Key Words: vaping, e-cigarettes, electronic cigarettes, combustible cigarettes, dual users, adolescents, sleep deprivation

# Exploring the Interplay of Sleep and Nicotine Vaping in Adolescents: An Evidence-Based Narrative Review.

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ABSTRACT ~ Introduction: Although adolescent use of combustible cigarettes (CC) has decreased, the rise of nicotine electronic vaping products (EVPs) presents new public health concerns. Nicotine vaping devices, with appealing packaging and flavors, are now the most commonly used nicotine delivery method among adolescents. While the long-term effects remain unclear, short-term effects include tachycardia, coughing, and wheezing. This review explores the relationship between nicotine vaping and sleep disturbances in adolescents. Methods: A PubMed search (2006-2024) using keywords "nicotine sleep adolescents," "vaping sleep adolescents," and "e-cigarette sleep adolescents" identified 159 articles. Filters for "Humans," "English," and "Age-Birth-18 years" narrowed the list to 124. Abstracts were independently screened for cross-sectional studies describing sleep disturbances, yielding nine articles. Outcome measures included insufficient sleep (< 7-8 hours/night) and sleep latency, assessed through self-reported hours and the Pittsburgh Sleep Quality Index (PSQI). Results: Data from 106,628 adolescents (12–18 years; males = females) revealed e-cigarette (most common vaping device used) and dual users (e-cigs + CC) reported significantly more insufficient sleep on school nights than non-users. Dual users exhibited increased sleep latency, particularly in males. Two studies suggested chronic insufficient sleep might lead to initiation or increased use of vaping devices, highlighting a bidirectional relationship. Conclusions: Many survey studies indicate vaping nicotine is associated with sleep disturbances in adolescents. Other studies determined sleep disturbances were associated with an initiation or increase in vaping nicotine indicating a cause-and-effect conundrum. Further investigation through longitudinal studies are needed to determine factors such as the causal relationship, doseresponse and product-specific effects. Psychopharmacology Bulletin. 2025;55(2):60–74.

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### INTRODUCTION

Although combustible tobacco cigarettes (CC) use has decreased amongst adolescents, the rapid emergence of popular electronic vaping products (EVPs) has unfortunately transformed the landscape of adolescent substance use in the US, becoming a critical public health issue. Vape pens, also referred to as "vapes", "electronic nicotine delivery systems (ENDS)", "e-cigarettes (e-cigs)", "e-cigars", "e-hookahs", and "hookah sticks", come in various forms that are packaged in cartridges to be placed within the vape. These products are sold in tobacco shops, malls, gas stations, and head shops. Vapes are devices that produce aerosolized nicotine, flavoring, and variable levels of other chemicals (including propylene glycol, glycerin, and potentially harmful excipients such as formaldehyde and metals). The device uses heat from a battery to create a vapor, which is inhaled by the user. <sup>2</sup>

E-cigarettes use has increased significantly since their entrance onto US markets in 2006. Since 2016, the FDA has regulated vaping devices, requiring manufacturers to submit applications for review prior to marketing, and often denying market entry. However, regardless of FDA oversight, there are many EVPs which are illegally marketed. On December 20, 2019, a federal law was enacted that raised the minimum legal age for purchasing all tobacco products, including e-cigarettes, from 18 to 21 nationwide.<sup>2</sup> However, the 2020 National Youth Tobacco Survey (NYTS) reported that 3.6 million middle and high school students were still current e-cigarette users.<sup>3</sup> The increased use amongst youth may be secondary to the widespread prevalence and easy access of these products. E-cigarette companies widely promote their products as "safer than conventional cigarettes" to gain business from experimenting adolescents who are more susceptible to addiction and risk-taking. Further, vaping "e-liquids" come in a variety of flavors such as cotton candy or bubblegum to accompany the sleek design of the EVP, enhancing their appeal to younger users.<sup>2</sup>

The American Academy of Sleep Medicine recommends that adolescents aged 13 to 18 get 8 to 10 hours of sleep per night to support their overall well-being<sup>5</sup> yet, seven in ten students in the general population report poor sleep quality on school nights. Chronic insufficient sleep can have serious health consequences, including an increased risk of obesity, diabetes, mental health issues, and behavioral problems. Additionally, poor sleep can impair cognitive development, hinder school performance, raise the risk of accidents, and negatively impact a student's overall functioning.<sup>6–8</sup> Lifestyle factors such as sedentary behaviors including watching TV or excessive screen time and physical inactivity are associated with insufficient sleep.<sup>9,10</sup> The psychosocial

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consequences of inadequate sleep include depression, anxiety, substance use (including nicotine), risk-taking behaviors, low self-esteem, and suicidal ideation. Adolescents may seek to cope with current mental disorders by vaping more or using stronger concentrations of nicotine in their products.

