Association between electronic cigarette use and tobacco cigarette smoking initiation in adolescents: A systematic review and meta-analysis

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Abstract

Aim: This systematic review of longitudinal cohort studies aimed to explore whether electronic cigarette (e-cigarette) use by adolescents, in Europe and North America, who had never smoked conventional tobacco cigarettes (tobacco cigarettes) at baseline was associated with subsequent initiation of tobacco cigarette smoking.

Methods: A key word search identified peer-reviewed literature published between 1 January 2005 and 2 October 2019 from seven bibliographic databases and one search engine. Using a predefined inclusion/exclusion criteria two authors independently screened abstracts, and subsequently, full text papers. Eligible papers were quality assessed and scored by two authors. Included papers had data on population characteristics, exposure and outcome measures extracted into an adapted Cochrane Data Extraction Form. Statistical analysis was preceded by a feasibility assessment, and included a pairwise random effects meta-analysis, and sensitivity and subgroup analyses.

Findings: From an initial 6,619 studies (6,510 papers from the initial searches, plus 109 papers from supplemental searches), 14 unique studies in 21 papers were identified. Nine of the 14 unique longitudinal studies with follow-up periods between 4 and 24 months were eligible for inclusion in a meta-analysis of the association between ever use of e-cigarettes and subsequent initiation of tobacco cigarette use. Based on primary study adjusted odds ratios, our meta-analysis calculated a 4.06 (95%confidence interval (CI): 3.00-5.48) times higher odds of initiating tobacco cigarette smoking for those who had ever used e-cigarettes at baseline, although the odds ratio was reduced slightly (to 3.71 times odds, 95%CI: 2.83-4. 86) when only the four high-quality studies were included. The initial meta-analysis model had a moderate to high statistical heterogeneity, sensitivity analysis restricted to high-quality studies had a low to moderate statistical heterogeneity.

Conclusion: The systematic review found that e-cigarette use was associated with initiation of tobacco cigarette smoking among adolescents in Europe and North America, identifying a potentially serious public health harm. Given the widespread availability and use of e-cigarettes, this study further supports urgent action by policymakers to prevent their use by adolescents to reduce direct harms in this vulnerable population group as well as to protect gains in reducing tobacco cigarette initiation.

Keywords

Electronic cigarette use, Vaping, Tobacco cigarette initiation, Smoking, Adolescents

Background

It is generally accepted that e-cigarettes were introduced to Europe in 2006 and to the United States of America (USA) in 2007 and as of 2017, 433 brands of e-cigarettes and 15,586 flavours had been identified [1]. Since then, their use has become increasingly prevalent. A study based on Eurobarometer surveys reported that 63 million (or 14.6%) of people living in European Union member states aged 15 or older had ever used e-cigarettes by 2017 (95% confidence interval [CI]: 59.9 million–66.2 million), and 7.6 million (95% CI: 6.5 million–8.9 million) or 1.8% were regular e-cigarette users [2]. Never smokers were less likely to be regular e-cigarette users than current and former smokers (12.8% versus 27.0% versus 41.3%).[2] In the USA, the self-reported prevalence of current e-cigarette use among adults was 3.2% in 2018. For young adults aged 18-24 years, the prevalence of current e-cigarette use was more than double at 7.6% [3].

The emergence of e-cigarettes is a disruptive change challenging tobacco control globally [4-6], and countries are adopting different approaches to public health policy [7]. While the balance of harms and benefits of e-cigarettes for established smokers continue to be debated [8], their toxicological profile and the impact of nicotine on the developing adolescent brain make their use among children and young people especially concerning [9, 10].

