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Risk Associated with E-Cigarette Use and Marketing Messages on Other Tobacco Products Use and Dependence Symptoms among Adolescents

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FLORIDA INTERNATIONAL UNIVERSITY

Miami, Florida

RISK ASSOCIATED WITH E-CIGARETTE USE AND MARKETING MESSAGES
ON OTHER TOBACCO PRODUCTS USE AND DEPENDENCE SYMPTOMS
AMONG ADOLESCENTS IN THE UNITED STATES

A dissertation submitted in partial fulfillment of the

requirements for the degree of

DOCTOR OF PHILOSOPHY

in

PUBLIC HEALTH

by

Rehab Auf

2017

To: Dean Tomás R. Guilarte
Robert Stempel College of Public Health and Social Work

This dissertation, written by Rehab Auf, and entitled Risk Associated with E-cigarette Use and Marketing Messages on Other Tobacco Products Use and Dependence Symptoms among Adolescents in the United States, having been approved in respect to style and intellectual content, is referred to you for judgment.

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Florida International University, 2017

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DEDICATION

To the true wealth and joy in my life.

To my children.

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My deep gratitude goes to my PhD committee's support throughout the difficult journey of PhD. I specially thank Professor Miguel Ángel Cano, my committee chair, for his personal support and scientific enrichment to my work from conception until publications. I am in debt for Professor Mary Jo Trepka for the friendly atmosphere she offers to all her students, while supporting them to achieve their self-best. I will always memorize her humane character and scientific rigorous as a role model who I aspire to follow in my prospective career.

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ABSTRACT OF THE DISSERTATION
RISK ASSOCIATED WITH E-CIGARETTE USE AND MARKETING MESSAGES
ON OTHER TOBACCO PRODUCTS USE AND DEPENDENCE SYMPTOMS
AMONG ADOLESCENTS IN THE UNITED STATES

by

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Florida International University, 2017

Miami, Florida

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E-cigarettes became available in the United States during 2007. Studies using national data have found an increase in e-cigarette use among adolescents as early as 2011. In 2014, e-cigarettes became the most commonly used tobacco product among adolescents; however, little is known about its association with other tobacco products use. Therefore, the present study aimed to: 1) Examine the association between initiating tobacco use via e-cigarettes and subsequent use of other tobacco products; 2) Examine the association between the exposure to e-cigarettes marketing messages and tobacco use; 3) Describe symptoms of nicotine dependence associated with e-cigarette use, compared with cigarette and dual use of e-cigarettes and cigarettes. All aims were carried out among data from the National Youth Tobacco Survey (NYTS) 2014 and 2015. The participants of NYTS were adolescents, and they self-reported their demographic characteristics and tobacco use in an anonymous 81-item pencil-paper questionnaire.

Findings from logistic regression modeling showed that initiating tobacco use via e-cigarettes was significantly associated with subsequent current use of cigarettes (adjusted

odds ratio (AOR)=2.7; 95% confidence interval [CI], 1.9-4.0), cigars (AOR= 1.7; 95% CI, 1.2-2.4), smokeless tobacco (AOR= 3.1; 95% CI, 2.2-5.4), or any tobacco products (AOR= 4.4; 95% CI, 3.5-5.6). In addition, living with someone who used e-cigarettes at home significantly increased the likelihood of using tobacco products. Notably, e-cigarette marketing exposure was significantly associated with current use of cigarettes (AOR: 1.3, 95% CI: 1.1-1.6), hookah (AOR: 1.3, 95% CI: 1.03-1.7), cigars (AOR: 1.3, 95% CI: 1.1-1.6), and polytobacco (i.e. more than one tobacco product) use (AOR: 1.8, 95% CI: 1.5-2.1). Among adolescent daily tobacco users, 35.6% of e-cigarette users and 85.3% of cigarette users reported one or more dependence symptoms. These proportions increased to 74.3% among e-cigarette and 93.3% of cigarette dual (i.e. combined) users. Strong cravings was the most commonly reported symptom with a range of 16.1-58.9% among different types of smokers in the study.

In conclusion, exposure to e-cigarette marketing messages and e-cigarette use were associated with use of other tobacco products. Furthermore, e-cigarette use is addictive. Despite cigarette and dual (i.e. e-cigarette and cigarette) users being more likely to report dependence symptoms than e-cigarette users, the addictiveness of e-cigarettes occurred at appreciable rates. Collectively, the findings suggest that e-cigarettes are associated with dependence symptoms and use of tobacco products and suggest that stricter regulations are needed to prevent adolescent access to and use of e-cigarettes.

TABLE OF CONTENTS

CHAPTER

PAGE

INTRODUCTION	1
References	7
OBJECTIVES	9
References	11
MANUSCRIPT 1	12
Abstract	12
Background	13
Methods	15
Results	19
Discussion	21
References	25
Tables and figures	29
MANUSCRIPT 2	33
Abstract	33
Introduction	34
Methods	36
Results	39
Discussion	40
References	44
Tables and figures	48
MANUSCRIPT 3	51
Abstract	51
Introduction	52
Methods	54
Results	56
Discussion	60
References	64

Tables and figures	68
CONCLUSIONS.....	73
VITA.....	77

INTRODUCTION

Tobacco use is a major preventable cause of extensive range of severe morbidity and mortality (Jha et al, 2015). Currently, it is estimated that tobacco kills approximately a third to half of its users, contributing to 5 million annual global deaths. Unfortunately, if tobacco use rates continue as observed, the expected number of associated deaths may be as high as one billion by the end of this century (Shafey O, 2009; WHO, 2008; Adcock IM, 2011; Koczulla AR, 2010). On average, smokers die 10 to 15 years earlier than non-smokers (USDHHS, 2004). Therefore, curbing tobacco use, especially among youth, is among the objectives of Healthy People 2020.

The stringent policy on restricting adolescent access to cigarettes, increasing taxes, and warning labels, along with other tobacco control efforts collectively led to achieving the 2020 cigarette use objective among youth by the year of 2013 (seven years ahead of time). In 2013, the CDC reported that the ever cigarette use was 15.7% among youth (the initiative had originally aimed to lower youth cigarette use to be 16% or less) (Healthy People 2020 Tobacco Use Report). The use of cigarettes is continuing to decline as reported in the NYTS for 2014 (CDC, 2015). However, the progress in tobacco control among other tobacco products - such as e-cigarettes - has not been as successful as that of conventional cigarettes, due to lack of a stringent control policy similar to those existing for cigarettes (CDC, 2015).

E-cigarettes are battery operated devices for nicotine delivery through vaping. Some of them look like cigarettes, albeit larger in size, and others might have other shapes and colors as well. E-cigarettes might have flavoring chemicals (examples of the flavors

are: menthol, fruits e.g. apple, desserts e.g. chocolate, and coffee) to appeal to customers, especially younger age groups (Johnston et al, 2016).

Although e-cigarettes were first invented in 2003, the prevalence of their use only were noted in 2011 due to its significant increase, especially among younger generations (Carroll and Wu, 2014). In the survey between years of 2011 to 2014, the annual e-cigarette use has almost tripled. In the NYTS (2014), it was reported that e-cigarettes became the most commonly used tobacco product among middle (3.9%) and high (13.4%) school students (CDC, 2015). The following year the rates continued to escalate; thus, in 2015 in the United States (US), 5.3% of middle school students, 16.0% of high school students, 13.6% of young adults (18-24 years), and 5.7% among young adults (above 25 years) reported using e-cigarettes within the past 30 days (USDHHS, 2016).

The surge in alternative tobacco products use in the U.S., mainly electronic cigarettes (e-cigarettes), has offset the observed decline in combustible cigarette use in the 2014 National Youth Tobacco Survey (NYTS) (Singh, et al, 2016). Indeed, in the NYTS 2015 e-cigarette ever users were double the numbers reported for cigarettes use (Singh et al, 2016). Similar trends were reported in Monitoring the Future National Survey (Johnston et al, 2016). The increasing prevalence of e-cigarette underscores the need to focus on new aspects of tobacco control, and hence to gear research questions to address these new challenges.

The sudden increase of e-cigarette use might warrant unexpected hazards on long term use. Indeed, decades of scientific debates passed before the danger of conventional tobacco products was asserted. Even though e-cigarettes are relatively new, several

studies reported significant potential hazards associated with chemicals found among its ingredients. Herman and Sofuglu (2010), detected various chemical substances and ultra-fine particles in e-cigarette aerosols, cartridges, refill liquids, and environmental emissions that are known to be carcinogenic and/or cause respiratory and heart distress. It has been estimated that e-cigarettes might be associated with cancer risk as high as 15 times - due to its inclusion of formaldehyde, a known carcinogen, relative to conventional cigarettes (Jensen et al, 2015). Some researchers report that e-cigarettes contain diacetyl, acetoin, and 2, 3-pentanedione, which is known to cause severe respiratory diseases such as popcorn lung disease (Allen et al, 2015). The current study does not focus on health hazards associated with e-cigarettes. However, the potential harms of e-cigarettes highlight the immediate need to understand the spectrum of factors that might have contributed to the sudden increase in e-cigarettes use.

Combating tobacco use among adolescents is key to reducing the global burden of tobacco for several reasons. First, tobacco initiation occurs most often among adolescents and young adults (USDHHS, 2016). Second, some literature suggests that exposure to tobacco during adolescence may have adverse developmental effects on the brain (USDHHS, 2014). Finally, the earlier the age of tobacco initiation during adolescence, the higher the risk of nicotine dependence and failure of smoking cessation later in life (Carroll and Wu, 2014; USDHHS, 2016). Therefore, reducing tobacco use among adolescents has been an important public health objective in the U.S., which witnessed considerable success in reducing the prevalence of tobacco use among adolescents after decades of tobacco control efforts (Auf et al, 2014). The present study's focus on adolescents stems from the same principles.

The addictive property of all tobacco products is attributed to nicotine, which most e-cigarettes contain (Schroeder and Hoffman, 2014). More than 90% of adolescents who use tobacco daily report cravings, irritability, and problems with concentration when they try to quit (CDC, 1994). Among smoking adolescents, craving is the most commonly reported symptom (DiFranza et al., 2002a; Panday et al., 2007). The younger the individuals are when they start using tobacco, the more likely they will develop nicotine dependence symptoms. Indeed, about three out of four adolescent smokers continue to smoke into adulthood due to nicotine dependence symptoms and are less likely to quit smoking compared to those who initiate smoking as adults (USDHHS, 2012). Moreover, adolescent smokers report symptoms of nicotine dependence even with low levels of exposure to nicotine as they are more prone to nicotine dependence than adult smokers (DiFranza et al., 2000; DiFranza et al., 2007a). Approximately 1 in 5 adolescent smokers will manifest symptoms of nicotine dependence within a month of the onset of smoking (O'Loughlin et al., 2003).

Animal models suggest that nicotine exposure during the period equivalent to adolescence leads to functional and structural changes in the brain such as alterations in the excitation and release of catecholamine and disruption of the dopamine and serotonin transporter function in prefrontal cortex and nucleus accumbens, leading to changes in serotonin function that may contribute to the increased incidence of mood disorders seen after adolescent smoking (Dwyer et al, 2009). Nicotine exposure leads to structural changes within the limbic and dopaminergic circuitry that underlies motivated behaviors, potentially enhancing the vulnerability to nicotine addiction (Dwyer et al, 2009).

Nicotine dependence is the most common type of substance dependence in the United States (CDC, 2010). Furthermore, in developed countries, nicotine dependence manifests early among adolescents (DiFranza et al., 2011). Not surprisingly, there is evidence that cigarettes, cigars, and smokeless tobacco use among youth leads to symptoms of dependence (Apelberg et al, 2014). Unfortunately, there is no published research that assesses the risk of nicotine dependence that is associated with e-cigarette use among adolescents in the United States. In addition, symptoms of nicotine dependence have not been described among e-cigarette adolescent users. For example, no study has examined either the relation of smoking intensity or the age of initiation for e-cigarette with symptoms of dependence among American adolescents. Thus, this study provided novel findings with a national representative sample that allows the generalizability of the results.

Using one tobacco product might increase the risk of trying other products through different pathways. One possibility is that using one tobacco product might stimulate the curiosity to use other tobacco products, increasing the risk for dual or poly tobacco use without developing dependence. Another, perhaps more important, pathway, is that once individuals develop nicotine dependence, they might seek using other tobacco products to satisfy their nicotine dependence. This can be driven by several factors, such as the cost to deliver sustainable nicotine levels, which can be an issue in e-cigarette. E-cigarettes currently are more expensive than traditional cigarettes. Therefore, this could be a driving force to shift adolescents to cigarettes once started on e-cigarettes. Therefore, an association of e-cigarettes with nicotine dependence precludes them being risk-free smoking methods (CDC, 2015).

In summary, this study aimed to assess e-cigarette use or its marketing messages and their association with other tobacco use; so as the dependence symptoms associated with e-cigarette use, which are all important aspects to examine to inform tobacco control. These are important and pivotal aspects to consider in order to avoid the rising e-cigarettes use disrupting the ongoing tobacco control efforts.

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OBJECTIVES

Smoking continues to be the most preventable cause of morbidity and mortality in the United States (Jha et al., 2015). Reducing smoking behaviors among adolescents is an important facet in tobacco control in order to develop a new generation who is less likely to use tobacco products. Indeed, it is estimated that about three out of four adolescent smokers continue to smoke into adulthood due to nicotine dependence symptoms and are less likely to quit smoking compared to those who initiate smoking as adults (USDHHS, 2012). Furthermore, the majority of adult smokers usually start to experiment with tobacco during adolescence; leading symptoms of dependence to start to develop during this period (USDHHS, 2012).