Though the long-term sequelae of vaping nicotine are poorly understood, the short-term medical effects include tachycardia, coughing, and wheezing. 14,15 Growing evidence suggests that nicotine use during adolescence is linked to changes in working memory and attention, as well as decreased activation of the prefrontal cortex. 16,17 Adolescent nicotine use has been linked to a range of long-term adverse effects, including academic challenges and an increased risk of developing psychiatric disorders. These disorders include major depressive disorder, agoraphobia, panic disorder, other substance use disorders, and antisocial personality disorder. 18,19 Research has established a link between substance use and impaired sleep.<sup>20</sup> While disrupted sleep and combustible cigarettes have a well-documented, bi-directional association in adolescents, <sup>21,22</sup> there remains a significant gap in research exploring the connection between regular nicotine vaping and sleep disruption among adolescents.<sup>23,24</sup> A 2018 systematic review and meta-analysis identified insomnia as one of the most prevalent adverse outcomes following e-cigs use in adults who attempted to quit CC use with the help of e-cigs. 25 Evidence is accumulating that vaping nicotine is associated with poor sleep health in adolescents. 26,27 Inversely, having poor sleep is known to increase anxiety, which may prompt nicotine or other substance use, further exacerbating sleep disturbances, causing a vicious cycle. In light of the short-term health risks and negative academic and psychosocial outcomes linked with insufficient sleep in adolescents,<sup>6</sup> an evidence-based review can help elucidate the interplay of sleep and nicotine vaping nicotine in this understudied population.

# **METHODS**

### Inclusion Criteria

All studies evaluating the interplay between sleep and nicotine vaping in individuals aged 12–18 years were included.

### Data Extraction

A PubMed search from 2006 to 2024 using the keywords "Nicotine sleep adolescents," "vaping sleep adolescents," and "e-cigarette sleep adolescents" yielded 159 articles. Activating the filters "Humans,"

"English," and "Age-Birth-18 years" reduced the list to 124 articles. Independent screening of abstracts by three authors (SB, BGB, and AR) for cross sectional studies that described sleep disturbances yielded 16 articles for inclusion. After carefully reading the methodology of each of the 16 articles, 7 articles were excluded as they did not meet the age range of less than 18 years. Following the above methodology, 9 articles remained to be included for the review. The data from various cross-sectional surveys, was pooled together. At least 4 of the 9 studies described below, utilized data from the Youth Risk Behavioral Survey. Methods flow chart shown in Figure 1.

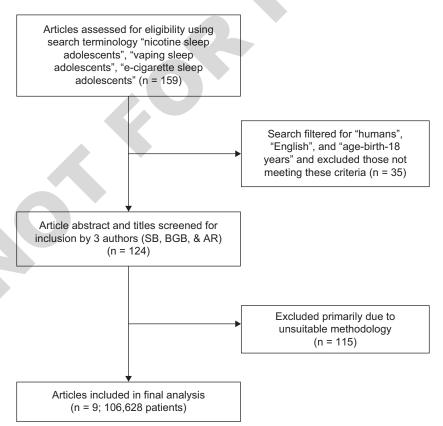
### **Outcome Measures**

The outcome measures of sleep duration and insufficient sleep, were classified categorically in self-reported hours. Due to research methods used in several studies, insufficient sleep was defined as less than 7 hours. Sleep latency and daytime dysfunction were assessed using Pittsburgh Sleep Quality Index (PSQI). The PSQI, a self-report questionnaire,

FIGURE 1

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# METHODOLOGY FLOW CHART



## **EVIDENCE BASED MEDICINE GUIDELINES**

"The categories of evidence were defined as IA: evidence from metaanalysis of randomized controlled trials (RCT); IB: evidence from at least one well designed RCT( large multi-site RCT); IIA: evidence from at least one well-designed controlled study without randomization; IIB: evidence from quasi-experimental study; III: evidence from nonexperimental descriptive studies such as case control/cross-sectional studies; and IV: evidence from national level expert committees/panels or opinions, not based on research".<sup>31</sup>

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### RESULTS

The initial search identified 159 articles of which nine articles were included in the final analysis. The 9 articles included publications from 2019–2023. Most of the articles included adolescents aged between 12–18 years (n=7 studies). While 2 studies included adolescents and young adults aged between 12–23 years, the mean age in both these studies included adolescents aged 17 years. With the exception of one study that was conducted in Canada, the remaining studies (n=8) were conducted in the US.

