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Demographics, Substance Use Behaviors, and Clinical Characteristics of Adolescents With e-Cigarette, or Vaping, Product Use–Associated Lung Injury (EVALI) in the United States in 2019

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IMPORTANCE To date, limited information is available on the characteristics of adolescents with e-cigarette, or vaping, product use–associated lung injury (EVALI).

OBJECTIVE To inform public health and clinical practice by describing differences in demographics, substance use behaviors, and clinical characteristics of EVALI among adolescents compared with adults.

DESIGN, SETTING, AND PARTICIPANTS Surveillance data reported to the Centers for Disease Control and Prevention during the 2019 EVALI outbreak were used to calculate adjusted prevalence ratios (aPRs) with 95% CIs and to test differences between 360 hospitalized or deceased adolescents vs 859 young adults and 936 adults with EVALI (N = 2155).

MAIN OUTCOMES AND MEASURES Demographics, substance use behaviors, and clinical characteristics.

RESULTS Included in this cross-sectional study were 360 hospitalized or deceased adolescents (age range, 13-17 years; 67.9% male) vs 859 young adults (age range, 18-24 years; 72.4% male) and 936 adults (age range, 25-49 years; 65.6% male) with EVALI. Adolescents diagnosed as having EVALI reported using any nicotine-containing (62.4%), any tetrahydrocannabinol (THC)-containing (81.7%), and both (50.8%) types of e-cigarette or vaping products. Informal sources for obtaining nicotine-containing and THC-containing e-cigarette or vaping products were more commonly reported by adolescents (50.5% for nicotine and 96.5% for THC) than young adults (19.8% for nicotine [aPR, 2.49; 95% CI, 1.78-3.46] and 86.9% for THC [aPR, 1.11; 95% CI, 1.05-1.18]) or adults (24.3% for nicotine [aPR, 2.06; 95% CI, 1.49-2.84] and 75.1% for THC [aPR, 1.29; 95% CI, 1.19-1.40]). Mental, emotional, or behavioral disorders were commonly reported; a history of attention-deficit/hyperactivity disorder was almost 4 times more likely among adolescents (18.1%) than adults (4.9%) (aPR, 3.74; 95% CI, 1.92-7.26). A history of asthma was more likely to be reported among adolescents (43.6%) than adults (28.3%) (aPR, 1.53; 95% CI, 1.14-2.05). Gastrointestinal and constitutional symptoms were more common in adolescents (90.9% and 97.3%, respectively) than adults (75.3% and 94.5%, respectively) (aPR, 1.20; 95% CI, 1.13-1.28 and aPR, 1.03; 95% CI, 1.00-1.06, respectively). Because of missing data, percentages may not be able to be calculated from data provided.

CONCLUSIONS AND RELEVANCE Public health and clinical professionals should continue to provide information to adolescents about the association between EVALI and THC-containing e-cigarette or vaping product use, especially those products obtained through informal sources, and that the use of any e-cigarette or vaping product is unsafe. Compared with adults, it appears that adolescents with EVALI more frequently have a history of asthma and mental, emotional, or behavioral disorders, such as attention-deficit/hyperactivity disorder, and report nonspecific problems, including gastrointestinal and constitutional symptoms; therefore, obtaining a confidential substance use history that includes e-cigarette or vaping product use is recommended.

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Since August 2019, the Centers for Disease Control and Prevention (CDC), US Food and Drug Administration (FDA), and state, local, and territorial health departments have been investigating a national outbreak of e-cigarette, or vaping, product use-associated lung injury (EVALI).[1] As of December 17, 2019, a total of 2506 hospitalized or deceased cases of EVALI, including 54 deaths from 27 states, had been reported to the CDC. Evidence indicates that EVALI is associated with e-cigarette or vaping products that contain tetrahydrocannabinol (THC) (the primary psychoactive ingredient in marijuana), particularly those obtained through informal sources (eg, family, friends, and in-person or online dealers): 82% of patients with EVALI reported using THC products and 78% reported obtaining their products from only informal sources.[2-6] Vitamin E acetate, a cutting or diluting agent sometimes used in THC-containing products, has been found in THC-containing e-cigarette or vaping products tested by the FDA and state laboratories and in bronchoalveolar lavage fluid from patients with EVALI tested by the CDC, suggesting an association between vitamin E acetate and EVALI.[7,8] The 2019 EVALI outbreak affected adolescents and young adults, with 16% of reported cases among patients aged 13 to 17 years and 38% among patients aged 18 to 24 years.[4]