Data from the 2011–2018 National Youth Tobacco Surveys in the USA, found that current e-cigarette use among high-school students, increased from 1.5% in 2011 to 20.8% in 2018 [11]. Surveys of 11–16-year-old children in the United Kingdom found between 7% and 18% had ever used e-cigarettes, and between 67% and 92% of children who regularly smoked had ever used e-cigarettes in 2015–2016 [12]. The surveys' range for ever use of e-cigarettes among 11–16-year-olds who regularly smoked tobacco cigarettes (i.e. dual users) was between 4% and 10%, while the range for regular e-cigarette use among the same

cohorts was between 0.1% and 0.5% [12]. The Health Behaviours in School Children study in Ireland reported that 22% of 12–17-year-old children reported that they had ever used e-cigarettes in 2018, and 9% of 12–17-year-olds reported that they had used e-cigarettes in the 30 days prior to the survey [13]. Perikleous *et al*. found that e-cigarette use in the USA and Europe was associated with older teenagers, male adolescents, tobacco cigarette smokers, peer influence, daily smoking, and heavier smoking [14].

In addition to the direct harm from e-cigarettes, one of the main concerns for this vulnerable group is potential for e-cigarette use to lead to tobacco cigarette use with its associated lifelong harms, and thereby undermining tobacco control initiatives. This is a critical area where evidence is required to inform public health policy [15].

Three previous systematic reviews were published examining this topic. Soneji *et al.* using seven studies found that e-cigarette use is associated with an increased risk of future cigarette smoking initiation and current cigarette smoking in young people aged 14–30 years, even after adjusting for potential confounding by demographic, psychosocial, and behavioural risk factors [16]. Glasser *et al.* concluded that e-cigarette use is associated with subsequent smoking in young people [17]. Aladeokin and Haighton included three studies in their meta-analysis and showed that United Kingdom (UK)-based adolescents who use e-cigarettes were six times more likely to smoke tobacco cigarettes. Only one of the three systematic reviews focused exclusively on adolescents, and these were UK-based adolescents [18].

Given the importance of the period of adolescence in establishing future smoking behaviour [19], the aim of the systematic review was to build on this work by determining if e-cigarette use by European and North American adolescents who never smoked tobacco cigarettes at baseline was associated with subsequent initiation of cigarette smoking through a meta-analysis of the longitudinal cohort studies.

Methods

Literature search strategy and inclusion-exclusion criteria

The peer-reviewed literature search on e-cigarettes published between 1 January 2005 and 15 April 2019 was structured and robust. It retrieved papers from seven databases and one search engine. These were Ovid MEDLINE (Appendix 1), Cochrane Library, Ovid PsycINFO, Elsevier Embase, PROSPERO, LILACS, CORE.ac.uk, and Google Scholar. The searches were updated twice, using Ovid MEDLINE, during the review period with an end date 2 October 2019. Our keywords were based on variations of English terms for e-cigarette for example, e-cig*, e-liquid, vape, vaping, cigalike, electronic nicotine delivery system (ENDS), and electronic non-nicotine delivery. Non-English terms for these concepts were also included, for example, e-sigaret*, E-zigarette, and e-papieros. We found 6,619 studies (6,510 papers from the initial searches, plus 109 papers from supplemental searches). Three rounds of screening were carried out by two independent authors using predefined inclusion/exclusion criteria (Table 1). We completed backward citation searching on all studies included in the review. Our PRISMA diagram is presented in Appendix 2. This systematic review followed the Centre for Reviews and Dissemination's guidance for undertaking reviews in health care [20].

Table 1 here

Quality assessment and data extraction

Two researchers independently assessed the quality of the included studies using the National Heart, Lung, and Blood Institute's (NHLBI's) 14-item quality assessment tool for observational cohort and cross-sectional studies (Appendix 3) [21]. One researcher extracted key population, exposure, and outcome data from the included papers into an

adapted Cochrane Data Extraction Form [22] and these extracted data were validated by another researcher.

Statistical analyses

A meta-analysis feasibility assessment was completed including the 14 studies in order to decide whether to complete meta-analysis and to decide which meta-analysis method would be most appropriate [23-25]. A pairwise random effects meta-analysis using the primary studies adjusted odds ratios, to compare outcomes of two-armed longitudinal studies exposures, was completed for the outcome 'initiated tobacco cigarette smoking' during the study follow-up period [26-28]. Sensitivity and subgroup analyses were also conducted where appropriate. A level of evidence [29] and a GRADE recommendation [30] were assigned to included data.

