reduce tobacco consumption (Breland et al., 2017; El Dib et al., 2017; Zhu, Zhuang, Wong, Cummins, & Tedeschi, 2017). On the other hand, e-cig use might lead to an escalation of smoking, due to frequent acute nicotine intakes that could worsen the dysregulation of the reward system (Conner et al., 2018; Doran et al., 2017; Volkow & Morales, 2015). Although a growing number of studies investigated the association between depression and e-cig use among selected samples, the interplay between depression, tobacco smoking and e-cig use is still poorly understood.

Some previous studies have shown cross-sectional (King, Reboussin, Spangler, Cornacchione Ross, & Sutfin, 2018; Leventhal et al., 2016; Pulvers et al., 2015; Spears, Jones, Weaver, Pechacek, & Eriksen, 2016) and longitudinal (Bandiera, Loukas, Li, Wilkinson, & Perry, 2017; Lechner, Janssen, Kahler, Audrain-McGovern, & Leventhal, 2017) associations between depressive symptoms and e-cig use, but negative findings have also been reported (Dunbar et al., 2017; Hefner et al., 2016; Spindle et al., 2017). Although smoking status might account for these discrepancies, only few studies have explored its influence on these associations (Dunbar et al., 2017; Lechner et al., 2017; Leventhal et al., 2016; Spindle et al., 2017). Likewise, although a dose-dependent relationship might provide some evidence for a causal relationship, only few cross-sectional studies have searched for it, yielding somewhat inconsistent results regarding the link between levels of psychological distress (i.e. symptoms of anxiety or depression) and e-cig use (Dunbar et al., 2017; Park, Lee, Shearston, & Weitzman, 2017). In addition, to our knowledge, the role of nicotine concentration in the liquid used in e-cigarettes (e-liquid) has never been explored. However, neurobiological studies support the hypothesis that depressed individuals may use nicotine as a “self-medication” to cope with depressive symptoms through enhanced short-term brain neurotransmission (Aubin, Rollema, Svensson, & Winterer, 2012; Dome, Lazary, Kalapos, & Rihmer, 2010). In the long run, however, chronic nicotine consumption may result in impaired monoamine functioning, contributing to promote or maintain depressive symptoms (Aubin et al., 2012; Dome et al., 2010). Furthermore, depression has been associated with lower rates of successful smoking cessation that could results from a poorer tolerance regarding nicotine withdrawal symptoms as well as a worsening of depressive symptoms during quit attempts (Brown, Lejuez, Kahler, & Strong, 2002). Finally, most previous studies were based on selected samples, restricted to current smokers (Pulvers et al., 2015), adolescents (Dunbar et al., 2017; Leventhal et al., 2016), students (Bandiera et al., 2017; King et al., 2018; Lechner et al., 2017; Spindle et al., 2017) or veterans using mental health and substance use disorders services (Hefner et al., 2016). The only population-based study was cross-sectional and did not use a validated measure of depression (Spears et al., 2016). Therefore, large-scale population-based studies are warranted to prospectively examine these associations.

The population-based Constances cohort study offers a unique opportunity to examine associations between depressive symptoms and e-cig use in both cross-sectional and longitudinal analyses, looking for a dose-dependent relationship and potentially different associations according to smoking status. Among e-cig users, we also aimed to explore associations between depressive symptoms and nicotine concentration in the e-liquid. Finally, associations between depressive symptoms at baseline and dual consumption of tobacco and e-cig at follow-up were investigated. We hypothesized that the risk of e-cig use would increase along with the intensity of depressive symptoms, following a dose-dependent relationship in both current and former tobacco smokers. Since depression is a risk factor of addictive behaviors, we expected depressed smokers to be both less likely to quit smoking and more likely to initiate e-cig use. In other words, we hypothesized that longitudinal analyses among depressed smokers would show increased risks of dual consumption rather than switching from one substance to the other.

2. Methods

2.1. Participants

The design and main objectives of the Constances cohort (www.constances.fr) have been previously described (Zins et al., 2015). Briefly, the Constances cohort includes volunteers aged 18–69 years at inception, who were randomly selected from French adults who are covered by CNAMTS (Caisse nationale d'assurance maladie des travailleurs salariés), which is the national health insurance of > 85% of the French population. Those who agree complete self-administrated questionnaires dealing with lifestyle, health, physical limitations, social and personal characteristics. They are invited to go to one of the twenty-one participating Health Screening Centers throughout France, to undergo an extensive health examination. An annual self-administered follow-up questionnaire is then completed by the participants at home, using either a paper questionnaire or internet. Recruitment of participants began mid-2012 and is still ongoing.

