Association between electronic nicotine delivery systems and electronic non-nicotine delivery systems with initiation of tobacco use in individuals aged < 20 years. A systematic review and meta-analysis

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Abstract

Background

This systematic review described the association between electronic nicotine delivery systems and electronic non-nicotine delivery systems (ENDS/ENNDS) use among non-smoking children and adolescents aged <20 years with subsequent tobacco use.

Methods

We searched five electronic databases and the grey literature up to end of September 2020. Prospective longitudinal studies that described the association between ENDS/ENNDS use, and subsequent tobacco use in those aged < 20 years who were non-smokers at baseline were included. The Joanna Briggs Institute Critical Appraisal Checklist was used to assess risk of bias. Data were extracted by two reviewers and pooled using a random-effects meta-analysis. We generated unadjusted and adjusted risk ratios (ARRs) describing associations between ENDS/ENNDS and tobacco use.

Findings

A total of 36 publications met the eligibility criteria, of which 25 were included in the systematic review (23 in the meta-analysis) after exclusion of overlapping studies. Sixteen studies had high to moderate risk of bias. Ever users of ENDS/ENNDS had over three times the risk of ever cigarette use (ARR 3.01 (95% CI: 2.37, 3.82; p<0.001, I²: 82.3%), and current
cigarette use had over two times the risk (ARR 2.56 (95% CI: 1.61, 4.07; p<0.001, I²: 77.3%) at follow up. Among current ENDS/ENNDS users, there was a significant association with ever (ARR 2.63 (95% CI: 1.94, 3.57; p<0.001, I²: 21.2%)), but not current cigarette use (ARR 1.88 (95% CI: 0.34, 10.30; p = 0.47, I²: 0%)) at follow up. For other tobacco use, ARR ranged between 1.55 (95% CI 1.07, 2.23) and 8.32 (95% CI: 1.20, 57.04) for waterpipe and pipes, respectively. Additionally, two studies examined the use of ENNDS (non-nicotine devices) and found a pooled adjusted RR of 2.56 (95% CI: 0.47, 13.94, p = 0.035).

Conclusion
There is an urgent need for policies that regulate the availability, accessibility, and marketing of ENDS/ENNDS to children and adolescents. Governments should also consider adopting policies to prevent ENDS/ENNDS uptake and use in children and adolescents, up to and including a ban for this group.

Introduction
Electronic Nicotine Delivery Systems (ENDS) and Electronic Non-Nicotine Delivery Systems (ENNDS) are systems that use devices to heat liquids to create aerosols that are inhaled by users. These are most commonly in the form of an ‘e-cigarette’, but come in other forms (e.g ‘e-pipe’, ‘e-shisha’, ‘e-cigars’). [1] These systems typically contain flavourings, propylene glycol, glycerine and, for ENDS–nicotine. ENDS/ENNDS were first introduced into markets in the 2000s and have been promoted aggressively by manufacturers as “reduced harm products” or “alternatives” to conventional cigarettes. [2] The use of ENDS/ENNDS among children and adolescents however is increasing in some countries, especially among those who had never used tobacco. [3] indicating that such products are not solely used or targeted at adults. [4] In many developed countries, including Canada and the United States (US), ENDS/ENNDS use far surpasses the rates of tobacco use among adolescents in high school. [5–7]

Of concern is an increasing body of evidence suggesting ENDS/ENNDS use may accrue a range of health risks for different age groups. [8, 9] Constituents of e-liquids, such as propylene glycol and glycerine form toxic aldehydes when heated, of which the long-term effects of exposure remains unknown. [10] ENDS/ENNDS use can also impact on the respiratory system and is associated with adverse effects on the developing brain. [10] A recent position statement by the European Association of Preventive Cardiology reported that e-cigarettes may have negative effects on cardiovascular health for both adolescents and adults. [11] There is a rapidly developing empirical evidence describing a longitudinal association between ENDS/ENNDS and cigarette use among young people.

The first review of three prospective cohort studies in those <20 years in 2016 commissioned by the World Health Organization (WHO), reported that non-smoking e-cigarette users had twice the odds of being a conventional cigarette user at follow-up. [3] Since then, there have been several systematic reviews including at time of conducting our review, the most recent by Khouja and colleagues. [12–16] The review by Khouja included 17 studies with individuals aged <30 years, published up to November 2018. The majority of studies were conducted in the US and found a significant adjusted association between ENDS/ENNDS use among non-smokers at baseline and later cigarette use (OR: 2.92 (95% CI 2.30, 3.71). Since this review a number of longitudinal studies have been published from a broader range of

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countries. [17, 18] An updated systematic review to reflect the contemporary evidence is warranted, as more countries are enacting or planning to enact policy or programs to deter ENDS/ENNDS use in young people globally. [19]

Therefore, this review synthesised findings from studies assessing the longitudinal association between ENDS and/or ENNDS use and later cigarette (primary outcome) and other tobacco product initiation (secondary outcome) among children and adolescents aged < 20 years, who were never smokers at baseline. Additionally, it sought to describe the longitudinal association of ENNDS and flavoured ENDS/ENNDS and subsequent tobacco use.

Methods

Search strategy and selection criteria

This systematic review and meta-analysis is undertaken consistent with guidance by Joanna Briggs Institute (JBI) [20] and reported in accordance with Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines. [21] It was prospectively registered in the PROSPERO database (CRD42020199485).

Studies were included if they were prospective longitudinal studies assessing the relationship between ENDS and/or ENNDS use at baseline and initiation of cigarette and other tobacco products at follow-up, among children and adolescents aged less than 20 years who were non-tobacco users at baseline. Case control, cross-sectional and retrospective studies were excluded to capture only studies with the lowest risk of bias for assessing association. [22] There were no restrictions on the year of publication, length or location of the study, peer review status, or language of publication.

We conducted an electronic search of the following databases: Medline, Web of Science, CINAHL, Embase and Wiley Cochrane Library using search terms for the following ‘electronic nicotine delivery systems (ENDS) electronic non-nicotine delivery systems (ENNDS),’ AND ‘prospective studies’ AND ‘children and adolescents’ (see S1 Appendix for search strategy) on the September 2020. The reference lists of all relevant reviews and eligible papers were also screened. We undertook a grey literature search based on guidance from previous reviews, [23] which included searching OpenGrey (a grey literature database) and Google and Google scholar to identify relevant studies using the following terms ‘electronic cigarette’, ‘e-cigarette’, ‘electronic nicotine delivery systems (ENDS),’ ‘electronic non-nicotine delivery systems (ENNDS),’ ‘e-hookah’ and ‘juul’. The first 500 titles of each search were sorted by relevance were assessed by one reviewer in October 2020 (SLY).