The 2019 EVALI outbreak occurred in the context of an epidemic of e-cigarette or vaping product use among US adolescents.[9] In 2019, 27.5% of high school students used e-cigarettes during the past 30 days.[10] As of 2016, an estimated one-third of US middle and high school students who ever used e-cigarettes had used marijuana in these products.[11] Furthermore, the proportion of high school students who reported use of THC-containing e-cigarette or vaping products during the past month increased from 7.5% in 2018 to 14% in 2019 based on survey results.[12] Adolescent and young adult nicotine and THC use can alter neurodevelopment in the long term and may lead to increased risk of substance use disorder and cognitive difficulties.[13-16]

Adolescents who develop EVALI may have characteristics that differ from those of young adults or adults with EVALI, such as how THC-containing products are obtained, medical history, and the frequency of initial symptoms. These differences may be important for tailoring EVALI-related prevention strategies, including messaging to adolescents through public health communication campaigns and by clinicians. Although characteristics of all patients with EVALI have been reported,[4,17-19] demographic, substance use, and clinical characteristics of adolescents with EVALI have not been separately described. We used surveillance data reported to the CDC during the 2019 EVALI outbreak to describe demographic characteristics, substance use behaviors, and clinical characteristics of 360 hospitalized or deceased adolescents vs 859 young adults and 936 adults with EVALI (N = 2155).

Key Points

Question Do adolescents with e-cigarette, or vaping, product use–associated lung injury (EVALI) differ from adults with EVALI?

Findings A total of 2155 patients were included in this cross-sectional study. Based on national surveillance data, adolescents with EVALI are more likely than adults with EVALI to report the use of informally sourced e-cigarette or vaping products that contain tetrahydrocannabinol and to have attention-deficit/hyperactivity disorder, asthma, and gastrointestinal and constitutional symptoms.

Meaning Public health and clinical efforts could include messaging to adolescents about the risks of tetrahydrocannabinol-containing e-cigarette or vaping products, especially those obtained from informal sources, and their association with EVALI.

Methods

Patients and Data Collection

Using case definitions and data collection tools developed by the CDC in collaboration with state health departments and the Council of State and Territorial Epidemiologists, jurisdictions voluntarily reported confirmed and probable hospitalized cases of EVALI and EVALI-associated deaths to the CDC as part of a national surveillance strategy for the 2019 EVALI outbreak. The EVALI surveillance was determined to be a nonresearch, public health surveillance activity exempt from institutional review board review by the CDC. Jurisdictions submit data from medical record abstractions and, if possible, patient interviews. Proxies (eg, parents) may be interviewed if patients are too ill or have died. Protocols for informed consent for medical record abstraction and patient interview were obtained at the jurisdictional level in accordance with jurisdictional practices for public health practice activities. The present cross-sectional study is limited to hospitalized or deceased patients with EVALI with known age younger than 50 years reported to the CDC as of December 17, 2019. At the time of this analysis, EVALI cases had been reported from all 50 states, the District of Columbia, the US Virgin Islands, and Puerto Rico. Patients with EVALI who were 50 years or older were excluded because they have a higher burden of chronic medical conditions and other risk factors for adverse EVALI-associated outcomes.[20,21] The analytic sample included 2155 patients with EVALI.

