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Nicotine matters in predicting subsequent smoking after e-cigarette experimentation: A longitudinal study among Finnish adolescents

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ABSTRACT

Background: Several studies indicate an association between e-cigarette use and subsequent smoking among youth. However, most previous studies lack measures of the nicotine content of e-liquid and have not usually measured regular smoking.

Methods: We tested the association between e-cigarette use, with and without nicotine, and subsequent daily use of conventional cigarettes and nicotine e-cigarettes among study population of 3474 students. A survey was conducted in lower secondary schools of the Helsinki metropolitan area, Finland, with 15 − 16-year-olds in 2014 (baseline) and in upper secondary schools in 2016 when the cohort was 17 − 18-year-olds (follow-up). Firth logistic regression and generalized linear mixed models (GLMM) were used.

Results: Of students, 25% had experimented with nicotine e-cigarettes at baseline and 40% at follow-up. Among baseline never-smokers, experimentation with or use of nicotine e-cigarettes predicted the uptake of daily smoking at follow-up (AOR 2.92; 95% CI 1.09–7.85), but baseline experimentation with non-nicotine e-cigarettes did not when compared with the non-e-cigarette experimenters. Nicotine e-cigarette experimentation at baseline predicted daily nicotine e-cigarette use at follow-up (AOR 2.96; 95% CI 1.22–7.22). Non-nicotine e-cigarette experimentation at baseline did not predict statistically significantly daily nicotine e-cigarette use at follow-up (AOR 3.13; 95% CI 0.98–10.02). The small number of cases may have diminished the statistical significance.

Conclusions: The findings suggest that experimentation with nicotine e-cigarettes serves as a gateway to subsequent use of conventional cigarettes as well as nicotine e-cigarettes. Our results support the actions to limit youths' access to e-cigarettes in order to prevent nicotine addiction.

1. Introduction

Electronic cigarette (e-cigarette) use has been increasing worldwide among adolescents (Grana et al., 2014; Pepper and Brewer, 2014). Adolescents' use and experimentation with e-cigarettes are more common among smokers but have been reported also among never-smokers (Bunnell et al., 2015; Carroll Chapman and Wu, 2014; Kinnunen et al., 2015, 2016). Liquids used in e-cigarettes usually contain nicotine (Grana et al., 2014; Glasser et al., 2017), but not in all cases (World Health Organization, 2016). Although nicotine is a highly addictive drug (Benowitz, 2010), most studies have analyzed use or experimentation of e-cigarettes without accounting for the nicotine content of e–liquid.

Several studies have shown the longitudinal association between adolescent e-cigarette use and use of conventional cigarettes (Barrington-Trimis et al., 2016a; Bold et al., 2018; Leventhal et al., 2015; Miech et al., 2017; Primack et al., 2015; Wills et al., 2017a). In their systematic review and meta-analysis, Soneji et al. (2017) concluded that e-cigarette use was associated with greater risk of subsequent cigarette smoking. This association has also been found to be stronger among adolescents with fewer risk factors for conventional smoking, e.g., among those with lower levels of rebelliousness and

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sensation-seeking (Morgenstern et al., 2018; Wills et al., 2017b), and among non-susceptible never-smokers (Aleyan et al., 2018). The longitudinal association between e-cigarette use and smoking initiation among never-smoking adolescents has also been confirmed from Germany (Morgenstern et al., 2018), UK (Conner et al., 2018; East et al., 2018), Scotland (Best et al., 2018), the Netherlands (Treur et al., 2018), Romania (Pénzes et al., 2018), Mexico (Lozano et al., 2017) and Canada (Aleyan et al., 2018; Hammond et al., 2017), as well as among young adults (Primack et al., 2018; Unger et al., 2016) and college students (Loukas et al., 2018; Spindle et al., 2017) in the USA. In their longitudinal study, Watkins et al. (2018) found that use of any other non-cigarette tobacco product, including e-cigarette, predicted cigarette smoking at follow-up among baseline never-smoking adolescents. Additionally, e-cigarette use has been found to be associated with progression to established cigarette smoking among adolescent cigarette experimenters (Chaffee et al., 2018). However, most of the longitudinal studies concern ever-smoking or past 30 day smoking. It is justified, as many adolescent smokers are non-daily smokers; a usual trajectory of smoking proceeds from experimentation to non-daily smoking, and then to daily smoking (Dierker et al., 2012). However, for the possible gateway effect, the initiation of regular use is also a key element. This has been studied previously only by Hammond et al. (2017) who found an association between past 30-day use of e-cigarettes at baseline and initiation of daily smoking at follow-up among baseline non-daily-smokers for 7 days.