An information specialist used EndNote version X9.2 software (Thomson Reuters, PA, U. S.) to filter duplicate studies. Title and abstract screening were undertaken using Covidence software [24] by two reviewers, and discrepancies resolved by consensus (SLY, AH). Full text was obtained and assessed for eligibility in accordance with the criteria described above by two reviewers (AL, ES). All conflicts were resolved by discussion and included a third reviewer (SLY), where necessary.

All data were extracted by a first reviewer (AG, FT, SLY or HT) and double checked by a second reviewer not involved in the original extraction of the study (SLY, HT or AL). Discrepancies were highlighted and checked by a third reviewer (AH). The following information was extracted: participant characteristics, study design, country, data collection modality and measure, sampling frame and recruitment, proportion and number of ENDS/ENNDS users separately where reported, tobacco users as well as non-users at each time point, relevant measures of association between ENDS and ENNDS users and future cigarette and other tobacco product initiation (e.g. risk ratios, odds ratios), estimates of variance and covariates adjusted for, follow-up time points, type of tobacco products assessed and flavours.
The JBI Critical Appraisal Checklist for prevalence studies was used to assess the quality of each study by two reviewers (AG, HT, FT, AL). Discrepancies were checked by a third reviewer (SLY). The tool consists of nine items examining the following: sample representativeness, sampling methods, adequacy of sample size, participant and setting descriptions, coverage of sample, objectivity and reliability of measures, appropriateness of statistical analysis, confounding factors identified and accounted for, and objective classification of subpopulations (Yes; No; Unclear; and N/A). An additional tenth criterion relating to participant retention was added to allow for assessment of attrition bias. Two reviewers also assessed four supplementary criteria detailed in the Bradford-Hill criteria relevant to establishing causality between exposure and outcome. [26] (see S1 Table)

Data analysis
All analyses were undertaken using Stata version 14.2. [27] Effect estimates (extracted or converted to Risk Ratios (RRs)) of the association between ENDS/ENNDS use at baseline and initiation of cigarette or other tobacco use at follow up were combined using the DerSimonian and Laird random effects method. [28]

The primary outcome variable was ever and current cigarette smoking. For ever cigarette smoking, this included lifetime ever use. For current cigarette use, this included use in the past 30 days, frequent and daily cigarette use. The exposure variable was ever and current ENDS/ENNDS use. For ever use of ENDS and/or ENNDS, this was defined as lifetime ever use. For current use of ENDS and/or ENNDS, this included use in the past 30 days, recent use and self-defined current use.

A p-value of 0.05 was used to determine a statistically significant association. Where it was not appropriate to undertake a meta-analysis (due to heterogeneity or small number of studies), study findings were narratively described.

For studies that did not report the unadjusted RRs, these were calculated using the data extracted from the original study or converted from an odds ratio (OR). In instances where studies reported an adjusted odds ratio (AOR) rather than an adjusted RR, these were also converted to an RR. The formula from the Cochrane Handbook (Section 15.4.4.4) [29] was used to convert ORs to RRs. The ACR was calculated on a per study basis as the risk of later smoking among controls, whereby the control was defined as no ENDS/ENNDS use at baseline. In instances where a study did not provide sufficient data to calculate a study-specific ACR, the average ACR from other studies was used.

Where multiple follow-up points were available, the furthest time from baseline was included. Additionally, when a study reported a slight variation for the same outcome, using overlapping datasets, the outcome most closely aligned with the aims was chosen. Where multiple effect estimates exist controlling for different confounders, we included the ones that controlled for demographics that had evidence of association with tobacco uptake (sex, age, socioeconomic status and susceptibility to tobacco use), where available.

A number of planned subgroup analyses were undertaken [12] including: country (grouped into US, United Kingdom (UK) and other), study quality (<7 and 7 or more on the Joanna Briggs scale), and Bradford-Hill’s causal inference score (≥ 3 and <3). Additionally, we also undertook a subgroup analysis by length of follow up (≤ 12 months and >12 months) and publication year (≤ 2018 and >2018). We planned to undertake sensitivity analysis by funding source (e.g. industry/non-industry), however no industry funded studies were included in the meta-analysis.

Heterogeneity of study effect estimates were evaluated using the I² statistic. A funnel plot and the Duval and Tweedie trim-and-fill method was used to examine possible publication bias and provide an estimate of the bias-adjusted pooled estimates. [30–32]
Results

Of the 1,668 studies included after removal of duplicates, 452 articles underwent full text screen, of which 35 were included (see Fig 1). Of those, 10 were excluded from the final analysis as there was overlap of data with other studies included in this review. A total of 25 studies were included in the review, of which 23 were included in any meta-analyses (Fig 1). [17, 18, 33–53]

The studies were conducted in the US (n = 13), Germany (n = 3), UK (n = 2), Scotland (n = 1), Canada (n = 1), Finland (n = 1), Mexico (n = 1), Taiwan (n = 1), Netherlands (n = 1) and Romania (n = 1) with data collection occurring from 2013–2016 at baseline (see Table 1). Sample sizes ranged from 164 to 17,318 and participants were aged between 11 to 26 years (as studies were eligible for inclusion if they had a mean age of <20). The follow-up period was between six to 24 months, and all studies used self-reported measures to assess cigarette (and/or tobacco) use at follow up. Overall, 21 studies assessed cigarette smoking only as an outcome, [17, 18, 34–41, 43–47, 49–54] three assessed cigarettes and other tobacco [33, 42, 48] and one assessed other tobacco only. [55] All studies referred to ENDS/ENNDS as e-cigarettes. Two studies specifically assessed the use of non-nicotine e-cigarettes [40, 51] while one study compared flavoured and non-flavoured e-cigarettes. [54]

