**E-cigarette use and subsequent smoking in adolescents and young adults: a perspective**

**Keywords:** Adolescent Behaviour; Electronic Cigarettes; Longitudinal Studies, Prevalence Studies; Tobacco Smoking

Cigarette smoking and its’ causal association with adverse health outcomes is well established. The introduction of electronic cigarettes (e-cigarettes) and their widespread marketing over the past decade as a safer alternative to combustible cigarettes, however, has also introduced a complex debate over their role in reducing tobacco-related harm. E-cigarettes, available in a variety of delivery systems, are considered to be significantly less harmful than combustible cigarettes and hence vaping is portrayed as a less risky alternative to smoking.(1) More recently, e-cigarettes have also been considered for their role in achieving smoking cessation among combustible cigarette users.(2) There are, nonetheless, concerns around their safety and long term health effects; research indicates that e-cigarette vapor can induce endothelial injury similar to cigarette smoke, alter the immune response and resistance to anti-microbial factors,(3) as well as induce respiratory symptoms in both adolescents and adults.(4, 5) It has also become a public health concern that the rapid surge in popularity of e-cigarettes among youth(6) could cause smoking rates in this age group to relapse by encouraging cigarette smoking among e-cigarette users. This is especially relevant to public health efforts in tobacco control, which focus heavily on prevention of smoking among adolescents and young adults.(7) The aim of this article is to highlight the current evidence on e-cigarettes, and explore if their use can lead to initiation and subsequent regular smoking among adolescents and young adults through a review of national tobacco surveys, published longitudinal studies and expert opinions.

**Prevalence of smoking and e-cigarette use among adolescents and young adults**

While the prevalence of smoking among adolescents worldwide continues to challenge global tobacco efforts (8), countries like the US and UK have observed a steady decline over the past decades, owing largely to the success of their tobacco control policies. In the UK, current (<1 cigarette/week) and regular (>1 cigarette/week) smoking rates among adolescents (aged 11-15 years) have fallen sharply from 1996 to 2016 (22% to 6% and 10% to 3%, respectively); a similar decline has been observed in young adults (18-24 years) across England, Scotland and Wales, where current smoking dropped from 25.8% in 2010 to 20.7% in 2015.(9) In the US, prevalence of past 30-day cigarette smoking declined linearly from 15.8% to 7.6% among 9-12 grade students (approx. 14-18 years), while a non-linear decrease from 4.3% to 2.1% was observed among 6-8 grade students (approx. 11-14 years) between 2011 and 2017.(10) The decline in smoking prevalence however, may now be challenged by the recent surge in the popularity of e-cigarettes. The ever use of e-cigarettes among 11-15 year olds in England increased from 22% in 2014 to 25% in 2016 in England. In the US, most recent estimates suggest that since 2011, past 30-day e-cigarette use has risen sharply from 1.5% to 20.8% among 9-12 grade students, while among 6-8 grade students, it has increased from 0.6% to 4.9%.(11) The knowledge and understanding of e-cigarette use among adolescents and young adults is constantly evolving; while some reports argue that most e-cigarette use reported may only be experimentation,(12) with regular e-cigarette use more likely in smokers only,(13, 14) others now suggest that exclusive e-cigarette use could be higher than the rates of smoking and dual use.(15-17) According to one UK study, up to 52.5% of all e-cigarette users reported only exclusive use.(18)

**E-cigarette use and subsequent smoking: Evidence from longitudinal studies**

We conducted a literature search on PubMed and Google scholar using search terms for e-cigarettes, cigarette smoking and adolescents/young adults in order to identify relevant cohort studies that reported on an association between e-cigarette use and subsequent smoking in this age group. Among these, we found a systematic review and meta-analysis, summarizing nine prospective cohort studies, that demonstrated significantly higher odds of smoking initiation (OR 3.50, 95% CI: 2.38-5.16) and past 30-day cigarette use (OR: 4.28, 95%CI: 2.52-7.27) among e-cigarette users.(19) A number of additional studies, conducted in North American(20-24) and European(25-27) settings, also suggested similar association between e-cigarette use and subsequent smoking, while adjusting for demographic, psychosocial and behavioral risk factors that predict smoking. Evidence also suggests that in addition to cigarettes, e-cigarette users are also likely to experiment with other combustible tobacco products (cigars, waterpipe).(28) Interestingly, the risk of smoking initiation or experimentation may be higher in exclusive e-cigarette users,(21) and comparable to the risk of subsequent smoking from baseline use of other tobacco products like waterpipe and smokeless tobacco.(29)