Data collected by the CDC include the following: e-cigarette or vaping product use, frequency, and product source; the use of nicotine-containing or combustible marijuana products; medical history; EVALI-compatible symptoms; and clinical course of the lung injury. Analytic demographic characteristics included sex (male or female) and race/ethnicity (non-Hispanic white or other race/ethnicity). Specific races/ethnicities were reported by jurisdictions based on medical record abstraction or patient interview but were further collapsed for this analysis because of small cell sizes for specific racial/ethnic categories by patient age group. Substance use history data included the following: nicotine use in the past 90 days (any use, exclusive use, or daily use of nicotine-containing e-cigarette or vaping product or any use of combustible tobacco); THC use in the past 90 days (any use, exclusive use, or daily use of THC-containing e-cigarette or vaping product or any use of combustible marijuana); and source of e-cigarette or vaping products, including formal sources (dispensary, vape or smoke shop, pop-up shop, or grocery, drug,

or convenience store) and informal sources (family or friend, illicit dealer, or online). Medical history data included a history of any mental, emotional, or behavioral disorder; diabetes; any heart disease; any chronic respiratory disease; EVALI symptoms reported (respiratory, gastrointestinal, and constitutional); and EVALI clinical course and treatment (location of first reported EVALI clinical encounter, corticosteroid treatment, intensive care unit admission, and intubation).

Statistical Analysis

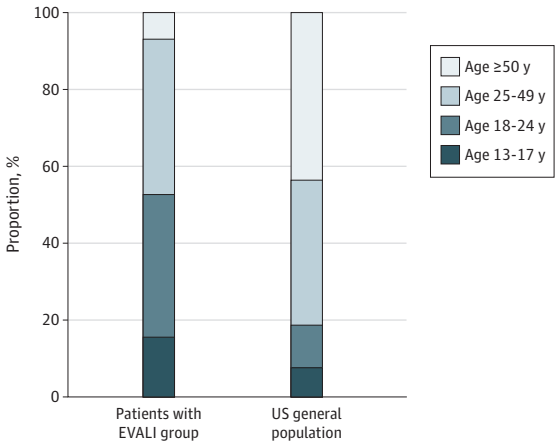
The age distribution of patients with EVALI was compared with the 2018 US Census population estimates to better understand the burden by age.[22] Selected demographic characteristics, substance use behaviors, medical history, and clinical course of EVALI for adolescents were compared with those for young adults and adults with EVALI. Because of missing data within each specific age stratum, percentages may not be able to be calculated from the counts provided. Adjusted prevalence ratios (aPRs) and 95% CIs were calculated using Poisson regression models with robust SEs[23,24]; binary outcomes were modeled with the log-link function and continuous outcomes with the identity link function. All models were adjusted for patient sex because of differences in distribution of sex by age; no other demographic characteristics were included in model adjustments because of percentage of item-level missingness. Analyses were performed using SAS, version 9.4 (SAS Institute Inc). A threshold of 2-sided $P < .05$ was used to define statistical significance.

Results

Included in this cross-sectional study were 360 hospitalized or deceased adolescents (age range, 13-17 years; 67.9% male) vs 859 young adults (age range, 18-24 years; 72.4% male) and 936 adults (age range, 25-49 years; 65.6% male) with EVALI. Compared with the US general population, patients with EVALI are disproportionately adolescents (16% vs 8%) or young adults (37% vs 11%) (**Figure 1**). A high proportion of adolescents with EVALI were non-Hispanic white (66.3%). Demographics for adolescents (n = 360), young adults (n = 859), and adults (n = 936) with EVALI are listed in **Table 1**.