Sixteen studies had high to moderate risk of bias (defined as meeting less than 7 of the 11 risk of bias criteria), [33, 34, 36–41, 44, 46–51, 53] while nine had a low risk (defined as meeting 7 or more criteria). [17, 18, 35, 42, 43, 45, 52, 54, 55] (See Fig 2). Key methodological issues identified in the studies were the sampling frame was not appropriately representative of the target population (n = 6 studies rated as high risk [37, 38, 42, 44, 50, 51] and 4 studies rated as unclear [46, 48, 49, 53]), lack of use of valid methods to identify the condition (n = 23 used self-reported measures without established psychometrics and were rated unclear [17, 18, 33–36, 38–41, 43–55]), and lack of information regarding whether the response rate was adequate or appropriately managed (n = 8 studies rated as high risk [18, 36, 39, 40, 43, 44, 50, 55] and 22 studies rated as unclear [17, 33–35, 37, 38, 41, 46–49, 51, 53, 54]). All 25 studies were rated as low risk on the criteria for appropriate statistical analysis and 18 were also rated as low risk for adequate sample size. [17, 18, 34–37, 39–44, 47, 50–52, 54, 55] For the Bradford-Hill criteria, 13 studies met three of the four criteria. [33–35, 37, 38, 41, 42, 45, 47, 49, 51, 54, 55]. All studies rated low risk for temporality, and most were also rated low risk for specificity (n = 24). Only three studies were rated low risk for the dose responsibility criteria. [34, 38, 47]. The majority of studies met the criteria for specificity and all met the criteria for temporality. All studies except one included in this review reported a positive association, with 13 reporting an adjusted odds ratio of > 4.

Seventeen studies assessed the association between ever ENDS/ENNDS use and subsequent ever cigarette use. [17, 18, 33, 35–38, 41–44, 46, 48, 49, 51, 53] The adjusted RRs ranged from 1.39 (95% CI: 1.01, 1.91) to 12.86 (95% CI: 3.59, 46.05); with a pooled RR of 3.01 (95% CI: 2.37, 3.82, p<0.001; I² = 82.3%, p <0.001) (see Fig 3). Most studies adjusted for covariates including sex and age or grade (n = 15), with the majority (n = 14) also adjusting for additional variables including susceptibility to smoking, influence by friends and family, psychological constructs and status, and exposure to advertising.

Six studies assessed the association between ever ENDS/ENNDS use at baseline and subsequent current cigarette use at follow-up. [34, 35, 40, 44, 46, 50] The adjusted RRs ranged from 1.40 (95% CI: 1.22, 1.60) to 3.53 (95% CI: 1.98, 6.30); with a pooled RR of 2.56 (95% CI: 1.61, 4.07, p<0.001; I² = 77.3%, p = 0.001) (see Fig 4).

Four studies assessed the association between current ENDS/ENNDS use at baseline and subsequent ever cigarette use at follow-up. [39, 45, 50, 52] The adjusted RRs ranged from 2.21
Two studies assessed association between current ENDS/ENNDS use at baseline and subsequent current cigarette use at follow-up. [47, 50] The adjusted RRs were $1.16 (95\% \text{ CI}: 0.11, 12.36)$ and $3.15 (95\% \text{ CI}: 0.27, 36.48)$, with a pooled RR of $1.88 (95\% \text{ CI}: 0.34, 10.30, p = 0.467; I^2 = 0\%, p > 0.05)$ (see Fig 6).

S3 Table lists the four studies that assessed the association between ENDS/ENNDS use at baseline and subsequent use of other tobacco products including hookah, cigar, pipe, and other tobacco products at follow-up, where significant associations were reported.
| Author name | Year of publication | Geographic region | Study design | Number of time points, length of follow-up | n analyzed, % retention rate | Sample characteristics (at baseline) | Sampling procedure | Data collection modality | Type of ENDS assessed | Main outcomes assessed (e.g. association between ever and current ENDS/ENNDS use) | Adjustments accounted for in analysis |
|-------------|---------------------|-------------------|--------------|-------------------------------------------|-----------------------------|------------------------------------|-------------------|------------------------|-----------------|---------------------------------|---------------------------------|
| Barrington-Truman 2016 | Southern California United States | Longitudinal prospective cohort study, 12 time points, follow-up: 12 months | n analysed: 149 (e-cigarette users), retention rate: 70.0% | Age: 13.4 (IQR: 12.6–14.2) Male-Female: 50-50% | Male-Female: 52-48% | Exposures frequency-matched cohort study, never-smoking e-cigarette users were contacted and a sample of never-smoking ever-e-cigarette users to complete a follow-up questionnaire. | Pen and paper | e-cigarette | Free use of ENDS/ENNDS at baseline and ever use of tobacco AND other tobacco products (pipes, cigars, hookah, any combustible product) | Gender, ethnicity, grade and highest parental education. |
| Berry 2019 | United States | Population Assessment of Tobacco and Health Study (PATH) | Projective cohort study, 12 time points, follow-up: 12 months | n analysed: 6123, retention rate: 80.9% | Age: 13 (IQR: 12), Male-Female: 50-50% | This longitudinal survey’s cohort was selected via a 6-stages stratified probability sample that was nationally representative. | Audiocomputer-assisted self-interviewing | e-cigarette | Free use of e-cigarette (baseline) and ever use of e-cigarette (follow-up) | Sex, age, race and ethnicity, grade, and study |
| Bhat 2018 | Scotland | Determining the Impact of Smoking Point of Sale Legislation Among Youth (DISPPLAY) study | Longitudinal prospective cohort study, 24 time points, follow-up: 12 months | n analysed: 2699, retention rate: 70.4% | Age: 14 (IQR: 13.5), Male-Female % NR, ethnicity NR | Schools were purposely selected to reflect two levels of urbanisation and two levels of socio-economic deprivation (derived from the population-weighted mean Scottish Index of Multiple Deprivation (SIMD) score for all data zones falling within the school catchment area and the proportion of children from each school receiving free school meals was weighted to ensure sample representativeness). | Pen and paper | e-cigarette | Free use of use of cigarette at baseline and ever use of tobacco follow-up | Sex, age, family influence, ethnic group, school smoking within the family, smoking friends and susceptibility to smoking |
| Chen 2019 | Taiwan | Taiwan Adolescent to Adult Longitudinal Study (TAALS) | Longitudinal prospective cohort study, 24 time points, follow-up: 24 months | n analysed: 1254, retention rate: 87% | Male-Female % NR, 7th grade (n=669) mean age=16 years, 8th grade (n=499) mean age=16 years, and vocational high school: 10th grade, (n=670) mean age=16 years | School was the primary sampling unit and the first wave included 5-year students from junior high school, 7th grade, senior high school, 10th grade and vocational high school students. | Pen and paper | e-cigarette | Free use of e-cigarette at baseline and ever use of tobacco follow-up | Smoking vulnerability at baseline, socio-demographic profile, psychological status, and peer support |
| Croon 2018 | England | National Child Development Study (NCDS) | Longitudinal prospective cohort study, 24 time points, follow-up: 12 months | n analysed: 1726, retention rate: 56% | Male-Female: 50-50% | Data collected as part of a 4-year cluster randomised controlled trial from adolescents in 20 control schools. Adolescents matched across time by randomly generated code. | Online | e-cigarette/quit-pieces | Free use of e-cigarette at baseline and ever use of tobacco follow-up | Friend smoking, sex, family smoking, irritations, attitudes, norms, perceived behavioral control, self-efficacy, free school meals |
| East 2018 | Great Britain | 2016 Action on Smoking and Health Great Britain Youth Longitudinal survey | Longitudinal prospective cohort study, 24 time points, follow-up: 4-6 months | n analysed: 923, retention rate: 50% | Male-Female: 53-47% | A non-probability quota sampling approach was adopted using GOR’s online panels to recruit respondents aged 11-18 years. Data was not in respect of age, gender, and Government Office Region (GOR) using data from Eurostat 2012 to ensure sample representativeness. | Online | e-cigarette | Free use of e-cigarettes at baseline and ever use of tobacco follow-up | Age, gender, school performance, problem behavior, monthly alcohol use, smoking susceptibility, friend smoking, friend e-cigarette use, parent smoking, parent-e-cigarette use, sibling smoking, sibling e-cigarette use, public approval of smoking, public approval of e-cigarettes |