Of the 9 studies included for analyses, eight were cross sectional surveys/studies and one was a prospective cohort study. A combined sample size of 106,628 adolescents (aged 12–18 years, males = females) was analyzed. With regards to the sample demographics recruited: Non-Hispanic White were the most common, followed by Hispanic and then Black.

Amongst all studies, E-cigs were the most common product used to vape nicotine. The other nicotine products mentioned are cigarettes, cigarillos, smokeless tobacco, e-cigars, combustible cigarettes and dual users (combustible cigarettes + e-cigs).

The sleep assessment parameters measured in the 9 studies were: total self-reported sleep hours, sleep quality as measured by the total PSQI score and self-reported sleep disturbances. Six of the 9 studies utilized self-reported sleep hours, of which one study described

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shortened sleep duration as self-reported of less or more than 7 hours. One amongst the 9 studies reported the PSQI sub measure. With regards to the other two remaining studies, one asked respondent for subjective sleep disturbances and the other one asked for self-reported sleep trouble including bad dreams, restless sleep, and daytime sleepiness. These items were drawn from the Global Appraisal of Individual Needs-Short Screener.<sup>32</sup>

The 9 studies in the pooled analysis, describing the interplay of sleep and nicotine in adolescents are described below (results summarized in Table 1):

A 2018 neurobiological study found that stronger connections in the laterobasal amygdala and the anterior insula predicted greater sleep problems, resulting in more depression and subsequent increased use of e-cigarettes.<sup>33</sup>

A cross-sectional study utilizing data from the Youth Risk Behaviors Survey investigated the role of sleep quantity as a moderator in the relationship between nicotine vaping and self-reported suicidality among adolescents (n = 10,520, M = F). The findings revealed that students who reported less than 7 hours of sleep on school nights (OR = 2.6; 95% CI = 2.1–3.3) and those who vaped nicotine in the past month (OR = 3.0; 95% CI = 2.1–3.9) had significantly higher odds of reporting a suicide attempt within the past year compared to their peers who did not vape.  $^{34}$ 

A study exploring the potential contribution of sleep deprivation to adolescents' initiation of EVPs involved 1,100 adolescents aged 13–17 years who participated in the Vaping Attitudes Youth Perspective Survey. The results indicated that adolescents who reported getting less than 6 hours of sleep per night had significantly higher odds of intending to try a nicotine vape within the next month (OR = 2.63, 95% CI = 1.30–5.31), even after controlling for confounders such as age, gender, race, and ethnicity.<sup>35</sup>

Adolescent (n = 609) data (aged 13–20, mean = 17.14 yrs) were isolated to assess age and parallel use of e-cigs, traditional tobacco, and dual use (e-cigs + traditional tobacco) with sleep quality and cough. The authors used PSQI to assess sleep quality. Dual use correlated with longer sleep latency than nonsmokers, but this was statistically significant only in male dual users.  $^{36}$ 

A cross-sectional questionnaire examining the frequency of e-cigs; identifying demographic features, risk-taking behaviors, beliefs about vaping, and determining symptoms associated with e-cigs were evaluated in 494 respondents (adolescents and young adults, aged 12–23, mean age = 17 yrs). 80% of responders were considered nonusers/experimenters (never tried or tried once) and 20% were considered

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	RESULTS	More sleep problems correlated with increased depressive	symptoms; increased depressive symptoms correlated with	increased e-cigs use.	An increased odds of suicide	attempt was seen in students achieving < 7 hours of sleep on	school nights who vaped within the past month.	Adolescents who reported		in the next month compared	to adolescents who reported	> 8hrs sleep/night.
	SLEEP ASSESSMENT TOOL/ PARAMETERS	Youth Self Report of Achenbach	System of Empirical Behavioral	Assessment. Items rated on 3-point Likert scale	Self-reported sleep	hours ( $<$ 7 vs $>$ 7 hours)		Self-renorted average	sleep duration in the	3–5hrs, 6–8 hrs or	> 8hrs)	
	TYPE OF VAPING PRODUCTS ASSESSED	E-cigs		S	E-cigs			F-cios	, 0			
	TYPE OF STUDY	Questionnaire			Cross-sectional	survey (Youth Risk Behaviors Survey)		Vaning Attitudes				
Ť	SAMPLE SIZE/ DEMOGRAPHICS	N = 146 $M > F$	Age 15–18 (mean 14.9) 88% White, 84%	Hispanic	N = 10,520	High School Students $M = F$	54.8% White, 9.2% Black, 17.1%,	Hispanic $N = 1100$	M = F Age 13–17	71% White, 12% Black,	13% Hispanic	
	AUTHOR/YEAR	Sutherland, BD et al.	2022		Welty, CW	et al. 2023		Holtz. KD	et al. 2022			