Questions about e-cig were first introduced in the 2013 follow-up questionnaire, then every year and in the inclusion questionnaire from 2015 onwards. For cross-sectional analyses, our study population was composed of all subjects included from January 2015 to December 2016, without missing data for selected variables (i.e. depressive symptoms, e-cig use, age, sex, years of education and tobacco smoking status). For longitudinal analyses, our study population consisted of all subjects included from February 2012 to December 2014, with at least one follow-up questionnaire without missing data for e-cig current use as well as for depressive symptoms, age, sex, years of education and tobacco smoking status at baseline.

All confidentiality, safety and security procedures were approved by the French legal authorities. According to French regulations, the Constances Cohort study has obtained the authorization of the National Data Protection Authority (Commission Nationale de l'Informatique et des Libertés - CNIL).

2.2. Depressive symptoms

Depressive symptoms were assessed at baseline using the validated self-administered Center for Epidemiologic Studies Depression scale (CES-D) (Führer & Rouillon, 1989; Radloff, 1977). This 20-item questionnaire has been designed for use in community studies. The CES-D scale evaluates the frequency of depressive symptoms during the previous week (e.g., I felt depressed, I felt everything I did was an effort, My sleep was restless). Responses range from 0 (hardly ever) to 3 (most of the time). Given the satisfactory internal consistency (Cronbach's alpha = 0.90 in the current sample), when < 5 items were missing, the total score was computed based on the mean value of available items multiplied by 20. The CES-D scale was used: either 1) as a binary variable based on the cut-off of ≥19 for both men and women, according to the validation of the French version (sensitivity/specificity for the diagnosis of major depression: 0.85/0.86) (Morin et al., 2011); or 2) as a continuous variable, using the whole range of CES-D scores with the interval between the 25th and the 75th percentile (i.e. 10 points) as the basic unit. The meaning of one-point increase in CES-D might indeed be difficult to figure out, whereas comparing participants in the middle of the upper half of the CES-D score distribution with those in the middle of the lower half is more intuitive.

2.3. E-cigarette (e-cig) use and nicotine concentration

For participants included from January 2015 to December 2016, ever and current e-cig use as well as the type of device used (i.e. disposable or rechargeable) were reported at study baseline. Participants were categorized into the following categories: never users, ex-users and current users of e-cig. Furthermore, nicotine concentration in mg/mL was collected at baseline in four categories: 0 (i.e. e-liquid without nicotine); < 6; 6–12; ≥ 13. Current e-cig use was also reported at follow-up, regardless of the date of inclusion.

2.4. Other variables

Age, sex, educational level, and tobacco smoking status were self-reported at study baseline. Educational level was categorized into three groups: less than or equal to high school degree (13 years or less of education), undergraduate degree (14–16 years of education) and postgraduate degree (17 years or more of education). Smoking status was categorized into three groups: never smokers, former smokers and current smokers. Participants were considered smokers or former smokers if they reported having consumed at least 100 cigarettes (or equivalent) and were currently or no longer smoking, respectively. At follow-up, current tobacco smoking was also reported.

2.5. Statistical analyses

In cross-sectional analyses, binomial logistic regressions were used to compute odds ratios (ORs) and their 95% confidence intervals (CI) for associations between depressive symptoms and e-cig use at baseline. The outcome was either ever e-cig use (vs. never use) or current e-cig use (vs. never or ex-use). We first examined these associations in univariable analyses and then in multivariable analyses adjusted for age, sex and education. Sex differences were systematically searched for by modelling sex by depression interactions, while simultaneously including both sex and depression in statistical models. In addition, since we had a priori hypotheses regarding a possible effect modification by smoking status, stratified analyses were planned for this variable. Among current users of rechargeable e-cig, associations between depressive symptoms and nicotine concentration were examined with a multinomial logistic regression, adjusted for age, sex and education, while taking a null nicotine concentration as reference category.