Two previous studies have examined the longitudinal associations according to the nicotine concentration of liquid used in e-cigarettes (e-liquids) (Goldenson et al., 2017; Treur et al., 2018). A six-month-long follow-up of high school students using e-cigarettes showed that high nicotine concentration increased both the frequency and intensity of smoking and vaping (Goldenson et al., 2017). Treur et al. (2018) found a longitudinal association between both nicotine and non-nicotine e-cigarettes to ever-smoking among never-smoking adolescents. To our knowledge, no previous study has investigated the longitudinal association between nicotine and non-nicotine e-cigarette use and onset of daily smoking among never-smoking adolescents.

Our longitudinal study aims at exploring whether nicotine and non-nicotine e-cigarette uses predict the daily use of two different nicotine products, namely conventional cigarettes and nicotine e-cigarettes. The study population includes Finnish adolescents aged 15–16 years who were followed for two and a half years.

2. Material and methods

2.1. Participants and study procedure

The participants of this study are from Metropolitan Longitudinal Finland (MetLoFIN), a longitudinal study of 12,248 children in the Helsinki metropolitan area of Finland. In spring 2014, 7738 of the students (response rate 63%) participated in the baseline school survey at the end of lower secondary education, in the 9th grade (15–16-year-olds). The follow-up-survey was conducted in 2016 in the beginning of the second year of upper secondary education (17–18-year-olds). The survey was conducted online in computer classrooms using personal user names and passwords. The sample of the current study consists of students who answered both surveys (n = 3474; 44.9% of the baseline n; Girls: 51.8%). The analytic sample in analyses for daily smoking as the outcome was restricted to adolescents who had not tried smoking by the baseline survey (n = 2016). The Ethical Committee of the National Institute for Health and Welfare, Finland, approved the study protocol. Participation in the survey was voluntary and no parental consent was required according to the ethical guidelines in Finland (National Advisory Board on Research Ethics, 2009).

2.2. Measures

In 2014 (baseline) and 2016 (follow-up), e-cigarette use was asked with the question “Have you sometimes used the following products?” with the options ‘No’, ‘I have tried once or twice’, ‘I have used 20 times or less’ and ‘I have used more than 20 times’. The use of nicotine and non-nicotine e-cigarettes was asked separately. As 78.8% of the students who reported trying or using e-cigarettes had tried both types of liquids, a combined variable was created to describe the e-cigarette use. It was categorized as follows: Not tried e-cigarettes, Tried/used only non-nicotine e-cigarettes (=those reporting only non-nicotine liquids), Tried/used nicotine e-cigarettes (=those reporting nicotine or both types of liquids). In 2016 (follow-up), ‘I use daily or almost daily’ was added as a new option. Here, we use a shorter term of daily use. For the analyses with daily use of nicotine e-cigarette as the outcome, the variable was dichotomized as 0 = No and 1 = Yes.

Smoking status was assessed with two questions:” Have you ever smoked? If you have, how many cigarettes have you smoked altogether until now?” with the options ‘I have never tried smoking’, ‘One’, ‘About 2 to 50′ and ‘More than 50′; and “Which option best describes your smoking nowadays?” with the options “I do not smoke at all”, “Less than once a week”, “Once a week or more often, but not daily” and “Once a day or more often”. The created categories were ‘Never tried’, ‘Tried but does not smoke’, ‘Occasionally’, ‘Weekly’ and ‘Daily’. For analyses with daily smoking as the outcome, a dichotomous variable was created with 0 = No and 1 = Yes.

