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The Age of E-cigarette Initiation and Association With Frequency of Use and Risk of Combustible Tobacco Cigarette Smoking Initiation

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THE AGE OF E-CIGARETTE INITIATION AND ASSOCIATION WITH FREQUENCY OF USE AND RISK OF COMBUSTIBLE TOBACCO CIGARETTE SMOKING INITIATION

By

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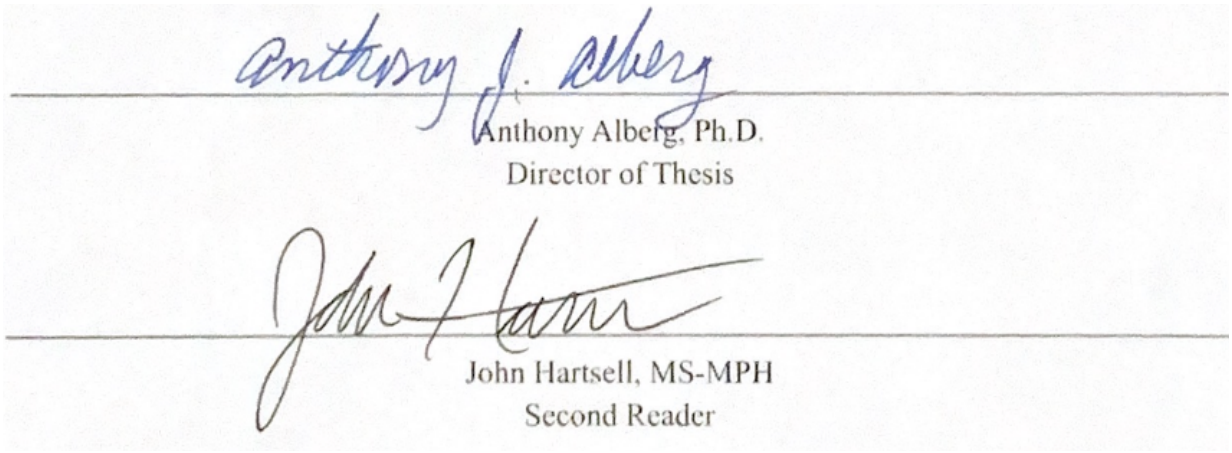

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Abstract

Background **-** Studies have shown that electronic nicotine delivery systems (ENDS) are unsafe for consumption. However, the prevalence of e-cigarette use among adolescents and young adults continues to increase, which is being addressed by research. Little attention has been paid to the effects of earlier age of ENDS initiation.

Purpose - This paper examined published research studies on the topic of the age of initiation of e-cigarette use in relation to 1) frequency of e-cigarette use and 2) risk of combustible tobacco cigarette smoking initiation. This research tested the hypothesis that an earlier age of e-cigarette initiation was associated with increased frequency of use and increased risk for combustible tobacco cigarette smoking.

Methods - A systematic review was performed by ascertaining, analyzing and interpreting published peer-reviewed articles obtained from PubMed's MEDLINE database. Peer-reviewed articles containing keywords related to the research question were filtered based on inclusion criteria and data were organized in evidence tables to synthesize the evidence on this topic.

Results - Three cross-sectional studies and two longitudinal studies were included in the review. Two of the studies showed that earlier age of initiation of e-cigarettes was associated with greater frequency of use, but one study found no association. Three studies found that earlier age of initiation was associated with increased risk of cigarette smoking.

Conclusion - Findings tended to support the hypothesis that a younger age of initiation would lead to more frequent e-cigarette use and risk of cigarette smoking initiation. Due to a limited number of eligible articles, further research regarding the age of e-cigarette initiation would be helpful to better draw conclusions with longitudinal data. The implications of these findings are

that future public health and government interventions can focus their efforts on decreasing exposure of young people to e-cigarette products to prevent further increases in prevalence and intensity. The importance in this research is that delaying the age of initiation can have public health benefits, even without changes in prevalence.

1. Introduction

Electronic nicotine delivery systems (ENDS) were introduced in the U.S. in 2007 [1], and the prevalence of vaping among youth has markedly increased since then, which has led to the current e-cigarette epidemic. Since the introduction of e-cigarettes to the U.S. market, marketing efforts by the vaping industry and Big Tobacco companies have not been regulated heavily. Tactics such as candy-flavored products, youth-oriented themes, and celebrity endorsement of these products have found their way into mainstream media avenues, contributing to the e-cigarette epidemic [2]. The prevalence of past 30-day use of e-cigarettes increased from 1.5% in 2011 to 11.3% in 2015, to 19.6% in 2020 among U.S. high school students and increased from 0.6% in 2011 to 4.7% in 2020 for middle school students, indicating the growing usage of e-cigarettes among adolescents [3]. Of current users of e-cigarettes, 38.9% of high school users and 20.0% of middle school users reported usage between 20 to 30 days within the past 30 days [3,4,5]. The emergence of e-cigarettes has been a challenge for tobacco control measures, despite a noticeable decrease in cigarette consumption, from 22.4% of high school seniors smoking daily two decades ago to 3.6% daily smokers in 2018 [4].