In longitudinal analyses, associations between depressive symptoms at baseline and current e-cig use at follow-up were examined with generalized estimating equations (GEE) logistic models. We first conducted univariable analyses and then multivariable analyses adjusted for age, sex and education. Sex differences were systematically searched for by modelling sex by depression interactions, while simultaneously including both sex and depression in statistical models. Again, analyses were a priori stratified by smoking status. Finally, associations between depressive symptoms at baseline and the pattern of current tobacco and e-cig use at follow-up were examined with a GEE multinomial logistic regression, with a 4-class computed dependent variable as follows: current tobacco smoking and e-cig use; current tobacco smoking without e-cig use; current e-cig use without tobacco smoking; no current tobacco smoking or e-cig use.

Statistical analyses were carried out with the Stata software (StataCorp, 2015), except for GEE multinomial logistic regressions for which R version 3.4 (R Core Team, 2018) and the package “multgee” were used (Touloumis, 2015).

3. Results

3.1. Cross-sectional analyses

A total of 35,337 participants enrolled from January 2015 to December 2016 were included in this analysis. Population selection is described in Supplementary Fig. S1 and participants with and without missing data are compared in Supplementary Table S1. Participants with missing data were older, more likely to be women, never smokers as well as to have a lower education and a higher CES-D score. The mean age (SD) of participants without missing data was 45.8 (13.9) years and 48.0% were men. Their mean (SD) CES-D score was 10.7 (9.0), with a difference of 10 points between the 25th and 75th percentiles, and 5631 participants (15.9%) had a score ≥ 19. Table 1 shows selected characteristics of study participants according to the use of e-cig. Lifetime e-cig use was associated with male sex, lower age and educational level, smoking and higher levels of depressive symptoms (all $p < 0.001$). Furthermore, compared to e-cig non-users (i.e. never or ex-users), current users had the same characteristics (all $p \leq 0.001$).

Table 2 displays the ORs and their 95% CI regarding associations between depressive symptoms and ever or current e-cig use. In the whole population, depressive symptoms were associated with both ever and current e-cig use, even after adjustment for age, sex and education. These associations were found in both men and women, with no indication of sex by depression interactions (all p for interaction > 0.14). To test a possible linear trend, the CES-D score was divided into quartiles. Whatever the outcome considered (i.e. ever or current e-cig use), a dose-dependent relationship was found between e-cig use and quartiles of CES-D (p for linear trend < 0.001, Supplementary Figs. S2 and S3). Although the interaction between depressive symptoms and smoking status was not significant, we had a priori decided to stratify by the smoking status. Associations between depressive symptoms and ever or current e-cig use were significant among tobacco smokers and former smokers, but not among never smokers (Table 2). In addition, in exploratory analyses, these associations were not statistically significant among casual smokers (i.e. < 1 cigarette/day, n = 544, all p-values > 0.05). However, when considering daily cigarette consumption in four categories (i.e. < 1, 1–10, 10–20, ≥ 20 cigarettes/day) and as a continuous variable, no dose-dependent relationship was found (all p for interaction > 0.26).

Among current e-cig users, the most prevalent type of device was rechargeable e-cig, either alone (n = 1425; 97.3%) or in conjunction with disposable e-cig (n = 24; 1.6%). Regarding relationships between depressive symptoms and nicotine concentration in the e-liquid (Fig. 1), there was a positive association with the highest concentration of nicotine compared to a null concentration (OR [95% CI]: 2.14 [1.29–3.53]). In addition, a significant trend following the increase in nicotine concentration levels was observed (p for linear trend = 0.001).

3.2. Longitudinal analyses

Among Constances participants included between February 2012 and December 2014, 30,818 individuals were included in longitudinal analyses. Population selection is described in Supplementary Fig. S4 and participants with and without missing data are compared in Supplementary Table S2. Participants with missing data were older, more likely to be former or never smokers as well as to have a lower education and a higher CES-D score. The mean (SD) follow-up duration was 1.88 (0.65) years, 45.4% of subjects who were included were male and their mean age (SD) was 49.3 (13.1) years. Their mean (SD) CES-D crude score was 10.4 (8.5), with a difference of 10 points between the 25th and 75th percentiles, and 4487 participants (14.6%) had a CES-D score ≥ 19. Table 3 shows selected characteristics of study participants at baseline according to the current use of e-cig at the longest follow-up. Current use of e-cig was associated with being male, younger, a current smoker and having a higher level of depressive symptoms (all $p < 0.001$).

