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*Experimenting first with e-cigarettes versus first with cigarettes and transition to daily cigarette use among adolescents: the crucial effect of age at first experiment*

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## **Abstract**

**Background and aims:** Most studies in English-speaking countries have found a positive association between e-cigarette experimentation and subsequent daily tobacco smoking among adolescents. However, this result may not be valid in other cultural contexts; in addition, few studies have assessed whether this association varies with the subject's age at the time of e-cigarette experimentation. This study aimed to estimate the association between experimenting first with e-cigarette (rather than tobacco) and subsequent daily smoking according to age at the time of experimentation.

**Design:** Secondary analysis; risk-ratios (RRs) computed using modified Poisson regressions with inverse probability weighting.

**Setting:** A cross-sectional nationwide representative survey performed in 2017 in France.

**Participants:** French adolescents (n=24,111), aged 17 to 18.5 years, who had previously experimented with either e-cigarettes or tobacco.

**Measures:** Exposure was defined as the experimentation with e-cigarettes first (whether or not followed by experimentation with tobacco); the outcome as daily tobacco smoking at the time of data collection. Gender, age, literacy, socioeconomic status, pre-exposure repeat school years and experimentation with 12 other licit and illicit drugs were adjusted for. Uncertainties about the sequence of events defining exposure were handled by the definition of three patterns of exposure, to avoid a misclassification bias.

**Findings:** Exposure reduced the risk of transition to daily smoking: RR=0.58, 95%CI=[0.54, 0.62]. This effect increased in linear manner with age at exposure (RR=0.87, 95%CI=[0.78; 0.98] for 1 year,  $p<0.001$ ): from RR=1.30 95%CI=[1.09; 1.54] at age 9 to RR=0.38, 95%CI=[0.32; 0.45] at age 17.

**Conclusions:** Experimenting with e-cigarettes first (as opposed to tobacco first) appears to be associated with a reduction in the risk of daily tobacco smoking among French adolescent at ages 17-18.5, but this risk varies negatively with age at experimentation, and early e-cigarette experimenters are at higher risk.

**Keywords**

E-cigarette; tobacco smoking; adolescents; propensity score; age at initiation

## INTRODUCTION

E-cigarette use, especially among adolescents, remains a controversial topic in public health (1-3). The first problem is the intrinsic danger of vaping. Vaping is predominantly considered to be safer than conventional cigarette smoking (3, 4), although there is currently insufficient evidence for disregarding any long-term toxicity (5, 6). The second problem is the potential relationship between e-cigarettes and tobacco: could e-cigarettes increase the risk of a transition to tobacco smoking, or could they reduce smoking prevalence by serving as a substitution product (7)? A third problem is the potential risk that the marketing and growing popularity of vaping products could eventually "renormalize" smoking, and thus undermine the current declining trends in tobacco use among young people (8, 9). Providing answers to these questions is of considerable importance for public health, as it could help in prevention campaigns targeting adolescents.

At population level, there is some evidence that, at least in the USA (10, 11) and New-Zealand (12), the spread of e-cigarettes has contributed to the decline of classic tobacco cigarettes among young people. In spite of this, many adolescent cohort studies have reported a strong positive link between vaping and subsequent tobacco experimentation (13) or daily smoking (14-18) and the same has been found in the general population (19, 20). For some authors, these positive links have not been clearly explained (17); for others (21), the patterns of use and the products themselves share so many features that these results can be biased by confounding factors that are almost impossible to control for, such as a common liability towards drug use, or the fact that the more substances a person uses, the more additional substances they are liable to experiment with (22-24). The apparent divergence between studies at individual level (positive association between e-cigarettes and tobacco smoking) and studies on population-trends (negative association between the two) could also result from the fact that e-cigarettes contribute to both tobacco initiation and to cessation (10, 25).

However, the association between e-cigarettes and tobacco use may also depend on the country: the marketing of tobacco and e-cigarettes, the regulations relating to the two products and their availability for adolescents undoubtedly play a role. Indeed, a recent study in France (26) found a negative association of e-cigarette initiation with subsequent daily tobacco use among classic cigarette experimenters: RR=0.62 95%CI [0.60; 0.64] and a complementary analysis showed a similar result for those who had experimented with e-cigarettes before experimenting with cigarettes, RR=0.76 95%CI [0.66; 0.89]. In fact, because e-cigarette experimenters who had never experimented with tobacco were excluded from this analysis, the real risk-ratio may have actually been lower.