Snus and water pipe uses were asked the same way as e-cigarette use. Use of drugs was assessed with a question: “Have you sometimes tried or used narcotic substances (e.g., cannabis, weed, ecstasy, cocaine or similar substances)?” with the options ‘No’, ‘Yes, once or twice’ and ‘Several times’. The proportion of missing answers was small for all variables (0.3–3.9%); no imputation was conducted. There were some inconsistent answers for e-cigarette use and smoking, i.e., some students reported ever trying them at the baseline but not at the follow-up. In these cases, the follow-up answers were corrected so that they coincided with the baseline answer.

Parents’ education was used as a proxy for socioeconomic background. It was measured separately for mother and father with the question “What kind of education do your parents have?” The options were ‘Comprehensive school’, ‘Vocational degree’, ‘Matriculation exam’, ‘University degree’ and ‘I have no mother/father’ (=missing).

2.3. Data analysis

For the analyses with daily smoking as the outcome, the analytic sample at baseline was restricted to adolescents who had never smoked a conventional cigarette (n = 2016). A series of cross–tabulations were initially performed to test the unadjusted associations between e-cigarette use and daily cigarette smoking and the daily use of nicotine e-cigarettes. Crude and adjusted binary logistic regression analyses were then conducted to analyze the associations between baseline e-cigarette use and the aforementioned outcomes. Adjusting variables included gender but not age, as it varied only slightly among the students. The adjusted models included also socioeconomic background, measured with parents’ education, and other tobacco product (snus and water pipe) and drug use to control for possible confounders. As the outcomes (daily smoking and daily use of nicotine e-cigarettes) were rare events, the crude and adjusted logistic regressions were also conducted with the Firth’s bias-reduced logistic regression (Cole et al., 2014). The variance at school-level in baseline e-cigarette and smoking questions was of small magnitude (1.2%–1.7%), but statistically significant; thus, adjusted logistic regression analyses were conducted also with generalized linear mixed models (GLMM) to account for school clustering, as it was not possible with the Firth logistic regression. The Pearson χ^2 test was used to test for statistically significant differences. All data analyses were conducted with IBM SPSS Statistics, V.23, except the

Firth logistic regression, which was conducted with function 'logistf' within 'logistf' –package in R version 3.3.0 (R Core Team, 2016).

2.4. Attrition analysis

To assess the attrition, the proportions of students in the final sample, i.e., those who answered both the surveys (n = 3474), and those who answered only the first but not the follow-up survey (n = 4264), were compared with χ^2 test of independence of baseline responses to key variables. The attrition had a statistically significant greater proportion of boys (52.9% vs. 48.2%; $p < .001$), ever cigarette smokers (50.9% vs. 39.7%; $p < .001$), ever-users of nicotine e-cigarettes (34.7% vs. 24.9%; $p < .001$), and ever-users of non-nicotine e-cigarettes (6.2% vs. 4.5%; $p < .001$). The students in the final sample had higher enrolment in general upper secondary school (76%) than the metropolitan area (61%), based on official statistics (Official Statistics of Finland, 2016), and correspondingly, lower enrolment in vocational upper secondary school. The attrition of vocational school students was caused by challenges in the data collection in the institutions of vocational upper secondary education, as all schools were not willing to participate.

3. Results

At the baseline, 24.9% (n = 839) of adolescents had tried or used nicotine e-cigarettes and 39.4% (n = 1309) had tried smoking, while the proportions were 40.4% (n = 1405) and 55.8% (n = 1928) at the follow-up, respectively (Table 1). Of those 70.6% (n = 2373) who had not tried e-cigarettes at the baseline, 75.9% (n = 1801) had not tried e-cigarettes during the follow-up; 18.4% (n = 436) had tried nicotine e-cigarettes; and 5.7% (n = 136) had tried only non-nicotine e-cigarettes. At the follow-up survey, 2.1% (n = 73) of the adolescents reported daily use of nicotine e-cigarettes and 6.8% (n = 235) reported using nicotine e-cigarettes more than 20 times but were not daily users, and 6.8% (n = 236) of the students were daily-smokers.