Some e-cigarette use among adolescents and young adults is limited to those who have already experimented with tobacco and is mostly experimental in nature [5]. However, there is still a concern that e-cigarette usage could lead to tobacco smoking for adolescents who have never smoked, as studies have shown that e-cigarette use presents a risk factor for cigarette smoking initiation [7,8,9]. For example, in a longitudinal survey of youth conducted in Great Britain in 2016, respondents who were ever e-cigarette users vs. never users, (53% vs. 8%, odds ratio [OR] = 11.89, 95% confidence interval [CI] = 3.56–39.72) were more likely to initiate smoking [6]. The hypotheses addressed in this study were that an earlier age of initiation of

ENDS use is associated with increased frequency of use and increased risk of progressing to cigarette smoking. Thus, the focus of the current study is to measure how the age of e-cigarette initiation is associated with the frequency of e-cigarette usage and risk of smoking combustible tobacco cigarettes (Figure 1). The age of initiation and its association with frequency of e-cigarette use has not been researched intensively but is important to advancing understanding the scope of the problem posed by e-cigarette use. In this study, frequency of e-cigarette use was assessed by self-reported use in the past 30 days.

The aim of this systematic review was to determine if e-cigarette use by adolescents was associated with more frequent usage and subsequent initiation of cigarette smoking. Although many experts view e-cigarettes as a harm reduction tool for tobacco smokers, e-cigarette use has been linked with youth progression toward combustible tobacco cigarette smoking [8]. Additionally, the Surgeon General has concluded that exposure to nicotine during adolescence can cause addiction and harm the developing adolescent brain [10]. Previous systematic reviews have investigated whether e-cigarette use leads to tobacco cigarette use [9,10]. However, the existing evidence on the age of e-cigarette initiation has not been carefully summarized before, even though it is an important factor that could contribute to more frequent e-cigarette use and risk of combustible tobacco cigarette smoking, henceforth referred to as ("cigarette smoking").

2. Methods

This review aimed to investigate whether e-cigarette use is associated with frequency of use and cigarette smoking initiation in adolescents and young adults. This search is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses

(PRISMA). The search was guided by determining keywords based on the research questions of the project (vaping, e-cigarettes, initiation, age, early, onset, frequency).

2.1. Study strategy

This review followed the principles of a systematic review. To begin the search, research questions were determined. The first study question was how does the age of e-cigarette initiation affect frequency of e-cigarette use among adolescents and young adults? The second question was how does the age of e-cigarette initiation affect the risk of combustible tobacco cigarette smoking initiation and usage? Keywords could then be identified for the association between the age of e-cigarette initiation and the two study outcomes of 1) frequency of use and 2) risk of combustible tobacco cigarette smoking initiation.

These questions led to search terms that guided the review on MEDLINE's PubMed. Articles were found by using the following search terms: (((age) AND ((initiation) OR (onset) OR (begin) OR (start)) AND ((e-cigarette) OR (vaping)) AND ((cigarette smoking) OR (vaping intensity))). No date restrictions were placed on the search strategy. While reviewing the initial pool of 245 articles, a review of 10 articles were added from previous systematic reviews [9,11,13,22,23,24] that related cigarette smoking and age of e-cigarette initiation as one of its outcomes. Four of these articles were duplicates so only six of them were added to the original search to create a final total of 251 articles (Figure 2).

2.2. Study selection

In this search, no restrictions were made for study design, but only cross-sectional and longitudinal studies were found. After the studies were compiled, they were put through a

screening process based on inclusion criteria. In the first round of screening, the titles and abstracts were manually screened based on presence of age of initiation, outcomes of interest, full-text availability, language, and relevance to the research questions, which led to 173 articles being excluded, leaving 48 full-text articles to be assessed. Next, 43 articles were excluded after screening the full-texts for age of e-cigarette initiation in association with either of the study outcomes, leaving five articles to be extracted and analyzed in the full-text review.

2.3. Quality assessment and data extraction

Using the National Heart, Lung, and Blood Institute's (NHLBI's) quality assessment tool for observational studies, all five studies were considered to be high-quality [12]. The study questions and responses used can be found in Table 2. After obtaining eligible articles, data extracted from each study included the following: study outcomes, location, study design, sample size, age range, mean age, and population characteristics. A table was created to summarize the study characteristics, such as the design and age of initiation measurements. Additionally, evidence tables were developed by adapting data extraction tables from other reviews [13,14]. Data were extracted and included in Tables 3 and 4 to describe the exposure to e-cigarettes, outcome of e-cigarette use, measures of association between age of e-cigarette initiation and either frequency of use or cigarette smoking initiation, confidence intervals, and any covariates included in the study.

3. Results

Of the five studies identified, two studies only examined frequency of e-cigarette use [15,16], another two only examined risk of cigarette smoking initiation [18,19], and the final

study examined both outcomes [17]. As shown in Table 2, most studies focused on adolescents and young adults from 13-19 years of age [16,17,18] and all studies had participants within the 11-19 year range. Two studies were longitudinal [15,17] while three studies were cross-sectional [16,18,19]. Finally, only one of the studies was performed outside of the US [17]. Two of the studies used grade level of initiation to report their findings [15,18].

3.1. Frequency of e-cigarette use

Three of the identified studies examined the age of initiation of e-cigarette use in relation to the outcome of frequency of e-cigarette use [15,16,17]. Based on previous studies, the frequency of e-cigarette use has been shown to be strongly related to nicotine dependence and health outcomes, which makes it an important factor to study [20]. E-cigarette use frequency is most commonly assessed by examining the number of days that the participant used an ENDS product in the past 30 days. Three studies examined frequency of e-cigarette usage associated with age of initiation.