Therefore, curbing the tobacco epidemic with focus on adolescents should lead to lowering the prevalence of tobacco use by cohort's effect. Indeed, the long ongoing tobacco control efforts have led to continuous decline in cigarette use among youth since the 1990s (Healthy People 2020 Tobacco Use Report). Therefore, the relationship of the expanding increase of e-cigarette use among adolescents and important aspects of tobacco control were examined in the present study. In other words, this study aimed to understand whether e-cigarette use might impact on other tobacco product use or not.

The study objectives are outlined for each manuscript below:

Manuscript 1 objective: Examine the association of tobacco initiation via e-cigarettes among never tobacco users' adolescents and subsequent other tobacco products ever

(lifetime) and current (past 30 days) use (namely: cigarettes, cigars, and smokeless tobacco).

Hypothesis: Tobacco initiation via e-cigarette is associated with higher odds to be ever or current user of cigarettes, cigars, and smokeless tobacco compared to those who did not use e-cigarettes among adolescent never tobacco users.

Manuscript 2 objective: Examine the association between the exposure to e-cigarette marketing messages and the ever (lifetime) or current (past 30 days) use of the most common tobacco products in use among adolescents (cigarettes, cigars, and hookah)

Hypothesis: Exposure to e-cigarette marketing messages is associated with higher likelihood to be ever or current user of cigarettes, cigars, and hookah compared to adolescents who were not exposed to such messages.

Manuscript 3 objective: Examine the association between reporting nicotine dependence symptoms and current (past 30 days) e-cigarette, cigarette, and dual (combined e-cigarettes and cigarettes) use among adolescents.

Hypothesis: E-cigarette users will demonstrate nicotine dependence symptoms that are expected to be less frequent than cigarette and dual user.

The Cross-sectional surveys for the year of 2014 and 2015 National Youth Tobacco Survey (NYTS) were used to conduct the outlined aims. The surveys included 39,318 participants from representative sample of middle and high school students in the United States.

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MANUSCRIPT 1 (revised and resubmitted)

E-cigarettes are associated with increased cigarette, cigar, and smokeless tobacco initiation among adolescent never tobacco users in the United States

Abstract

INTRODUCTION:

E-cigarette use is becoming increasingly common among never tobacco-using adolescents, and the effect of this on tobacco use at national level is unknown.

METHODS:

Longitudinal events were constructed from a cross-sectional representative sample of US adolescents (n=39,718) who completed the 2014 & 2015 National Youth Tobacco Survey (NYTS). Logistic regression models estimated the adjusted odds ratio (AOR) of cigarettes, cigars, and smokeless tobacco initiation among never tobacco users associated with initiation via e-cigarettes compared to those who did not initiate via e-cigarettes; while controlling for factors that are known to be associated with tobacco initiation.

RESULTS:

Adolescent never tobacco users who initiated tobacco use via e-cigarettes were significantly younger (15.1 years) than those initiated via cigarettes (15.6 years), cigars (16.1 years), and smokeless tobacco (15.8 years). E-cigarette initiators were more likely to have ever tried cigarettes (AOR=3.7; 95% confidence interval (CI), 3.1-4.5), cigar (AOR=2.5; 95% CI, 2.0-3.1), smokeless tobacco (AOR= 4.1; 95% CI, 2.9-5.7), and any tobacco product (AOR= 6.0; 95% CI, 5.1-7.2) compared to others. Similarly, e-cigarette initiators had significantly higher odds of current use of cigarettes (AOR=2.7; 95% CI, 1.9-4.0), cigars (AOR= 1.7; 95% CI, 1.2-2.4), smokeless tobacco (AOR= 3.1; 95% CI,

2.2-5.4), or any tobacco products (AOR= 4.4; 95% CI, 3.5-5.6). Also, having someone using e-cigarette at home significantly increased the likelihood to use tobacco products.

CONCLUSIONS AND SCIENTIFIC SIGNIFICANCE:

The earlier age of initiation of e-cigarettes and the association of adolescent tobacco use initiation via e-cigarette or use by other family/household with subsequent tobacco use suggest that e-cigarettes may lead to increased use of tobacco among adolescents. This is the first study from a large and representative sample of American adolescents that shows such an association. Therefore, it can contribute to policy formation and suggests the need for continuous monitoring for e-cigarette use among adolescents.

Background

Tobacco use continues to be the most preventable cause of premature death in the United States (U.S.) (1). Combating tobacco use among adolescents is key to reducing the global burden of tobacco for several reasons. First, tobacco initiation occurs most often among adolescents and young adults (2). Second, some literature suggests that exposure to tobacco during adolescence may have adverse developmental effects on the brain (3). Finally, the earlier the age of tobacco initiation during adolescence, the higher the risk of nicotine dependence and failure of smoking cessation later in life (1, 2). Therefore, reducing tobacco use among adolescents has been an important public health objective in the U.S., which witnessed considerable success in reducing the prevalence of tobacco use among adolescents after decades of tobacco control efforts (4).

The surge in alternative tobacco products use in the U.S., mainly electronic cigarettes (e-cigarettes), has offset the observed decline in combustible cigarette use in

the latest National Youth Tobacco Survey (NYTS) (5). In the 2011 NYTS, e-cigarettes were the least commonly reported tobacco product (ever use: 1.4% of high school students), but e-cigarette use doubled over the following two survey years. By 2014, e-cigarettes became the most prevalent lifetime used tobacco product reported in the NYTS (13.4% among high school students). In the 2015 NYTS, 16% of adolescents reported life-time use of e-cigarettes, about double the reported rate of ever use of cigarettes (5). Similar trends were reported in Monitoring the Future National Survey (6).

Generally, e-cigarettes have been promoted as a less harmful tobacco product due to the absence of many harmful chemicals that are typically emitted from cigarettes (7, 8). However, some research has indicated that e-cigarettes also contain harmful substances, although at lower levels, that may lead to adverse health outcomes such as cancer and cardiovascular diseases (9, 10). Additionally, most e-cigarettes contain nicotine, which is the active substance responsible for dependence (11). Because of nicotine's addictive properties (12), there is concern that adolescents using e-cigarettes may later use tobacco products (13, 14). Indeed, it has been shown that using one tobacco product is associated with higher risk to use other tobacco products (15), thus polytobacco use is becoming the more common (16, 17).

We are aware of five studies that investigated whether the use of e-cigarette is associated with subsequent increased risk of tobacco initiation among adolescents or not (14, 18-21). In each of these studies, e-cigarette use was associated with higher risk of initiating the use tobacco products among people who had never smoked. Despite the strength of those studies, their reported results may not be generalizable to the general

population of U.S. adolescents because they either used data from one city, one state, or had a small sample size that did not reflect the actual rate of e-cigarettes and tobacco use.

Building on previous research, the aim of the present study is to examine if e-cigarette initiation among never tobacco users is associated with increased odds to use other tobacco products including cigarettes, cigars, and smokeless tobacco products. Exposure to nicotine is reported to be associated with an increased risk of other tobacco products and substance use (i.e. gateway), which provides the scientific plausibility of the association this study aims to examine. (15). Also, we examined the association between e-cigarette use and the use of tobacco products. This study is of public health significance because it is the first study to report from a national representative sample for US adolescents, while controlling for important socioecological factors that are associated with tobacco use.

Methods:

Study population

The NYTS obtained a nationally representative cross-sectional sample of middle and high school students (grades 6-12 with age ranging from 12-19 years) using a three-stage cluster probability sampling design without replacement. Non-Hispanic black and Hispanic/Latino students were oversampled. Parents or legal guardians consented for their children's participation. A total of 22,007 and 17,711 adolescents participated (91.4% and 87.4% response rate) from 207 and 185 schools (80.2% and 72.6% response rate) in the 2014 and 2015 surveys respectively totaling 39,718 from the two years' surveys. All students responded to an anonymous self-administered 81-item, pencil and paper

questionnaire. The NYTS is designed to inform national and state tobacco prevention and control programs (23).

Ethics statement

The Institutional Review Board at Florida International University deemed the study non-human subjects research because of using non-identifiable public access data.

Measures

For simplicity, we will refer to “cigars, cigarillos, or little cigars” as “cigars” and “chewing tobacco, snuff, or dip” as “smokeless tobacco” throughout this report.

Consistent with reports from the Centers for Disease Control and Prevention [CDC], we list e-cigarettes as a tobacco product. To make the comparison uniform between different tobacco products’ definition of use, we did not take into account the number of cigarettes smoked because no similar questions were available for the other included products (e-cigarettes, cigars, and smokeless tobacco). This is consistent with the published reports by the CDC (5) and facilitates the comparison of our results with other published research. Participants were asked about lifetime use (ever) and current use (past 30 days) of cigarettes, cigars, smokeless tobacco, and e-cigarettes. Lifetime and current use of the cigarettes, cigars, and smokeless tobacco was further grouped into at least one product use versus none.

Tobacco initiation was defined by responding with “yes” to one of the choices in the question: “Which of the following tobacco products did you try first? (CHOOSE ONLY ONE ANSWER).” Participants who selected e-cigarettes constituted the e-cigarettes initiators. Those who were never tobacco users at its time, formed the comparison group in the analysis. Having never tobacco users as the comparison group is

consistent with published research which based the risk estimate on a comparison group of never tobacco users (14). The newly introduced question about smoking initiation method in the 2014 and was also available at the 2015 NYTS allowed the construction of a timeline of events within the cross-sectional design, similar methodology was used in previous research (24). It has to be noted that the method of initiation is different from lifetime and current smoking status. An adolescent can initiate smoking via one method, but later on move to explore other methods.

The peer influence to use a tobacco product was measured by the question “If one of your best friends were to offer you would you smoke it? “, which was available for cigarettes and cigars, but not for smokeless tobacco. Likert-type scale responses: “definitely yes, probably yes, probably no, and definitely no” were reverse coded, so higher scores indicated higher probability. Participants were asked to report all tobacco products used at home by household members. We considered the reported e-cigarette, cigarette, cigar, and smokeless tobacco use at home as “household use.”

Covariates included age, race/ethnicity, and gender as detailed below. We used the readily available recoded question for single race classification and collapsed all categories other than non-Hispanic Whites, non-Hispanic Blacks, and Hispanics/Hispanic into “other.”

Data Analysis

Data from 2014 and 2015 NYTS were pooled to examine the association of tobacco initiation via e-cigarettes and subsequent tobacco use. The Proc Survey procedure in SAS v9.4 was used to adjust for the survey’s complex design. Each survey year’s weights and the survey procedures were applied to account for the stratified

clustered sampling design of the NYTS to adjust for nonresponse, the probability of selection, and to match the sample's sociodemographic characteristics with those of U.S. middle and high school students in 2014 (23).

We used the chi-square test for categorical variables and t-test for continuous variables i.e. age at initiation of tobacco product use. Logistic regression models were used to estimate the odds ratio (OR) and corresponding 95% confidence interval (CI) of tobacco initiation via e-cigarette, lifetime, and current e-cigarette use associated with lifetime and current use of cigarettes, cigars, and smokeless tobacco. The OR and corresponding 95% CI were further adjusted by models that included age, gender, race/ethnicity, probability to smoke the specific tobacco product if offered by a friend, and home (i.e. household) tobacco use in separate models for ever and current use of each tobacco product. Using e-cigarettes at home was included to control for parents' (or other household members) influence and accessibility of e-cigarettes. The included covariates are known risk factors for tobacco use among adolescents (25, 26), which were collected at the NYTS 2014 and 2015. The year of survey did not change the outcome of the models. So, the findings remained consistent if we analyzed the data for each year separately or for the pooled data from the two survey years. However, the pooled data provided narrower confidence intervals. Missing data were excluded from the analysis. Statistical significance was set to 0.05. All tests were 2-tailed, and Bonferroni-Holm correction for multiple tests was applied (27).

Results:

Descriptive analysis

A total of 39,718 adolescents participated in the 2014 & 2015 NYTS with 11,047 (28.3%) lifetime users and 4,181 current users of either cigarettes, cigars, or smokeless tobacco (10.6%) (Data not shown). A total of 2,477 (6.2%), 5,057 (12.7%), 1,521 (15.0%), and 1,055 (2.7%) reported e-cigarettes, cigarettes, cigars, and smokeless tobacco to be their method for tobacco initiation from the entire study population; respectively. E-cigarette initiators were more likely to be younger than other tobacco product initiators (15.1 years vs. 15.6, 16.1, and 15.8 years for cigarette, cigar, and smokeless tobacco – $p < 0.05$; respectively). There was a higher percentage of Hispanics/Latino who initiated tobacco use via e-cigarette (26.9%) compared to among those who initiated with other tobacco use methods (23.1% of cigarette, 15.8% of cigar, and 8.7% of smokeless tobacco), but this observation was not consistent among Blacks or Whites. One third of e-cigarette initiators were middle school students, which is higher than the proportions for cigarette (22.6%), cigars (13.5%), and smokeless tobacco (21.3%) initiators.

Of the 39,718 participants, 8,887 (23.4%) and 3,973 (10.3%) reported lifetime and current use of e-cigarettes respectively. A higher percentage of Hispanics, and whites were lifetime and current e-cigarette users compared with other racial/ethnic groups. High school and male students were more likely to be lifetime and current e-cigarette users compared to middle students ($p < 0.001$, table 2).

Association between tobacco use initiation via e-cigarette among never tobacco users and subsequent lifetime cigarette, cigar, and smokeless tobacco use

After controlling for demographic and important tobacco product use factors, e-cigarette initiators had a significantly higher adjusted odds for lifetime use of combustible cigarettes (adjusted OR (AOR); 3.7; 95% confidence interval (CI), 3.1-4.5), cigars (AOR=2.5; 95% CI, 2.0-3.1), smokeless tobacco (AOR= 4.1; 95% CI, 2.9-5.7), and any tobacco product (AOR= 6.0; 95% CI, 5.1-7.2) (Table 3); in comparison to never tobacco users at its time retrospectively.