SUMMARY OF RESULTS\*

Dual (CC + e-cigs) use correlated with longer sleep latency than non-smokers in surveyed males.	Frequent (20%) users (those using EVPs once a month/once a week/once a day) are more likely to demonstrate sleep disturbances.	The majority of students reported inadequate sleep and vaping. The prevalence of the past 30-day vaping increased by 216% among male and 416%	E-cigarette, CC, and dual use were associated with higher odds of sleep-related complaints compared to no use. E-cig users were associated with more sleep complaints than CC and dual users. F had higher odds of sleep complaints than M.
	Self-reported sleep Fr disturbances in the past 6 months	Self-reported sleeping Theours in the past 1 week (< 8 hours/ night considered inadequate)	Self-reported sleep Errouble (bad dreams, restless sleep, daytime sleepiness) in the past year (from Global Appraisal of Individual Needs-
E-cigs, CC & dual Pittsburgh Sleep users Quality Index (PSQI)	E-cigs, vape & hookah pen	CC, cigars, smokeless tobacco, e-cigs, hookah	E-cigs, CC & dual users
Online survey	Self-administered cross-sectional study	Cross-Sectional study	Prospective cohort study (self-reported survey questionnaire)
N = 609 Age 13–20 (mean 17.14), F > M, 92% non-Hispanic, 5% Hisbanic	Benyo SE et al. $N = \frac{1}{494}$ 2021 Age 12–23 (mean 17) F > M 72.5%, 5.5% Black,	N = 44,740 High School Students $M = F,$ 74% White	N = 9,588 Age 12–17 M > F 70.9% White ,14.9% Black, 14.2% Other Race
Malhotra, CK et al. 2021	Benyo SE et al. 2021	Cole AG et al. 2021	Riehm KE et al. 2019

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# SUMMARY OF RESULTS\*

	RESULTS	F had higher rates of CC and	dual product use. 73.4% of	respondents reported inadequate	sleep. Exclusive e-cig users	were at $3.2 \times \text{increased odds}$ ,	and dual product users were	at 3.26 $\times$ increased odds to	report insufficient sleep when	compared with exclusive	CC smokers after adjusting	covariates.	22.6% reported using EVPs,	19.2% were former EVP users.	76.5% reported inadequate
SLEEP ASSESSMENT TOOL/	PARAMETERS	Self-reported school	night sleep hours	(< 8  hours)	night considered	inadequate)							Self-reported school	night sleep hours	(< 8 hours/
TYPE OF VAPING	PRODUCTS ASSESSED	E-cigs, CC & dual	users										EVPs: E-cigs,	y e-cigars,	e-hookahs, vape
	TYPE OF STUDY	Secondary analysis of	2017 Youth Risk	Behavior School	Based Survey								2017 and 2019 Youth EVPs: E-cigs,	Risk Behavior Survey	
	SAMPLE SIZE/ DEMOGRAPHICS	N = 11,296	Age 13–18	$\mathrm{F}>\mathrm{M}$	53.4% White,	13.8% Black, 22.1%	Hispanic						Baiden P et al. $N = 28,135$	Age 13–18	$\mathrm{F}>\mathrm{M}$
	AUTHOR/YEAR	$Merianos\ AL$	et al. 2021										Baiden P et al.	2022	

\*= Level III evidence-based medicine guidelines; M = males; F = females; E-cigs = e-cigarettes; CC = combustible cigarettes, dual use = E-cigarettes + combustible cigarettes; EVPs = electronic vaping products.