In *Harrell, et al*., it was found that among past 30-day users of e-cigarettes, an increase in usage was associated with younger age of initiation ($p < 0.01$). The study compared average e-cigarette use frequency ($\bar{x}$) between early initiators (13-14 years old), mid initiators (14-15 years old), and late initiators (15-16 years old). In the 6th grade cohort, the past 30-day e-cigarette use was higher for those that initiated early ($\bar{x}$ > 15 days/month) compared to those that initiated later ($\bar{x}$ < 10 days/month) by 16 years of age. In the 8th grade cohort, by 18 years of age, the past 30-day e-cigarette use for early initiators ($\bar{x}$ ~ 15 days/month) was lower than mid initiators ($\bar{x}$ > 20 days/month), but both were higher than late initiators ($\bar{x}$ ~ 5 days/month). In 10th grade, by 19 years of age, the past 30-day e-cigarette use was highest for early initiators ($\bar{x}$

~ 22 days/month), followed by mid initiators ($\bar{x}$ ~ 15 days/month), and late initiators ($\bar{x}$ ~ 10 days/month) [15]. There was an overall trend in the data, with the exception of the 8th grade cohort, that an earlier age of initiation and subsequent escalation in use was associated with higher frequency of use at follow-up. However, the 8th grade data still showed that the latest age of initiation group had the lowest frequency of use. U.S. national cross-sectional data indicate that an earlier age of first time using an e-cigarette or using them daily were both strongly associated with a greater likelihood of heavily using them later on [10].

In *Bold, et al.,* the authors examined the association between impulsivity and e-cigarette frequency with the age of initiation of e-cigarette use as a potential mediator on this pathway [16]. The authors found that an earlier age of e-cigarette initiation predicted more frequent use of e-cigarette use in the past month while controlling for impulsivity. It is important to note that mediation is present in the authors' analysis; they compare their unadjusted models and their adjusted models to examine how age of e-cigarette initiation is a mediator between impulsivity and frequency of use, but also examine the direct association between age of initiation and frequency of use. From this study, Figure 3 was used to show a nonlinear, negative relationship between frequency of e-cigarette use and age of initiation. Additionally, the data in Table 3 show that there was a significant association between an earlier age of initiation of e-cigarette use and more frequent use of e-cigarettes in the past month in both the unadjusted (B = -0.18, SE = 0.04, $p < 0.001$) and adjusted regression model output (B = -0.28, SE = 0.08, $p < 0.001$).

Finally, *Conner, et al.* used a hierarchical linear model (HLM) to examine the association between age of e-cigarette initiation and likelihood of regular e-cigarette use [17]. The authors expanded the HLM to explain the data between and within subject variability. In this study, regular e-cigarette use was defined as using more than once a week, based on self-reported data

and confirmed by breath carbon monoxide levels (CO). The odds ratio (OR) was reported at 12-month and 24-month follow up periods, showing differences in regular e-cigarette use between early and late users (Reference group: Early users, OR = 0.76, *95% CI* = 0.45, 1.28, p = 0.292), which shows that the odds of using e-cigarettes regularly were higher for those that initiated e-cigarette use earlier on (Table 3). However, this data became insignificant when reporting the adjusted odds ratio (AOR), which meant controlling for covariates (AOR = 0.96, *95% CI* = 0.84, 1.11, p = 0.602). As a result, this study did not find a strong association between age of e-cigarette initiation and frequency of use.

3.2. Risk of combustible tobacco cigarette smoking initiation

The studies of age of initiation of e-cigarette use in relation to risk of combustible tobacco cigarette smoking showed that the age of initiation had a significant association with initiation of cigarette smoking [17,18,19]. Smoking initiation does not necessarily lead to regular cigarette smoking use, but can be seen as a starting point with the potential of progressing to regular use of cigarettes. Three studies examined cigarette smoking behavior in e-cigarette users based on age of e-cigarette initiation.

Conner, et al. compared ever users and regular users of cigarettes based on age of e-cigarette initiation. Regular cigarette use was defined as smoking at least one cigarette a week, based on self-report and validated by breath CO levels. Ever-cigarette use was defined as having smoked before, used to smoke but quit, or smokes less than one cigarette a week. The authors found that ever-cigarette use was significantly lower in late users compared to early users before (OR = 0.48, *95% CI* = 0.35, 0.66, $p < 0.001$) and after adjusting for covariates (AOR = 0.61, *95% CI* = 0.46, 0.81, $p < 0.001$). However, the association between age of e-cigarette initiation

and regular cigarette use was only strong before adjustment (OR = 0.69, *95% CI* = 0.35, 1.37, *p* = 0.282), but after adjusting for covariates (AOR = 0.94, *95% CI* = 0.83, 1.07, *p* = 0.347), found that the association was very weak. Based on these data, adolescents in England who reported initiating e-cigarettes at earlier ages have higher rates of initiating cigarette use, but not regular use, than adolescents who reported initiating e-cigarettes later on [17].