Association between tobacco use initiation via e-cigarette among never tobacco users and subsequent current cigarette, cigar, and smokeless tobacco use

The adjusted odds ratios indicated significant associations between initiation of tobacco use via e-cigarettes and current use of cigarettes (AOR=2.7; 95% CI, 1.9-4.0), cigar (AOR= 1.7; 95% CI, 1.2-2.4), smokeless tobacco (AOR= 3.4; 95% CI, 2.2-5.4), and any tobacco products (AOR= 4.4; 95% CI, 3.5-5.6) in comparison to never tobacco users at its time point (Table 4).

In all models for lifetime and current use of three examined tobacco products, household e-cigarette use, peer influence, and household use of the outcome tobacco product were important factors associated with lifetime and current smoking of cigarettes, cigars. Household use of e-cigarettes was not associated with current use of smokeless tobacco, but it was for its lifetime use. Other factors with statistical significance were consistent for lifetime and current use of smokeless tobacco as described for other tobacco products.

Association between e-cigarette use and smoking cigarettes, cigars, and smokeless tobacco (lifetime and current)

Lifetime and current e-cigarette users (irrespective to their method of initiation) were consistently more likely to be lifetime or current users of cigarettes, cigars, or smokeless tobacco, and at least one of the three products (Table 3 & 4). The association of ever and current e-cigarette use and tobacco use was significant after adjusting for other risk factors and were also observed for current use of the examined tobacco products (Table 4).

Discussion:

Using a nationally representative sample, our results indicate that e-cigarette initiation among never tobacco users is associated with increased risk of tobacco initiation. This finding is consistent with other published studies (13, 14, 16, 18-20, 28) that have small samples with limited generalizability.

Adolescents who initiated tobacco use via cigarettes, analysis is not shown, had higher odds to lifetime and current use of e-cigarettes as reported elsewhere (14). Therefore, our results support a bidirectional relationship between cigarette and e-cigarette use. The bidirectional association of e-cigarette and the use of tobacco products can be explained by having common socio-ecological risk factors (14). Some putative direct and indirect mechanisms might be contributing to the shift of e-cigarette into the use of tobacco products or dual use (29). Directly, this can be attributed to the nicotine gateway mechanism given nicotine is the active substance in all tobacco products leading users to use them in alternating orders (15). However, given the relationship between e-

cigarettes and other tobacco products is bidirectional (i.e. no specific order is required) and can be attributed to other factors beyond nicotine (detailed later), the common liability theory might be a good fit to describe the observed association (30-32).

Our results indicate that, on average, adolescents initiate e-cigarette at a significantly younger age compared to cigarettes, cigars, and smokeless tobacco products. One possible explanation is that e-cigarettes were not as highly regulated as a tobacco product when the underlying survey was conducted. Therefore, adolescents were able to access it an earlier age compared to regulated tobacco products. It would be interesting to reexamine this observation after the FDA regulating e-cigarettes as tobacco products. Nevertheless, the younger age of initiation combined with the increasing prevalence of e-cigarettes among adolescents (5, 22) warns of e-cigarettes potentially becoming a gateway for initiating other tobacco products, and possibly substance use, based on the direct nicotine pathway and common liability theory. Such mechanisms lend themselves as a support to the observed increasingly common poly-tobacco use reported in several studies (16, 17). In other words, the commonly observed polytobacco use supports the hypothesis that using one tobacco product is a gateway to using other tobacco products, which provides plausibility and coherence to our findings. The commonality of polytobacco, besides possibly circumventing public smoking ban, makes it not unexpected for never tobacco users who initiate via cigarette to subsequently try e-cigarettes as we reported in this study.

Furthermore, the indirect mechanisms may include marketing messages (33, 34) renormalization of tobacco use within public spaces, and societies (35), while sale restrictions have proven to be ineffective in controlling adolescents' tobacco use (36-38).

Therefore, a rebound increase in tobacco use might be observed over the coming years if the prevalence of e-cigarette continues to escalate (29) among adolescents in the U.S (5, 22). and other parts of the globe (e.g. South Korea) (39). If this were to occur, it could potentially reverse decades of tobacco control and increase the prevalence of tobacco use.

The younger age of e-cigarette initiator compared to other tobacco products is problematic for several considerations. Exposure to nicotine during the period of adolescence leads to structural changes in the brain enhancing the vulnerability to nicotine dependence (40). In developed countries, nicotine dependence manifests early among adolescents (41). Therefore, the younger age of initiation among e-cigarette users would increase their risk of nicotine dependence. Nicotine dependence at an early age may hinder the opportunity to quit tobacco products later on in life (12, 41). Also, adolescence is a critical period in brain development. Exposure to nicotine during this period might disrupt the dopamine and serotonin transporter leading to mood disorders and subsequently lower likelihood of quitting smoking and transition into heavier smoking (40). It also leads to structural changes in the brain enhancing the vulnerability to nicotine dependence (40).

Interestingly, in the adjusted model testing for the effect of initiation via e-cigarette on subsequent tobacco use, we reported a new association between household e-cigarette use and tobacco initiation, but it was not consistently found in the models testing for life-time and current e-cigarette use. One possible explanation is that having someone use e-cigarettes at home may increase the likelihood of an adolescent initiating tobacco use via e-cigarette and then shift to subsequent tobacco use. This suggests that promotion of e-cigarettes for adults as a smoking cessation tool might increase the

likelihood of children initiating tobacco use via e-cigarette and becoming tobacco products users. Consistent with published research (25, 26), peer influence and smoking practice at home are significant factors associated with tobacco use. This underscores the interplay between known risk factors of tobacco use and e-cigarettes, which further complicates tobacco control efforts.

The adjusted models included presumable socio-ecological factors that might influence tobacco use (25, 26), yielding robust statistically significant associations (adjusted odds ratio ranging from 3.5 to 7.0, depending on the product in question). The reported odds ratio provides the first representative national estimate of the risk of tobacco initiation among never tobacco users who were first exposed to e-cigarettes. Also, the estimated adjusted OR for the association between lifetime (range 6.0-8.1) or current e-cigarette use (range 4.1-6.0) and the outcome tobacco products are the first reported in a representative sample of American adolescents, while controlling for important factors that are associated with tobacco use. Although a previous study reported a significant association between lifetime and current use of e-cigarettes and smoking cigarettes from the 2011 and 2012 NYTS (13), it was focused only on cigarette smokers and did not adjust for the factors we controlled for in the logistic regression models. Also, e-cigarettes were not the most prevalent tobacco products used by adolescents in the previous NYTS as the case in the 2014 NYTS& 2015 NYTSs, which are used in the current study.

The current study has some limitations. The analysis was bound by the available variables at NYTS; therefore, it did not allow including other variables. Those who initiated cigarettes, cigar, and smokeless tobacco later on might have done so with or

without the preceding e-cigarette initiation (i.e. adolescence is the time where most smokers initiate smoking). However, the referred to five published cohort studies suffered from similar limitations. Also, despite the limitations of causal inference from cross-sectional design, our estimated adjusted odds ratio for cigarettes, cigars, and smokeless tobacco initiation was within the range of previously published research, which underscores the consistency of our results to similar research supporting possible a causal relationship. Recall bias is possible and the exact age of initiation could not be ascertained for all products.

In conclusion, the results suggest that e-cigarette use in the homes of adolescents and among adolescents themselves is a risk factor to initiation and use of other tobacco products. Future studies should focus on progression to current use, intensity to smoke, and difficulty of quitting among e-cigarette initiators and -cigarette users.

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Table 1: Characteristics of tobacco users according to the reported tobacco use initiation method among the NYTS 2014 and 2015 participants.

Characteristics	Tobacco use Initiation method^b				Overall^b
	E-cigarettes	Cigarettes	Cigars	Smokeless	
Respondents, No. (%)	2,477	5,057	1,521	1,055	10,110
Age, mean (SD), y**	15.1 (1.8)	15.6 (1.9)	16.1 (1.8)	15.8 (1.9)	15.5 (1.9)
Gender, No. (%)**					
Male	1,319 (52.0)	2,466 (46.9)	928 (60.1)	883 (84.7)	5,596 (54.4)
Female	1,131 (48.0)	2,546 (53.1)	584 (39.9)	164 (15.3)	4,425 (45.6)
Race, No. (%)**					
White	1,153 (56.0)	2,456 (57.1)	686 (55.0)	806 (82.3)	5,101 (59.4)
Black	243 (9.5)	680 (11.7)	420 (24.2)	34 (2.8)	1,377 (12.1)
Hispanic/Latino	859 (26.9)	1,452 (23.1)	316 (15.8)	136 (8.7)	2,763 (21.3)
Other	123 (3.7)	239 (4.0)	42 (1.8)	29 (2.0)	433 (3.4)
Unknown	99 (3.8)	230 (4.0)	57 (3.3)	50 (4.2)	436 (3.9)
Grade, No. (%)**					
Middle school	860 (31.1)	1,210 (22.6)	230 (13.5)	236 (21.3)	2,536 (23.1)
High school	1,592 (68.9)	3,812 (77.3)	1,282 (86.2)	813 (78.7)	7,499 (76.7)

** P < .001

^a Respondents with missing values were excluded.

^b Percentages (weighted) are by column.

Table 2: Characteristics of the study population according to e-cigarette use among the participants of the 2014 and 2015 NYTS.

Characteristics	All ^b	E-cigarette use ^c	
		Life-time	Current
Respondents, No. (%)	39,718 (100)	8,887 (23.4)	3,973 (10.3)
Age, mean (SD), y	14.5 (2.1)	15.6 (1.9)**	15.7 (1.8)**
Gender, No. (%)			
Male	20,108 (50.7)	4,925 (25.4)**	2,327 (11.8)**
Female	19,267 (49.3)	3,888 (21.5)	1,605 (8.7)
Race, No. (%)			
White	18,375 (54.7)	4,305 (23.9)**	2,022 (10.9)**
Black	5,971 (14.0)	994 (17.6)	335 (5.8)
Hispanic/Latino	10,930 (21.7)	2,828 (27.8)	1,264 (12.1)**
Other	2,421 (4.6)	410 (19.9)	191 (9.6)
Unknown	2,021 (4.9)	350 (18.7)	161 (8.8)
Grade, No. (%)			
Middle school	18,589 (44.0)	2,270 (11.8)**	958 (4.6)**
High school	20,832 (55.9)	6,543 (32.5)	2,974 (14.7)
Unknown	36 (0.1)	13 (51.9)	9 (39.5)
Life-time cigarette, No. (%) ^d			
Never	30,390 (77.9)	3,262 (11.2)**	1,161 (3.9)
Life-time	8,569 (22.1)	5,409 (66.5)	2,694 (32.8)
Current cigarette, No. (%) ^d			
Non-user	36,374 (93.7)	6,611 (19.2)**	2,455 (7.0)**
Current	2,473 (6.3)	1,947 (81.8)	1,327 (55.6)
Life-time cigars, No. (%) ^d			
Never	32,075 (82.6)	4,336 (14.0)**	1,557 (4.8)
Life-time	6,714 (17.4)	4,309 (67.0)	2,282 (35.2)
Current cigars, No. (%) ^d			
Non-user	36,254 (94.5)	6,923 (19.9)**	2,642 (7.4)
Current	2,200 (5.5)	1,567 (75.6)	1,085 (52.7)
Life-time smokeless tobacco No. (%) ^d			
Never	35,805 (91.7)	6,674 (19.2)**	2,693 (7.6)
Life-time	3,076 (8.3)	2,057 (69.7)	1,170 (39.3)**
Current smokeless tobacco, No. (%) ^d			
Non-user	37,613 (96.2)	7,802 (21.4)**	3,200 (8.6)**
Current	1,401 (3.8)	998 (75.1)	710 (52.0)

** P < .001

Ever use indicates lifetime trial and current use indicates past 30 days use.

^a Respondents with missing values for e-cigarettes and tobacco use variables were excluded.

^b Percentages are by column.

^c Percentages are by row.

^d All percentages are

weighted.

^e Tobacco products are limited to the tested groups i.e. cigarettes, cigars, and

smokeless tobacco.

Table 3: Association of smoking initiation via e-cigarettes (and e-cigarette use) with life-time use of cigarettes, cigars, and smokeless tobacco from the 2014 and 2015 NYTS.