Finally, while early cigarette initiation has consistently been shown to be associated with subsequent daily smoking and nicotine dependence (27), less is known regarding the age at e-cigarette initiation. Age at initiation has been reported to be younger in more recent cohorts in one study (28), but to remain approximately constant and older than for cigarette initiation in another (11). However, research on the effects of age at e-cigarette initiation on later e-cigarette and tobacco use is scarce, although young age is a major determinant in addiction research (27, 29, 30). Only one study has investigated this topic, finding that early e-cigarette use increased the risk of subsequent cigarette use (31).

The aim of the present study was twofold: first to provide a more accurate estimate of the effect of experimenting first with e-cigarettes on subsequent daily tobacco smoking in France (considering all e-cigarette experimenters, whether or not they experimented with tobacco afterwards); second, to study how the age at e-cigarette initiation affects subsequent daily smoking. The results will be discussed in detail in the light of national specificities in terms of tobacco and e-cigarette marketing and regulation.

## **METHODS**

### **Design**

A large national representative cross-sectional sample of adolescents and a self-administered questionnaire including questions on the first occurrence of a number of behaviours were used. This analysis was not pre-registered and the results should be considered exploratory.

### **Data**

The French Monitoring Centre for Drugs and Drug Addiction has conducted the ESCAPAD Survey (survey on health and substance use) regularly since 2000 (32). All nationals are required to attend a one-day session of civic and military information, known as the National Defence and Citizenship Day (JDC), shortly after having turned 17. Because the JDC attendance certificate is compulsory for all public examinations, enrolment at university and the driving license, very few young people postpone this session by one year or fail to fulfil this requirement. Participation in the ESCAPAD survey for its part is confidential and anonymous but not compulsory: everyone is able to refuse by not completing the self-administered paper questionnaire, as stated in the introductory video presentation and in the questionnaire guidelines. The survey gained the Public Statistics General Interest seal of approval from the National Council for Statistical Information.

The data was derived from the eighth yearly session in metropolitan France: the data collection took place from the 13th to the 25th of March 2017. All adolescents having attended a JDC session during that period were invited to complete the questionnaire (43,892): 42,751 completed the questionnaire, yielding a participation rate of 97%. The initial survey sample included 39,115 French adolescents aged from 17 to 18.5 years (mean=17.4, std=0.3, 8.7% of the respondent sample being 18-18.5 years old): the older respondents were removed. The respondent sample can be considered representative of the French population aged 17-18.5 years.





## **Sample analysed**

Tobacco experimentation (at any time) was defined from the question: “During your life, have you ever smoked [cigarettes], [cigars or cigarillos]?” with the following possible answers “never; once; several times” recoded in as “never” or “yes”. Age (in years) at experimentation of each product was recorded and the lowest was defined as the age at tobacco experimentation. E-cigarette experimentation and age at e-cigarette experimentation were defined from the same questions relating to the use of an “electronic cigarette”. Individuals were removed from the analysis if they had missing values for classic cigarette consumption in the last 30 days, for lifetime use of e-cigarettes, for lifetime use tobacco, and for their age at first e-cigarette use, at first cigarette or at transition to daily smoking, because these variables were necessary to define exposure and outcome. In the initial sample of 39,115 respondents, 240 did not answer the question defining the outcome variable (see below); 79 did not answer the question about tobacco experimentation while 1,285 tobacco experimenters did not provide any age at tobacco experimentation; 286 did not answer the question defining experimentation with e-cigarettes while 2,538 e-cigarette experimenters did not provide any age at e-cigarette experimentation. The sample analysed therefore comprised 24,111 respondents who reported having at some time experimented with either tobacco (n=21,701) or e-cigarettes (n=14,801).

## **Outcome variable**

The outcome was the report of daily use of at least one tobacco cigarette in the past 30 days (yes/no) with the question “in the last 30 days, have you smoked cigarettes?” (never; less than once a week; less than once a day; 1-5 per day; 6-10 per day; 11-20 per day; more than 20 per day). Daily smoking, which is associated with known health hazards, is a classic indicator in public health.