Results

Study and population characteristics

We identified 21 papers for inclusion in the study (Appendix 2); comprising 14 unique longitudinal cohort studies (Appendices 4 – 8). The data in the primary studies were collected between 2013 and 2016 and the longitudinal follow-up period ranged from 4 months to 2.5 years. Only one study had two follow-up time points [31]. Fifteen primary papers were completed using North American data [31-45] and six primary papers were based on European data [46-51]. The included studies had a range of research questions related to e-cigarette use; 17 asked about ever use of e-cigarettes [31, 34-38, 40, 42-51], and 4 asked about e-cigarette use in the past 30 days [33, 38, 41, 42]. No study provided information on e-cigarette type, generation or liquid. All papers measured tobacco cigarette smoking during follow-up as an outcome variable: 18 papers investigated ever use of tobacco cigarettes between baseline and follow-up [31, 33, 35-50], and 4 asked about past 30-day use of tobacco cigarettes [37, 38, 40, 42]. All publications which conducted

regression analysis included potential confounding variables as covariates in their regression model, ranging from the inclusion of 3 variables to the inclusion of 17. Based on previous research, we grouped the covariates into three groups: demographic (e.g. ethnicity, family affluence), interpersonal (e.g. number of friends/family members that smoke) or intrapersonal (e.g. such impulsivity, sensation seeking, rebellion) [17]. One paper [34] only included variables from one domain, while eight papers [33, 36, 41, 44, 45, 48, 49, 51] included variables from two domains, and ten papers [31, 32, 37, 38, 40, 42, 43, 46, 47, 50] included variables from all three domains. The age of the included population was between 13 and 19 years at baseline.

Quality assessment

Overall, using the NHLBI quality assessment tool [21], we judged four studies to be high-quality as they had a representative and clearly defined sample with a participation rate of more than 50%, a loss to follow-up rate of 20% or less, and a sample size justification or variance calculation for the main outcomes (Appendix 3).

Feasibility assessment

In order to ascertain whether a meta-analysis was appropriate and which studies should be included, a feasibility analysis was conducted, taking outcome, exposure, unit of measurement, and length of time to follow-up into account as they employed the same method of analysis (Appendix 9). Based on these criteria, nine studies with 16,808 participants were considered eligible for meta-analysis of ever using e-cigarette at baseline and smoked tobacco cigarettes at any time during the follow-up period (Figure 1), while four studies of past-30-day e-cigarette use at baseline and smoked tobacco cigarettes at any time during the follow-up period were eligible.

Ever e-cigarette use at baseline and subsequent cigarette smoking at follow-up

Our ever e-cigarette-use meta-analysis was based on the primary study adjusted odds ratios and calculated a combined 4.06 (95%CI: 3.00-5.48, I^2 68%) times higher odds of initiating smoking tobacco cigarettes for those who had ever used e-cigarettes at baseline, although this combined odds was reduced slightly to 3.71 times (95%CI: 2.83-4. 86, I^2 35%) when only the four high-quality studies [37, 42, 45, 50] were included in a sensitivity analysis(Appendix 10).

Figure 1 here

A further sensitivity analysis was conducted on the six studies [31, 37, 42, 46, 47, 50] which controlled for the three domains of covariates – that is, demographic, interpersonal, and intrapersonal factors. The results of this analysis (OR: 3.82; 95% CI: 2.66–5.48; I2 69%) were similar to the results for the high-quality studies assessment, but the level of heterogeneity remained moderate to high(Appendix 10).

Three subgroup analysis were completed(Appendix 10). The first considered studies which collected data pre-2014 [31, 37, 45] in comparison with those which collected their initial data from 2014 onwards [36, 42, 46, 47, 49, 50], due to the increase in e-cigarette use that was observed around this time [52]. The combined OR for studies which collected data from 2014 onwards increased substantially (pre-2014 AOR: 2.81, 95%CI: 2.45–3.72); compared to 2014 onwards (5.16, 95%CI: 3.69–7.21). However, the confidence intervals overlap indicating that they are not statistically significantly different.

The second subgroup analysis considered the length of time to follow-up, as studies included in the analyses had follow-up periods which ranged from 4 months to 2 years. However, as only two studies had follow-up periods of less than 1 year [47, 49] including one study which had a very small sample size, the meta-analysis for this subgroup did not provide meaningful results.