The associated probability between age of initiation of e-cigarette use and cigarette smoking behaviors were also analyzed by *McCabe, et al.,* who used multivariate logistic regression models [18]. The adjusted odds ratios found for lifetime cigarette smoking indicated higher probabilities of cigarette smoking at an earlier age of e-cigarette initiation (Reference group: Grade 12, Grade 11: AOR = 1.38, *95% CI* = 0.71, 2.68, Grade 10: AOR = 1.89, *95% CI* = 0.81, 4.09, Grade 9 or earlier: AOR = 2.83, *95% CI* = 1.06, 7.51, $p < 0.05$). The data show a trend in the AOR as an earlier age of e-cigarette initiation confers greater odds of cigarette smoking. The results were significant for those who initiated e-cigarettes at Grade 9 or earlier, with 2.83 times the likelihood to initiate cigarette smoking than those in Grade 12. Some of the age of initiation data is summarized in Figure 5. This graph shows the trend of decreasing likelihood of cigarette use as the age of e-cigarette initiation increases. Overall, this study shows that an earlier age of e-cigarette initiation is associated with a greater likelihood of ever using cigarettes.

In *Lanza, et al*., the authors sought to examine the age trends stemming from e-cigarette use and cigarette use, and any association between these behaviors among U.S. adolescents. The findings of this study suggest that age of e-cigarette initiation and likelihood of cigarette smoking are associated among youths, and that e-cigarette use is more strongly linked with cigarette smoking during adolescence [19]. Odds ratios of cigarette smoking initiation are graphically

shown to be associated with age of e-cigarette initiation in Figure 4. By interpreting this figure, it is shown that the odds of initiating smoking are 40 times as likely for those who initiate e-cigarette use at age 11 than their peers who never used e-cigarettes. On the other hand, those who initiated e-cigarette use at age 16 are 12 times as likely to initiate cigarette smoking than their peers who never initiated e-cigarette use. This study shows that an earlier age of e-cigarette initiation is associated with an increased likelihood of cigarette smoking initiation.

4. Discussion

E-cigarette use has become an epidemic in the U.S. during the past decade. Despite efforts to reduce tobacco consumption, e-cigarettes have become the primary source of nicotine among adolescents and young adults [4]. The chemicals contained in e-cigarettes are harmful to the human body, and risk factors associated with e-cigarette use can be measured by looking at frequency of use as well as risk of cigarette smoking initiation. In adolescents, the age of initiation of cigarette smoking has been studied in association with nicotine dependence, smoking intensity, and smoking cessation. E-cigarette research, on the other hand, is not as extensive and there are not many studies done on age of e-cigarette initiation and frequency of use. However, e-cigarette usage is known to have an association with combustible tobacco cigarette smoking, so the present study examined how the age of e-cigarette initiation can lead to regular use and subsequent combustible tobacco cigarette use. In this review, results from five peer reviewed studies examined the relationship between the age of e-cigarette initiation and 1) frequency of e-cigarette use or 2) risk of combustible tobacco cigarette smoking. Measures of association tended to support the hypothesis that an earlier age of initiation would lead to more frequent e-cigarette usage and higher risk of initiation of cigarette smoking. Some trends to be

noted from the studies are that an earlier age of e-cigarette initiation tends to be associated with greater frequency of e-cigarette and cigarette use [16]. From the results, age of initiation of e-cigarette use presents a risk factor for cigarette smoking initiation and smoking behaviors [20]. It was hypothesized that an earlier age of e-cigarette initiation is associated with more frequent usage and higher risk of cigarette smoking initiation.

The first research question investigated the relationship between age of e-cigarette initiation and frequency of e-cigarette use. For the outcome of frequency of use of e-cigarettes, two of the three studies found that younger age of initiation of e-cigarette use was associated with increased frequency of e-cigarette use while one study found no association. The second research question evaluated the relationship between age of e-cigarette initiation and initiation of cigarette smoking. For the outcome of risk of cigarette smoking, all three studies found that earlier age of initiation of e-cigarettes was associated with increased likelihood of smoking cigarettes.

E-cigarettes are dangerous for addiction because e-cigarette aerosols contain highly oxidizing free-base nicotine, the most addictive form of nicotine [21]. As a result, e-cigarette users may be more inclined to experiment with and transition to combustible cigarettes and other forms of inhalable nicotine to more effectively satiate their nicotine cravings.

4.1. Strengths and limitations

This is the first systematic review we are aware of to relate the age of e-cigarette initiation to frequency of e-cigarette use and to cigarette smoking initiation. The current study contains strengths and limitations that are important in interpreting the findings. A strength is that the studies occurred over a short period and that they were published recently, which confers

a better representation of current habits of e-cigarette and cigarette usage. However, the novelty of e-cigarette data also limited the number of studies found and amount of data pertaining to this topic. The small number of included studies limits the evidence to make inferences, so ongoing data collection and future research studies are needed to increase the evidence base. Specifically, only two studies were longitudinal and three were cross-sectional, which restricts the understanding of the initiation and progression in e-cigarette and cigarette behaviors. The studies that were longitudinal showed significant associations between age of initiation and the study outcomes. However, since the developmental stage of adolescence is often characterized by many changes in behavior, it cannot be concluded with certainty whether the associations between age of e-cigarette initiation and 1) frequency of e-cigarette use 2) cigarette smoking initiation are causal or not. Another strength is that the review was not limited to U.S. participants, and examined students in the UK, which demonstrates that the e-cigarette epidemic is not a U.S. specific issue. Overall, the present study is significant in summarizing the evidence that tended to show that first experimentation of e-cigarettes confers more frequent use of e-cigarettes and a high risk of cigarette smoking initiation. The systematic review found that e-cigarette use was temporally associated with frequency of use in the past 30 days and initiation of tobacco cigarette smoking among teenagers in the U.S. and the UK, which helps identify an important health-related harm.