Table 4 displays the ORs and their 95% CI regarding the associations between depressive symptoms at baseline and current e-cig use at follow-up. The interaction between depressive symptoms and time was not significant and thus was not included in the final models. In the whole population, these associations were statistically significant, even

Table 1
Characteristics of the participants included in cross-sectional analyses according to e-cig use (n = 35,337).

	E-cig use	
	Never users (n = 31,788)	Ever users (n = 3549)
Sex, n (%)		
Men	15,267 (48.0)	1832 (51.6)
Women	16,521 (52.0)	1717 (48.4)
Age (years), mean (SD)	46.53 (13.92)	39.38 (12.15)
Education, n (%)		
Less or equal to high school degree	12,845 (40.4)	1669 (47.0)
Undergraduate degree	10,996 (34.6)	1197 (33.7)
Postgraduate degree	7947 (25.0)	683 (19.2)
Smoking status, n (%)		
Current smokers	4548 (14.3)	2525 (71.1)
Former smokers	11,252 (35.4)	945 (26.6)
Never smokers	15,988 (50.3)	79 (2.2)
CES-D score, mean (SD)	10.44 (8.74)	13.29 (10.29)
CES-D score ≥ 19, n (%)	4785 (15.1)	846 (23.8)
	Never or ex-users (n = 33,873)	Current users (n = 1464)
Sex, n (%)		
Men	16,309 (48.1)	790 (54.0)
Women	17,564 (51.9)	674 (46.0)
Age (years), mean (SD)	45.98 (13.97)	41.94 (12.10)
Education, n (%)		
Less or equal to high school degree	13,853 (40.9)	661 (45.2)
Undergraduate degree	11,700 (34.5)	493 (33.7)
Postgraduate degree	8320 (24.6)	310 (21.2)
Smoking status, n (%)		
Current smokers	6111 (18.0)	962 (65.7)
Former smokers	11,718 (35.6)	479 (32.7)
Never smokers	16,044 (47.4)	23 (1.6)
CES-D score, mean (SD)	10.60 (8.85)	13.55 (10.69)
CES-D score ≥ 19, n (%)	5274 (15.6)	357 (24.4)

CES-D: Center for Epidemiologic Studies Depression scale.
All p-values are ≤0.001 for differences between never and ever users or between non-users (i.e. never or former users) and current users ($\chi 2$ or *t*-test for categorical or continuous variables, respectively).

Table 2
Cross-sectional associations between depressive symptoms and e-cig use (n = 35,337) in the whole population and stratified by smoking status.

Ever vs. never use	Crude OR (95% CI)	Adjusted OR (95% CI)
Total population		
CES-D score ≥ 19	1.77 (1.63–1.92) ***	1.67 (1.53–1.82) ***
CES-D continuous score[a]	1.36 (1.31–1.41) ***	1.33 (1.28–1.38) ***
Current smokers		
CES-D score ≥ 19	1.41 (1.25–1.58) ***	1.39 (1.24–1.56) ***
CES-D continuous score[a]	1.19 (1.13–1.25) ***	1.19 (1.13–1.25) ***
Former smokers		
CES-D score ≥ 19	1.41 (1.19–1.68) ***	1.31 (1.09–1.57) **
CES-D continuous score[a]	1.27 (1.18–1.36) ***	1.21 (1.13–1.31) ***
Never smokers		
CES-D score ≥ 19	1.05 (0.57–1.95)	0.94 (0.50–1.75)
CES-D continuous score[a]	1.23 (0.98–1.54)	1.15 (0.90–1.46)
Current vs. never or ex-use	**Crude OR (95% CI)**	**Adjusted OR (95% CI)**
Total population		
CES-D score ≥ 19	1.75 (1.55–1.98) ***	1.73 (1.53–1.96) ***
CES-D continuous score[a]	1.36 (1.29–1.43) ***	1.36 (1.29–1.43) ***
Current smokers		
CES-D score ≥ 19	1.31 (1.12–1.53) **	1.35 (1.15–1.58) ***
CES-D continuous score[a]	1.16 (1.09–1.24) ***	1.18 (1.11–1.26) ***
Former smokers		
CES-D score ≥ 19	1.60 (1.27–2.01) ***	1.58 (1.25–1.99) ***
CES-D continuous score[a]	1.33 (1.21–1.45) ***	1.32 (1.20–1.45) ***
Never smokers		
CES-D score ≥ 19	1.24 (0.42–3.64)	1.05 (0.35–3.13)
CES-D continuous score[a]	1.34 (0.90–1.98)	1.22 (0.80–1.86)

