# Electronic Vaping Product Use Among Adolescents in the Era of the COVID-19 Pandemic: An Updated Scientific Review for Clinicians

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## ABSTRACT

**Introduction:** In light of increased rates of hospitalizations among adolescents diagnosed with severe symptoms of COVID-19, as well as the prevalence of electronic vaping product (EVP) use among this population, this review highlights the public health and clinical implications of EVP use during an ongoing respiratory disease pandemic.

**Objectives:** This review assesses evidence of pulmonary effects of EVP use from pathophysiological and epidemiological research and explores EVP use as a risk factor for COVID-19.

**Methods:** An updated, yet concise, literature review of recent scientific evidence examining trends of EVP use among adolescents during the COVID-19 pandemic was conducted. Included in this review are studies examining the pulmonary effects of EVP use and scope of the problem relating to its use among adolescents within the context of COVID-19.

**Conclusions:** Preclinical and theoretical models establish pulmonary harm associated with EVPs. Based on the limited epidemiological studies, the contribution of EVP use to the risk of contracting COVID-19 is mixed. EVP-associated lung injury could present as a diagnostic challenge for clinicians during COVID-19 and requires greater attention. Clinicians should effectively screen for and discourage EVP use among adolescents.


## INTRODUCTION

Electronic vaping products (EVP) are battery-powered devices that heat a liquid (e-liquid) to create an inhalable aerosol. The e-liquid in an EVP contains solvent propylene glycol (PG) and vegetable glycerin (VG) with flavorings. EVPs are often used with an optional addition of nicotine, tetrahydrocannabinol (THC) extract, or other addictive substances, thereby increasing the harmful effect of the vaped or inhaled aerosol.[1] The use of EVPs is commonly referred to as "vaping" or "juuling."[2,3] Aerosols from heated e-liquid containing PG and VG consist of more than 100 volatile organic compounds, such as propylene oxide, acrolein, acetaldehyde, and formaldehyde, with diverse toxic properties. Additionally, some studies have reported that potentially carcinogenic and teratogenic compounds, aldehydes, and heavy metals may be formed during the heating process of EVPs.[4]

During 2017-2018, a national survey noted an increase in EVP use of 78% (from 11.7% to 20.8%) and 48% (from 3.3% to 4.9%) among high-school and middle-school students, respectively.[5] The use of EVP-cannabis among high school students doubled from 2018 to 2019—the second-largest 1-year increase in the history of Monitoring the Future survey,[6] a nationwide survey by the National Institute on Drug Abuse deployed annually to adolescent students. The drastic increase in EVP use among younger people led the US Surgeon General to declare youth EVP use an epidemic in 2018.[7] On a positive note, the rapid increase of adolescent EVP use from 2017 to 2019 plateaued during early 2020. Factors that contributed to this pause were the emergence of the e-cigarette or vaping product use-associated lung injury (EVALI) epidemic during the summer of 2019 and a national media campaign that warned adolescents and young adults against EVP use.[8] US Food and Drug Administration policies restricting the manufacture and sale of certain EVP flavors, such as fruit and mint

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flavors,[9] and Tobacco 21 legislation[10] that increased the minimum age for the sale of tobacco products from age 18 to 21, also played a role in limiting EVP access to adolescents. Despite these regulations, mint and fruit flavors were still the most commonly used EVP flavors by adolescents in 2020.[8] Given that EVP content varies markedly and national surveys define EVP differently, prevalence rates of EVP use should be interpreted with caution.