4.2. Comparison with previous systematic reviews

Previous systematic reviews have investigated whether e-cigarette use led to combustible tobacco cigarette use [11,22,23,24]. However, this systematic review examines the independent variable of age of e-cigarette initiation in association with cigarette use, which has not been

reported in detail. No systematic reviews were found that examined the independent variable of age of e-cigarette initiation in association with the dependent variable of frequency of e-cigarette use. These previous findings reported moderate evidence that adolescents and young adults who have never smoked but experiment with e-cigarettes are at least two times more likely to experiment with smoking later, which follows the same trend as the data in the present study [22].

4.3. Future research

The systematic review found that most but not all the evidence supports the hypothesis that an earlier age of initiation is associated with frequency of e-cigarette use and initiation of cigarette smoking. However, due to a small number of articles identified and small sample sizes included in the study, there was an inconsistency in the findings for e-cigarette frequency that needs to be accounted for. An important question that remains to be answered is what the long-term effects of e-cigarette usage are and how age of initiation is associated with the severity of these outcomes, so future research should continue examining this research question with longitudinal data. Despite a plateauing of e-cigarette usage in recent years, the prevalence of e-cigarettes remains high. Tobacco use in adolescents and young adults is a complicated topic as there are many more products that contain tobacco than just e-cigarettes and combustible tobacco cigarettes (snus, hookahs, cigars, etc.). The relationship between age of initiation and future use has not been examined for e-cigarettes extensively, but there is substantial evidence that youth who first try cigarette smoking at an earlier age are at increased risk for heavier long-term use, greater nicotine dependence, and lower smoking cessation [25,26]. By examining the associations of age of e-cigarette initiation and these outcomes, a better understanding of the

dangers of e-cigarettes can be gathered to develop better strategies to combat tobacco abuse. Future research can also expand the scope of studies worldwide since many eligible studies may have been excluded based on language criteria. The e-cigarette epidemic is not a U.S. specific issue, demonstrated by Conner and colleagues, so it should be addressed on a global scale. The paper that did examine e-cigarette behavior outside of the U.S. was conducted in an upper income European country, however, so it would be useful to test the hypotheses in African, Asian, and South American countries as well. The marketing of e-cigarettes can also be looked into further. The introduction of a variety of flavors to the e-cigarette market by tobacco companies is the the simplest issue to address. To combat marketing tactics, the U.S. Food and Drug Administration (FDA) may focus on regulating the advertising and variety of products that Big Tobacco corporations use to appeal to younger consumers [20]. Additionally, the illegal sale of ENDS products to minors and those under 21 may require tighter regulations by law enforcement.

5. Conclusion

Although there have been efforts to mitigate the spread of e-cigarette use, the prevalence remains at a high level in the U.S. The present study assessed the relationship between the age of initiation of e-cigarette use and frequency of e-cigarette use and subsequent cigarette smoking. The findings of this review suggest that an earlier age of initiation of e-cigarette use tends to be associated with an overall trend of more frequent e-cigarette use and higher likelihood of initiating combustible tobacco cigarette smoking. Only five peer-reviewed articles were included in this study, indicating that future research is necessary to examine the hypothesis of this study in greater detail. Although the results did not indicate a consistent trend in the age of e-cigarette

initiation, delaying the use of e-cigarettes and other tobacco products is important, even to just reduce the amount of lifetime use that occurs. Given the results of this study, future research on this topic and public health interventions may consider focusing their efforts on decreasing exposure of young people to e-cigarette products and delay initiation of e-cigarette use to prevent further increases in prevalence and intensity among adolescents and young adults. A current law to delay the age of initiation is tobacco 21, which has made it more difficult for young people to purchase and consume tobacco products. Although the law has not has a dramatic effect on e-cigarette usage, the delayed initiation of e-cigarette use will lead to gradual reductions in prevalence and intensity over time.

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Tables and Figures

Table 1. Summary of Studies

Author, Year	Study Design	Study Objective	Age of Initiation Measurement	Age Measurements	Sample Size	Outcome Measured
Harrell, 2021	Prospective cohort or longitudinal study. Texas Adolescent Tobacco & Marketing Surveillance Study (TATAMS). Complex, multi-stage, probability sampling design - 9 waves of an e-cigarette use survey were completed from 2014 to 2019	Identify and examine differing developmental trajectories of e-cigarette use.	Grade level where regular e-cigarette usage began	Range = 11-19	3,907	Frequency of use
Bold, 2017	Cross-sectional mediation analysis done with paper-and-pencil surveys distributed school-wide during homeroom periods in Spring 2015.	Examines the association between impulsivity and e-cigarette frequency with the age of initiation of e-cigarette use as a mediator	Age at first use	Mean = 16.2 Range = 14-19 SD = 1.2	927	Frequency of use
Conner, 2021	Longitudinal, prospective hierarchical linear model (HLM) with 2 levels. 4-year cluster randomized controlled trial of a school-based intervention. 12- and 24-month follow-up of e-cigarette/cigarette use with data from an intervention. Only students from wave 3 are analyzed here.	Examined the difference between regular and ever cigarette use between user groups	Age at first reported use	Range = 13-14	3,289	Frequency of use and Cigarette Initiation
McCabe, 2018	Self-administered cross-sectional questionnaires part of the Monitoring the Future (MTF) study in Spring 2015 among high school seniors	Examine the associated probability between age of initiation of e-cigarette use and cigarette smoking behaviors.	Grade level at first use	Range = 17-18	2,299	Cigarette Initiation
Lanza, 2017	Cross-sectional data from the 2014 National Youth Tobacco survey (NYTS) were collected to study use among adolescents.	Examined the age trends stemming from e-cigarette use and cigarette use	Age at first experimentation	Mean = 14.5 Range = 11-19	22,007	Cigarette Initiation