Crude Odds ratios (ORs) and their 95% confidence intervals (95% CI) were computed with univariable binomial logistic regressions and adjusted OR (95% CI) were computed with multivariable binomial logistic regressions, adjusting for age, sex, and education.
CES-D: Center of Epidemiologic Studies Depression scale.
[a] ORs are expressed per 10-point increase in CES-D score (i.e. the interval between the 25th and the 75th percentile).
** p < 0.01.
*** p < 0.001.

after adjustment for age, sex and educational level, and with no indication of sex by depression interactions (all p for interaction > 0.05). Furthermore, a dose-dependent relationship was observed in using quartiles of CES-D p for linear trend < 0.001, (Fig. 2). With the a priori stratification by smoking status, the associations were significant for all categories, except for never smokers where the association was only significant when depressive symptoms were considered as a continuous variable (Table 4). The interaction between depressive symptoms and smoking status was significant only for the continuous measure of depressive symptoms (p = 0.01). In addition, in exploratory analyses, the association between depressive symptoms and e-cig use was examined among current smokers at baseline, according to their level of daily cigarette consumption (i.e. < 1, 1–10, 10–20, ≥ 20 cigarettes/day). This association was not statistically significant for casual smokers (i.e. < 1 cigarette/day, n = 424, all p-values > 0.66) and no dose-dependent relationship was found when considering this variable as continuous (all p for interaction > 0.79).

Associations between depressive symptoms at baseline and the pattern of current tobacco and e-cig use follow-up according to smoking status at baseline are presented in Table 5. Given the small number of e-cig users at follow-up among never smokers (n = 9), only former and current tobacco users were considered. Among smokers at baseline, higher levels of depressive symptoms were positively associated with dual consumption of tobacco and e-cig at follow-up and negatively associated with having quitted tobacco without e-cig use at follow-up. Among former smokers at baseline, higher levels of depressive symptoms were positively associated with tobacco use relapse as well as e-cig use at follow-up. A positive association was also found between the continuous CES-D score and dual consumption of tobacco and e-cig at follow-up.

4. Discussion

The present study aimed to examine cross-sectional and longitudinal associations between depressive symptoms and e-cig use. In cross-sectional analyses, depressive symptoms were positively associated with both ever and current e-cig use, with a dose-dependent relationship, even after adjustment for age, sex and educational level. Among e-cig users, depressive symptoms were positively associated with the use of the highest nicotine concentration in the e-liquid and a linear trend following the increase in nicotine concentration levels was found. In longitudinal analyses, depressive symptoms at baseline were positively associated with current e-cig use at follow-up, with a similar dose-dependent relationship, even after adjustment for age, sex and education. Among smokers, depressive symptoms were positively associated with dual consumption of tobacco and e-cig at follow-up, and negatively associated with quitting tobacco without e-cig use. Among former smokers, depressive symptoms were associated with relapse of tobacco smoking and with e-cig use only at follow-up. Finally an association was also found between depressive symptoms and dual consumption at follow-up, when the continuous CES-D score was used.