While the literature on the association between e-cigarette use and subsequent smoking continues to grow rapidly, the current evidence base is not without its limitations. Most studies reported only ever-use or any use in past 30-day as smoking outcomes, which although clearly identify the risk of initiation and experimentation (also reported in the NASEM report(30)) however, offers a weak explanation for a risk of subsequent regular or daily smoking. Other studies that have demonstrated an association between baseline e-cigarette use with “established” current smoking (defined as a combination of >100 cigarettes smoked and past 30-day use), daily smoking (smoking in the past 7 days)(23, 31) and with higher frequency (OR: 2.17, 95%CI: 1.95-2.42) and heaviness of smoking (OR: 2.19, 95% CI: 1.85-2.58) at follow up(32) included smokers at the baseline.

Based on the above observational studies, there is now sufficient and strong evidence to suggest an association between e-cigarette use and subsequent smoking initiation. In comparison, the evidence on the relationship between e-cigarette use and regular smoking is still growing. The divisions over the issue of e-cigarette use and smoking in youth appears to be less about its evidence base and more about its two different explanations, as discussed below.

The “gateway effect” has been suggested as one of the explanations for the relationship between e-cigarette use and subsequent cigarette smoking among youth. The theory states that e-cigarette users become addicted to nicotine, which leads to subsequent cigarette smoking. The notion, which also underpins the NASEM report,(30) that e-cigarette use leads to subsequent smoking in adolescents and young adults is largely based upon this theory. However, in addition to the development of nicotine dependence,(33) e-cigarettes may also act by encouraging affiliations with smoking peers, (34) diluting the harm perceptions of cigarettes, (35) and prompting smoking behaviors through use of both nicotine as well as non-nicotine containing e-cigarettes.(26)

An alternative explanation for this relationship, called the “common liability” has also been used; this theory suggests that young people who use e-cigarettes and transition to smoking cigarettes, may do so due to other factors that make them susceptible to both behaviors.(33) This explanation has previously been suggested in reports that demonstrated an association between e-cigarette use and smoking experimentation only, little e-cigarette use in non-smokers, and the continuous decline in smoking rates in this age group.(36) Based on this understanding, Public Health England (PHE) currently states that there is insufficient evidence to support e-cigarettes as a potential entry point into smoking for adolescents or non-smokers. (37) There is however, emerging evidence that baseline non-smokers with a low risk profile for smoking may also transition into cigarette smoking at follow-up (34, 38); this is likely to affect the current applicability of the common liability theory in the context of e-cigarettes and cigarette smoking.

In the absence of any strong evidence for either of the two explanations (gateway effect and common liability), it is imperative that these two are considered as hypotheses and not facts. Any future longitudinal research in this area faces a tough challenge of controlling for this common liability(39) before confirming a causal inference between e-cigarette use and smoking. Furthermore, given the low prevalence of daily smoking in adolescents, it may be unrealistic to expect studies, which conclude in this age bracket, to show a transition from e-cigarette use to established smoking. It is possible that this transition may happen during young adulthood, which would require studies to include follow-ups longer than just 12 or 24 months.

The use of e-cigarettes has increased considerably among adolescents and young adults with potential for further spread globally, given that only 68 countries currently regulate e-cigarette products.(40) In such circumstances, special attention must be given to emerging products like JUUL, a novel electronic device which aims directly at youth with its distinctive, technological appeal and has already established itself as the leading e-cigarette brand in the US.(41) Longitudinal studies among non-smoking adolescents and young adults using e-cigarettes point unanimously toward an association between e-cigarette use and smoking initiation, warranting the need for vigilance. This includes, but is not be limited to, a restriction of sales and marketing to non-smoking groups, and the regularization and testing of products for safety, especially considering its potential to affect respiratory health. Lastly, while routine and ongoing surveillance of e-cigarette trends in this age group is needed, future research will need to place more emphasis on gathering robust observational data using long term follow-ups, and adopting standardized measures that demonstrate the risk of transition into established or daily smoking among e-cigarette users.

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