(Continued)
| Author name, year of publication, geographic region | Survey name | Study design, number of time points, length of follow-up | n analysed, % retention rate | Sample characteristics (at baseline) (sex, age, ethnicity) | Sampling procedure | Data collection modality | Type of ENDS assessed (specify duration if applicable) | Main outcomes assessed (e.g. association between ever and current ENDS/ENNDS use) | Adjustments accounted for in analysis |
|--------------------------------------------------|-------------|----------------------------------------------------------|-----------------------------|---------------------------------------------------------------|-----------------|------------------------|---------------------------------|-----------------------------------------------------------------|---------------------------------|
| Friedman 2020 United States [56] | Population Assessment of Tobacco and Health Study (PATH) | Prospective cohort study, 2 time points, follow-up: 5 years total, including waves 1-4 | n analysed: 164, Wave 1 response rates were 73% for the youth, Wave 3 response rates (within the wave 1 cohort) were 79% | Male: 51.4%, Female: 48.6%, Age: 12-17 years, mean reported 66.9% white | This longitudinal survey cohort was selected via a multistage, stratified probability sample, such that weightable analyses were nationally representative for the noninstitutionalized US civilian population | Randomly were unweighted with audio computer-assisted self-interviewing in English or Spanish | e-cigarettes | Initiated flavoured/unflavoured current e-cigarettes use (wave 2) and cig current use (up to 30 days) wave 3 | Sex, race (Black and other, with whites as the reference group), Hispanic ethnicity, age group, household income categories (3 categories), parental reports for youth, and an indicator for ever tried conventional cigarettes at wave 1 as well as a missing observation indicator for each of these variables. Additionally, youth regressions controlled for potential selection at baseline (high school graduate or equivalent, some college or college graduate, high school graduate as the reference group). |
| Hammond 2017 Ontario and Alberta Canada [30] | COMPASS | Longitudinal prospective cohort study, 2 time points, follow-up: 12 months | n analysed: 17318, retention rate: 43% | Male: 51%, Female: 49%, age: <14 or >18 years, race/ethnicity: White: n = 14940 (77.3), Black: n = 6303 (3.6), Asian: n = 3056 (1.7), Aboriginal: n = 6782 (3.5), Latin American Hispanic: n = 805 (0.6), Other/missing: n = 1125 (0.6) | Pen and paper | Mixed (online and pen and paper) | e-cigarette | Current e-cigarette use at baseline and ever use of tobacco use at 5th wave follow-up | Student clustering within schools (school as a random effect) and the post-wave variables (baseline values of age, race/ethnicity, spending money and past 30-day e-cigarette use as fixed effects). |
| Hansen 2020a, Baden-Württemberg Mecklenburg-West Pomerania North Rhine-Westphalia, Schleswig-Holstein and Saxony Germany [57] | DAK prevention radar | Longitudinal cohort study, 2 time points, follow-up: 24 months | n analysed: 2328, retention rate: 56% | Male: 50.3%, Female: 49.6%, mean age at baseline: 12 years, type of school (government) 48%, Migration background 41.1%, SES mean (SD) 6.7 (1.0) | Each state was randomly selected from one of six Nielsen regions. A total of 667 secondary schools were identified in randomly selected sub-regions within each state, and all of them were invited to participate in the study. | Mixed (online and pen and paper) | e-cigarette | Ever use of e-cigarette use at baseline and ever use of tobacco use at follow-up | Age, gender, migration background, sensation seeking, school performance, SES, type of school, peer substance use. |
| Hansen 2020b, Baden-Württemberg Mecklenburg-West Pomerania North Rhine-Westphalia, Schleswig-Holstein, Saxony, and Schleswig-Holstein Germany [57] | DAK prevention radar | Longitudinal cohort study, 2 time points, follow-up: 12 months | n analysed: 3771, retention rate: 76.2% | Male: 51.5%, Female: 48.4%, mean age at baseline: 13 years, type of school (government) 51.5% | Each state was randomly selected from one of six Nielsen regions. A total of 667 secondary schools were identified in randomly selected sub-regions within each state, and all of them were invited to participate in the study. | Mixed (online and pen and paper) | e-cigarette | Ever use of e-cigarette use at baseline and ever use of hookah at follow-up | Age, gender, migration background, sensation seeking, SES, type of school, peer substance use. |
| Kinnunen 2019 Helsinki Finland [41] | Metropolitan Longitudinal Finland (MetaLonF) | Longitudinal cohort study, 2 time points, follow-up: 24 months | n analysed: 2,016, retention rate: 49.9% | Male: 49.2%, Female: 50.8%, Age at baseline: 15-16 years | NR | Online | Electronic Non-invasive Delivery Systems (ENDS) | Ever ENDS use at baseline and current tobacco use at follow-up | Gender, SES, other tobacco product and drug use, School clustering was accounted for. |