Table 2. Quality assessment tool

#	Study Characteristics	Harrell et al. 2021	Bold et al. 2017	Conner et al. 2021	McCabe et al. 2018	Lanza et al. 2017
1	Was the research question or objective in this paper clearly stated?	Y	Y	Y	Y	Y
2	Was the study population clearly specified and defined?	Y	Y	Y	Y	Y
3	Was the participation rate of eligible persons at least 50%?	CD	Y	CD	Y	Y
4	Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	Y	Y	Y	Y	Y
5	Was a sample size justification, power description, or variance and effect estimates provided?	Y	Y	Y	Y	Y
6	For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	Y	Y	Y	Y	Y
7	Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	Y	N	Y	N	N
8	For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?	Y	Y	Y	Y	Y
9	Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Y	Y	Y	Y	Y

10	Was the exposure(s) assessed more than once over time?	Y	N	Y	N	N
11	Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Y	Y	Y	Y	Y
12	Were the outcome assessors blinded to the exposure status of participants?	NA	NA	NA	NA	NA
13	Was loss to follow-up after baseline 20% or less?	Y	Y	Y	Y	Y
14	Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	CD	CD	CD	CD	CD

NA = Not Applicable

CD = Couldn’t Determine

Table 3. Age of initiation and frequency of use association

Study, Year	Exposure	Outcome	Measure of Association	Lower 95% CI	Upper 95% CI	Covariates	Conclusions
Harrell, 2021	First reported use	Frequency of use	$\bar{x}$ is the average number of days used in the past 30 days 6th Grade: Early: $\bar{x} > 15$ Late: $\bar{x} < 10$ 8th Grade: Early: $\bar{x} \sim 15$ Mid: $\bar{x} > 20$ Late: $\bar{x} \sim 5$ 10th Grade: Early: $\bar{x} \sim 22$ Mid: $\bar{x} \sim 15$ Late: $\bar{x} \sim 10$ P < 0.01	—	—	Age, sex, race/ethnicity, SES	Association data shows that in all three cohorts, those who initiated e-cigarette use later used e-cigarettes less frequently than those who initiated earlier.
Bold, 2017	First time using	Frequency of use	Unadjusted: B = -0.18 SE = 0.04 P < 0.001 Adjusted: B = -0.28 SE = 0.08 Beta = -0.54 t = -3.66 P < 0.001	—	—	Sex, race, e-cigarette use with peers, number of other tobacco products tried	This study implemented age of initiation as a mediator variable. The unadjusted and adjusted regression model data listed here shows a strong, nonlinear relationship between age of initiation and e-cigarette use frequency.
Conner, 2021	First reported use	Regular e-cigarette use	Reference: Early user (Odds Ratio = 1.00) **Odds Ratios** listed are for late users Unadjusted: OR = 0.76 P = 0.292 Adjusted: AOR = 0.96 P = 0.602	 0.45 0.84	 1.28 1.11	Sex, ethnicity, family affluence, free school meals, friend smokers, family smokers, impulsivity, intentions, attitude, perceived norms, perceived behavioral control, self-efficacy	The association between age of initiation and frequency of use was robust without covariates. After adjusting for covariates, the association became very weak and does not support the hypothesis.

Table 4. Age of initiation and risk of cigarette smoking association

Study, Year	Exposure	Outcome	Measure of Association	Lower 95% CI	Upper 95% CI	Covariates	Conclusions
Conner, 2021	First reported use	Regular and Ever Cigarette Smoking	Reference: Early User (Odds Ratio = 1.00) **Odds Ratios** listed are for late users Unadjusted: Ever Use: OR = 0.48 P < 0.001 Regular use: OR = 0.69 P = 0.282 Adjusted: Ever: AOR = 0.61 P < 0.001 Regular: AOR = 0.94 P = 0.347	 0.35 0.35 0.46 0.83	 0.66 1.37 0.81 1.07	Sex, ethnicity, family affluence, free school meals, friend smokers, family smokers, impulsivity, intentions, attitude, perceived norms, perceived behavioral control, self-efficacy	The association between age of e-cigarette initiation and ever cigarette use is strong, before and after adjusting for covariates. However, the association between age of e-cigarette initiation and regular cigarette use was robust before adjustment and very weak after adjusting for covariates.
McCabe, 2018	First reported use	Lifetime Cigarette Smoking	**Adjusted Odds Ratios** Grade 12: Ref. Grade 11: 1.38 Grade 10: 1.89 Grade 9 or earlier: 2.83	Ref. 0.71 0.81 1.06	Ref. 2.68 4.09 7.51	Age, sex, race, level of parental education, geographic region, metropolitan statistical area, college plans	There is a clear trend in the Odds Ratios from Grade 12, 11, 10, and 9, which shows a dose-response trend with greater risk of cigarette smoking initiation associated with an earlier age of e-cigarette initiation. Additionally, the odds ratio at Grade 9 was statistically significant.
Lanza, 2017	First reported use	Risk of Cigarette smoking	See Fig. 4			Sex, race/ethnicity, age	The reference group was never users of e-cigarettes. Odds of cigarette smoking initiation decrease significantly compared to never-user peers at the earlier ages and begin flattening out around 16 years of age. Younger initiators were much more likely to initiated cigarette smoking than later initiators

Figure 1.