Finally, given the importance of the context of these studies (including social norms, regulatory environment, etc.), we conducted a subgroup analysis of the European studies as compared with the studies from the USA. The combined OR was higher in the European studies (OR: 6.22, 95%CI: 3.73–10.38) [46, 47, 49, 50] as compared with the USA studies (OR: 3.18, 95%CI: 2.26–4.47) [31, 36, 37, 42, 45]. However, the confidence intervals overlap indicating that they are not statistically significantly different.

Past-30-day e-cigarette use at baseline and subsequent cigarette smoking at follow-up

Four studies examined the impact of past-30-day e-cigarette use at baseline and subsequent cigarette smoking at follow-up [33, 38, 41, 42]. A meta-analysis was conducted using the primary studies adjusted odds ratios(Appendix 10). The analysis included 30,018 participants from three of four studies measuring past-30-day e-cigarette use at baseline, and found a significant positive association between past-30-day e-cigarette use at baseline and subsequent cigarette smoking initiation at follow-up (OR: 2.14; 95% CI: 1.75–2.62; I2 0%) (Figure 2) [33, 38, 42].

Figure 2 here

Level and certainty of evidence

We assigned a level of evidence of 3 using British Medical Journal guidelines [29], as this is a systematic review of cohort studies, some of which had high loss to follow-up and/or very small sample sizes. However, with respect to certainty of evidence [30], we have moderate confidence that the true effect is probably close to the estimated effect for initiating smoking at follow-up for those who had ever used e-cigarettes at baseline.

Discussion (1541)

We found a four-fold increased likelihood between e-cigarettes use and initiating smoking tobacco cigarettes in adolescents in a combined analysis of nine cohort studies conducted

with follow-up periods between 4 and 24 months. Sensitivity and subgroup analysis support the relationship between ever using e-cigarettes and initiating smoking tobacco cigarettes. Six studies controlled for confounding under three domains (demographic, interpersonal, and intrapersonal) while examining the association between using e-cigarettes and initiating smoking tobacco cigarettes, and had a similar, significant estimate of effect in meta-analysis. The four high-quality studies also had a similar estimate of effect but lower statistical heterogeneity. The remainder of the studies were judged to be moderate quality because of their small sample sizes and/or high loss to follow-up.

The cohort study design used to assess the relationship between e-cigarette use and initiation of tobacco cigarette smoking allows researchers to build a case towards a causal relationship. The findings are consistent across all studies included in the meta-analysis and the strength of association is statistically significant across all primary research studies in the meta-analysis. Furthermore, the use of e-cigarettes which occurred before initiating smoking, fulfils the criteria for a temporal relationship and two studies in this review have illustrated a dose-response relationship. We have moderate confidence that the true effect is probably close to the estimated effect for initiating smoking at follow-up for those who had ever used e-cigarettes at baseline, as all meta-analyses indicate that there is a significant positive association between using e-cigarettes at baseline and smoking tobacco cigarettes at follow-up, and this effect size is quite large; the findings are statistically significant, consistent, and the exposure occurred before the outcome

Strengths and limitations

One limitation of the research in this area is the lack of specificity of the exposure (e-cigarette) in terms of generation, product type, e-liquid and its nicotine content, etc. None of the included studies asked specific questions, and only two [49, 51] of the 21 studies measured the differences between nicotine and non-nicotine e-cigarettes. This is

particularly pertinent as the world of e-cigarettes is fast-moving, with new products developing rapidly.

The most common measure of both e-cigarette and cigarette use was 'ever use' of either product, a measure which has been criticised by commentators [53]. 'Past-30-day use' has received the same criticism, as it does not identify whether people used the product once in the past 30 days, or if they used it regularly. However, the use of these measures has been justified by a number of publications, with a recent study by Birge et al. reporting that more than two-thirds of smokers who tried as little as a single puff during adolescence became, for a time, regular smokers [54].