Strengths of our study include a large, randomly-recruited,

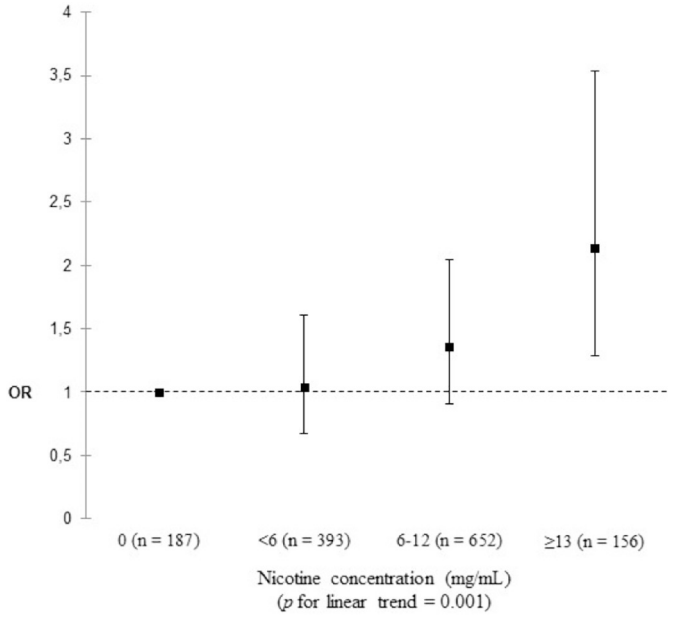

Fig. 1. Cross-sectional associations between depressive symptoms and nicotine concentration, among current users of e-cig (n = 1388).
Odds ratios (ORs) and their 95% confidence intervals (95% CI) were computed with a multivariable multinomial logistic regression, adjusting for age, sex and education, while taking a nicotine concentration of 0 mg/mL as reference category. Depressive symptoms were considered as a binary variable based on a CES-D (Center for Epidemiologic Studies Depression scale) score ≥ 19.

Table 3
Baseline characteristics of the participants included in longitudinal analyses according to the current use of e-cig at follow-up (n = 30,818).

	E-cig non-users at follow-up (n = 30,084)	E-cig users at follow-up (n = 734)	P[a]
Sex (men), n (%)	13,616 (45.3)	388 (52.9)	< 0.001
Age (years), mean (SD)	49.43 (13.08)	45.02 (11.78)	< 0.001
Follow-up duration, n (%)			0.25
6 months to 1.5 years	13,143 (43.7)	342 (46.6)	
1.5 years to 2.5 years	11,696 (38.9)	276 (37.6)	
≥ 2.5 years	5245 (17.4)	116 (15.8)	
Education, n (%)			0.45
Less or equal to high school degree	12,454 (41.4)	321 (43.7)	
Undergraduate degree	10,699 (35.6)	250 (34.1)	
Postgraduate degree	6931 (23.0)	163 (22.2)	
Smoking status, n (%)			< 0.001
Current smokers	4682 (15.6)	562 (76.6)	
Former smokers	11,055 (36.7)	163 (22.2)	
Never smokers	14,347 (47.7)	9 (1.2)	
CES-D score, mean (SD)	10.34 (8.49)	13.63 (10.21)	< 0.001
CES-D score ≥ 19, n (%)	4308 (14.3)	179 (24.4)	< 0.001

CES-D: Center for Epidemiologic Studies Depression scale.
[a] Difference between users and non-users at the longest follow-up ($\chi 2$ or t-test for categorical or continuous variables, respectively).

population-based sample of adults and a prospective design for some of the analyses. Depressive symptoms were assessed with a well-known validated tool and data regarding e-cig use included the type of device as well as nicotine concentration. In addition, we also examined the risk of e-cig use according to smoking status and our findings were adjusted for age, sex and education. Potential sex differences were also systematically searched for by modelling sex by depression interactions in both cross-sectional and longitudinal analyses. Follow-up duration was longer than 1.5 years for > 50% of participants while no study on this topic had, to our knowledge, a follow-up of > 1 year.

This study has some limitations. First, even if participants were randomly selected, they may not be representative of the general population. In particular, because of selection bias, they might be more aware of the benefits of quitting smoking. In addition, excluding participants with missing data might have increased a selection bias toward healthier participants, as it is often observed in population-based

Table 4
Longitudinal associations between depressive symptoms at baseline and current use of e-cig at follow-up (n = 30,818) in the whole population and stratified by smoking status at baseline.

	Crude OR (95% CI)	Adjusted OR (95% CI)
Total population		
CES-D score ≥ 19	1.98 (1.69–2.32) ***	2.02 (1.72–2.37) ***
CES-D continuous score[a]	1.45 (1.36–1.54) ***	1.47 (1.38–1.58) ***
Current smokers		
CES-D score ≥ 19	1.37 (1.14–1.65) **	1.46 (1.21–1.76) ***
CES-D continuous score[a]	1.19 (1.10–1.29) ***	1.23 (1.14–1.33) ***
Former smokers		
CES-D score ≥ 19	1.79 (1.26–2.55) **	1.83 (1.28–2.62) **
CES-D continuous score[a]	1.45 (1.25–1.67) ***	1.49 (1.28–1.73) ***
Never smokers		
CES-D score ≥ 19	2.88 (0.74–11.15)	2.59 (0.66–10.23)
CES-D continuous score[a]	1.99 (1.20–3.29) **	1.99 (1.15–3.44) *

Crude odds ratios (ORs) and their 95% confidence intervals (95% CI) were computed with univariable binomial generalized estimating equations (GEE) logistic regressions, and adjusted ORs (95% CI) were computed with multivariable binomial GEE logistic regressions, adjusting for age, sex and education.
CES-D: Center for Epidemiologic Studies Depression scale.
[a] ORs are expressed per 10-point increase in CES-D score (i.e. the interval between the 25th and the 75th percentile).
* $p < 0.05$.
** $p < 0.01$.
*** $p < 0.001$.