| Kong 2019 California and Connecticut United States [41] | Southern California Children’s Health Study (CCHS), Happiness and Health (HAMH) Study, Yale Adolescent Survey Study (YASS) | Longitudinal prospective cohort study, 2 time points, follow-up: 12-18 months | n analysed: 487 Retention rate NR | Male: 48.7%, Female: 55.3%, Mean age: 15 years (SD 1.0), Ethnicity: Non-Hispanic White: 1897 (38.6), Hispanic: 1704 (34.6), Other: 1185 (23.4), Non-Hispanic Black: 124 (2.3), Asian: 364 (6.1), Other including Bir- and Multi-Racial: 47 (9% | Sampling strategies CCHS: a cohort that has been followed yearly since enrollment in 2003-2005, when participants were in kindergarten or first grade, from entire classrooms in school districts in communities throughout California. HAMH: Approximately 40 public high schools in the Los Angeles metropolitan area were approached about participating in this study. These schools were chosen because of their diverse demographic characteristics and proximity. Ten schools agreed to participate in the study and the schools from different DRG’s in Connecticut were invited to participate of these, four agreed to participate. | Pen and paper | e-cigarette | Ever use of nicotine at baseline and ever use of tobacco use at follow-up | Baseline measures of ever cigarettes, ever e-cigarette use, gender, gender, race, ethnicity (White, Hispanic, Other), and site (CCHS, HAMH, YASS). |
| Leventhal 2015 Los Angeles California United States [42] | NR | Longitudinal cohort study, 3 time points, follow-up: 6 months | n analysed: 2,535, retention rate: 79.0% at 6 months, 96.6% at 12 months | Male: 46.8%, Female: 53.2%, Age: 9th grade, ethnicity: American Indian: n = 21 (0.4), Asian: n = 472 (18.9), Black: n = 119 (4.6), Native Hawaiian: n = 99 (3.9), White: n = 4,016 (16.2), Other: n = 142 (5.7), Multiethnic: n = 144 (5.7) | Ten public high schools in Los Angeles were recruited through convenience sampling | Pen and paper | e-cigarette | Ever use of e-cigarette at baseline and e-cigarette use at follow-up and other tobacco products at follow-up (hookah, cigars, any combustible product) | Age, sex, ethnicity, lives with biological parents, substance use, family history of smoking, parental education, peer smoking, depressive symptoms, impulsivity, delinquency, smoking susceptibility and expectancies. | (Continued) |
| Author name, year of publication, geographic region | Survey name | Study design, number of time points, length of follow up | n analysed, % retention rate | Sample characteristics (at baseline) | Sampling procedure | Data collection modality | Type of ENDS used (specify duration, non-smoker) | Main outcomes assessed (e.g. association between ever and current ENDS/ENNDS use) | Adjustments accounted for in analysis |
|--------------------------------------------------|-------------|-----------------------------------------------------------|-------------------------------|-------------------------------------|-------------------|------------------------|---------------------------------------------|--------------------------------------------------------------------------------|-----------------------------------|
| Isumaru 2020                                     | Texas United States [63] | Longitudinal design, 2 time points, follow-up every four months for three waves (around 3–5 years) | n analysed: 2,307, retention rates = 91% at wave 1 and 88% at wave 2 | Male: 52.6%, Female: 47.4%, age: 18–25 (mean age: 19), ethnicity: non-Hispanic white = 73%, Hispanic/Latino = 20.8%, Asian = 2.4%, Native American/Black = 3.2% | Online | e-cigarette, vapes, nicotine, or ever used hookah | Retention rates: 90% at baseline and ever use of ENDS/ENNDS | Age, sex, race, socioeconomic status, parental smoking status, perceived risk of smoking, peer use, interventions among non-users, school type, cohort size, and time of study. | Adjustments for age, sex, race, and baseline ENDS/ENNDS use. |
| Isumaru 2017                                     | Mexico City, Guadalajara, and Monterrey Mexico [64] | Longitudinal cohort study, 2 time points, follow-up: 20 months | n analysed: 626, retention rate: 70% | Male: 45.9%, Female: 48.7%, age: 18–25 (mean age: 20), ethnicity: non-Hispanic white = 55% | Online | e-cigarette, or ever used hookah | Retention rates: 69% at baseline and ever use of ENDS/ENNDS | Age, sex, race, parental education, and baseline ENDS/ENNDS use. | Adjustments accounted for in analysis. |
| March 2017                                       | United States [65] | Monitoring the Future study Longitudinal prospective cohort study, 2 time points, follow-up: 13.4 months | n analysed: 1,064, retention rate: 96% | Male: 52.6%, Female: 48.7%, age: 18–25 (mean age: 20), ethnicity: non-Hispanic white = 54% | Online | e-cigarette, or ever used hookah | Retention rates: 89% at baseline and ever use of ENDS/ENNDS | Age, sex, race, parental education, and baseline ENDS/ENNDS use. | Adjustments accounted for in analysis. |
| Munich 2018                                     | Bavarian Saxony and Schleswig-Holstein Germany [66] | Longitudinal cohort study, 2 time points, follow-up: 4 months | n analysed: 625, retention rate: 89% | Male: 52.6%, Female: 47.4%, age: 18–25 (mean age: 19), ethnicity: non-Hispanic white = 73%, Hispanic/Latino = 20.8%, Asian = 2.4%, Native American/Black = 3.2% | Online | e-cigarette, or ever used hookah | Retention rates: 86% at baseline and ever use of ENDS/ENNDS | Age, sex, parental education, and baseline ENDS/ENNDS use. | Adjustments accounted for in analysis. |