EVP use among adolescents and young adults is especially concerning because nicotine, THC, and other potentially addictive substances are often used in the EVP e-liquid. These substances negatively affect the developing brain due to their ability to alter neurochemistry.[11] In addition, the use of addictive substances in this age group is correlated with future medical harms and psychiatric comorbidities.[12] Adolescents often use EVPs as a way of using cannabis because of easy concealment in public spaces.[13] The lack of awareness that exists among adolescents and young adults regarding the type of e-liquid they use is also problematic. A study found that 63% of youth were unaware that popular EVP "JUULL" contains nicotine and unknowingly used EVPs that contained nicotine.[14] These results suggest that self-reported data may not be accurate, and current data on the use of EVP nicotine among adolescents and young adults is likely underestimated.[15] Even though there has been a recent change in perceived risk,[8] a significant number of young people still perceive use of EVPs as less harmful, less addictive, and a healthier alternative to combustible or traditional cigarettes.[16-19] This misattribution of the level of danger leads to greater use of these products, potentially exposing users to harmful substrates. EVP manufacturing companies claim that their products assist in tobacco smoking cessation and, thus, reduce medical comorbidities associated with tobacco smoking, but mounting evidence suggests that many adolescents and young adults who use EVPs have never tried traditional cigarette smoking.[20,21] In addition, studies show that EVP use is associated with later smoking of tobacco cigarettes among nonsmokers,[22] and those who smoke cigarettes may continue to smoke cigarettes despite using EVPs.[23,24]

As society at large currently grapples with the COVID-19 pandemic, it is especially important to consider the implications that EVP use has on a disease that has deleterious effects on the lungs. In light of the increased hospitalization rates among young people diagnosed with severe symptoms of COVID-19, this review highlights serious yet preventable health risks of EVP use among adolescents amidst the COVID-19 pandemic. It will assist clinicians in initiating EVP use prevention and treatment efforts, in addition to current public health attempts to decrease EVP use.

## Pulmonary Effects of EVP Use

In 2018, several youth including adolescents were diagnosed with EVALI. Their symptoms ranged from shortness of breath and fever to compromised lung function.[25] Approximately 95% of patients with EVALI were hospitalized, and one-fourth of those patients required intubation and mechanical ventilation.[26] A longitudinal analysis of Population Assessment of Tobacco and Health Waves 1, 2, and 3 (2013–2016) showed that individuals who use EVPs increase their risk of developing lung disease by about 30% compared with nonusers and that EVP use could be an independent risk factor for developing respiratory diseases.[27] Preclinical studies have demonstrated that, similar to tobacco cigarette smoke, EVP use is damaging to pulmonary structures and alters platelet function, resulting in alveolar airspace enlargement and disappearance of peripheral vasculature.[28] In addition, EVP use increases the inflammatory profile of respiratory pathogens through an increase in platelet-activating factor receptor expression, thus increasing susceptibility to pneumonia.

The first and only human trial to assess biological responses to EVP use among 10 never smokers and individuals without exposure history to EVP found that acute inhalation of EVP aerosols resulted in altered transcriptomes of small airway epithelium and alveolar macrophages for all subjects (with and without nicotine).[29] Mounting evidence suggests that the pulmonary effect of EVP use depends on its constituents in e-liquid. PG and VG are the solvent carriers for flavors and nicotine in e-liquids and are "generally regarded as safe" by the US Food and Drug Administration (FDA) when used in foods and cosmetics. In animal models, however, heated PG and VG lead to increased inflammatory infiltrates, cytokine production, lung infections, reactive oxygen species, and gene expression.[30] To assess the effects of EVP use with only PG and VG (no nicotine or flavors) on human lungs, Song et al conducted a series of bronchoscopies over 4 weeks in never-smokers (n = 30), where subjects were randomized in 2 groups (intervention or to a no-use control group) and found that intervention (PG and VG) did not exhibit change in mRNA or miRNA gene expression. In addition, no significant differences were observed in changes in bronchoalveolar lavage fluid inflammatory cell counts or cytokines between baseline and follow-up, comparing the control and intervention group.[31]

## EVP-Associated Lung Injury During COVID-19 Pandemic: A Diagnostic Dilemma

The symptomatic (pulmonary, gastrointestinal, and constitutional symptoms), radiological (bilateral multifocal ground glass opacities), and laboratory results (inflammatory markers) showing similarities between EVALI and COVID-19 present a unique diagnostic dilemma. Several cases have been described in the literature highlighting these diagnostic challenges.[32,33] These similarities emphasize the importance of eliciting history of EVP use and a high index of suspicion for EVALI in adolescents who present with unexplained respiratory distress while excluding COVID-19. Highlighting these complexities and diagnostic


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challenges, physicians should counsel their patients—especially adolescents—against using EVP.