Most adolescent patients with EVALI reported using THC-containing e-cigarette or vaping products (81.7%); this proportion of patients was similar to that of young adults (81.3%) and adults (77.2%) with EVALI (Table 1). Among adolescents reporting the use of THC-containing products, 57.9% reported daily use; this practice was less common compared with young adults (76.5%; aPR, 0.76; 95% CI, 0.64-0.89) and adults (78.0%; aPR, 0.74; 95% CI, 0.63-0.87). Nicotine-containing e-cigarette or vaping product use was more commonly reported among adolescents (62.4%) than adults (46.3%) (aPR, 1.35; 95% CI, 1.20-1.51). Among adolescents with EVALI reporting nicotine-containing product use, daily use was common (74.4%). However, adolescents used nicotine-containing products daily less commonly than adults (91.9%; aPR, 0.81; 95% CI, 0.72-0.91). Daily use of these products was similar among adolescents and young adults. Exclusive nicotine-containing product use was similar across all 3 age categories (range, 10.9%-14.4%; $P > .05$); exclusive use of THC-containing products was less common among adolescents (28.0%) than adults (37.3%) (aPR, 0.75; 95% CI, 0.61-0.92). Reporting use of both nicotine-containing and THC-containing products was more common among adolescents (50.8%) compared with adults (30.4%) (aPR, 1.66; 95% CI, 1.43-1.94). Combustible marijuana use was more common in adolescents (55.5%) than adults (44.7%) (aPR, 1.25; 95% CI, 1.05-1.47); combustible tobacco use was less common among adolescents (16.8%) than young adults (31.7%) (aPR, 0.53; 95% CI, 0.38-0.75) and adults (40.4%) (aPR, 0.42; 95% CI, 0.29-0.61).

Figure 1. Age Distribution of Patients With e-Cigarette, or Vaping, Product Use–Associated Lung Injury (N = 2315) Compared With the Age Distribution of the US General Population



Data for patients with known age with e-cigarette, or vaping, product use–associated lung injury (EVALI) are from national EVALI surveillance reports to the Centers for Disease Control and Prevention as of December 17, 2019. Data for the general population are from annual estimates of the resident population by single year of age and sex for the United States from April 1, 2010, to July 1, 2018, by the US Census Bureau. Ages 0 to 12 years were excluded from the graph because no EVALI cases have been reported in that age group.

More adolescent patients with EVALI reported obtaining THC-containing products through informal sources (96.5%) compared with young adults (86.9%) (aPR, 1.11; 95% CI, 1.05-1.18) and adults (75.1%) (aPR, 1.29; 95% CI, 1.19-1.40). Specifically, adolescents obtained THC-containing products more frequently from family or friends (61.0%) than young adults (42.2%) (aPR, 1.41; 95% CI, 1.14-1.75) and adults (40.5%) (aPR, 1.52; 95% CI, 1.22-1.88). Adolescent patients with EVALI also reported obtaining nicotine-containing products more frequently from informal sources (50.5%) than young adults (19.8%) (aPR, 2.49; 95% CI, 1.78-3.46) and adults (24.3%) (aPR, 2.06; 95% CI, 1.49-2.84). Among adolescents with EVALI who reported using nicotine-containing products, most reported obtaining at least some (69.0%) of their nicotine-containing e-cigarette or vaping products through formal sources, such as recreational dispensaries or convenience stores, although less commonly than young adults (92.5%) (aPR, 0.75; 95% CI, 0.65-0.87) or adults (88.9%) (aPR, 0.78; 95% CI, 0.67-0.90).

Reported history of any mental, emotional, or behavioral disorder was common across all age groups with EVALI in our

Table 1. Differences in Demographics and Substance Use Behaviors Between Adolescent and Young Adult or Adult Hospitalized or Deceased Patients With e-Cigarette, or Vaping, Product Use–Associated Lung Injury (N = 2155) in the US in 2019[a]