| O’Regan 2020                                     | United States [67] | Population Assessment of Tobacco and Health Study (PATH) Prospective cohort study, 2 time points, follow-up: 24 months | n analysed: 625, retention rate: 89% | Male: 52.6%, Female: 47.4%, age: 18–25 (mean age: 19), ethnicity: non-Hispanic white = 73%, Hispanic/Latino = 20.8%, Asian = 2.4%, Native American/Black = 3.2% | Online | e-cigarette, or ever used hookah | Retention rates: 86% at baseline and ever use of ENDS/ENNDS | Age, sex, parental education, and baseline ENDS/ENNDS use. | Adjustments accounted for in analysis. |
| Furuoka 2018                                     | United States [68] | Longitudinal cohort study, 2 time points, follow-up: 48 months | n analysed: 625, retention rate: 89% | Male: 52.6%, Female: 47.4%, age: 18–25 (mean age: 19), ethnicity: non-Hispanic white = 73%, Hispanic/Latino = 20.8%, Asian = 2.4%, Native American/Black = 3.2% | Online | e-cigarette, or ever used hookah | Retention rates: 86% at baseline and ever use of ENDS/ENNDS | Age, sex, parental education, and baseline ENDS/ENNDS use. | Adjustments accounted for in analysis. |
| Primack 2015                                     | United States [69] | National Youth Tobacco Survey (NYTS) | n analysed: 625, retention rate: 89% | Male: 52.6%, Female: 47.4%, age: 18–25 (mean age: 19), ethnicity: non-Hispanic white = 73%, Hispanic/Latino = 20.8%, Asian = 2.4%, Native American/Black = 3.2% | Online | e-cigarette, or ever used hookah | Retention rates: 86% at baseline and ever use of ENDS/ENNDS | Age, sex, parental education, and baseline ENDS/ENNDS use. | Adjustments accounted for in analysis. |
| Spinelle 2017                                    | United States [70] | Monitoring the Future study Longitudinal prospective cohort study, 2 time points, follow-up: 13.4 months | n analysed: 625, retention rate: 89% | Male: 52.6%, Female: 47.4%, age: 18–25 (mean age: 19), ethnicity: non-Hispanic white = 73%, Hispanic/Latino = 20.8%, Asian = 2.4%, Native American/Black = 3.2% | Online | e-cigarette, or ever used hookah | Retention rates: 86% at baseline and ever use of ENDS/ENNDS | Age, sex, parental education, and baseline ENDS/ENNDS use. | Adjustments accounted for in analysis. |
| Treue 2018                                       | Netherlands [71] | Longitudinal cohort study, 3 time points, follow-up: 12 months | n analysed: 625, retention rate: 89% | Male: 52.6%, Female: 47.4%, age: 18–25 (mean age: 19), ethnicity: non-Hispanic white = 73%, Hispanic/Latino = 20.8%, Asian = 2.4%, Native American/Black = 3.2% | Online | e-cigarette, or ever used hookah | Retention rates: 86% at baseline and ever use of ENDS/ENNDS | Age, sex, parental education, and baseline ENDS/ENNDS use. | Adjustments accounted for in analysis. |
| Author name, year of publication | Survey name | Study design, number of time points, length of follow up | Sample characteristics (at baseline) | Sampling procedure | Data collection modality | Type of ENDS assessed (specify nicotine/non-nicotine) | Main outcomes assessed (e.g. association between ever and current ENDS/ENNDS use) | Adjustments accounted for in analysis |
|--------------------------------|-------------|------------------------------------------------------|------------------------------------|-------------------|------------------------|---------------------------------|-------------------------------------------------|-----------------------------------------------|
| Watkins 2018 United States [52] | Population Assessment of Tobacco and Health Study (PATH) | Longitudinal prospective cohort study, 2-time points, follow-up: 1 year | Follow-up n = 10,304, retention rate: 87.9% Male: 50.9%, Female: 49.1%, mean age: 14.3 (71 years, range 12-17 years, 52.5% white, 13.9% African American, 22.3% Latinx, 11.3% other | A 4-stage, stratified probability sample design. Adults (age ≥18 years, up to 2 per household) were oversampled for tobacco users, African American individuals, and young adults (age 18–24 years). The PATH youth sample consists of individuals whose parents were sampled for the PATH adult survey. Up to 2 youths were selected per household; sample and replicate weights were generated so that the sampled population reflected the non-institutionalized youth population at baseline. | In-person computer-assisted interviews at home. | e-cigarette | Ever use of e-cigarettes at baseline and ever use of tobacco at follow-up, Current ENDS/ENNDS use at baseline and ever tobacco use at follow-up, Current ENDS/ENNDS use at baseline and current tobacco use at follow-up | Model includes all ever tobacco use categories and the following wave 1 covariates: female, age, race/ethnicity, parental educational level, sensation seeking, alcohol ever use, living with tobacco user, notice of cigarette warning labels, tobacco advertising receptivity, and summer season |
| Wills 2017 Oahu Hawaii United States[53] | NR | Longitudinal prospective cohort study, 2-time points, follow-up: 12 months | Analyzed: 1136, retention rate: 70% and 67% at follow up | Male/Female: NR, Age Grades 9-10 at baseline; ethnicity: NR | Pen and paper | e-cigarette | Use of e-cigarette at baseline and current use of follow up | NR |