Of those baseline never-smokers who had tried or used nicotine e-cigarettes by the baseline survey (n = 103), 8.7% (n = 9) had become daily-smokers during the follow-up compared to 0.8% (n = 15) of those who had not tried e-cigarettes (n = 1820) ($p < 0.001$) (Table 2). Baseline experimentation or use of nicotine e-cigarettes was significantly associated with follow-up daily smoking at the follow-up survey (AOR 2.92; 95% CI 1.09–7.85 with GLMM). As the outcome was a rare event, the analyses were conducted also with the Firth's bias-reduced logistic regression, but the statistical significances or ORs did not change considerably. (Table 2.)

Baseline experimentation or use of nicotine e-cigarettes (AOR 2.96; 95% CI 1.22–7.22 with GLMM) was significantly, but baseline experimentation or use of non-nicotine e-cigarettes was not significantly (AOR 3.13; 95% CI 0.98–10.02 with GLMM) associated with the daily use of nicotine e-cigarettes by the follow-up survey (Table 3). With Firth logistic regression, the results did not change considerably for baseline experimentation or use of nicotine e-cigarettes. In contrast, the AOR for baseline experimentation or use of only non-nicotine e-cigarettes became statistically significant; yet, the estimate was not adjusted for school clustering (Table 3).

Table 1
Descriptive statistics of the study population, %.

	Baseline, % (n)	Follow-up, % (n)
Gender		
Boys	48.2 (1676)	
Girls	51.8 (1798)	
E-cigarettes		
Never tried	70.6 (2373)	53.7 (1866)
Tried only non-nicotine e-cigarettes	4.5 (151)	5.8 (203)
Tried nicotine e-cigarettes	24.9 (839)	40.4 (1405)
Smoking		
Never tried	60.6 (2016)	44.2 (1527)
Tried but does not smoke	23.7 (787)	35.5 (1227)
Occasional smoker	6.5 (215)	9.7 (335)
Weekly smoker	2.9 (98)	3.8 (130)
Daily smoker	6.3 (209)	6.8 (236)

4. Discussion

The findings of this study indicate that youths' experimentation with nicotine e-cigarettes is common, as evidenced by 25% and 40% of the study participants who had tried nicotine containing e-cigarettes by middle adolescence and late adolescence, respectively. Furthermore, the findings indicate that nicotine e-cigarette experimentation or use, but not non-nicotine e-cigarette experimentation or use, predicts the onset of daily cigarette smoking, and that nicotine e-cigarette experimentation predicts the daily use of nicotine e-cigarettes.

Our results coincide with the findings from previous studies, which have shown the gateway from e-cigarettes to cigarette smoking (Aleyan et al., 2018; Barrington-Trimis et al., 2016a; Best et al., 2018; Bold et al., 2018; Conner et al., 2018; East et al., 2018; Hammond et al., 2017; Leventhal et al., 2015; Loukas et al., 2018; Lozano et al., 2017; Miech et al., 2017; Morgenstern et al., 2018; Pénzes et al., 2018; Primack et al., 2015, 2018; Soneji et al., 2017; Spindle et al., 2017; Treur et al., 2018; Unger et al., 2016; Watkins et al., 2018; Wills et al., 2017a, 2017b). In our study, the odds of becoming a daily smoker after trying or using nicotine e-cigarettes was almost three-fold compared to adolescent who had not tried e-cigarettes. In the study of Hammond at al. (2017), the corresponding odds was almost two (1.79) but it did not take the type of e-liquid into account. The other longitudinal studies are not quite comparable because they have investigated smoking initiation and past-30-day-use among never-smoking adolescents after e-cigarette experimentation or use, and the nicotine content of e-liquids has not been taken into account. We chose daily cigarette smoking as our primary outcome because the behavior is more predictive of the long-term health hazards associated with smoking, and it gives stronger indication of the possible nicotine addiction and thus showing the potential gateway effect compared to smoking initiation.