### EVP Use a Risk Factor for COVID-19?

Recent evidence shows that smokers and chronic obstructive pulmonary disease (COPD) patients are shown to be at a higher risk of contracting COVID-19 infection due to increased expression of angiotensin-converting enzyme II (ACE-2) expression (cellular entry receptor used by theSARS-CoV-2 virus that causes COVID-19) in small airways, which is mediated by α7-subtype nicotinic receptors (α7-nAChR).[34] The detrimental effects of EVP use on lung function and structure described above and the association between nicotine/tobacco and ACE-2 raised concerns that EVP use also may increase the risk and severity of COVID-19.[35] To explore this particular association, Lee et al compared a cohort of EVP users (with and without nicotine and flavorings) and tobacco smokers based on ACE-2 expression and inflammatory response. They found that, as reported in prior studies, tobacco cigarette use increased ACE-2 expression, but EVP use—irrespective of nicotine status—did not increase the expression of ACE-2, a finding that differs from prior preclinical studies. Of note, however, EVPs with only nicotine/flavor, as opposed to nonflavored and non-nicotine-containing, led to cytokine dysregulation and potential inflammasome activation.[36]

Epidemiological studies examining the association of EVP use and development of COVID-19 infection are limited. The studies that exist vary markedly in their findings and are limited in scope to studying the risk of contracting COVID-19 infection and not the severity of the illness. For example, a cross-sectional study conducted among US adolescents and young adults aged 13–24 years showed that ever EVP-nicotine users—but not current users—were 5 times more likely to be diagnosed with COVID-19.[37] Conversely, a study conducted among individuals >18 years old in the United Kingdom found no difference in self-reported COVID-19 infection between never, current, and past-EVP users.[38] Two other US studies reported conflicting findings as well.[39,40] Larger epidemiological studies and metanalysis would be helpful to confirm theoretical models to examine this association and to better guide clinicians.

### Pattern of EVP Use During COVID-19 Pandemic

A cross-sectional study among adolescents and young adults conducted in May 2020 found that half of the participants (56.4%) reported changes in their EVP use since the beginning of COVID-19 pandemic. Out of those who reported a change, one-third quit EVP use, another third reduced EVP use, while the rest switched to another nicotine or cannabis product.[41] Another study among adolescents compared past 30-day EVP use before (January 1–March 13, 2020) and after stay-at-home directives (March 14–June 29, 2020) during the COVID-19 pandemic and found that EVP use was significantly lower during the stay-at-home directives.[41] Decreased accessibility to EVPs because of stay-at-home orders and closed shops during the pandemic were the most-cited reason in aforementioned studies.[41,42] The results of these studies show that access to EVP is one of the major determinants for EVP use among adolescents and young adults. Interventions to limit access to underage youth may accelerate a downward trajectory of adolescent and young adult EVP use.

### Management of EVP Use Among Adolescents

To date, no published randomized trials exist for vaping cessation among adolescents. A variety of treatment strategies exist for smoking cessation among adults, including behavioral and pharmacotherapy. However, relevance of these guidelines in relation to EVP use cessation among adolescents still needs to be investigated. EVP use treatment strategies are complicated because of varying motivation to quit and willingness to enter an EVP cessation program, diverse EVP use patterns and nicotine level in devices, and co-use of other substances. Discussions with young people on the reasons that motivate them to use EVPs could be helpful. For example, some adolescents use EVPs to socialize, some use them to quit smoking cigarettes, and some perceive EVP use as less harmful than smoking cigarettes. Interventions identifying these subgroups and targeting the reasons that motivate them to use EVPs through education and involving support services were found to be helpful.

## CONCLUSION

The correlation between EVP use and COVID-19 is mostly drawn from preclinical and theoretical models. Based on current but limited epidemiological research, the evidence for EVP use as a risk factor for COVID-19 is mixed. Large-scale epidemiological studies are needed to concretely establish the association between EVP use and occurrence of COVID-19. From a clinical standpoint, since COVID-19 respiratory failure and respiratory failure due to EVALI have many overlapping clinical presentations, clinicians need to be vigilant when managing these cases and thoroughly discuss EVP history with patients—especially adolescents and young adults. The existing evidence demonstrates the need for clinicians to screen for EVP use among adolescents and educate them about potential harms associated with use, especially during the ongoing pandemic.

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