## **Exposure variable**

The first experimentation with either e-cigarettes or cigarettes was used to classify the subjects as exposed (e-cigarette first: value=1) and unexposed (tobacco first: value=0). In the sample analysed,

3,983 respondents were directly classified as exposed, while for 4,579 subjects the classification was indeterminate because the two experimentations occurred at the same age (ties). Another question was then used to classify them: "Did you ever also smoke manufactured or hand-rolled cigarettes at the time when you first tried e-cigarettes?" (No, yes). Thus 1,603 ties were recoded as unexposed and 633 as exposed, while 2,343 non-responses remained as indeterminate. To avoid any potential misclassification bias, handling the non-classified cases correctly was crucial. Three versions of the exposure variable were therefore considered: one in which the remaining unclassified subjects were unexposed ("strict" exposure), another version where they were considered exposed ("inclusive" exposure) and a third ("intermediate" exposure, hereafter simply labelled "exposure") where 50% of the remaining unclassified subjects were randomly recoded as unexposed and the other half as exposed. Only the results for this "intermediate" exposure are presented (Tables 1-3): the analyses for the "strict" and the "inclusive" exposures are available online (Tables S1-S3).

### **Pre-exposure covariates**

The 6 following sociodemographic variables were considered as time-invariant because it was hard to imagine a causal mechanism whereby the experimentation with either tobacco or e-cigarette could prove to be linked: gender, parental socio-economic status (SES) (5-level ordinal variable based on the higher parental occupational category); the Family Affluence Scale (FAS) score (33) in three categories (low; moderate; high); family structure (nuclear family; step-family; single-parent family/others) (34, 35); difficulty reading and writing in French (no; yes, sometimes; yes, often). Age at the time of the survey (in months) was also used as a control variable.

Experimentation with 3 substances were taken into account (hookah, alcohol and cannabis) as well as the first experience of drunkenness. The questions were: "During your life, have you ever: smoked tobacco with a [hookah], [drunk alcohol], [been drunk], [smoked cannabis]?" and "How old were you the first time?" Similarly, a dichotomous variable was built based on experimentation and age at experimentation with at least one illicit drug among 8 (hallucinogenic mushrooms, poppers,

inhalants, ecstasy/MDMA, amphetamine/speed, LSD, crack/freebase, cocaine, heroin) and one for a repeat school year. This last variable was defined from the following question: "Did you ever repeat a school year?" (No, yes: please specify); we used compulsory schooling at age 6 to deduce the age at which the first repeat year occurred. Six dichotomous pre-exposure covariates were derived from these six variables (value 1 if the corresponding event had occurred at least one year prior to exposure, 0 otherwise). For each of the covariates, half of the unclassified cases (when the age at experimentation/repeat year was that of the exposure) were independently and randomly considered as having occurred before exposure, the other half as having occurred after.

### **Statistical analysis**

No age at experimentation was imputed (a missing value equating to no experimentation). Only missing data for family structure (n=243), FAS (n=206) and literacy (n=102) were imputed using a random hotdeck based on age at the time of the survey, gender, school situation, repeat school years and SES.

Our aim was to estimate the overall effect of experimentation with e-cigarettes before any experimentation with tobacco. All the above-mentioned covariates were intended to describe the situation of the subjects before exposure with no change afterwards. Assessment of this effect required comparison of exposed and unexposed groups that had the same pre-exposure covariates in the Rubin Causal Model (36). For this purpose, inverse propensity score weighting (IPW) was used to compute the "average treatment effect weighting". It was estimated using a multivariate dichotomous logistic regression modelling the exposure variable and controlling for the 13 covariates plus age at exposure and its square, plus all bivariate interactions across these 15 covariates (120 effects). The distribution of the propensity scores is shown in Figure 1.

The balance between the exposed and unexposed groups was assessed with Standardized Mean Differences (SMD) for each covariate, an absolute value |SMD| below 0.1 indicating a good balance (37). The impact of e-cigarette experimentation on daily tobacco smoking was estimated using IPW-

weighted risk ratios, obtained by modified Poisson regression (38) modelling the outcome: first with exposure as the sole covariate (labelled RRraw); second, with adjustment for exposure and all main effects of the 15 covariates – labelled RRfull, thus providing a doubly robust estimation (36). Finally, the third model used the full IPW-weighted multivariate model and added an interaction between exposure and age at exposure and its square to estimate the effect of age at exposure.

Statistics were computed using SAS® V9.4.

## RESULTS

In the sample analysed, 90.0% of the subjects (n=21,701) were tobacco experimenters (among whom 57.1% were e-cigarette experimenters: n=12,391), 61.4% (n=14,801) were e-cigarette experimenters (among whom 83.7% were tobacco experimenters: n=12,391); 26.0% had smoked e-cigarettes in the last 30 days (3.0% on a daily basis), while 39.9% were daily tobacco smokers (n=9,608).