Comparison with previous systematic reviews

The results of this up-to-date and comprehensive systematic review are in line with two previous meta-analyses, Soneji *et al.* [16] and Aladeokin and Haighton [18], that also found an association between initiation of e-cigarette use and subsequent smoking. However, this systematic review consolidates and extends the evidence base for public health policy because it used nine studies concentrating on adolescents who resided in a wider geographical region, and the analysis also took account of quality and confounding. The World Health Organization, based on the Academies of Sciences systematic narrative review, reported that there is moderate evidence that young never smokers who experiment with e-cigarettes are at least two times more likely to experiment with smoking later, which is lower but in line with our findings [55]. The study presented in this paper, however, includes newer studies not analysed in that review.

Future research

A key question remaining relates to causality and the underlying drivers in the relationship between e-cigarette and tobacco cigarette use. Three theories that attempt to explain the move from using e-cigarettes to smoking tobacco cigarettes include the gateway theory,

[56], the common liability theory [57-60], and the catalyst model [61]. Future research should focus on designing studies which specifically set out to test these three theories (or elements thereof).

In terms of the most appropriate study design for assessing causality, Etter recommended large longitudinal epidemiological studies which measure smoking onset, control for confounders, and include a propensity score measure of liability to smoking [53]. In addition to this, we suggest exploring the association using explorative and in-depth quantitative and qualitative research approaches.

Most research has taken place in Europe and North America: there is a need for research for cross-country research including low- and middle-income countries where the burden of tobacco cigarette use is the highest.

No study provided information on e-cigarette type, generation or liquid. It is important to note that e-cigarettes and their e-liquids were not a standard intervention in the included studies; rather, they are an umbrella term for a device that delivers nicotine and other products including flavourings [62]. The content of the e-liquids was another confounding factor due to the variation in nicotine dosages and other contents [62]. Independent longitudinal research over a number of years is required into e-cigarette devices and their liquids to determine their long-term effects on human health.

Implications for policymakers

Given over six million deaths attributable to smoking worldwide each year[63], tackling tobacco use continues to be a global health priority, with countries at different stages in controlling the epidemic and some high-income countries signalling intent to transition from tobacco control to tobacco endgame [64, 65]. E-cigarettes are a disruptive innovation raising new questions for health policy-makers [4-6]. Debate on the harms and potential benefits of e-cigarettes has dominated tobacco control discourse [66], and became even

more charged with the emergence of e-cigarette, or vaping, product use–associated lung injury (EVALI) in 2019 [67]. Two viewpoints, which often appear conflicting emerge: a harm minimisation approach is proposed to leverage a potentially favourable balance of harms and benefits for people who smoke so as to mitigate the overwhelmingly bleak odds they face from their use of combustible tobacco products [68], while a precautionary approach is advised given the many unknowns regarding e-cigarette use, evidence of tobacco industry interference, and previous false dawns of "safer" tobacco products [69].

To find a way forward through these competing viewpoints, policy-makers must carefully appraise evidence on risk, benefits, and trade-offs while understanding the framing and wider context of the debate [15, 70-72]. The U.S. National Academies of Sciences, Engineering, and Medicine, were commissioned by the Food and Drugs Administration to systematically review scientific evidence to inform e-cigarette policy [73], while in Europe the Scientific Committee on Health, Environmental and Emerging Risks has been mandated to assist the European Commission in assessing the most recent scientific and technical information on e-cigarettes as part of its review of the Tobacco Products Directive 2014/40/EU [74]. Similarly, the study presented in this paper was conducted as part of broader programme of evidence review to inform and support public health policy in Ireland, which included mapping of the harms and benefits of e-cigarettes (and their e-liquids) [62] and a systematic review of e-cigarettes role in smoking cessation [75]. We found that e-cigarettes (and their e-liquids) lead to acute harms such as poisoning, lung injury, and burns and blast injuries, a finding aligned with six other systematic reviews [55, 73, 76-79], and highlighted a need for continuing study using robust methods to measure the long-term health impacts of their use as these are not yet known. We also found that approved and regulated nicotine replacement therapies with established safety profiles were as effective as e-cigarettes in helping smokers quit [75].