Life-time use	At least one	Cigarettes	Cigars	Smokeless tobacco
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Adjusted models				
Initiation via e-cigarette				
Initiation via e-cigarette	6.0 (5.1-7.2)**	3.7 (3.1-4.5)**	2.5 (2.0-3.1)**	4.1 (2.9-5.7)**
Age (per year)	1.4 (1.3-1.4)**	1.3 (1.3-1.4)**	1.5 (1.4-1.6)**	1.3 (1.2-1.4)**
Male (Ref= female)	1.3 (1.1-1.5)**	1.3 (1.1-1.5)**	1.2 (1.0-1.4)	3.0 (2.2-4.2)**
Race				
White	1	1	1	1
Black	2.5 (2.0-3.1)**	2.1 (1.7-2.7)**	3.2 (2.5-4.2)**	1.1 (0.7-1.8)
Hispanic/Latino	2.0 (1.7-2.3)**	2.0 (1.7-2.4)**	1.6 (1.4-2.0)**	1.3 (1.0-1.6)*
Peer influence	-----	4.5 (4.0-5.2)**	6.2 (5.4-7.1)**	-----
Household e-cigarette use	1.7 (1.4-2.0)**	1.8 (1.4-2.2)**	1.5 (1.2-1.8)*	1.9 (1.3-2.8)*
Household tobacco use	1.7 (1.5-1.9)**	1.7 (1.4-2.0)**	2.2 (1.7-2.8)**	2.7 (2.0-3.7)**
Life-time e-cigarette				
Life-time e-cigarette use	12.9 (11.8-14.1)**	7.3 (6.6-8.0)**	5.7 (5.1-6.3)**	7.8 (6.5-9.4)**
Age (per year)	1.39 (1.36-1.44)**	1.3 (1.3-1.4)**	1.5 (1.4-1.5)**	1.3 (1.2-1.3)**
Male (Ref= female)	1.3 (1.2-1.4)**	1.1 (1.0-1.2)*	1.4 (1.2-1.5)**	4.5 (3.8-5.3)**
Race				
White	1	1	1	1
Black	1.6 (1.3-1.9)**	1.5 (1.3-1.8)**	2.3 (2.0-2.8)**	0.3 (0.2-0.4)**
Hispanic/Latino	1.1 (1.0-1.2)	1.2 (1.1-1.4)**	1.0 (0.9-1.1)	0.5 (0.4-0.6)**
Peer influence	-----	4.5 (4.2-4.9)**	5.5 (5.0-6.1)**	-----
Household e-cigarette use	1.1 (0.9-1.2)	1.2 (1.0-1.3)*	0.9 (0.8-1.1)	0.9 (0.8-1.1)
Household tobacco use	2.4 (2.2-2.6)**	2.2 (2.0-2.4)**	2.7 (2.3-3.1)**	4.9 (4.0-6.1)**
Current e-cigarette				
Current e-cigarette use	11.4 (10.1-13.0)**	4.6 (4.1-5.3)**	4.1 (3.6-4.7)**	6.2 (5.3-7.2)
Age (in years)	1.5 (1.4-1.5)**	1.4 (1.35-1.44)**	1.5 (1.5-1.6)**	1.3 (1.3-1.4)**
Male (Ref= female)	1.3 (1.2-1.4)**	1.1 (1.0-1.3)*	1.4 (1.2-1.5)**	4.4 (3.6-5.3)**
Race				
White	1	1	1	1
Black	1.4 (1.2-1.7)**	1.5 (1.2-1.7)**	2.1 (1.8-2.5)**	0.3 (0.2-0.4)**
Hispanic/Latino	1.2 (1.1-1.3)**	1.3 (1.2-1.5)**	1.1 (1.0-1.2)	0.6 (0.5-0.7)**
Peer influence	-----	5.4 (5.0-5.9)**	6.4 (5.8-7.2)**	-----
Household e-cigarette use	1.4 (1.2-1.5)**	1.4 (1.3-1.6)**	1.1 (0.9-1.2)	1.0 (0.8-1.2)
Household tobacco use	2.6 (2.4-2.8)**	2.3 (2.1-2.6)**	2.6 (2.3-3.0)**	5.2 (4.3-6.4)**

* p < 0.05 ** p < 0.

^aAll OR are weighted. ^bThe variable " Having someone smoke this product at home" refers to the outcome tobacco products in the columns.

Table 4: Association of initiation via e-cigarettes (and e-cigarette use) with current use of cigarettes, cigars, and/or smokeless tobacco from the 2014 and 2015 NYTS.

Current use	At least one	Cigarettes	Cigars	Smokeless tobacco
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Adjusted models				
Initiation via e-cigarette				
Initiation via e-cigarette	4.4 (3.5-5.6)**	2.7 (1.9-4.0)**	1.7 (1.2-2.4)*	3.4 (2.2-5.4)**
Age (per year)	1.4 (1.4-1.5)**	1.3 (1.2-1.5)**	1.4 (1.3-1.6)**	1.3 (1.3-1.5)**
Male (Ref= female)	1.8 (1.4-2.3)**	1.6 (1.2-2.2)*	1.7 (1.2-2.2)*	3.6 (2.3-5.6)**
Race				
White	1	1	1	1
Black	1.7 (1.3-2.4)**	1.5 (1.0-2.4)	2.7 (1.8-3.9)**	1.4 (0.8-2.5)
Hispanic/Latino	1.9 (1.5-2.3)**	2.1 (1.5-2.9)**	1.8 (1.2-2.6)**	1.7 (1.3-2.4)*
Peer influence	-----	7.7 (6.6-8.9)**	6.5 (5.7-7.4)**	-----
Household e-cigarette use	2.0 (1.5-2.5)**	2.2 (1.5-3.4)**	1.7 (1.0-2.8)*	1.5 (0.9-2.3)
Household tobacco use	2.1 (1.7-2.5)**	2.1 (1.5-2.8)**	2.7 (1.8-4.0)**	3.5 (2.3-5.5)**
Life-time e-cigarette				
Life-time e-cigarette use	9.4 (8.2-10.8)**	5.4 (4.4-6.5)**	3.9 (3.3-4.7)**	8.2 (6.4-10.5)**
Age (per year)	1.4 (1.3-1.4)**	1.3 (1.2-1.3)**	1.3 (1.3-1.4)**	1.2 (1.2-1.3)
Male (Ref= female)	1.9 (1.7-2.2)**	1.4 (1.2-1.6)**	1.5 (1.3-1.7)*	5.5 (4.3-7.0)**
Race				
White	1	1	1	1
Black	1.0 (0.8-1.2)	0.9 (0.7-1.3)	2.3 (1.8-3.1)**	0.3 (0.2-0.5)**
Hispanic/Latino	0.8 (0.7-0.9)**	1.0 (0.8-1.3)	1.3 (1.1-1.5)*	0.6 (0.5-0.7)**
Peer influence	-----	6.7 (6.1-7.3)**	4.0 (3.7-4.4)**	-----
Household e-cigarette use	1.1 (0.9-1.2)	1.2 (1.0-1.4)	1.0 (0.8-1.3)	0.8 (0.6-0.99)*
Household tobacco use	2.3 (2.0-2.6)	2.4 (2.0-2.8)**	3.2 (2.5-4.0)	5.5 (4.4-7.0)**
Current e-cigarette				
Current e-cigarette use	11.0 (9.7-12.5)**	5.2 (4.4-6.2)**	5.0 (4.2-6.0)**	9.4 (7.4-11.9)**
Age (in years)	1.4 (1.4-1.5)**	1.3 (1.3-1.4)**	1.4 (1.3-1.4)**	1.3 (1.2-1.4)**
Male (Ref= female)	1.9 (1.7-2.2)**	1.3 (1.1-1.6)**	1.5 (1.2-1.7)**	5.5 (4.2-7.2)**
Race				
White	1	1	1	1
Black	1.0 (0.8-1.2)	0.9 (0.7-1.2)	2.4 (1.8-3.0)**	0.4 (0.3-0.6)**
Hispanic/Latino	0.9 (0.8-1.0)	1.1 (0.9-1.3)	1.3 (1.1-1.6)**	0.6 (0.5-0.8)**
Peer influence	-----	7.0 (6.4-7.6)**	4.1 (3.8-4.4)**	-----
Household e-cigarette use	1.0 (0.8-1.1)	1.1 (0.9-1.4)	0.9 (0.7-1.2)	0.7 (0.5-0.9)*
Household tobacco use	2.7 (2.4-3.0)**	2.6 (2.2-3.1)**	3.4 (2.7-4.2)**	6.7 (5.3-8.6)**

* p < 0.05

** p < 0.001

^a All OR are weighted.

^b The variable " Having someone smoke this product at home" refers to the outcome tobacco products in the columns.

**E-cigarette marketing exposure and combustible tobacco use among adolescents in
the United States**

Abstract

Introduction

E-cigarette advertising has been shown to be associated with use of e-cigarettes, but its association with tobacco use has not been studied. Therefore, we examined the association between e-cigarettes advertisement and tobacco use.

Methods

Data from a nationally representative sample of 22,007 middle and high school students (grades 6-12) were used to conduct the analysis. Logistic regression models estimated the adjusted odds ratios (AOR) of ever and current use of cigarette, hookah, cigar, and polytobacco use. Odds ratios were weighted and adjusted for study design, non-response rates, school level, gender, race/ethnicity, e-cigarette use, and smoking at home. E-cigarette marketing exposure was significantly associated with ever use of cigarettes (AOR: 1.3, 95% CI: 1.1-1.5), hookah (AOR: 1.4, 95% CI: 1.2-1.7), cigars (AOR: 1.5, 95% CI: 1.4-1.6), and polytobacco (AOR: 1.7, 95% CI: 1.5-1.8). Likewise, E-cigarette marketing exposure was significantly associated with current use of cigarettes (AOR: 1.3, 95% CI: 1.1-1.6), hookah (AOR: 1.3, 95% CI: 1.03-1.7), cigars (AOR: 1.3, 95% CI: 1.1-1.6), and polytobacco use (AOR: 1.8, 95% CI: 1.5-2.1).

Conclusions

The results suggest that e-cigarette advertisement is associated with use of cigarettes, hookah, cigars, and polytobacco products. These results add to the evidence about the

risks of e-cigarette marketing and highlight the need for stricter regulation of e-cigarette advertisements.

Introduction

Electronic cigarettes (e-cigarettes) were introduced to the United States (US) market in 2007 and also globally around this time. However, the increasing use of e-cigarette among adolescents started to gain attention in 2011, and there were dramatic increases in the following years (Singh, Arrazola, et al., 2016). For example, data from the National Youth Tobacco Survey (NYTS) show that 1.1% of middle and 4.5% of high school students in the United States used e-cigarettes in 2013, and by 2014 the prevalence had nearly tripled (3.9% in middle school and 13.4% in high school (Singh, Arrazola, et al., 2016). Similar increases in e-cigarette use have been observed in other countries (Bauld, MacKintosh, Ford, & McNeill, 2016; Durmowicz, 2014; Lee, Grana, & Glantz, 2014). Notably, the US sales of e-cigarettes have been doubling each year and reached \$1 billion in 2013 (Robehmed, 2013), \$2.5 billion in 2014, and are projected to reach \$10 billion by the year 2017 (Herzog, Gerberi, & Scott, 2014).

During the same time period, there was a plethora of e-cigarettes marketing on the Internet and in newspapers, magazines, public places (e.g. stores), and television advertisements. In 2011, it was estimated that \$6.4 million was spent on e-cigarette advertising in the US (Kim, Arnold, & Makarenko, 2014), and spending increased to \$115.3 million in 2014 (Truth Initiative, 2015). However, the expenditure on advertisements does not precisely reflect the extent of marketing because many marketing methods require little to no cost such as the Internet, which has been widely used for e-cigarette advertisements (Duke et al., 2014; Grana & Ling, 2014). The

marketing expansion also occurred in other countries such as the United Kingdom (UK) (de Andrade, Hastings & Angus, 2013).

E-cigarette advertisements pose several concerns. First, they allow once again television advertisements for a nicotine product after a 45 year-ban on tobacco products from television advertisements (Eckard, 1991). The themes of e-cigarette advertisements are reminiscent of the old tobacco marketing methods designed to appeal to adolescents and young adults (Grana & Ling, 2014; USHHS, 2012). Themes used to specifically target young people include having celebrities back the product, promoting it as a “life choice”, associating it with sports events, stating it is a “smarter alternative”, using social media platforms such as Facebook and Instagram, or claiming romantic appeal for using e-cigarettes (de Andrade et al., 2013; Farrelly et al., 2015; Grana & Ling, 2014; Laestadius, Wahl, & Cho, 2016). It is notable that adolescents aged 12 to 17 years are increasingly exposed to e-cigarette advertisement; for example, from 2011 and 2013 their exposure increased by 256% in the US (Duke et al., 2014). Data from the NYTS indicate that seven out of ten American youth are exposed to some sort of e-cigarette marketing (Singh, Marynak, et al., 2016). In another survey, it was estimated that 84% of adolescents and young adults aged 13-21 years in the US were aware of e-cigarette advertising (Truth Initiative, 2015).

Empirical research has linked exposure to e-cigarette marketing with an increased risk of e-cigarette use (Dai & Hao, 2016; Singh, Agaku, et al., 2016), which is analogous to the documented higher risk of tobacco use associated with exposure to tobacco advertisements (Pierce, Choi, Gilpin, Farkas, & Berry, 1998). A study among middle and high school students in the US found a positive association between pro tobacco

marketing (not related to e-cigarettes) and e-cigarette use (Agaku & Ayo-Yusuf, 2014). However, there is no published research that has examined the association between exposure to e-cigarette marketing and tobacco products use especially cigarettes. A study among daily smokers, intermittent smokers, and former smokers suggested that e-cigarette advertising increases the urge to smoke cigarettes and actual smoking among smokers (Maloney & Cappella, 2016). Also former smokers who viewed the e-cigarette advertisements reported lower intentions to abstain from smoking compared to those who did not view cue advertisements (Maloney & Cappella, 2016). More importantly, perhaps, there is a concern that e-cigarette use and marketing will renormalize tobacco smoking, which might disrupt tobacco control efforts (Cataldo, Petersen, Hunter, Wang, & Sheon, 2015; Fairchild, Bayer, & Colgrove, 2014). Therefore, there is a gap in the literature about the relationship between e-cigarette marketing and tobacco use. According, the objective of this study was to assess the relationship between e-cigarette marketing and tobacco use among adolescents using a nationally representative sample.

Methods

Study population

The NYTS is a nationally representative sample of middle and high school students (grades: 6-12 – age: 9-19 years) from the US that used a three-stage cluster probability sampling design without replacement. Non-Hispanic black and Hispanic students were oversampled. Parents or legal guardians consented to their children's participation. A total of 22,007 adolescents participated in the 2014 anonymous, self-administered pencil and paper survey (91.4% response rate) from 207 schools (80.2% response rate) (Centers for Disease Control and Prevention [CDC], 2014). The Florida

International University Institutional Review Board deemed the study non-human subjects research because of using non-identifiable public access data.