The definition of "intermediate" exposure yielded 5,616 exposed cases (and 18,495 unexposed cases), among which the proportion of tobacco experimenters was 57.1% (n=3,206) (Table 1). A large proportion of adolescents who had first experimented with e-cigarettes thus never became tobacco experimenters. The proportion of subsequent tobacco experimenters decreased continuously with age at exposure, from 95% at age 11 or under (n=35/37) to 25.3% at 17 years (n=(3,203-3,068)/(5,602-5,069)). The mean age at the first experimentation with either tobacco or e-cigarettes was 15.14 years (standard deviation –std=1.20) among exposed subjects and 14.24 (std=1.68) among unexposed subjects (standard mean difference SMD =0.62, Table 2).

Boys were overrepresented among the exposed subjects (58.8% vs 47.5%, SMD=0.23) while the mean ages at the time of the survey were very similar between exposed and unexposed subjects (17.4 years). Exposed subjects more often reported belonging to nuclear families (SMD=0.10) but their socio-economic status (FAS or the SES scale), their literacy and repeat school years yielded values similar to those observed for the non-exposed subjects (|SMD|<0.1). The exposed subjects

also more frequently reported alcohol and hookah experimentation (SMD=0.19 and 0.27) but less frequently cannabis experimentation (SMD=-0.07). The proportion of daily smokers among the 17-18.5-year-olds (i.e. the outcome) was significantly higher ( $p<0.001$ ) among the unexposed subjects (46.3%,  $n=8,559$ ) than among the exposed subjects (18.7%,  $n=1,049$ ).

The common support (i.e. the shared range of variation of the propensity score used to define comparable exposed and unexposed groups) was very broad: only 47 observations (0.3%) fell outside in the unexposed group and 5 in the exposed group (0.1%), which is negligible. The balance of the IPW-weighted distributions between the exposed and unexposed groups improved, with all SMD below 0.1 in absolute values (Table 2).

The risk ratio measuring the association between exposure and outcome was below 1 ( $RR_{raw}=0.59$ ,  $95\%CI=[0.56; 0.62]$ ;  $RR_{full}=0.58$ ,  $95\%CI=[0.54, 0.62]$ ) (Table 3), which means that the adolescents who experimented with e-cigarettes first had about 40% less risk of becoming daily smokers at the time of data collection than those who had first experimented with tobacco. The interaction between age at exposure and exposure was significant ( $p=0.0103$ ), but not the interaction with age at exposure squared ( $p=0.1995$ ) (Table 3). The linear interaction term showed a decline with age at exposure ( $RR_{full}=0.87$ ,  $95\%CI=[0.78; 0.98]$  for one additional year). The effect varied from  $RR_{full}=1.30$   $95\%CI=[1.09; 1.54]$  at age 9 and  $RR_{full}=1.06$   $95\%CI=[0.93; 1.22]$  at age 10 to  $RR_{full}=0.38$ ,  $95\%CI=[0.32;0.45]$  at ages 17-18.5. All the results for the "strict" and "inclusive" exposures were similar (online Tables S1-S3):  $RR_{full}(strict)=0.63$   $95\%CI=[0.59; 0.67]$ , from  $RR=1.40$   $95\%CI=[1.19; 1.65]$  at age 9 to  $RR=0.41$   $95\%CI=[0.34; 0.50]$  at age 17;  $RR_{full}(inclusive)=0.54$   $95\%CI=[0.51; 0.57]$ , from  $RR=1.26$   $95\%CI=[1.04; 1.54]$  at age 9 to  $0.34$   $95\%CI=[0.29; 0.40]$  at age 17.

## DISCUSSION

### Findings

Our first finding was that 42.9% of the adolescents who had first experimented with e-cigarettes never became tobacco experimenters (54.4% and 35.6% respectively in "strict" and "inclusive" exposure groups) and that experimenting with e-cigarettes first was negatively associated with subsequent daily smoking (RR<sub>full</sub>=0.58, 95%CI=[0.54, 0.62]). This effect is stronger than that computed by Chyderiotis *et al.* (2020) from the same survey (RR=0.76 95%CI=[0.66; 0.89]), with non-overlapping confidence intervals. This was expected because our sample included e-cigarette experimenters who never became tobacco experimenters afterwards (n=2,410).