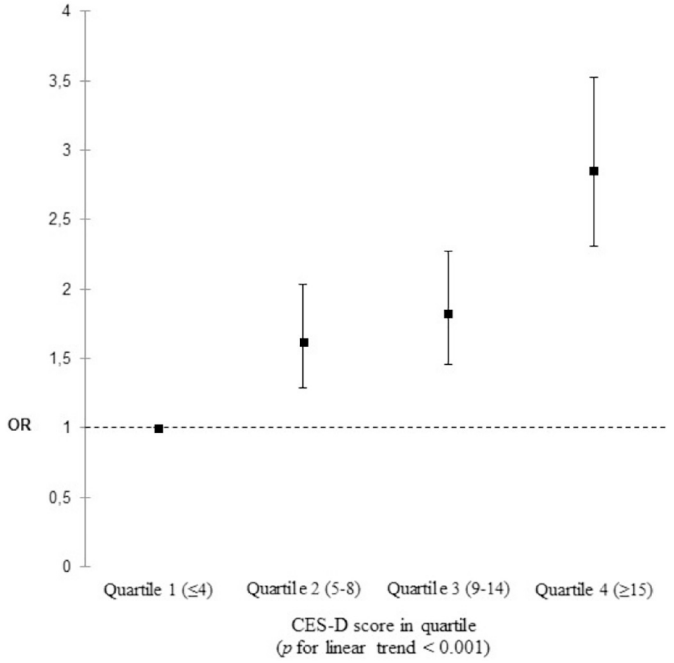

Fig. 2. Longitudinal associations between depressive symptoms at baseline and current use of e-cig at follow-up (n = 30,818).
Odds ratios (ORs) and their 95% confidence intervals (95% CI) were computed with a multivariable generalized estimating equations (GEE) binomial logistic regression, adjusting for age, sex and education. Depressive symptoms were considered as a variable in four categories based on quartiles of the CES-D (Center for Epidemiologic Studies Depression scale) score.

Table 5
Longitudinal associations between depressive symptoms at baseline and patterns of current tobacco and e-cig use at follow-up according to smoking status at baseline (n = 16,402).

Current smokers at baseline	T(−)/E(−) (n = 1359)	T(+)/E(−) (n = 3303)	T(−)/E(+) (n = 235)	T(+)/E(+) (n = 319)
CES-D score ≥ 19	0.71 (0.65–0.77) ***	Ref.	1.00 (0.85–1.17)	1.58 (1.41–1.77) ***
CES-D continuous score[a]	0.84 (0.81–0.87) ***	Ref.	1.06 (1.00–1.13)	1.26 (1.20–1.32) ***

Former smokers at baseline	T(−)/E(−) (n = 10,622)	T(+)/E(−) (n = 404)	T(−)/E(+) (n = 126)	T(+)/E(+) (n = 34)
CES-D score ≥ 19	Ref.	1.52 (1.34–1.73) *	2.02 (1.64–2.49) ***	1.11 (0.73–1.68)
CES-D continuous score[a]	Ref.	1.31 (1.24–1.38) ***	1.48 (1.35–1.61) ***	1.45 (1.30–1.62) ***

Adjusted Odds ratios (ORs) and their 95% confidence intervals (95% CI) were computed with multivariable generalized estimating equations (GEE) multinomial logistic regressions, adjusting for age, sex and education.
CES-D: Center of Epidemiologic Studies Depression scale.
T: tobacco use; E: e-cig use.
(+): current use at follow-up.
(−): no current use at follow-up.
N are given for the longest follow-up of each participant.
[a] ORs are expressed per 10-point increase in CES-D score(i.e. the interval between the 25th and the 75th percentile).
* $p < 0.05$.
*** $p < 0.001$.