Our study discovered that experimenting or using non-nicotine e-cigarettes might increase the risk for daily use of nicotine e-cigarettes. The association was not statistically significant with GLMM, possibly due to small number of cases. With Firth's bias-reduced logistic regression, the association was statistically significant, but the model did not account for school clustering. However, the odds were over three-fold with both methods. This means that non-nicotine e-cigarette use might lead to the habit of vaping, which in turn may lead to use of nicotine-containing e-liquids. Further, use of nicotine e-cigarettes may lead to daily cigarette smoking as demonstrated in our study. This potential sequence of events is troubling and supported by data indicating that some adolescents who would not otherwise have tried tobacco have actually tried e-cigarettes (Barrington-Trimis et al., 2016b), and the adolescents who had no intention to smoke were more at risk for becoming a smoker after e-cigarette use (Barrington-Trimis et al., 2016a).

Schneider and Diehl (2016) have introduced a "catalyst model" to explain adolescents' transition from experimenting with e-cigarettes to tobacco smoking. They suggest that some adolescents perceive e-cigarettes as healthier and more acceptable to peers than conventional cigarettes, while, others are attracted to e-cigarettes because of product characteristics (e.g., flavorings). Consequently, adolescents' experimentation with e-cigarettes may lead to nicotine dependence and the subsequent use of conventional cigarettes (Schneider and Diehl, 2016). Sensation-seeking behavior (Zuckerman et al., 1972) has also been used as an explanation to adolescents' experiment with e-cigarettes, and it has been found to predict e-cigarette use (Hanewinkel and Isensee,

Table 2
Prevalence (%), crude (OR) and adjusted (AOR) odds ratios and 95% CI for follow-up daily smoking by baseline e-cigarette use among baseline never-smokers.

	Follow-up daily smoking among baseline never-smokers			
Baseline e-cigarette use (n)	% (n)	OR (95% CI)[#]	AOR (95% CI)[¥]	AOR (95% CI)[¶]
Not tried e-cigarettes (1820)	0.8 (15)	1.0	1.0	1.0
Tried/used only non-nicotine e-cigarettes (65)	1.5 (1)	1.88 (0.25, 14.45) [2.71 (0.29, 11.14)]	2.50 (0.25, 12.05)	0.94 (0.22, 4.08)
Tried/used nicotine e-cigarettes (103)	8.7 (9)	11.52 (4.91, 27.01)** [11.70 (4.91, 26.56)]**	8.50 (2.14, 29.19)*	2.92 (1.09, 7.85)*
Intercept				0.042 (0.022, 0.081)**

CI denotes Confidence Interval.
** $p < 0.001$.
* $p < 0.05$.
[#] OR in [square brackets] is from Firth logistic regression.
[¥] Firth logistic regression, not accounted for school clustering.
[¶] Logistic regression with generalized linear mixed models (GLMM) to account for school clustering.

Table 3
Prevalence (%), crude (OR) and adjusted (AOR) odds ratios and 95% CI for follow-up daily use of nicotine e-cigarettes by baseline e-cigarette use.

	Follow-up daily use of nicotine e-cigarettes			
Baseline e-cigarette use (n)	% (n)	OR (95% CI)[#]	AOR (95% CI)[¥]	AOR (95% CI)[¶]
Not tried e-cigarettes (2373)	0.6 (15)	1.0	1.0	1.0
Tried/used only non-nicotine e-cigarettes (151)	3.3 (5)	5.38 (1.93, 15.02)** [5.71 (1.94, 14.52)]**	3.71 (1.13, 10.73)*	3.13 (0.98, 10.02)
Tried/used nicotine e-cigarettes (839)	6.1 (51)	10.17 (5.69, 18.20)** [9.94 (5.74, 18.22)]**	3.24 (1.36, 7.91)*	2.96 (1.22, 7.22)*
Intercept				0.002 (0.001, 0.004)**

CI denotes Confidence Interval.
** $p < 0.001$.
* $p < 0.05$.
[#] OR in [square brackets] is from Firth logistic regression.
[¥] Firth logistic regression, not accounted for school clustering.
[¶] Logistic regression with generalized linear mixed models (GLMM) to account for school clustering.