Measures

Exposure to e-cigarette marketing was examined with four questionnaire items which asked participants to report exposure to marketing messages on the internet, television, newspapers, and in stores. Participants who responded to any question with “never” or “rarely” were considered not exposed. Others who selected “sometimes,” “most of the time,” or “always” were considered exposed to the particular marketing method. A new variable was created to sum all sources of e-cigarette marketing exposures. A participant was considered exposed if s/he was exposed to at least one of the four listed marketing methods. We followed the CDC approach of assessing exposure to e-cigarette marketing to assure consistency and facilitate comparison with other published work (Singh, Marynak, et al., 2014; Singh, Agaku, et al., 2016). Also, a full description of the marketing variables and level of the study population’s exposure to them has been published elsewhere (Singh, Marynak, et al., 2014; Singh, Agaku, et al., 2016).

The outcome variables were cigarette, hookah, cigar, and polytobacco ever and current use. Since the study population are adolescents, they are in the stage of experimentation. Therefore, ever and current tobacco use offer important aspects in the developing smoking behavior; hence both were considered. For simplicity, cigars, cigarillos, or little cigars will be referred to as “cigars” throughout this report. Participants were asked about ever (lifetime use) and current (past 30 days) use of cigarettes, cigars, and hookah. Cigarettes, hookah, and cigars were selected because in

the 2014 NYTS they were the most commonly reported nicotine products used (CDC, 2015). Polytobacco use was defined as reporting use of more than one of the following nicotine products: cigarettes, hookah, cigars, snus, chewing tobacco, pipe, bidi, and dissolvable tobacco.

Participants were asked to report all tobacco products smoked at home by parents and other family members, and available responses were used in the present study as the household tobacco use variable (see data analysis section). Other covariates included school level, race/ethnicity, and gender. We used the readily available recoded question for single race classification and collapsed all categories other than non-Hispanic Whites, non-Hispanic Blacks, and Hispanics into “other”.

Data Analysis

The Proc Survey procedure in SAS v9.4 was used to adjust for the survey’s complex design. Weights and the survey procedures were applied to account for the stratified clustered sampling design of the NYTS to adjust for nonresponse, the probability of selection, and to match the sample’s sociodemographic characteristics with those of US middle and high school students in 2014.(CDC, 2014).

We used the chi-square test for categorical variables and t-test for age; in order to test the association between e-cigarette marketing exposure and participant characteristics listed in Table 1. Logistic regression was used to estimate the odds ratio (OR) and corresponding 95% confidence interval (CI) of ever and current cigarette, hookah, cigar, and polytobacco use that is associated with exposure to e-cigarette marketing. The OR and corresponding 95% CI were further adjusted by models that included school level, gender, race/ethnicity, and household tobacco use in separate models for ever and current

use of each tobacco product. The included covariates were known risk factors for tobacco use among adolescents (Cardenas et al., 2015; Tyas & Pederson, 1998). The analysis was limited to the variables available within the NYTS 2014 for all the examined tobacco products to ensure consistency of the models. Statistical models further controlled for e-cigarette use, given it is associated with both e-cigarette marketing and tobacco use (Barrington-Trimis, Urman, et al., 2016; Dai & Hao, 2016; Leventhal et al., 2015; Primack, Soneji, Stoolmiller, Fine, & Sargent, 2015; Singh, Agaku, et al., 2016; Wills, Knight, Williams, Pagano, & Sargent, 2015). Most adolescents used e-cigarettes in conjunction with other products (e.g., 80% of current cigarette smokers tried e-cigarettes in the underlying study population); therefore, it was decided to control for e-cigarette use rather than to stratify the analysis with it to have adequate power to control for the included variables in the employed logistic regression models. E-cigarette use was defined by participants reporting using e-cigarettes in the past 30 days.

Of the participants, 3.5% had missing data and were excluded from analysis. Significance was set to $p < 0.05$. All tests were two-tailed, and Bonferroni-Holm correction for multiple comparisons was applied (Holm, 1979).

Results

A total of 21,055 study participants had valid responses for e-cigarette marketing exposure out of the 22,007 who participated in the 2014 NYTS (96.5% of the total study participants). The full description of the study population is presented in Table 1. More than two thirds (69.1%) of adolescents were exposed to e-cigarette marketing. Exposure was similar between both genders and racial/ethnic groups. However, high school students had higher odds of exposure (OR: 1.2; 95% CI: 1.1-1.3) compared with middle

school students. Ever and current users of cigarettes, hookah, cigars, or polytobacco had higher odds of exposure to e-cigarette marketing messages than non-tobacco users.

The logistic regression models controlling for school level, gender, race/ethnicity, e-cigarette use, and smoking the specified tobacco product at home indicated that those exposed to e-cigarette marketing were more likely to be ever users of the examined tobacco products – Table 2. Adolescents who were exposed to e-cigarette marketing messages had an adjusted odds ratio (AOR) 1.3 (95% CI: 1.1-1.5) to be ever cigarette users. Likewise, e-cigarette marketing exposure was more likely to be associated with the ever use of hookah (AOR: 1.4, 95% CI: 1.2-1.7), cigars (AOR: 1.5, 95% CI: 1.4-1.6), and polytobacco products (AOR: 1.9, 95% CI: 1.7-2.1).

The adjusted odds ratio for e-cigarette marketing exposure and current use of tobacco products are shown in Table 3. E-cigarette marketing exposure was associated with current use of cigarettes (AOR: 1.3, 95% CI: 1.1-1.6), hookah (AOR: 1.3, 95% CI: 1.03-1.7) and cigars (AOR: 1.3, 95% CI: 1.1-1.6).

Discussion

Our results suggest that exposure to e-cigarette marketing is associated with ever and current cigarette, hookah, cigar, or polytobacco use among adolescents. Adolescents who were exposed to e-cigarette marketing had AOR ranging 1.3-1.9 of being an ever user and 1.3-2.4 of being a current user of the examined tobacco products. Thus, exposure to e-cigarette marketing is associated with tobacco use among adolescents after controlling for e-cigarettes and other key factors.

These results are consistent with those of a study among high school students in Los Angeles that found that exposure to an e-cigarette social environment increases the susceptibility to cigarette smoking (Barrington-Trimis, Berhane, et al., 2016).

E-cigarette marketing exposure may lead to an increase in tobacco smoking via two putative mechanisms. The first is through increasing e-cigarettes use (Dai & Hao, 2016; Singh, Agaku, et al., 2016), which in turn may increase the risk for cigarette and other tobacco products use as previously published research suggests (Barrington-Trimis, Urman, et al., 2016; Leventhal et al., 2015; Primack et al., 2015; Wills et al., 2015). As such, we have controlled for e-cigarette use in our models to eliminate the possibility that the observed association resulted from this route. The second is a direct pathway by increasing the susceptibility to use tobacco products (e.g., cigarettes; Barrington-Trimis, Berhane, et al., 2016) and actual use of tobacco products. The similarity in shape between e-cigarette and its reminiscent marketing strategies that appeal to younger people (see the introduction section for details) might lead to increasing the risk of tobacco use (de Andrade et al., 2013).

One study indicated that e-cigarette advertising was associated with increased urges and thoughts to smoke cigarettes among smokers (Kim, Lee, Shafer, Nonnemaker & Makarenko, 2015). This study suggests that e-cigarette advertisements may induce a desire to use tobacco, hence provides plausibility for our observed associations. Also, our finding extends the previously observed association between the exposure to conventional tobacco advertisement exposure with the use of both cigarettes and alternative tobacco products (Agaku & Ayo-Yusuf, 2014).

Notably, nicotine is known to cause developmental problems and increases the risk of nicotine dependence among adolescents and difficulty to quit later on as adults (Goriounova & Mansvelder, 2012; Kandel & Kandel, 2014). E-cigarettes can interfere with tobacco control efforts through several avenues; mainly the renormalization of tobacco smoking (Stanwick, 2015) and initiation of tobacco smoking among adolescents who had previously never smoked (Barrington-Trimis, Urman, et al., 2016; Leventhal et al., 2015; Primack et al., 2015; Wills et al., 2015). The disruption of tobacco control does not necessarily lead to an increase in rates of cigarette and other tobacco products use. However, it can possibly reduce the magnitude of decline in those rates despite of all the spent tobacco control efforts, which would be pivotal issue to address in tobacco control policies.

This study raises concerns about the efforts to reduce tobacco use among adolescents, given the expanding marketing for e-cigarettes (Kim et al., 2014; Kornfield, Huang, Vera & Emery, 2015). It is of particular concern that e-cigarette marketing expanded almost 20-fold from 2011 to 2014 (Kim et al., 2014; "Truth Initiative," 2015), and adolescents' exposure to e-cigarette marketing tripled (Emery, Vera, Huang & Szczypka, 2014).

Due to the cross-sectional design of the present study, the temporality of the associations cannot be ascertained. However, a causal relationship was documented in marketing exposure and tobacco use from research on tobacco marketing (Biener & Siegel, 2000; USHHS, 2012). The limitation of cross-sectional design does not allow a similar conclusion to be drawn in the present study. Recall bias is possible, but some of the reported rates in this survey are consistent with those of other national surveys (e.g.,

Monitoring the Future Survey; Johnston, O'Malley, Miech, Bachman, & Schulenberg, 2015). There is a possibility of attention bias as well. Those who use tobacco products might be more likely to notice e-cigarette marketing compared to those who do not use tobacco products. However, the same bias might be applicable to all tobacco marketing and tobacco use. However, longitudinal research provided evidence that marketing messages increases the risk to use tobacco products, while attention bias remains a possibility too (Biener & Siegel, 2000; USHHS, 2012).

Our findings suggest that a longitudinal study is warranted to examine possible causal effect of e-cigarette marketing on tobacco use. Nevertheless, the reported odds ratio was significantly associated with higher risk for tobacco use due to e-cigarette marketing exposure after controlling for important factors predicting cigarette, hookah, and cigar use such as grade, gender, household smoking, and e-cigarette use, which highlights the robustness of our analysis.

Our results along with previous work indicate that it would be prudent to implement stricter regulations for e-cigarette marketing. This might be critical as the Food and Drug Administration announcements on e-cigarettes are pending, but no formal nationwide regulations are in place in the US (Kim et al., 2014; Kornfield et al., 2015). Although this study was conducted among adolescents in the US, similar associations are possible and expected in other countries. Hence this report might contribute and inform tobacco control policies in the US as well as other countries in order to protect adolescents from exposure to e-cigarette marketing and a risk of tobacco product use.

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Table 1: Characteristics of the study population by exposure to e-cigarette marketing among adolescents surveyed at the NYTS 2014.

Characteristics	All ^b	Exposed to e-cigarette marketing ^c		Crude OR (95% CI)
		No	Yes	
Respondents, No. (%)	21,055 (100)	6,583 (30.9)	14,472 (69.1)	
Age, mean (SD), in years	14.5 (2.1)	14.4 (2.1)	14.6 (2.1)**	1.1 (1.0-1.1)**
Gender, No. (%)				
Male	10,613 (49.9)	3,353 (30.8)	7,260 (69.2)	1 (0.9-1.1)
Female	10,287 (50.1)	3,184 (30.9)	7,103 (69.1)	1
Race, No. (%)				
White	9,676 (56.2)	2,876 (29.4)	6,800 (70.6)**	1
Black	3,182 (14.2)	974 (31.3)	2,208 (68.7)	0.9 (0.8-1.0)
Hispanic	5,823 (20.7)	1,811 (31.0)	4,012 (69.0)	0.9 (0.8-1.0)
Other	1,349 (4.3)	554 (41.6)	795 (58.4)	0.6 (0.5-0.7)**
Unknown	1,025 (4.7)	368 (37.4)	657 (62.6)	0.7 (0.6-0.9)**
School level, No. (%)				
Middle school	9,945 (43.8)	3,368 (33.4)	6,577 (66.6)**	1
High school	109,85 (56.2)	3,180 (28.9)	7,805 (71.1)	1.2 (1.1-1.3)**
Unknown	11 (0.1)	4 (28.8)	7 (71.2)	1.2 (0.3-5.1)
Ever cigarette, No. (%) ^d				
Never	16,093 (77.8)	543 (33.2)	10,662 (66.8)**	1
Ever	4,617 (22.2)	1,053 (22.8)	3,564 (77.2)	1.6 (1.5-1.9)
Current cigarette, No. (%) ^d				
Nonsmoker	19,354 (93.7)	6,213 (31.7)	13,141 (68.3)**	1
Smoker	1,322 (6.3)	267 (18.8)	1,055 (81.2)	2.0 (1.7-2.3)
Ever hookah, No. (%) ^d				
Never	17,546 (85.3)	5,769 (32.7)	11,777 (67.3)**	1
Ever	2,872 (14.7)	629 (21.0)	2,243 (79.0)	1.8 (1.6-2.1)
Current hookah, No. (%) ^d				
Nonsmoker	19,230 (93.6)	6,148 (29.6)	13,082 (64.0)**	1
Smoker	1,301 (6.4)	265 (19.2)	1,036 (80.8)	1.9 (1.6-2.4)
Ever cigars No. (%) ^d				
Never	17,097 (82.5)	5,675 (33.0)	11,422 (67.0)**	1
Ever	3,607 (17.5)	811 (21.3)	2,796 (78.7)	1.8 (1.7-2.0)
Current cigar, No. (%) ^d				
Nonsmoker	19,410 (94.7)	6,191 (31.5)	13,219 (68.5)**	1
Smoker	1,117 (5.3)	239 (19.3)	878 (80.7)	1.9 (1.6-2.3)
Ever polytobacco, No. (%) ^d				
Never or one product	15,195 (77.7)	5,214 (34.1)	9,981 (65.9)**	1
Ever more than one product	4,353 (22.3)	922 (20.8)	3,431 (79.2)	2.0 (1.8-2.2)
Current polytobacco, No. (%) ^d				
Nonsmoker	18,244 (92.1)	5,941 (96.0)	12,303 (90.4)	1
Smoker	1,525 (7.8)	258 (15.8)	1,267 (84.2)	2.5 (2.2-3.0)

Abbreviations: OR = odds ratio, CI = confidence interval.