Research questions of this study

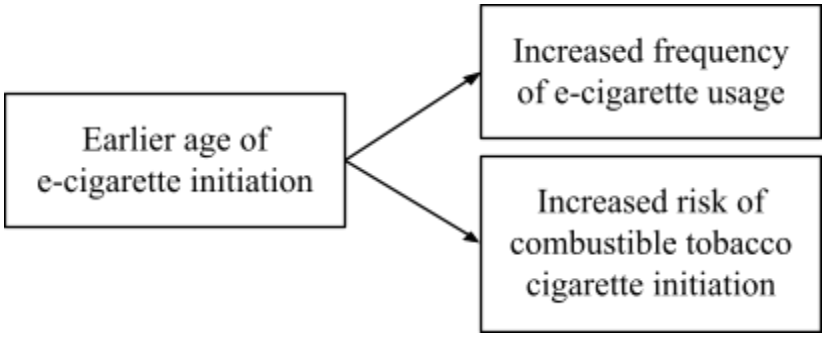

Figure 2.

PRISMA Flow Diagram of Study Screening

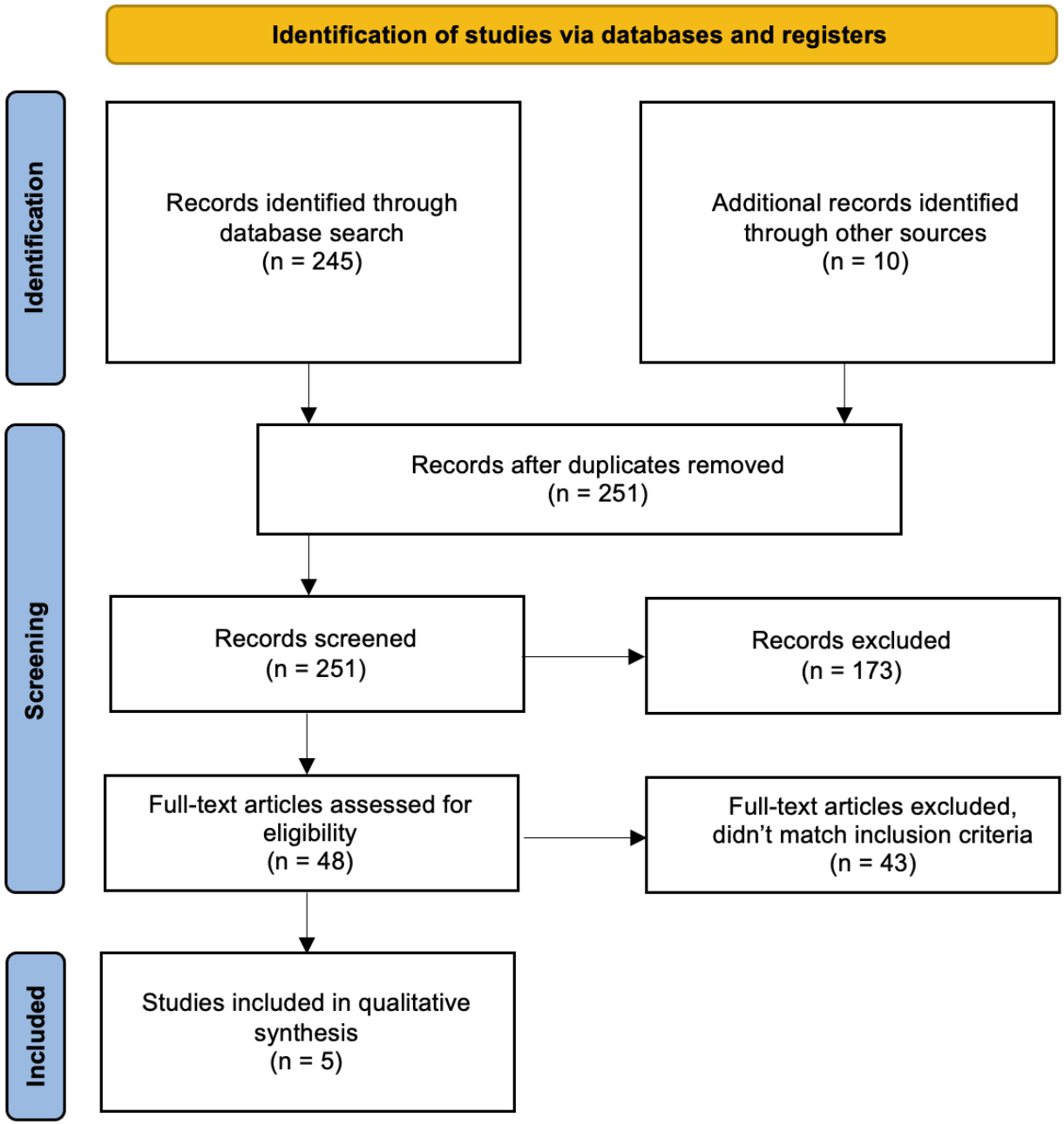

Figure 3. Age of e-cigarette initiation and e-cigarette usage in past 30 days [16]