 $1.\bar{3}3 \times \text{higher odds of reporting}$ insufficient sleep in comparison

to non-users.

sleep. Former and current users reported between a 1.29 imes and

night considered (< 8 hours/

bens

46.7% White, 17.5% Black, 24.2%

Hispanic

inadequate)

frequent users (at least once in 30 days). Frequent users were more likely to endorse sleep disturbances when compared to non-users.<sup>37</sup>

Evaluating health and risk behaviors among Grade 12 cohorts over time is crucial for identifying intervention opportunities. A cross-sectional study analyzed trends in health and risk behaviors among 12th-grade students (n = 44,740), focusing on movement (physical activity, screen time, sleep) and substance use (smoking and vaping). The findings revealed that over 91% of students reported engaging in at least one health risk behavior, with a significant rise in inadequate sleep and vaping behaviors over time. Notably, the prevalence of past-month vaping surged by 216% among male and 416% among female students.<sup>38</sup>

A cross-sectional study investigating the association between exclusive e-cigarette use, exclusive combustible cigarette (CC) use, and dual-product use with sleep-related complaints among adolescents (n=9,588) found that all three nicotine-containing products were significantly linked to higher odds of sleep complaints compared to adolescents who used neither nicotine product (e-cigs: OR=1.61, 95% CI 1.34–1.94; CC: OR=1.62, 95% CI 1.26–2.09; dual product use: OR=2.00, 95% CI 1.63–2.46). Additionally, female adolescents had higher odds of experiencing sleep complaints than their male counterparts.<sup>23</sup>

A secondary data analysis of the Youth Risk Behavior Survey, which included 11,296 high school students, was conducted to investigate the relationship between current exclusive e-cigarette use, exclusive combustible cigarette (CC) smoking, and dual use of e-cigarettes and CC with insufficient sleep. Insufficient sleep was defined as getting less than 8 hours and less than 7 hours of sleep per night. Overall, 73.4% of adolescents reported insufficient sleep of less than 8 hours per night. The analysis revealed that, compared to non-tobacco users, exclusive e-cigarette users and dual-product users were more likely to report insufficient sleep (both < 8 hours and < 7 hours per night). After adjusting for covariates, exclusive e-cigarette users had 3.20 times higher odds, and dual-product users had 3.26 times higher odds of reporting insufficient sleep compared to exclusive CC smokers.<sup>24</sup>

A study investigating the cross-sectional association between EVP use and insufficient sleep pooled data from the Youth Risk Behavioral Survey, including 28,135 adolescents. Among the participants, 22.6% were current EVP users, and 58.2% were never users. More than three in four adolescents (76.5%) reported getting less than 8 hours of sleep on an average school night. After adjusting for demographics and other covariates, the study found that adolescents who currently used EVPs had 1.33 times higher odds of experiencing insufficient sleep, and

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those who had previously used EVPs had 1.29 times higher odds of insufficient sleep compared to non-users.<sup>39</sup>

### **DISCUSSION**

To our knowledge, this is the first evidence-based narrative review exploring the interplay between vaping nicotine and sleep abnormalities in adolescents. This report contributes to the existing literature by synthesizing known information from disparate studies and highlighting future research needs on this topic. Adolescents are an understudied population in the field of sleep medicine.<sup>36</sup> The primary results of our review are: Firstly, nicotine vaping and insufficient sleep are highly prevalent in adolescents. Secondly, e-cigs were the most common vaping devices used, and e-cig users and dual users had increased odds of reporting < 7-8 hours of sleep on school nights when compared to non-users. E-cigs and dual users are more likely to have insufficient sleep (as measured as less than 7 hours) than those who only used CC. Finally, in adolescent males, dual use was associated with increased sleep latency (mean difference = 6.27 minutes; confidence interval = 1.40-11.13 minutes) measured by PSQI. This finding related to sleep latency correlates with the known effects of nicotine, of which dual users have a higher intake, such that dual users are more likely to experience greater side effects specific to nicotine compared to other users. Prior research has demonstrated that a wide range of substances like alcohol, marijuana and CC are associated with sleep disturbances.<sup>22</sup> Our review expanded this literature further by suggesting that not only CC, but e-cig and dual product users struggle with sleep-related complaints. The odds ratios for sleep abnormalities were statistically significant for both e-cigs and dual-product users and also e-cigs alone when compared to non-users. 23,24,39