** P < .001

Ever use indicates lifetime trial and current use indicates use during past 30 days.

^a Respondents with missing values for e-cigarettes and tobacco use variables were excluded.

^b Percentages are by column.

^c Percentages are by row.

^d All percentages are

weighted. ^e Tobacco products are limited to the tested groups i.e. cigarettes, cigars, and chewing tobacco.

Polytobacco use refers to more than one tobacco product use.

Table 2: Association of demographic factors and e-cigarettes marketing exposure with ever use of cigarettes, cigars, hookah and polytobacco use from the 2014 NYTS (n= 21,055).

Ever use	Cigarettes AOR (95% CI)	Hookah AOR (95% CI)	Cigars AOR (95% CI)	Polytobacco AOR (95% CI)
High school (Ref= middle school)	3.1 (2.5-3.9) **	4.6 (3.7-5.7)**	4.6 (3.8-5.5)**	4.6 (3.8-5.5)**
Male (Ref= female)	1.1 (0.97 – 1.3)	0.9 (0.8-1.1)	1.7 (1.5-1.9)**	1.3 (1.2-1.5)*
Race				
White	1	1	1	1
Black	1.0 (0.9-1.2)	0.8 (0.7-0.97)*	1.5 (1.2-1.9)**	0.7 (0.6-0.9)*
Hispanic	1.3 (1.1-1.5)	1.6 (1.4-1.9)**	1.1 (0.98-1.3)	1.2 (0.9-1.4)
E-cigarette marketing exposure	1.3 (1.1-1.5)**	1.4 (1.2-1.7)**	1.5 (1.4-1.6)**	1.9 (1.7-2.1)**
E-cigarette use	10.2 (8.5-12.4) **	8.2 (6.6-10.1)**	8.7 (7.3-10.5)**	-----
Household tobacco use	2.7 (2.4-3.0) **	11.2 (7.6-16.4) **	4.1 (3.4-4.8)**	-----

Abbreviations: AOR = adjusted odds ratio, CI = confidence interval, Ref=referent.

* p < 0.05 ** p < 0.001

^a All OR are weighted and adjusted for study design (selection and clustering), non-response rates, school level, gender, race, e-cigarette use, and smoking at home.

^b The variable " Household tobacco use " refers to the outcome tobacco products in the columns. Polytobacco use refers to more than one tobacco product use.

Abbreviations: AOR =adjusted odds ratio.

Table 3: Association of demographic factors and e-cigarettes marketing exposure with current use of cigarettes, cigars, hookah and polytobacco use from the 2014 NYTS (n= 21,055).

Current use	Cigarettes	Hookah	Cigars	Polytobacco
	AOR (95% CI)	AOR (95% CI)	AOR (95% CI)	AOR (95% CI)
High school (Ref= middle school)	2.7 (2.0-3.5)**	3.0 (2.3-3.9)**	3.3 (2.5-4.4)**	5.1 (4.1-6.3)**
Male (Ref= female)	1.3 (1.1-1.6)*	0.8 (0.7-0.99)*	2.0 (1.6-2.5)**	1.5 (1.3-1.8)**
Race				
White	1	1	1	1
Black	0.6 (0.5-0.8)**	0.9 (0.6-1.3)	1.5 (1.2-2.0)*	0.3 (0.2-0.5)**
Hispanic	0.97 (0.77-1.2)**	1.8 (1.4-2.2)**	1.2 (0.9-1.5)	0.9 (0.7-1.1)
E-cigarette marketing exposure	1.3 (1.1-1.6)**	1.3 (1.03-1.7)*	1.3 (1.1-1.6)*	2.4 (2.0-2.8)**
E-cigarette use	12.9 (10.8-15.5)**	11.5 (9.3-14.3)**	11.2 (8.8-14.1)**	-----
Household tobacco use	2.9 (2.6-3.3)**	9.9 (6.9-14.2)**	6.3 (5.2-7.6)**	-----

Abbreviations: AOR = adjusted odds ratio, CI = confidence interval, Ref=referent.

* $p < 0.05$ ** $p < 0.001$ ^a All OR are weighted and adjusted for study design (selection and clustering), non-response rates, school level, gender, race, e-cigarette use, and smoking at home. Polytobacco use refers to more than one tobacco product use.

^b The variable " Household tobacco use " refers to the outcome tobacco products in the columns.

MANUSCRIPT 3 (Submitted)

Symptoms of Nicotine Dependence Among Adolescent E-cigarette, Cigarette, and Dual Users Who Participated in the 2014 & 2015 National Youth Tobacco Surveys (NYTS)

Abstract

Introduction:

E-cigarette use is expanding among adolescents dramatically and there is no previous research to examine its addictiveness among them. We aimed to examine the association between reporting dependence symptoms and e-cigarettes cigarettes, and dual use.

Methods:

Cross-sectional National Youth Tobacco Survey (NYTS) 2014 and 2015 of 39,718 middle and high school students (grades 6-12) representing adolescents in the US. Main exposure: E-cigarette, cigarette, and dual use. Main outcome measures: Logistic regression models estimated the adjusted odds ratios (AOR) with their 95% confidence intervals (CI) of strong craving, feeling restlessness, and wake-up tobacco use dependence symptoms that is associated with e-cigarette, cigarette, dual use after controlling for important factors.

Results:

Among adolescent daily tobacco users, 35.6% of e-cigarette users and 85.3% of cigarette users reported one or more dependence symptoms. These proportions increased to be 74.3% of e-cigarette and 93.3% of cigarette dual users. Strong cravings was the most reported symptom with a range of 16.1-58.9% among different study groups. There was a dose-response association between reporting dependence symptoms and the frequent

tobacco use for e-cigarette and cigarette users. Starting to use tobacco before age 11 had consistent association of reporting dependence (AOR 1.4-3.0), but the odds were almost two folds for e-cigarette users compared to cigarette users. Dual users had the highest odds to report dependence symptom (AOR: 1.8-3.2) followed by cigarette users (AOR: 1.9-2.6) compared to e-cigarettes as the reference group.

Conclusions:

Our results suggest that e-cigarettes are addictive as demonstrated by reporting the three examined symptoms, more dependence reporting among early initiators, and dose response association. Despite cigarette and dual users showed higher odds of reporting dependence, the addictiveness of e-cigarettes occurred at appreciable rates. This is further confirmed by the higher rates among daily e-cigarette users. Early age of tobacco use (i.e. eleven years) was consistently associated with reporting dependence among e-cigarette users with higher AOR compared to cigarette users and had around two folds of odds to report dependence symptom among e-cigarette compared to cigarette. These findings call to control adolescents' access to e-cigarettes to limit its use among them.

Introduction

Although e-cigarettes were first invented in 2003, the prevalence of their use increased significantly starting in 2011, especially among younger generations.¹ In 2015 in the United States (US), 5.3% of middle school students, 16.0% of high school students, 13.6% of young adults, and 5.7% among young adults (18-24 years) reported using e-cigarettes within the past 30 days.² This is particularly problematic as e-cigarettes exposed non-tobacco users to nicotine; the addictive substance in tobacco products.³

Empirical research has shown that e-cigarette use among non-tobacco using adolescents is associated with a higher risk of initiating the use of tobacco products such as cigarettes, cigars, and chewing tobacco.^{4,5}

Some putative pathways might be contributing to tobacco use after e-cigarette use.⁶ One is directly through the nicotine gateway mechanism⁷ i.e. nicotine dependence.⁸ Nicotine dependence is a critical factor contributing to tobacco use, hence it ought to be examined for several reasons. First, inhaling nicotine is more addictive than other forms of nicotine administration because nicotine absorbed via the pulmonary system (e.g. e-cigarettes and cigarettes) reaches the brain faster than absorption via the venous system (e.g. in skin patches).⁹ Furthermore, dependence can develop shortly after initiating tobacco and even before daily use.^{10,11} The link between e-cigarettes and nicotine dependence might jeopardize decades of tobacco control efforts by introducing children to nicotine from e-cigarettes which would put them at higher risk for tobacco use.^{4,5} Therefore, it is of public health significance to study nicotine dependence among e-cigarette adolescent users.

Limited research among current and former adult tobacco users has compared symptoms of nicotine dependence among e-cigarette users to their dependence on other tobacco products and/or nicotine gums.¹²⁻¹⁶ Examining dependence among ex-smokers can create recall and selection bias since successful quitting is an indicator of less dependence, and ex-smokers might be inaccurate in reporting their old dependence symptoms.¹⁷ Also, the majority of adult smokers usually start to experiment with tobacco during adolescence; leading symptoms of dependence to start to develop during this period.^{17,18}

Therefore, it is ideal to describe dependence symptoms among adolescents when the nicotine dependence is first developing. To our knowledge, no research has been published to describe dependence symptoms among adolescent e-cigarette users. There has been only one study of nicotine dependence among e-cigarette users from a national sample (Population Assessment of Tobacco and Health [PATH] Study), and it included only adults.¹⁶ The other limited research among e-cigarette users mainly focused on adult volunteer samples which limits its generalization.¹²⁻¹⁵ The current study aims to fill the gaps in the literature by comparing nicotine dependence symptoms between e-cigarette and cigarette users from a nationally representative sample of adolescents who participated in the 2014 and 2015 National Youth Tobacco Survey (NYTS).

Methods:

Study population

The data were obtained from the 2014 and 2015 National Youth Tobacco Survey (NYTS). This survey aimed to obtain a nationally representative cross-sectional sample of middle and high school students (grades 6-12 with age ranging from 12-19 years). A total of 22,007 and 17,711 adolescents participated (91.4% and 87.4% response rate) in the 2014 and 2015 surveys respectively (total=39,718).

Ethics statement

The Institutional Review Board at Florida International University deemed the study to be non-human subjects research because it used non-identifiable public access data.

Measures

The nicotine dependence symptoms were measured by five survey items. The first three were measured both survey years, and the last two were only present in one year. This paper is restricted to the 3 dependence symptoms which were present in the two years to facilitate the interpretation of the results.

1) During the past 30 days, have you had a strong craving or felt like you really needed to use a tobacco product of any kind? (yes/no), will be referred to as “strong craving”;

2) I feel restless and irritable when I don’t use tobacco for a while? (I do not use tobacco/not at all true/sometimes true/often true/always true), will be referred to as “restless”;

3) How soon after you wake-up do you want to use a tobacco product? (I do not use tobacco/within 5 minutes/from 6 to 30 minutes/from more than 30 minutes to 1 hour/after more than 1 hour but less than 24 hours/I rarely want to use tobacco), will be referred to as “wake-up tobacco use”;

The Yes/No response were used as the binary outcome in logistic regression in “strong craving”. The “restless” responses were categorized into: (i) those who reported “sometimes true/often true/always true,” to indicate being restless; (ii) otherwise indicated not having this dependence symptom. The responses for “wake-up tobacco use” were grouped into either tobacco use within 30 minutes or more than this. Published research suggest reliability¹⁹ and construct validity^{20,21} in predicting failed cessation, progression to tobacco use, and measures of smoking in adolescents for such dependence symptoms.

E-cigarette and cigarette users were defined as participants who reported using one product, but not the other, at least once in the past month i.e. current users. Dual users are those who reported using both products. Age of initiation was dichotomized at 11 years similar to previous research.²² Other tobacco products was the self-report use of other than cigarettes and e-cigarettes in the past 30 days (cigars, smokeless tobacco, pipe, bidi, hookah, snus, and dissolvable tobacco).

Data Analysis

Proc Survey procedure in SAS v9.4 was used to adjust for the survey's complex design in the pooled 2014 and 2015 NYTS.²³

Distribution and demographics were presented by numbers and weighted frequencies of the study population. Each dependence symptom was used as the binary outcome in separate multivariate logistic regression models to estimate the odds ratio (OR) and corresponding 95% confidence interval (CI) of more dependence that is associated with one of the study groups. The OR and corresponding 95% CI were adjusted by including the year of survey, age, gender, race/ethnicity, age of initiation of e-cigarettes and cigarettes, number of days smoked e-cigarettes and cigarettes in the past 30 days, and current use of other tobacco products.

Missing data were excluded from the analysis due to lower percentage that is not expected to affect the results. Statistical significance was set to 0.05. All tests were 2-tailed, and Bonferroni-Holm correction for multiple tests was applied.²⁴

Results

The prevalence of current e-cigarette use, cigarette use, and dual use in the combined survey years were 7.0%, 2.9%, 3.4% (data not shown); respectively. Table 1 describes the demographic and tobacco use characteristics of current e-cigarette and

cigarette users. There was a higher percentage of middle schoolers and Hispanics among e-cigarette users compared to cigarette or dual users.

A larger proportion of cigarette only users (27.0%) started to smoke before the age of 11 years compared to the two other groups (15.1% of e-cigarette only and 21.8% of dual users) (Table 1). Dual users were more likely to use daily both e-cigarettes (17.8%) and cigarettes (23.4%) compared to e-cigarette only users (5.5%) and cigarette only users (17.3%). Furthermore, cigarette and dual users (57.0%) were more likely to use other tobacco products compared to the e-cigarette users group (43.7%).

Figure 1-A shows the frequency of e-cigarette and cigarette use among different study groups. In general, dual users were more likely to use e-cigarettes and cigarettes more frequently in the past 30 days compared to those who used only one of the two products (Chi Square test, $P < 0.05$). Cigarette users were more frequent days of tobacco use compared to e-cigarette users. For example, 17% used cigarettes every day compared to 6% of e-cigarette users ($P < 0.05$). Likewise, cigarette use was more frequent than e-cigarette among the dual users (23% used cigarettes daily in comparison to 18% of e-cigarette dual users, $P < 0.05$).