The rare negative associations between e-cigarettes and tobacco have been reported by studies that have modelled population trends (10, 11). Conversely, most individual longitudinal studies (16, 17, 39, 40) have reported a positive association between e-cigarette experimentation and subsequent daily smoking. How can we interpret our finding of a strong negative association in France?

First, in France, tobacco smoking is much more common than in English-speaking countries, whereas the reverse is true for e-cigarette use. In 2018, 27.3 % of French high-school students (aged 15 to 18) reported having smoked in the past 30 days (41), whereas the figures were 8.1 % among US high-school students (42) and 15 % among 15 year-olds in the UK in 2016 (43). More specifically, in the US, particularly for the 12<sup>th</sup> graders (mostly aged 17-18), the prevalence of daily tobacco smoking in the past 30 days was 4.2% while the prevalence of any e-cigarette use was 16.6% in 2017 (44) (11.7% for daily vaping in 2019 (45)). In the ESCAPAD survey (adolescents aged 17-18.5 interviewed in 2017), the corresponding figures were 25.1% for daily smoking, 16.8% for any vaping and 1.9% for daily vaping.

These differences should be interpreted in a general framework. Tobacco use is higher in France than in the USA, it is declining less rapidly, and the social gradient is not yet as pronounced for women

(46). Using the theoretical framework of the "tobacco epidemic" (based on levels of use and associated mortality (47)), extending it to take into account variation according to socio-economic levels (48) and using the theory of innovations (49) (men and the upper classes acting as pioneers in the adoption and later cessation of smoking), it could be concluded that France is lagging behind the USA in this theoretical model. If e-cigarette use can be considered as a new stage in this epidemic, France is also expected to lag behind the USA regarding e-cigarette use. In this perspective, French adolescents who first experimented with e-cigarettes could be considered as pioneers who opted for a supposedly less harmful and more attractive smoking behaviour than tobacco smoking. The association between e-cigarette and tobacco use could thus depend on the stage in the epidemic reached by the country and vary over time.

Second, regulations on nicotine vaping products, which could shape the trends in e-cigarette use, vary greatly across countries. In the European Union, e-liquid bottles with nicotine concentrations greater than 20mg/ml are considered as medicinal products and the refillable tank capacity has been limited to 2 mL since 2016 (50). In the UK, selling nicotine products to minors has been forbidden since 2015; in Australia, nicotine vaping products have been banned from retail, while they require special approval in Canada (51). In France, advertising and sales of these products to minors have been banned since 2016, as well as their use in schools and other public places; furthermore, a warning on the packaging of these e-devices and e-liquids is required, indicating that they are not recommended to non-smokers. Liquids with concentrations of nicotine exceeding 20 mg/ml are prohibited, which is not the case in the USA (52), Canada, the UK or Australia (50). These distinct regulatory environments appear to influence the levels of social acceptability of e-cigarette use, typically lower in Australia compared to the US, Canada, and the UK in 2016 (53). In the USA, the JUUL brand is very popular and its devices can contain e-liquids with concentrations of nicotine salt up to 59 mg/ml, while most adolescents are not even aware of the presence of nicotine in them (54). Since it is more regulated and less addictive, e-cigarette use is less widespread and could be less likely to favour transition to daily smoking in France.

It is also worth noting that a recent meta-analysis concluded that the longitudinal studies published that have found finding a strong positive association between e-cigarette use and tobacco smoking are very likely to be marred by non-corrected high attrition rates, as well as insufficient numbers of controls, including common liability to use drugs (18).

Our second finding concerns age at e-cigarette experimentation: to our knowledge, our study is among the first to have investigated the effect of early e-cigarette use on tobacco use. In line with results reported by McCabe *et al.* on US adolescents, we found that the later exposure to e-cigarettes occurred, the lower was the risk of transition to daily smoking (31). Similar results were found in the general population study in the PATH survey, where 18-34 year-olds had significantly higher risks of transitioning to tobacco than their older counterparts (RR=3.8, 95%CI=[1.1-13.2]) (19).

One reason for the apparent disinterest of research in early e-cigarette initiation may be that e-cigarette use has mostly been studied in schools. In classic school cohorts, age at inclusion is young and thus the variation in age at e-cigarette experimentation is too narrow to be a matter of concern (14, 15, 40). In our methodology (as in Mac Cabe' study that included pupils in grade 12 –aged 17-18: (31)), exposure was defined for any age up to the age at the time of data collection; therefore, its variance was greater and analysis of the effect of younger age was therefore more straightforward.