Several potential explanations could be inferred from the above findings. E-cig use in adults is associated with insomnia.<sup>25</sup> This finding could be extrapolated to adolescents, as exposure to nicotine stimulates nicotine-acetylcholine receptors, which in turn triggers the release of several neurotransmitters, including acetylcholine, dopamine, serotonin, and norepinephrine. These neurotransmitters have activating effects on the central nervous system, which can disrupt normal sleep patterns.<sup>40</sup> Also, sleep alterations are an important symptom of nicotine withdrawal.<sup>41</sup> Additionally, nicotine cravings could predispose adolescents who use e-cigs to wake up in the middle of the night.<sup>39</sup> Interestingly, considering the potential causal directionality between insomnia and e-cigarette use, adolescents experiencing sleep problems may turn to vaping as a coping mechanism. The moodiness, attention issues, and

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daytime sleepiness that often accompany insufficient sleep could lead adolescents to use e-cigarettes as a way to self-medicate.<sup>26</sup> It's possible that e-cigs could help sleep-deprived adolescents stay alert and awake during the day, masking the negative consequences of insufficient sleep. Furthermore, the cross-sectional association between vaping nicotine and insufficient sleep could be bidirectional. Insufficient sleep may pre-dispose adolescents to use e-cigarettes as a way to cope with moodiness, attention issues, and low energy, while the use of e-cigarettes could, in turn, disrupt sleep, creating a vicious cycle of sleep deprivation and nicotine use. Based on evidence-based guidelines,<sup>31</sup> all the nine articles included in our review were cross-sectional studies which corresponds to Level III category of evidence. Hence, the cross-sectional relationship between e-cigs/dual users and sleep are merely speculative and further longitudinal studies are required to determine causality.

Insufficient sleep at night, as observed in our study subjects, leads to excessive daytime sleepiness, which is strongly correlated with poor academic outcomes, mental health issues, and increased substance use. Our review findings suggest that school-based tobacco and vaping abstinence programs could play a crucial role in promoting sleep health in adolescents. This study suggests that E-cigs, dual use and tobacco use should be the key targets of school prevention programs for students. Adolescents should also be educated about sleep hygiene and the consequences of insufficient sleep and provided guidance on inculcating healthy practices that include avoiding substance use including nicotine in e-cigs, and, excessive use of daytime stimulating products. Prevention programs should be encouraged on the medical and psychiatric consequences of nicotine use and its use serving as a gateway to other substances including alcohol, marijuana and other illicit/recreational drugs. 15,42

### LIMITATIONS

The papers described above have several limitations. All the nine studies included in the review were either cross-sectional studies or surveys. Cross-sectional studies are limited to association and do not allow readers to infer causality. A majority of the surveys utilized a school-based sample, which may not be fully representative of all youth in the United States. Future studies addressing the present research questions or longitudinal research are required to address the bidirectional association between sleep problems and vaping nicotine. Additionally, future studies should consider measuring e-cigarette use with greater detail. This could include assessing factors such as the number of days e-cigarettes were used in the past month, the number of puffs or vaping

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episodes per day, the specific type of e-pen used, and the nicotine levels of the e-liquids.

The other significant limitation is the self-report nature of the vaping and sleep-related measures. There could be significant amount of recall bias in adolescents self-reporting the vaping use and the sleep hours. Not all studies accounted for potential covariates such as preexisting mental health comorbidities, other substance use disorders and medical conditions. The lack of specificity in measuring sleep could have contributed to the measurement error. Actigraphy or polysomnography, sleep diaries, self-report sleep questionnaires could have been utilized for specific sleep measures. Additionally, other potential covariates like caffeine intake and school start times could have affected sleep hours. Finally, E-cig use, and sleep measure covariates were not always cleanly separated and directly measured in relation to one another alone.

### CONCLUSIONS

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Survey studies indicate the interplay between vaping nicotine and sleep disturbances in adolescents is complex. Compared to adolescents who reported eight or more hours of sleep, those who reported getting less than 7–8 hours of sleep were at increased odds of initiating e-cigarette use in the following month. Additionally, sleep disturbances could predispose individuals to vape nicotine suggesting a possible bidirectional association between vaping nicotine and sleep alterations. Further investigation through longitudinal studies is needed to determine factors such as the causal relationship and dose-response effects. Clinicians should educate children, adolescents, and parents about potential detrimental effects of the interplay between vaping and sleep during healthcare visits or school seminars. •

### **DISCLOSURES**

Disclosures of Potential Conflict of Interest.

Mr. Birur, Drs. Burk, Fargason, Alhassan and Reddy have no conflict of interest to disclose in the preparation of this manuscript.

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