NR, not reported
Only two studies [40, 51] assessed the association between ENDS use at baseline and subsequent cigarette use (current or ever) at follow-up. The pooled adjusted RR of 2.56 (95% CI: 0.47, 13.94, $I^2 = 77.5\%$, $p = 0.277$) (see Fig 7). No study reported on association between ENDS use with subsequent use of other tobacco products.

The unadjusted estimates are available as supplementary materials (S2 and S3 Tables, S1–S3 Figs).

One study [54] reported no difference in uptake of ENDS/ENNDS use at follow up between flavoured vs unflavoured e-cigarette use at baseline (RR: 0.24 (95% CI 0.05, 1.0) when controlling for sex, age, state, school type, migration background, parent’s qualifications, socio-economic status (SES), multiple personality traits, and consumption of five substances.

The adjusted RRs were similar by geographic location, year of publication, and length of follow up (see S4A–S4C Fig). There were some differences in effect sizes by study quality, with higher quality studies reporting lower adjusted RRs (risk of bias ≥7 (higher quality): 2.16 (95% CI: 1.47, 3.16, $p<0.001$; $I^2 = 85.0\%$, $p < 0.001$) compared to lower quality studies (risk of bias scores <7: 3.57 (95% CI: 2.69, 4.73, $p<0.001$; $I^2 = 76.9\%$, $p < 0.001$)) see S4D Fig. Studies that scored $> = 3$ on the Bradford-Hill criteria for causal inference had higher adjusted RRs of 4.47 (95% CI: 3.28, 6.09, $p<0.001$; $I^2 = 65.0\%$, $p = 0.006$) relative to studies that scored <3: 2.21 (95% CI: 1.80, 2.70, $p<0.001$; $I^2 = 64.1\%$, $p = 0.004$) (see S4E Fig).

The adjusted RRs for baseline ever ENDS/ENNDS use and current cigarette use at follow-up were similar by geographic location, year of publication, length of follow up, study quality, and score for Bradford-Hill causal inference (S5A–S5E Fig).

We did not undertake subgroup analysis examining other associations due to the small number of studies included in the main meta-analyses (four or less).

For ever ENDS/ENNDS use at baseline and ever cigarette use at follow-up the adjusted results, three studies were estimated as missing due to funnel plot asymmetry. Results from the trim-and-fill analysis found that the bias-adjusted pooled RR was 2.75 (95% CI: 2.16, 3.49), which was only slightly lower than the adjusted pooled RR from the primary analysis (see Fig 8).

For ever ENDS/ENNDS use at baseline and current cigarette use at follow-up, the adjusted results two studies were estimated as being missing due to funnel plot asymmetry. Results from the trim-and-filled analysis found that the bias-adjusted pooled RR was 2.21 (95% CI: 1.55, 3.17), which was slightly lower than the original estimate (see Fig 9).

**Discussion**

This review supports evidence of a longitudinal association between ENDS/ENNDS use at baseline and subsequent tobacco use in those aged <20 years. Studies included in the meta-
analysis found a significant positive adjusted association between ever ENDS/ENNDS and current cigarette use (2.56 (95% CI: 1.61, 4.07) at follow-up among children and adolescents aged <20 years. A positive association was also found between current e-cigarette use and current cigarette use at follow-up (RR: 1.88 (95% CI: 0.34, 10.30)), and ENNDS use at baseline and later cigarette use (RR: 2.56 (95% CI: 0.47, 13.94)). Despite the relatively large effect size, evidence of these associations was not statistically significant potentially due to the small number of studies included, and thus require further exploration in prospective studies.

Our findings are similar, albeit slightly weaker, to those reported by Khouja et al. [12] where a significant association between e-cigarette use among non-smokers and later tobacco smoking was found. The similarity may, in part, be due to the inclusion of many of the same studies. However, our review included more recently published studies, included a broader...
representation of study locations outside of the US (13/25 studies), focused entirely on children and adolescents (whereas the review by Khouja et al. included those up until the age of 30) [12], and excluded case-control studies that are at risk of increased bias. Consequently, this study has improved both the robustness, precision of aggregate analysis and international applicability of findings from prior reviews.

In our exploratory subgroup analysis, we found that higher quality studies had small estimates than lower quality studies. The impact of different methodological biases have been explored in a recent review examining the association between e-cigarette use and initiation of conventional cigarette use. [15] This review described potential bias relating to attrition, where studies that reported on findings from complete case analyses found larger effect sizes than when imputed data was included. Additionally, studies that adjusted for a more comprehensive list of known confounders also reported smaller estimates, compared to those that adjusted for fewer confounders. [15, 56] Future studies need to better consider and address such methodological differences to provide better estimates of the association between e-cigarette use and conventional cigarette uptake. All but one of the studies included in this review reported a positive association (RR>1) between ENDS/ENNDS use and future cigarette use among children and adolescents. The only industry-funded study that met the eligibility

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**Table:**

| Author (Year) | Country       | ES (95% CI)       | Weight |
|---------------|--------------|-------------------|--------|
| Barrington-Trimis 2018 United States | 3.53 (1.98, 6.30) | 17.81 |
| Berry 2019 United States | 2.87 (1.65, 5.00) | 18.19 |
| Kinnunen 2019 Finland | 2.94 (1.09, 7.90) | 11.62 |
| Lozano 2017 Mexico | 1.40 (1.22, 1.60) | 24.07 |
| Morgenstern 2018 Germany | 2.88 (1.54, 5.39) | 16.99 |
| Spindle 2017 United States | 3.33 (1.21, 9.20) | 11.32 |
| **Overall (I-squared = 77.3%, p = 0.001)** | **2.56 (1.61, 4.07)** | **100.00** |

**NOTE:** Weights are from random effects analysis
criteria for this review was excluded from the meta-analysis due to overlap of data with other studies. The authors of this study undertook various sensitivity analysis adjusting for multiple confounders. [56, 57] Whilst the authors concluded that adjustment for various confounders including propensity to smoke reduced the strength of the association, all adjusted odds ratios were larger than one, consistent with findings from non-industry sponsored studies.

Our review found evidence of a consistent positive association between ENDS/ENNDS use and cigarette smoking across a large number of studies internationally. This provides strong evidence to support the causal relationship between ever ENDS/ENNDS and ever smoking for this age group. These findings are of concern as other cross-sectional studies have reported that children and adolescents who use ENDS and/or ENNDS have different psychological profiles to current smokers, and would have otherwise have been at low risk of smoking. [58–61] As such, there is an urgent need for governments internationally to take action to regulate the availability and marketing of ENDS/ENNDS products to children and adolescents.

Further, the US Surgeon General’s Report concluded that ENDS/ENNDS were unsafe for use among children and adolescents due to a range of health-related adverse effects. [62] The use of ENDS/ENNDS may also contribute to increased burden of tobacco-related harms on individuals and communities. [63] In part due to such an association, modelling weighing the
potential health benefits (e.g. cessation among established smokers) and harms associated with e-cigarettes found, overall, that ENDS/ENNDS use would yield a net harm and lead to 1,510,000 years life lost in the US. [63] This modelling is based on results from a single clinical trial of ENDS/ENNDS provided as part of medically-supervised cessation benefits. Such findings are consistent with later reviews of randomised trials assessing the use of ENDS/ENNDS, [64, 65] however presents an overestimation of benefit when used as consumer products in the general population. As presented in a synthesis of observational studies, there are no apparent population-level increase in cessation when using e-cigarettes as a consumer product [65].