Against a backdrop of often clashing harm reduction and precautionary viewpoints on e-cigarettes, mobilising evidence, while necessary, is difficult for policy-makers This difficulty is exacerbated when the relationship between evidence and policy is seen as a linear "know-do-gap", instead of recognising the "muddling through" of the policy process [80]. The harms, benefits and trade-offs to be considered by policy-makers in the area of e-cigarettes are likely to be different across population groups and require a finely balanced blend of policies which are precautionary for vulnerable groups while retaining potential prospect of harm reduction for some highest-risk groups not amenable to other risk management measures.

In the case of children, young people, and non-smokers, e-cigarettes offer no benefits and present potential for harm from nicotine dependence and exposure to known toxins The mandate for policy action to maximise protection of children and adolescents is further strengthened by the systematic review presented in this paper, in which we found that e-cigarettes were associated with initiation of tobacco cigarette smoking among adolescents. This is a potentially serious harm which undermines hard-won progress in tobacco control, that have been largely delivered through preventing smoking initiation in youth. Other researchers have noted that two-thirds of these adolescents may go on to smoke tobacco cigarettes for a period [54]. Children and adolescents should be offered the same protection from e-cigarettes as conventional tobacco cigarettes through a well-enforced regulatory regime of measures including: age restriction on purchase, control of availability through licensing outlets, limits to product visibility and attractiveness, and appropriate pricing through taxation. Before exploring the potential for harm reduction for highest-risk groups and those for whom regulated pharmaceutical interventions do not work, policy-makers should assure protection of children, adolescents and never smokers as their next evidence-informed, precautionary step through this complex and challenging policy process, so as to

reduce direct harms from e-cigarettes in these vulnerable populations and to protect gains in reducing tobacco use initiation.

Conclusion

The systematic review found that e-cigarette use was associated with initiation of tobacco cigarette smoking among adolescents in Europe and North America, identifying a potentially serious public health harm. Given the widespread availability and use of e-cigarettes, this study further supports urgent action by policymakers to prevent their use by adolescents to reduce direct harms in this vulnerable population group as well as to protect gains in reducing tobacco cigarette initiation.

Supplementary information

Appendix 1 Medline literature search strategy and Appendix 2 presents the study PRISMA flow chart. Appendix 3 presents the quality assessment tool and results. Appendix 4 presents characteristics of included studies. Appendix 5 presents primary research AOR for ever e-cigarette and cigarette use among adolescents in the selected longitudinal cohort studies. Appendix 6 presents primary studies ever use of e-cigarettes and cigarettes among adolescents in the selected longitudinal cohort studies using statistical measures such as adjusted relative risk, estimates, or standardised coefficient. Appendix 7 presents AORs for different frequencies of e-cigarette and cigarette use among adolescents in the selected longitudinal cohort studies. Appendix 8 presents adjusted relative risk for different frequencies of e-cigarette and cigarette use. Appendix 9 presents the feasibility assessment for meta-analysis and Appendix 10 presents the results of the meta-analysis, sensitivity analysis, and subgroup analysis.

See attached Excel file.

Abbreviations

AOR: adjusted odds ratio; CI: confidence interval; e-cigarette: electronic cigarette; e-liquid: electronic liquid for e-cigarette; EVALI: e-cigarette, or vaping, product use–associated lung injury; NHLBI: National Heart, Lung, and Blood Institute; OR: odds ratio; UK: United Kingdom; USA: United States of America

Acknowledgements

We would like to thank the Department of Health in Ireland for setting this interesting research question.

Authors' contributions

DOB conceptualized the research question and developed the search, screening and analysis plan jointly with AMcC, CL, JQ and JL. DOB, AMcC and CL screened the literature. DOB completed data extraction with JL as second reviewer and both DOB and JL completed the quality assessment. DOB, JQ and JL analyzed the data. JL and DOB drafted the manuscript, and PK, AMcC, JQ and CL read and contributed to revising the manuscript. All authors read and approved the final manuscript.

Funding

The systematic review was funded as part of the routine work of the Health Research Board.

Availability of data and materials

The primary research papers are available through bibliographic databases. The PRISMA flow chart, quality assessment sheet, and data extraction sheet is provided as part of the supplementary materials.

Ethics approval and consent to participate

As all data is published in primary papers, ethics approval for this analysis was not required.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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