cohorts (Goldberg et al., 2001). However, as this study focused on relationships between variables (measures of association), this limitation is less problematic than in merely descriptive studies (measures of prevalence or incidence) (Rothman, Gallacher, & Hatch, 2013). Second, we did not have data on medications to support tobacco weaning (e.g., nicotine replacement therapy). Third, in the longitudinal analyses, we did not have data about baseline e-cig use. However, e-cig use was marginal in France before 2014 and thus began to be assessed in national surveys from that date (Andler et al., 2016). These data might be helpful in further studies to better distinguish between the risks of maintaining versus initiating e-cig use, and to explore the prospective association between e-cig use and subsequent depressive symptoms. Fourth, the CES-D does not capture major depression, so that our conclusions may merely apply to the broader issue of depressive symptoms. Fifth, the possibility of unmeasured confounding cannot be completely ruled out. However, with an OR of 1.67 (95% CI 1.53–1.82), which is the smallest OR value obtained with the binary measure of depressive symptoms in our study, the unmeasured confounders should be associated with both depressive symptoms and e-cig use with an OR of 2.73 (95% CI 2.43–3.04) to entirely explain the present findings (Vanderweele & Ding, 2017). Finally, even though our sample is large, some analyses, such as those looking for a dose-dependent relationship with daily tobacco consumption, might have been underpowered which warrants future investigations with larger samples.

The observational nature of the present study does not allow drawing causal conclusions about the nature of the association between depression and e-cig use. However, the dose-dependent relationship between depressive symptoms and risk of e-cig use, identified in both cross-sectional and prospective analyses, as well as the gradient between nicotine concentration and risk of depressive symptoms among e-cig users, are both consistent with a causal relationship. The former is in line with Park et al. (Park et al., 2017) but the latter is, to our knowledge, a new finding and supports the hypothesis that nicotine per se could be causally involved in the association between depressive symptoms and e-cig use, whatever the direction. These results may indeed have clinical implications regardless of the direction of the association. Overall, the stratification by smoking status at baseline did not substantially change the results. Associations between depressive symptoms and e-cig use appear to be of the same magnitude among current and former smokers. With respect to the results for never smokers, no conclusions can be drawn since there were only nine e-cig users at follow-up. Among current smokers, e-cig use in the context of depressive symptoms may result from their enhanced tendency toward addictive behaviors. On the other hand, e-cig use might be an attempt to limit the increase of tobacco consumption driven by an increased craving due to depressive symptoms (Kushnir et al., 2013). In both cases, a standardized assessment of depressive symptoms should therefore be proposed to both e-cig users and tobacco smokers. Among former smokers, depressive symptoms can precipitate relapse. In this subgroup, however, the odds ratio for e-cig isolated use at follow-up tends to be somewhat higher than the odds ratio of smoking alone at follow-up. Nevertheless, when used as a continuous variable, depressive symptoms at baseline also predict dual consumption at follow-up. Consequently, former smokers should benefit from periodical assessments of depressive symptoms in order to reduce the risk of relapse by treating depression as early as possible.

In this large-scale population-based sample, depressive symptoms were associated with past, current and future e-cig use with a dose-dependent relationship. Interestingly, this association seems to be driven by the use of high concentrations of nicotine, further suggesting biological mechanisms. Further studies assessing depressive symptoms and e-cig use at both baseline and follow-up are needed to better understand the nature and the direction of these mechanisms. However, the present results are sufficient to recommend, without further delay, screening for depression as a routine procedure, not only among individuals who experience trouble quitting smoking, but also among those using e-cig.

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Contributors

EW, GA and CL designed the study. MG and MZ acquired the data. EW, GA and CL conducted the statistical analysis. All authors contributed to the interpretation of data. EW, GA and CL wrote the first draft of the manuscript and all authors contributed to and have approved the final manuscript.

Conflict of interest

GA has received speaker and consulting fees from Lundbeck and Pfizer, outside the submitted work. FL has received speaker and

consulting fees from AstraZeneca, Euthérapie-Servier, Janssen, Lundbeck, Otsuka Pharmaceuticals France and Roche, outside the submitted work. CL reports grants, personal fees and non-financial support from Lundbeck, personal fees from Servier, Daiichi-Sankyo and Janssen, non-financial support from Otsuka Pharmaceuticals, outside the submitted work. All other authors declare that they have no conflicts of interest.

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