Given such considerations, a report by WHO provides a range of policy options including a ban on their sale; product taxation; and preventing the use of ENDS/ENNDS indoors and in areas to prevent use in in children and adolescents but also uptake in adults more broadly [66, 67]. These are supported by recommendations and policy statements nationally and internationally. [67, 68] Given the susceptibility of children and adolescents to marketing and the appeal of flavouring, governments should restrict all forms of promotion and marketing to children and adolescents and ban all characterising flavours. [68, 69] A number of recently published studies have also reported promising findings regarding the impact of local retail regulations, [70] and the prohibition of the sale of flavoured products on ENDS/ENNDS use in youth, [71] however, rigorous evaluation of the impacts of comprehensive policy approaches is warranted. Early findings from two studies suggest mixed findings between

![Forest plot of adjusted risk ratios assessing the association between current e-cigarette use at baseline and subsequent current cigarette use at follow-up.](https://doi.org/10.1371/journal.pone.0256044.g006)
| Author      | Country     | ES (95% CI)     | Weight |
|-------------|-------------|-----------------|--------|
| Kinnunen 2019 | Finland    | 0.94 (0.21, 4.12) | 42.64 |
| Treur 2018  | Netherlands | 5.40 (2.75, 10.60) | 57.36 |
| Overall (I-squared = 77.5%, p = 0.035) |            | 2.56 (0.47, 13.94) | 100.00 |

NOTE: Weights are from random effects analysis

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**Fig 7.** Forest plot of adjusted risk ratios assessing the association between ever ENNDS use at baseline and subsequent current or ever cigarette use at follow-up.

https://doi.org/10.1371/journal.pone.0256044.g007

**Fig 8.** Funnel plot illustrating results from trim-and-fill analysis of adjusted log RRs for outcome ever e-cigarette use at baseline and ever cigarette use at follow-up.

https://doi.org/10.1371/journal.pone.0256044.g008
ENNDS and cigarette smoking. Whilst, still inconclusive, precautionary principles should be in place when considering the regulation for all forms of e-cigarettes, including those that do and do not contain nicotine.

There were few studies that measured association between current ENDS/ENNDS and current cigarette use. Further studies are needed to establish whether current ENDS/ENNDS result in current cigarette given this. Similarly, there were few studies assessing the impact of non-nicotine and flavoured tobacco products, and as such any conclusions need to be interpreted in light of this. Most studies were conducted in high-income countries. Consequently, the study results may be limited in their generalisability. The data from included studies may also be subject to social desirability and other reporting biases due to the self-report nature of the data collection methods. There was high heterogeneity in the meta-analysis, unexplained by the subgroup analysis, indicating that the reasons for the variation remains unknown. The trim and fill funnel plots suggest there may be some publication bias, but the bias-adjusted estimates were similar to those calculated from the main analysis. Finally, despite efforts to select outcomes that controlled for pre-specified confounders, restricting outcomes that controlled for these confounders only was not always possible. Consequently, there were differences between studies in terms of the characteristics that were controlled for, which may contribute to the high level of heterogeneity.

Nonetheless, the findings provide consistent evidence from observational studies of an association between ENDS/ENNDS use among non-smoking children and adolescents, and subsequent tobacco use, in particular cigarettes. Government regulation and implementation to prevent use of ENDS/ENNDS among youth however varies considerably globally. [69, 72] The experience of global efforts to combat the use of conventional cigarettes and other tobacco products suggests that such efforts are inadequate to sufficiently avert the projected harms, if the current trajectory continues. There is a need for countries internationally to prioritise the adoption and implementation of comprehensive measures as outlined in the WHO Framework Convention on Tobacco Control to prevent uptake of ENDS/ENNDS and regulates availability in children and adolescents, up to imposing a ban, to prevent uptake of ENDS/ENNDS for this group.
Supporting information

S1 Checklist.
(DOC)

S1 Fig. Forest plot of unadjusted risk ratios assessing the association between ever e-cigarette use at baseline and ever cigarette use at follow-up.
(DOCX)

S2 Fig. Forest plot of unadjusted risk ratios assessing the association between ever e-cigarette use at baseline and current cigarette use at follow-up.
(DOCX)

S3 Fig. Forest plot of unadjusted risk ratios assessing the association between current e-cigarette use at baseline and ever cigarette use at follow-up.
(DOCX)

S4 Fig. (A) Forest plot of adjusted risk ratios assessing the association between ever e-cigarette use at baseline and ever tobacco use at follow-up by country. (B) Forest plot of adjusted risk ratios assessing the association between ever e-cigarette use at baseline and ever tobacco use at follow-up by year of publication. (C) Forest plot of adjusted risk ratios assessing the association between ever e-cigarette use at baseline and ever cigarette use at follow-up by length of follow-up. (D) Forest plot of adjusted risk ratios assessing the association between ever e-cigarette use at baseline and ever cigarette use at follow-up by overall risk of bias score. (E) Forest plot of adjusted risk ratios assessing the association between ever e-cigarette use at baseline and ever cigarette use at follow-up by Bradford Hill’s criteria for causal inference.
(DOCX)

S5 Fig. (A) Forest plot of adjusted risk ratios assessing the association between ever e-cigarette use at baseline and current tobacco use at follow-up by country. (B) Forest plot of adjusted risk ratios assessing the association between ever e-cigarette use at baseline and current tobacco use at follow-up by year of publication. (C) Forest plot of adjusted risk ratios assessing the association between ever e-cigarette use at baseline and current tobacco use at follow-up by length of follow-up. (D) Forest plot of adjusted risk ratios assessing the association between ever e-cigarette use at baseline and current tobacco use at follow-up by overall risk of bias score. (E) Forest plot of adjusted risk ratios assessing the association between ever e-cigarette use at baseline and current tobacco use at follow-up by risk of bias score for causal inference.
(DOCX)

S1 Table. Additional Bradford-Hill causal inference criteria.
(DOCX)

S2 Table. Unadjusted and adjusted risk ratios for association between ENDS/ENNDS and cigarette use.
(DOCX)

S3 Table. Unadjusted and adjusted risk ratios for association between ENDS/ENNDS and other tobacco products.
(DOCX)

S1 Appendix. Search strategy.
(DOCX)

S1 Data.
(XLS)
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