These methodological considerations set apart, experimenting with e-cigarettes early in life is likely to be more culturally transgressive than later in life and therefore could be associated with personality traits involving greater impulsiveness, novelty and sensation-seeking. It is thus possible that early e-cigarette experimenters are keener to experiment with drugs, including tobacco, but that they choose to experiment first with e-cigarettes because they appear less hazardous, more readily available and more appealing, especially when there are different flavours to choose from (55, 56). The fact that early experimentation with e-cigarettes favours the transition to tobacco smoking before a certain age may therefore not be due to an effect of the e-cigarette itself (which could be described as a “gateway effect”) but could rather reflect a self-selection mechanism via an “addiction



liability” phenotype (23). There is however another explanation: in France, the popularity, appeal, and accessibility of vaping have been increasing regularly for ten years, while the reverse is true for tobacco (57): tobacco prices have increased regularly since 2003, smoking in public places, bars and restaurants has been banned since 2007, and sales to minors have been prohibited since 2009. As a consequence, tobacco experimentation and smoking have become less common among e-cigarette experimenters over the years. Again, the phase reached by France in the tobacco epidemic could play a crucial role: in ten years from now, the image of vaping and tobacco could appear roughly constant throughout a retrospective period assessed in a similar survey, and the hypothesis of interaction with age may not hold any longer.

If the association between e-cigarette use and tobacco smoking does in fact vary with age at e-cigarette experimentation, a part of the negative association that was found could reflect the fact that we considered older subjects with exposure at older ages than was the case with many school cohort studies (except the cross-sectional study by Mac Cabe (31)): for example, all the subjects included were aged 12-15 in a school cohort using the PATH survey (16), and 66% were aged 14-15 in the COMPASS study (17). However, comparing results from different surveys remains difficult because they all use different patterns to define exposure, outcomes, follow-up durations and covariates.

Finally, national specificities (the stage reached in the tobacco/e-cigarette epidemic as well as in regulations) certainly play a role in the fact that many adolescents (42.9% in our study) experimenting first with e-cigarettes never became tobacco experimenters, and in the fact that the association with daily smoking was negative (RR=0.58) even among tobacco experimenters (RR=0.76 in *Chyderiotis et al.* (26)).

### **Limitations**

Our study was based on a large representative sample with a high response rate; we followed a classic analytical methodology in the field of causal estimation (36) and our results are robust for a

variety of exposure definitions which helped prevent misclassification biases. But there are some limitations. Our study does not extend beyond the ages 17 to 18.5 years; this limitation is shared by all school cohorts but, as transition to daily use requires time, this certainly contributed to our two findings. Furthermore, the reduced risk of transition from e-cigarette experimentation to daily smoking could disappear at an older age, while e-cigarette use could result in e-cigarette addiction *per se* (58).

Because a cross-sectional representative sample of the population was used, there was no attrition, which is a considerable problem in longitudinal studies (18) but all the recalled ages could be subject to recall bias. But recall bias is generally considered limited in adolescence because experimenting with psychoactive substances is an important “rite of passage” (59) occurring only a few years previously (60); in addition, our results were robust to different versions of exposures accounting for a large share of recall biases. The narrow age range of our subjects contributes to the internal validity of our study, as the respondents shared the same birth cohort environment and the stage in the tobacco and e-cigarette epidemics, but it limits the comparability of our results to populations with a wider age range.

We restricted our sample to experimenters of e-cigarettes and/or tobacco and the unexposed group was therefore composed of subjects who had first experimented with tobacco. Including subjects who had never experimented with tobacco would have certainly changed the results.

Finally, our study lacked measures of several confounders that could limit the causal interpretation of our results: we lacked psychological variables (61) and the nicotine content of e-liquids, a considerable limitation pointed out by Khouja *et al.* (20): our global negative association could reflect the fact that e-liquids delivering high doses of nicotine are not available in France, or again the widespread preference for e-liquids without nicotine.

## **Conclusion**

Overall, experimenting with e-cigarette first (as opposed to tobacco first) was associated with a reduction in the risk of daily tobacco smoking by the age of 17-18.5. The association varied with age at experimentation, and an early age of experimentation actually increased the risk. National specificities as to the stage in the tobacco/e-cigarette epidemic and their regulation could play a role in the fact that many adolescents experimenting first with e-cigarette never became tobacco experimenters and that the association with daily smoking was negative even among tobacco experimenters.