2015).

Wills et al. (2016) have studied the mediating effect of cognitive and social factors between adolescent e-cigarette use and smoking onset. They did not find a significant direct effect from e-cigarette use to smoking onset, but e.g., changes in expectancies and affiliations partly mediated the effect (Wills et al., 2016). However, the direct effect from ever e-cigarette use to smoking initiation was found in a study in UK (East et al., 2018). So, there is a need for more research to shed light on this issue.

In our study, the transition from experimenting with or using nicotine e-cigarettes to daily cigarette smoking is likely to be attributed to the addictive properties of nicotine (Benowitz, 2010), based on our observation that a significant association was not observed with the non-nicotine e-cigarette. As e-cigarette experimentation can serve as a gateway to smoking among adolescents, it is important to restrict the availability of e-cigarettes for minors.

Limitations of this study include use of self-reported data, small number of cases, and a possible attrition bias. We cannot exclude the possibility that some adolescents have reported incorrectly on smoking or e-cigarette use, as they may have wanted to answer in a socially acceptable way in the classroom setting (Krumpal, 2013). However, adolescents' self-report of e-cigarette use is comparable to adolescents' self-report of conventional cigarette smoking, which has been found to be valid (Dolcini et al., 2003; Kentala et al., 2004; Post et al., 2005). All adolescents may not have known about the content of the e-liquids they were using (Kinnunen et al., 2015, 2016), why we combined also those who reported both nicotine and non-nicotine e-cigarettes to the nicotine e-cigarette group. This may dilute the real effect of nicotine containing e-cigarettes on subsequent smoking. Due to attrition, the respondents at the follow-up were selected according to their smoking status, use of e-cigarettes and the type of school. Knowing the addictive nature of nicotine (Benowitz, 2010), the results are, however, expected. Even though the attrition bias may have affected the strength of the associations, it is unlikely that it would have affected the direction of the associations. Although we controlled for other tobacco product (snus, water pipe) and drug use, we were not able to adjust the models for all known confounders, e.g., peer smoking and sensation seeking, as these indicators were not available in the surveys. Finally, as smoking has become less and less frequent among Finnish adolescents (Kinnunen et al., 2017), and e-cigarette daily use is also very rare, the small number of cases may have diminished the statistical significance of the results. This concerns especially the results of non-nicotine e-cigarettes. Weekly smoking as the outcome was considered, but not chosen, as the modest gain in sample size did not outweigh the importance of focusing on daily smoking.

Despite these limitations, the strength of this study is the longitudinal design offering a chance to study the transition from experimentation with or use of e-cigarettes to subsequent cigarette smoking and daily use of nicotine e-cigarettes with a certainty of chronological sequence over a relatively short interval (2.5 years). Our study also covered the age range when adolescents commonly adopt smoking and transfer from experimenters to regular users (Dierker et al., 2012).

5. Conclusions

Among never-smoking adolescents, e-cigarette experimentation with nicotine e-liquid increases the risk of becoming daily smoker while experimentation with non-nicotine e-liquid does not. Additionally, e-cigarette experimentation with nicotine e-liquid increases the risk of daily use of nicotine e-cigarettes. Nicotine containing e-cigarettes can

be considered as a gateway to conventional smoking why access to e-cigarettes should be limited by legislation in order to prevent nicotine addiction.

Contributors

JK formulated the research design and research questions, reviewed the literature, carried out the statistical analyses, and wrote and commented the manuscript. JK contributed to the data collection. HO participated in formulating the research design and research questions, reviewed the literature, and contributed for writing and commenting the manuscript. JM commented the research design and research questions and contributed for writing and commenting the manuscript. PL commented the research design and research questions and wrote and commented the manuscript. PL contributed to the data collection. DT participated in commenting the research design and research questions and contributed for writing and commenting the manuscript. AR contributed to the data collection and commented the research design and the manuscript. All authors read and accepted the final version of the article.

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