Figure 1-B shows the number of dependence symptoms according to frequency of use. Cigarette users were more likely to demonstrate one or more dependence symptoms compared to e-cigarette users according to the frequency of use, but the difference was less pronounced among dual users. Among daily dual users, as high as 74% of e-cigarettes users reported dependence symptoms compared with 93.3% among cigarette users. Overall, there was a dose- response effect i.e. reporting dependence symptoms

increased the number of tobacco use in the past 30 days increased among e-cigarette and cigarette users.

The most prevalent dependence symptom was strong craving - which was demonstrated in one third of the study population, and the least common was wake-up tobacco use (14.7%) (Table 1). Interestingly, there was a consistent increasing trend in the prevalence of all the examined dependence symptoms among the three smoking groups with the lowest prevalence of any dependence symptom was observed among e-cigarette users, followed by cigarette users, and dual users having the highest proportion of participants demonstrating dependence symptoms (Table 2). For example, more than half of dual users demonstrated symptoms of strong craving (58.9%) and feeling restless (53.3%) in comparison to 16.1% and 12.2% among the e-cigarettes only users, which increased to 45.5% and 40% among the cigarette only users; respectively.

In the multivariate logistic regression (Tables 2-4) dual users had the highest odds ratio of reporting dependence symptoms in each model followed by cigarette users when compared to e-cigarette users as the reference group in the overall study population models. The only exception was the wake-up tobacco use dependence symptom's model in which both cigarette and dual users had similar odds ratio in comparison to the e-cigarette users.

The year of survey had no difference in the odds of reporting all the examined dependence symptoms (Tables 2-4). Among the dual users group, middle school students had higher odds of reporting dependence symptoms compared to high school students, but the difference in odds were not statistically significant. Other tobacco use groups did not have consistent direction regarding school grades and the differences were

statistically insignificant as well. Males were less likely to report the strong craving, and feeling restless when not using tobacco with around 70-80% of the odds of developing dependence among females (odds ratio ranging 0.7-0.8 for males, while having females as the reference group). No difference between males and females was observed in the wake up tobacco use model.

Starting to smoke before the age of 11 was consistently associated with higher odds of reporting dependence in all models with odds ratio ranging from 1.4 – 1.7 among the entire study population. The same association was observed among e-cigarette and cigarette users for the three dependence symptoms models. Interestingly, the early initiation of tobacco use (before 11 years) was associated with higher odds to develop dependence among the e-cigarette users (odds ratio ranging from 1.9-3.0) compared to the cigarettes users group (odds ratio ranging from 1.5-1.8) for all the underlying dependence symptom in each model in the entire population model.

The more the days of e-cigarette or cigarette use in the past 30 days were, the higher the odds to report the examined dependence symptoms after controlling for all the included covariates. This association was observed in all models for dependence symptoms among both the entire population and the study subgroups; except for the past 30 days e-cigarette use and feeling “restless” (Table 3) or “wake-up tobacco use” (Table 4) dependence symptoms models among dual users. Use of other tobacco products was controlled for in all models, and it had significant association with reporting the various examined dependence symptoms with odds ratio ranging from 1.6 to 4.7 in most the multivariate regression models with few exceptions (see tables 2-4). Noteworthy, in all models the odds of reporting the examined dependence symptoms that is associated

with other tobacco use was higher among the e-cigarette users compared to the overall population, cigarette users, and dual users in all the employed multivariate regression models.

Discussion

This study demonstrated that using e-cigarettes is associated with reporting dependence symptoms such as strong craving, feeling restless, and using e-cigarettes within 30 minutes after wakeup among adolescents. Also, there was a dose response association between days of e-cigarette use and reporting dependence symptoms. Despite the lower proportion of e-cigarette users reporting dependence symptoms compared to dual and cigarette users, their magnitude remains appreciable. The overall results demonstrated that among all study groups starting to smoke before the age of 11 years, the more numbers of cigarette and/or e-cigarettes used in the past 30 days, and the use of other tobacco products were all associated with higher odds to demonstrate the three examined dependence symptoms. There was no difference in the odds of reporting the examined dependence symptoms by the year of survey in all models. Furthermore, school grade, gender, and race were not consistently associated with the examined dependence symptoms.

No consistent association was observed between gender and reporting the dependence symptoms (except for few models where girls had higher odds to report a dependence symptom e.g., strong craving). However, none of the e-cigarette models showed such difference even when it was demonstrated in other smokers' groups (see Table 2). This might be attributed to lower prevalence of dependence symptoms among e-cigarette users and our inability to exclude no nicotine e-cigarette users from the

analysis. A previous national survey showed girls had a higher likelihood to report dependence compared to boys;²² which was reported in other populations reporting dependence symptoms such as urges and strong cravings^{20,22,25-27} that is consistent with gender reporting of strong cravings in this study. However, as in the current study, gender differences is not consistently reported^{21,28} and boys might be more likely to report dependence.²⁹ Reports from previous years of the NYTS were inconsistent as well in the detecting an association between school grade and reporting nicotine dependence symptoms.^{22,25}

Initiating cigarette or e-cigarettes before the age of 11 years was consistently associated with reporting all the examined dependence symptoms compared to older initiators. Also, the magnitude of the association was consistently higher among e-cigarette users compared to cigarette users. Dependence among adolescents has been reported for other than cigarettes tobacco products as well^{30,31}

In the current study, strong craving was the most commonly observed dependence symptom, followed by feeling restless and the least frequent dependence symptom was “wake-up tobacco use”; consistently among all study groups. This might be explained by the earlier development of craving symptom in the dependence milestone. Craving and restlessness are among the most frequent dependence symptoms in adolescents that indicates early onset.³² The same conclusion extends to adult populations.¹³ In other words, the longer the tobacco use duration, the more dependence symptoms will develop. Hence, earlier symptoms will be captured at a higher frequency. Research among adolescents is sensitive to the milestones of nicotine dependence since relatively limited time is available to capture the developing dependence symptoms. Moreover, observing

similar distribution of dependence symptoms frequency for the e-cigarette and cigarette user groups supports common natural history of dependence development for both products.

Our findings that dual and cigarette users were more likely to report dependence symptoms compared to e-cigarettes only users among adolescents is consistent with previous research among adults.¹²⁻¹⁶ However, several factors should be considered when interpreting the “addictive” property of e-cigarettes.

First, the limited research that compared dependence symptoms among e-cigarette to that of cigarette users was conducted among ex-smokers which raises the possibility of recall bias (by the failure to accurately recall the dependence symptoms they had with cigarette use in the past) and selection bias (successful quitting is an indicator of less dependence¹⁷).

Second, it was reported that never tobacco users adolescents who used e-cigarettes were at higher odds to subsequently use other tobacco products among this population and elsewhere.^{4,5} Such association suggests dependence might have played a role to shift e-cigarette users into tobacco. Although it is known that e-cigarettes deliver lower nicotine levels compared to cigarettes, this might be optimum to develop “tolerance” (a symptom of dependence) then users use tobacco products to deliver higher levels of nicotine;^{11,33-36} and dependence can develop at very low doses of nicotine with infrequent use.^{17,37}

Third, e-cigarette’s newer generations deliver comparable levels of nicotine to the blood stream as that for cigarettes.³⁸ Such progress might increase the likelihood to

manifest dependence symptoms more frequently and sooner among e-cigarette users than reported in this study and previous research. Therefore, an increase in dependence symptoms reporting among e-cigarette users may be observed in future studies.

Furthermore, it is known that low nicotine content tobacco products do not lead to neither smoking less nor lower dependence,³⁹ that can be an analogy to the e-cigarette use.

Fourth, the fact that the highest prevalence of reported dependence symptoms was observed among dual users (compared to those who used either e-cigarettes or cigarettes only), besides the dose response association, further supports the addictiveness of e-cigarettes. It is plausible that dual users were more likely to use nicotine e-cigarettes, hence had higher reporting of dependence symptoms.

Finally, we argue that e-cigarettes is addictive and this is warning. Therefore, even if e-cigarette use would lead less people to develop nicotine dependence in comparison to cigarettes this should not be considered an open invitation to use e-cigarettes due to the concerns outlined here. Notably, a recent report suggested that e-cigarettes should be discouraged among never smokers as it has no benefits, but possible harms, which agrees with the view we take here.⁴⁰

The current study is limited by its cross-sectional nature that hindered describing and comparing the trajectory of dependence among different types of smokers. However, its national representation among US adolescents where evidence on the risk of e-cigarettes on tobacco use have been presented⁴ supports the addictiveness of e-cigarettes. Also, we were unable to exclude none nicotine containing e-cigarettes or adjust for the known variations to its nicotine content.⁴¹ This might have lowered the percentage of e-cigarette users reporting dependence symptoms. This study is school

based, therefore the results cannot be generalized on home schooled and drop out adolescents.

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Table 1: Characteristics of the study groups from the NYTS 2014 and 2015.

	Entire population (n=5,119)	E-cigarette users (n= 2,646)	Cigarette users (n= 1,146)	Dual users (n=1,327)
	N (%)	N (%)	N (%)	N (%)
Year of Survey				
2014	2,684 (46.4)	1,292 (42.8)	667 (50.8)	725 (49.9)
2015	2,435 (53.6)	1,354 (57.2)	479 (49.2)	602 (50.1)
Grade*				
Middle School	1,169 (19.3)	702 (21.6)	211 (18.2)	256 (15.7)
High School	3,895 (80.4)	1,918 (78.4)	921 (81.3)	1,056 (83.6)
Sex				
Male	2,990 (57.8)	1,540 (58.2)	663 (57.4)	787 (57.4)
Female	2,081 (42.2)	1,080 (41.8)	476 (42.6)	525 (42.6)
Race**				
White, non-Hispanic	2,601 (58.5)	1,261 (55.9)	579 (58.4)	761 (64.1)
Black, non-Hispanic	489 (8.7)	251 (9.3)	154 (11.8)	84 (4.8)
Hispanic	1,567 (24.6)	902 (26.6)	303 (21.9)	362 (22.8)
Other	462 (8.2)	231 (8.2)	110 (7.9)	120 (8.4)
E-cigarette/cigarette initiation**				
≤ 11 years	1,198 (21.8)	431 (15.1)	313 (27.0)	1,198 (21.8)
> 11 years	3,921 (78.2)	2,215 (84.9)	833 (73.0)	3,921 (78.2)
Current use of other tobacco**				
Yes	2,830 (55.1)	1,157 (43.7)	660 (57.2)	1013 (76.9)
No	2,289 (44.9)	1,489 (56.3)	486 (42.8)	314 (23.1)
Strong craving for tobacco**				
Yes	1,650 (33.4)	403 (16.1)	489 (45.5)	758 (58.9)
No	3,304 (66.6)	2,167 (83.9)	606 (54.5)	531 (41.1)
Wake-up tobacco use**				
Yes	732 (14.7)	124 (4.3)	223 (20.8)	385 (31.3)
No	4,240 (85.3)	2,468 (85.7)	870 (79.2)	902 (68.7)

*P < 0.05

**P < 0.001

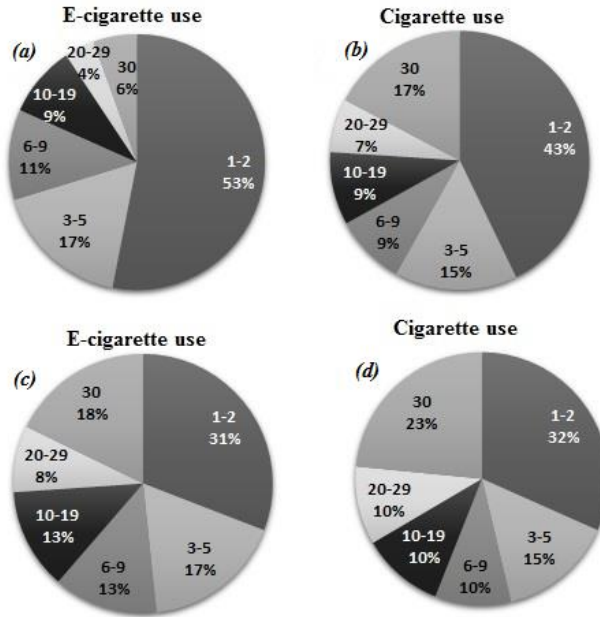


Figure 1-A: Frequency of e-cigarette and/or cigarette use in the past 30 days among the participants 2014 and 2015 NYTS; study groups: a- E-cigarette users; a- Cigarette users, c- Dual users.

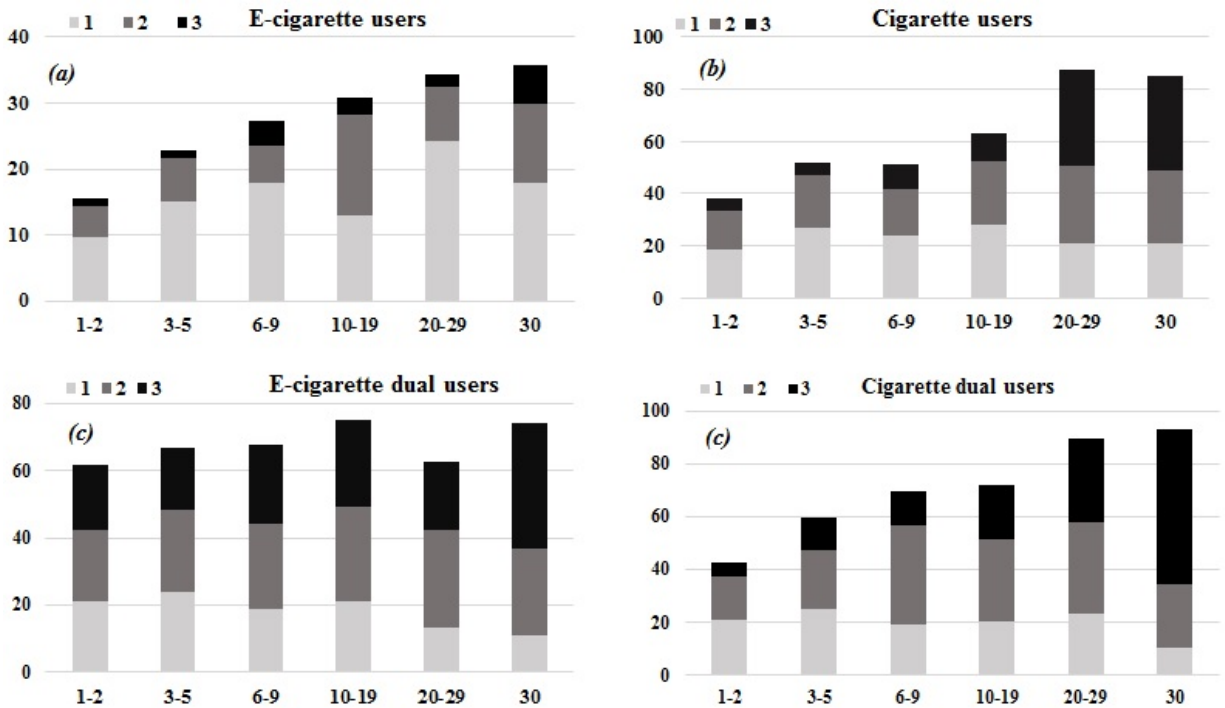


Figure 1-B: Number of dependency symptoms according to the frequency of use among the participants 2014 and 2015 NYTS; study groups: a- E-cigarette users; a- Cigarette users, c- Dual users.