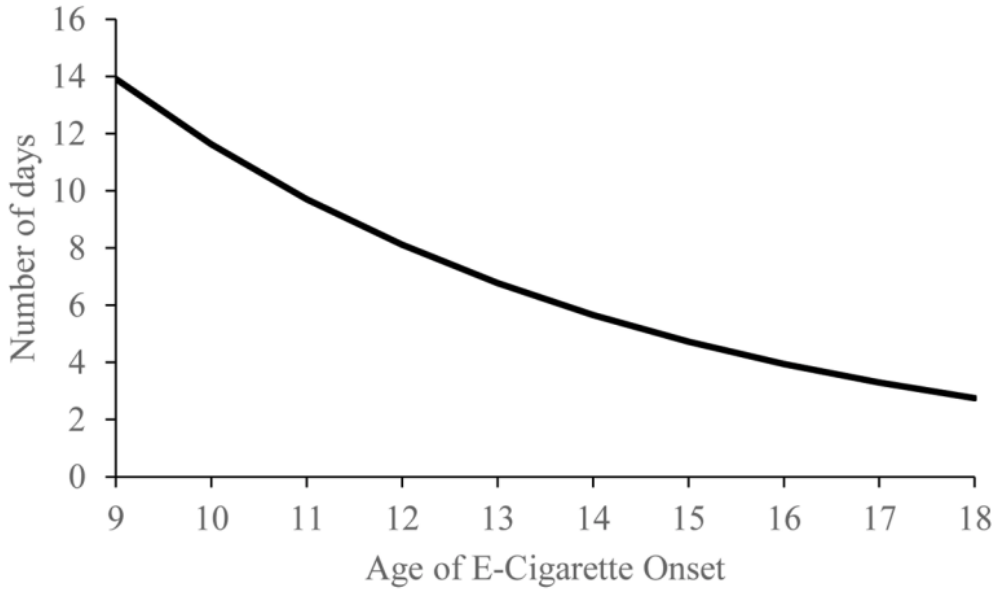

Figure 4. Age of cigarette initiation and odds of cigarette smoking initiation [19]

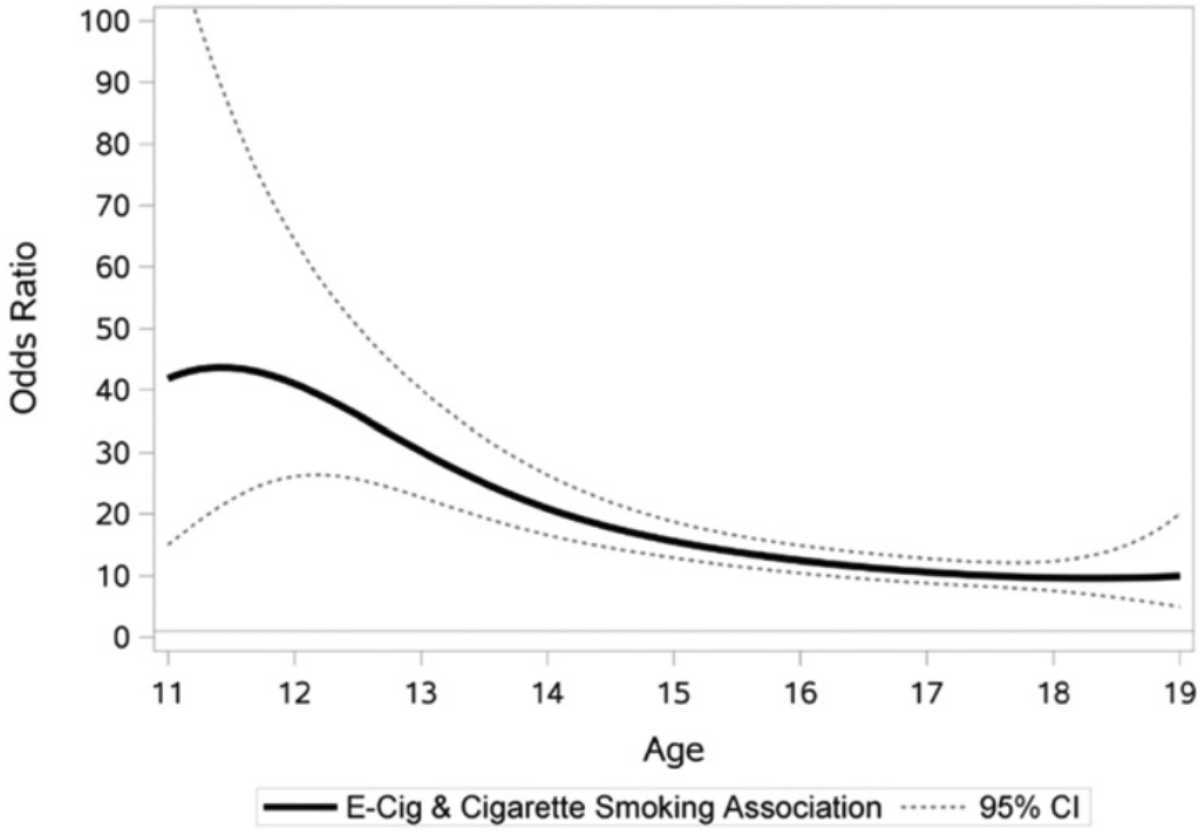

Figure 5: Grade of initiation and estimated percentage of cigarette smoking [18]