Table 1: joint distribution of retrospective age (1) and exposure

Retrospective age	Unexposed	Exposed	Cumulate number of exposed subjects	Cumulate number of subsequent tobacco experimenters among exposed subjects	% of future tobacco experimenters among exposed subjects
4	6	0	0	0	--
5	10	2	2	2	100.0%
6	15	2	4	4	100.0%
7	38	0	4	4	100.0%
8	63	1	5	5	100.0%
9	123	2	7	7	100.0%
10	304	10	17	16	94.1%
11	608	20	37	35	94.6%
12	1366	97	134	110	82.1%
13	2435	316	450	353	78.4%
14	4275	998	1448	1064	73.5%
15	5044	1807	3255	2163	66.5%
16	3526	1814	5069	3068	60.5%
17	666	533	5602	3203	57.2%
18	16	14	5616	3206	57.1%
Total :	18495	5616	5616	3206	57.1%
Age at first tobacco experimentation (if any): mean (sd)	14.2 (1.7)	15.4 (1.1)			
Age at first e-cigarette experimentation (if any): mean (sd)	15.4 (1.1)	15.1 (1.2)			

Exposure= experimentation with e-cigarette first (exposure=1) or experimentation with tobacco first (exposure=0)

Retrospective age is the age in the past, as opposed to the current age at data collection.

Number of exposed subjects = 5616 (among whom 1187 classified for experimentation with both tobacco and e-cigarette in the same year); Number of unexposed subjects= 18495 (among whom 1156 classified for experimentation with both tobacco and e-cigarette in the same year).

Table 2: Sample description before and after inverse propensity weighting according to (intermediate) exposure

		Unexposed	Exposed	Initial SMD	IPW SMD
	N=	18495	5616		
<b>Time-invariant covariates</b>					
Boys (%)		47.5	58.8	0.23	0.03
Age at the time of the survey (years)		17.43	17.39	-0.13	0.00
	(sd)	(0.33)	(0.31)		
SES	low	9.4	9.2	-0.04	-0.04
	1	33.1	34.6		
	2	30.3	30.7		
	3	20.1	19.4		
	high	7.2	6.1		
FAS (%)	low	1.5	1.3	0.03	-0.03
	intermediate	20.2	18.9		
	high	78.4	79.8		
Family type (%)	nuclear	60.4	65.1	0.10	-0.02
	step family	11.8	10.9	-0.03	0.04
	single parent/other	27.8	24.0	-0.09	-0.01
Reading difficulties (%)	never	86.0	88.3	-0.07	-0.01
	sometimes	12.8	10.8		
	often	1.3	0.9		
Writing difficulties (%)	never	74.4	75.5	-0.03	0.03
	sometimes	22.5	21.9		
	often	3.2	2.7		
<b>Other covariates</b>					
Repeat school year (%)		21.9	24.2	0.05	-0.01
Alcohol use (%)		46.0	55.6	0.19	-0.01
Drunkenness (%)		15.4	17.8	0.06	-0.01
Hookah (%)		19.3	31.1	0.27	-0.01
Cannabis (%)		12.0	9.7	0.07	0.00
Other drugs (%)		1.9	2.1	0.02	-0.01
Age at exposure (years)		14.24	15.14	0.62	-0.05
	(sd)	(1.68)	(1.20)		
(Age exposure) <sup>2</sup>		205.57	230.82	0.63	-0.04
	(sd)	(44.95)	(35.14)		

SMD: standard mean deviation

Table 3 Association of (intermediate) exposure with transition to daily smoking (risk ratios and 95% confidence intervals)