Table 2: Characteristics associated with having strong cravings for tobacco product during the past 30 days among the study groups from 2014 and 2015 NYTS.

	Entire population (n=4,954)	E-cigarette users (n= 2,570)	Cigarette users (n= 1,095)	Dual users (n=1,289)
	AOR (95% CI)	AOR (95% CI)	AOR (95% CI)	AOR (95% CI)
Year of Survey				
2014	1.1 (0.9-1.3)	1.0 (0.7-1.3)	1.2 (0.9-1.6)	1.3 (0.9-1.9)
2015	1.0	1.0	1.0	1.0
Grade				
Middle School	1.0 (0.7-1.4)	1.2 (0.8-1.7)	0.5 (0.3-1.0)*	1.4 (0.9-2.1)
High School	1.0	1.0	1.0	1.0
Sex				
Male	0.7 (0.5-0.9)**	0.8 (0.7-1.1)	0.6 (0.4-0.9)*	0.5 (0.3-0.7)**
Female	1.0	1.0	1.0	1.0
Race				
White, non-Hispanic	1.0	1.0	1.0	1.0
Black, non-Hispanic	0.7 (0.5-0.9)*	1.0 (0.6-1.5)	0.5 (0.3-0.8)*	0.4 (0.2-0.7)
Hispanic	0.7 (0.6-0.9)*	0.7 (0.5-1.0)	0.6 (0.4-0.97)*	0.8 (0.5-1.1)
Other	0.6 (0.4-0.99)*	0.8 (0.4-1.4)	0.4 (0.1-1.1)	0.6 (0.3-1.1)
E-cigarette/cigarette initiation				
≤ 11 years	1.4 (1.1-1.7)**	2.0 (1.4-2.8)**	1.5 (1.0-2.0)*	1.0 (0.7-1.4)
> 11 years	1.0	1.0	1.0	1.0
Past 30 D e-cig. use	1.02 (1.01-1.04)**	1.03 (1.02-1.05)**	-----	1.02 (1.01-1.03)*
Past 30 D cig. use	1.1 (1.06-1.09)**	-----	1.06 (1.05-1.08)**	1.09 (1.07-1.1)**
Current use of:				
E-cigarette	1.0	-----	-----	-----
Cigarette	2.1 (1.7-2.6)**		-----	-----
Dual use	2.5 (2.0-3.1)**		-----	-----
Current other tobacco				
Yes	2.1 (1.7-2.6)**	3.0 (2.2-4.0)**	1.8 (1.3-2.5)**	1.5 (1.1-2.1)*
No	1.0	1.0	1.0	1.0

*P < 0.05

**P < 0.001

Table 3: Characteristics associated with feeling irritable or restless when not using tobacco for a while among the study groups from 2014 and 2015 NYTS.

	Entire population (n=4,947)	E-cigarette users (n= 2,566)	Cigarette users (n= 1,089)	Dual users (n=1,292)
	AOR (95% CI)	AOR (95% CI)	AOR (95% CI)	AOR (95% CI)
Year of Survey				
2014	0.9 (0.7-1.0)	0.7 (0.5-1.0)	1.1 (0.7-1.5)	0.9 (0.7-1.3)
2015	1.0	1.0	1.0	1.0
Grade				
Middle School	1.2 (0.8-1.7)	1.0 (0.7-1.3)*	0.6 (0.3-1.2)	1.5 (1.0-2.1)*
High School	1.0	1.0	1.0	1.0
Sex				
Male	0.8 (0.7-1.0)*	1.0 (0.7-1.3)	0.7 (0.5-1.1)	0.8 (0.6-1.1)
Female	1.0	1.0	1.0	1.0
Race				
White, non-Hispanic	1.0	1.0	1.0	1.0
Black, non-Hispanic	0.9 (0.6-1.2)	1.1 (0.7-1.9)	0.8 (0.4-1.4)	0.7 (0.4-1.2)
Hispanic	0.8 (0.6-0.95)*	0.8 (0.6-1.2)	0.8 (0.5-1.1)	0.7 (0.5-0.9)
Other	0.8 (0.5-1.3)	0.8 (0.4-1.5)	1.5 (0.4-5.4)	0.6 (0.3-1.1)
E-cigarette/cigarette initiation				
≤ 11 years	1.4 (1.1-1.8)*	1.9 (1.3-2.8)*	1.5 (1.0-2.1)*	1.2 (0.8-1.8)
> 11 years	1.0	1.0	1.0	1.0
Past 30 D e-cig. use	1.01 (1.0-1.03)*	1.03 (1.01-1.04)*	-----	1.0 (1.0-1.02)
Past 30 D cig. use	1.07 (1.06-1.08)**	-----	1.07 (1.05-1.09)**	1.07 (1.05-1.09)**
Current use of:				
E-cigarette	1.0	-----	-----	-----
Cigarette	2.6 (1.9-3.7)**	-----	-----	-----
Dual use	3.2 (2.5-4.2)**	-----	-----	-----
Current other tobacco				
Yes	1.9 (1.6-2.3)**	3.6 (2.6-5.0)**	1.0 (0.8-1.4)	1.7 (1.3-2.3)**
No	1.0	1.0	1.0	1.0

*P < 0.05

**P < 0.001

Table 4: Characteristics associated with first time to wake-up tobacco use among the study groups, 2014 and 2015 National Youth Tobacco Survey.

	Entire population (n=4,972)	E-cigarette users (n= 2,592)	Cigarette users (n= 1,093)	Dual users (n=1,287)
	AOR (95% CI)	AOR (95% CI)	AOR (95% CI)	AOR (95% CI)
Year of Survey				
2014	0.9 (0.7-1.2)	1.0 (0.6-1.6)	0.9 (0.6-1.5)	0.9 (0.6-1.2)
2015	1.0	1.0	1.0	1.0
Grade				
Middle School	1.0 (0.7-1.3)	0.8 (0.5-1.4)	1.01 (0.6-1.7)	1.0 (0.6-1.8)
High School	1.0	1.0	1.0	1.0
Sex				
Male	1.1 (0.8-1.5)	2.0 (1.2-3.5)	1.0 (0.6-1.6)	1.0 (0.7-1.6)
Female	1.0	1.0	1.0	1.0
Race				
White, non-Hispanic	1.0	1.0	1.0	1.0
Black, non-Hispanic	0.9 (0.6-1.3)	1.8 (0.8-4.4)	1.0 (0.5-1.8)	0.4 (0.2-0.7)*
Hispanic	0.7 (0.5-0.99)*	1.2 (0.7-2.0)	0.5 (0.3-0.9)*	0.7 (0.4-1.1)
Other	0.7 (0.4-1.2)	1.4 (0.6-3.1)	0.4 (0.1-1.8)	0.7 (0.3-1.3)
E-cigarette/cigarette initiation				
≤ 11 years	1.7 (1.2-2.3)**	3.1 (1.7-5.9)**	1.8 (1.04-3.1)*	0.8 (0.4-1.7)
> 11 years	1.0	1.0	1.0	1.0
Past 30 D e-cig. use	1.03 (1.01-1.04)*	1.04 (1.02-1.06)*	-----	1.0 (1.0-1.04)
Past 30 D cig. use	1.1 (1.09-1.1)**	-----	1.1 (1.08-1.1)**	1.1 (1.09-1.1)**
Current use of:				
E-cigarette	1.0	-----	-----	-----
Cigarette	1.9 (1.4-2.7)**	-----	-----	-----
Dual use	1.8 (1.3-2.6)*	-----	-----	-----
Current other tobacco				
Yes	2.5 (1.8-3.4)**	4.7 (2.6-8.2)**	2.0 (1.3-3.2)*	1.9 (1.2-3.0)*
No	1.0	1.0	1.0	1.0

*P < 0.05

**P < 0.001

CONCLUSIONS

E-cigarette use has expanded dramatically among adolescents in the United States and is now the most commonly used tobacco product among them. Such expansion was mainly driven by extensive marketing messages (Singh et al, 2016) and lack of strict regulation as what in place for e-cigarettes, while few studies have examined the consequences of this expansion on other tobacco products use. This research provided the first insights from a large and representative American Adolescents (i.e. NYTS 2014 and 2015) into the association of tobacco initiation via e-cigarettes and subsequent tobacco use, exposure to e-cigarette marketing messages and its association with tobacco use, and symptoms of nicotine dependence among e-cigarette users compared to cigarette users and dual (combined) e-cigarette and cigarette users.

The first manuscript tackled an important research question about the association of initiating tobacco via e-cigarettes and subsequent tobacco use (cigarettes, cigars, and smokeless tobacco). It was interesting to note that around 25% of those reported initiating tobacco use by either e-cigarettes, cigarettes, cigars, and smokeless tobacco were e-cigarette users. E-cigarette users were more likely to be male, white, and high school students in the general demographic description.

There was a consistent and significant association between initiating tobacco use via e-cigarettes and subsequent ever and current use of cigarettes, cigars, and smokeless tobacco. It was interesting to note that those who initiated tobacco use via e-cigarettes

were significantly younger than adolescents who initiated tobacco use via cigarettes, cigars, or smokeless tobacco. This may be related to more accessibility to e-cigarettes in comparison to other products and should be monitored as the future governmental regulations on e-cigarettes are implemented. It is important to note that there was an association between exposure to e-cigarette use by members in the household and adolescents' use of cigarettes, cigars, and smokeless tobacco. These findings should be explored in further research as it identifies possible negative outcome of e-cigarette use among adults for their children.

The second manuscript examined the association between e-cigarette marketing messages and tobacco use among adolescents. The e-cigarette marketing messages were accessible to millions of American adolescents via social media, television, newspapers, and at stores. E-cigarettes marketing messages were reminiscent of older tobacco advertisements targeting adolescents after decades of banning tobacco advertisement in the US (Singh et al, 2016). The use of social media makes it accessible to adolescents, given their common use of such media.

This study showed that exposure to one or more forms of e-cigarette marketing messages (i.e. at social media, television, newspapers, and at stores) was significantly associated with ever and current use of cigarettes, hookah, and cigars after controlling for e-cigarette use and other important factors. This study represented the first insight into the association of e-cigarettes marketing and tobacco use among adolescents that can help formulating policies to regulate such marketing messages and adolescents' exposure to them.

The third manuscript addressed an important facet in tobacco use, which is nicotine dependence. Nicotine dependence is a driving factor in ongoing use of tobacco products and hinders tobacco cessation. This study showed that e-cigarettes are addictive as demonstrated by the reporting of the three examined symptoms. Among adolescent daily tobacco users, 35.6% of e-cigarette users and 85.3% of cigarette users reported one or more dependence symptoms. These rates increased to be 74.3% of e-cigarette and 93.3% of cigarette dual users. Strong cravings was the most reported symptom with a range of 16.1-58.9% among different tobacco user groups. Early initiation of smoking (before the age of eleven years) was associated with reporting dependence symptoms among e-cigarette, cigarette, and dual (combined cigarette and e-cigarette) users. Also, the more the past 30 days of e-cigarettes and cigarettes, the higher the proportion who reported dependence symptoms indicating dose-response association.

Despite cigarette and dual users showed a higher odds of reporting nicotine dependence symptoms, the addictiveness of e-cigarettes occurred at appreciable proportions. This is further confirmed by the higher proportions of reporting nicotine dependence symptoms among daily e-cigarette users. Early age of tobacco use (i.e. at or before eleven years) was consistently associated with reporting nicotine dependence symptoms among e-cigarette users with higher AOR (of the three examined nicotine dependence symptoms) compared to the AOR (for the corresponding nicotine dependence symptom) estimated among the cigarette users (i.e. e-cigarette users had around two fold of odds to report dependence symptoms compared to cigarette users). These findings indicated that control of adolescent access to e-cigarettes needs to be explored.

Overall the present study results indicated that e-cigarettes use among adolescents is associated with reporting symptoms of nicotine dependence and also use of other tobacco products; and that exposure to e-cigarette marketing messages was associated with tobacco use. The reported dependence symptoms among e-cigarette user (third manuscript) and the association of its marketing messages with tobacco use (second manuscript) lend themselves as putative possibilities, among other potential sociodemographic factors, to explain the plausibility of the association we reported here of cigarette, cigar, and smokeless tobacco use and tobacco initiation via e-cigarettes (first manuscript).

Therefore, collectively our findings suggest e-cigarette use is not risk free and support the need for regulations for access and use among adolescents.

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