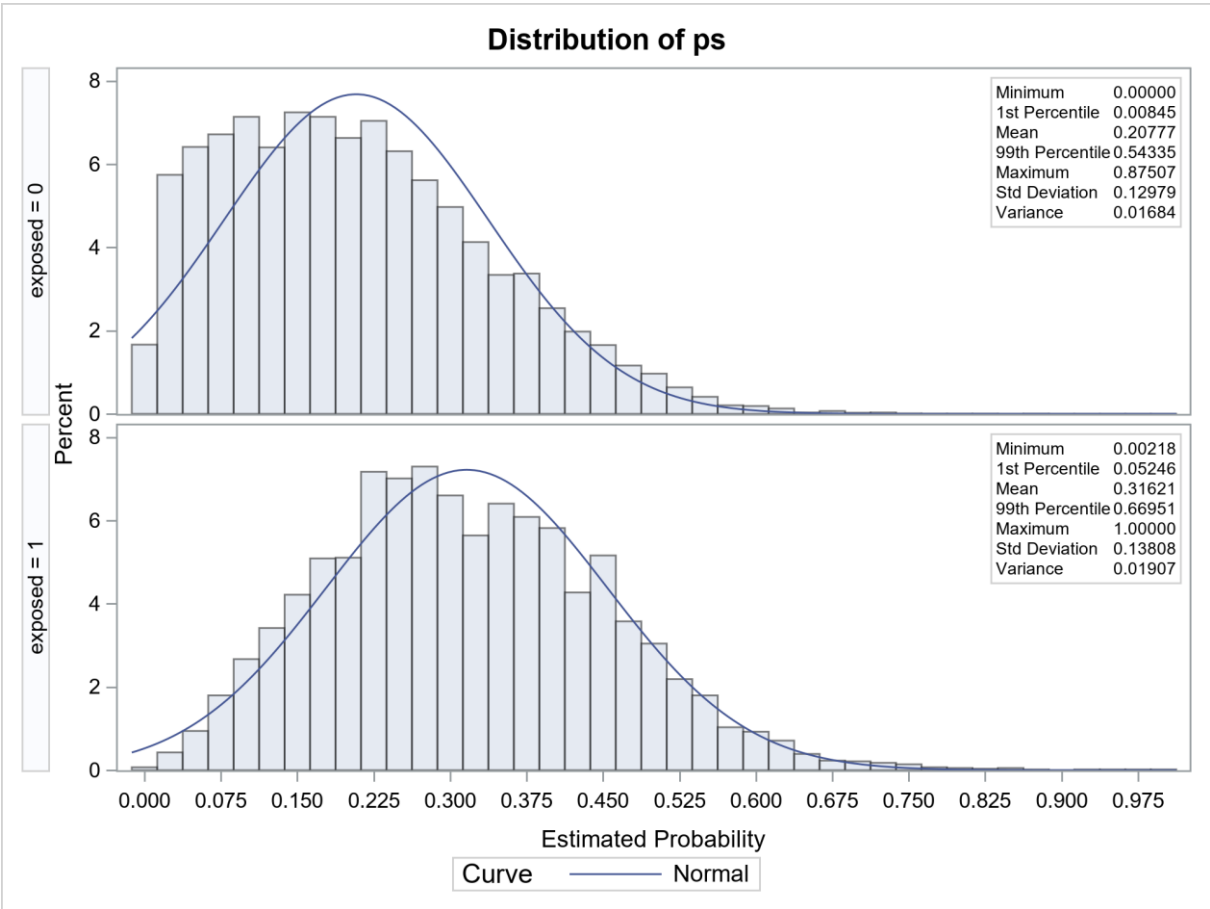
Bivariate IPW estimate	RR_raw	95%CI	
	<b>0.59</b>	0.56	0.62
Doubly-robust estimate	RR_full	95%CI	
Global (1)	<b>0.58</b>	0.55	0.62
With interaction with age at exposure (2)	RR_full	95%CI	
exposure at 9	<b>1.30</b>	1.09	1.54
exposure at 10	1.06	0.93	1.22
exposure at 11	<b>0.88</b>	0.78	1.00
exposure at 12	<b>0.74</b>	0.67	0.83
exposure at 13	<b>0.63</b>	0.58	0.70
exposure at 14	<b>0.55</b>	0.51	0.59
exposure at 15	<b>0.48</b>	0.45	0.51
exposure at 16	<b>0.42</b>	0.39	0.47
exposure at 17	<b>0.38</b>	0.32	0.45

In bold type: significant RR at 0.05 level.

(1): Inverse propensity-weighted, controls: for all covariates as main effect: gender, age at the time of the survey, age at exposure, (age at exposure)<sup>2</sup>, reading difficulties, writing difficulties, SES, FAS, history of repeat school years, pre-exposure to hookah use, alcohol, drunkenness, cannabis and other drugs

(2): Inverse propensity-weighted, controls: model (1) plus interactions between exposure and age at exposure and (age at exposure)<sup>2</sup>; p-value for interaction between exposure and (age at exposure) and (age at exposure)<sup>2</sup>=0.0103 and 0.1995, respectively

Figure 1: Propensity score distribution for (intermediate) exposure



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