Variable	No.[b]	Age, No. (%)			Adolescents vs young adults		Adolescents vs adults	
		13-17 y (n = 360)	18-24 y (n = 859)	25-49 y (n = 936)	aPR (95% CI)[c]	*P* value	aPR (95% CI)[c]	*P* value
Demographics								
Sex	2141							
Male		243 (67.9)	618 (72.4)	609 (65.6)	0.94 (0.86-1.02)	.12	1.04 (0.95-1.13)	.41
Female		115 (32.1)	236 (27.6)	320 (34.4)				
Race/ethnicity	1547							
Non-Hispanic white		171 (66.3)	459 (74.8)	522 (77.3)	0.89 (0.80-0.98)	.02	0.86 (0.78-0.94)	.002
Other race/ethnicity		87 (33.7)	155 (25.2)	153 (22.7)				
Substance use history								
Nicotine use in past 90 d								
Any nicotine-containing e-cigarette or vaping product use	1793	194 (62.4)	452 (62.5)	351 (46.3)	1.00 (0.90-1.11)	.98	1.35 (1.20-1.51)	<.001
Exclusive nicotine-containing e-cigarette or vaping use	1793	34 (10.9)	90 (12.5)	109 (14.4)	0.85 (0.59-1.23)	.39	0.76 (0.53-1.10)	.14
Nicotine-containing e-cigarette or vaping daily use	603	90 (74.4)	226 (83.1)	193 (91.9)	0.89 (0.79-1.00)	.06	0.81 (0.72-0.91)	<.001
Use of combustible tobacco	1190	32 (16.8)	153 (31.7)	209 (40.4)	0.53 (0.38-0.75)	<.001	0.42 (0.29-0.61)	<.001
THC use in past 90 d								
Any THC-containing e-cigarette or vaping product use	1793	254 (81.7)	588 (81.3)	586 (77.2)	1.01 (0.94-1.07)	.86	1.06 (0.99-1.13)	.10
Exclusive THC-containing e-cigarette or vaping use	1793	87 (28.0)	207 (28.6)	283 (37.3)	0.97 (0.78-1.20)	.76	0.75 (0.61-0.92)	.005
THC-containing e-cigarette or vaping daily use	784	70 (57.9)	250 (76.5)	262 (78.0)	0.76 (0.64-0.89)	<.001	0.74 (0.63-0.87)	<.001
Use of combustible marijuana	1020	101 (55.5)	231 (54.7)	186 (44.7)	1.03 (0.88-1.20)	.74	1.25 (1.05-1.47)	.01
e-Cigarette use of both nicotine-containing and THC-containing products	1793	158 (50.8)	353 (48.8)	231 (30.4)	1.05 (0.92-1.20)	.46	1.66 (1.43-1.94)	<.001
Source of e-cigarette or vaping products								
Source of nicotine-containing e-cigarette, or vaped								
Shop or store, formal	518	62 (69.0)	221 (92.5)	168 (88.9)	0.75 (0.65-0.87)	<.001	0.78 (0.67-0.90)	<.001
Recreational dispensary, vape or smoke shop, or pop-up shop	517	35 (38.9)	118 (49.6)	119 (63.0)	0.81 (0.61-1.09)	.17	0.61 (0.46-0.81)	<.001
Grocery, drug, or convenience store	518	34 (37.8)	132 (55.2)	66 (34.9)	0.68 (0.51-0.91)	.009	1.11 (0.80-1.54)	.54

(continued)

Table 1. Differences in Demographics and Substance Use Behaviors Between Adolescent and Young Adult or Adult Hospitalized or Deceased Patients With e-Cigarette, or Vaping, Product Use–Associated Lung Injury (N = 2155) in the US in 2019[a] (continued)

Variable	No.[b]	Age, No. (%)			Adolescents vs young adults		Adolescents vs adults	
		13-17 y (n = 360)	18-24 y (n = 859)	25-49 y (n = 936)	aPR (95% CI)[c]	*P* value	aPR (95% CI)[c]	*P* value
In-person or online, informal	520	47 (50.5)	47 (19.8)	46 (24.3)	2.49 (1.78-3.46)	<.001	2.06 (1.49-2.84)	<.001
Family or friend	518	30 (33.0)	30 (12.6)	20 (10.6)	2.57 (1.64-4.03)	<.001	3.04 (1.82-5.08)	<.001
Illicit dealer[d]	518	9 (9.9)	6 (2.5)	3 (1.6)	4.12 (1.44-11.76)	.008	6.33 (1.70-23.64)	.006
Online[d]	517	9 (10.0)	13 (5.5)	26 (13.8)	1.71 (0.74-3.96)	.21	0.73 (0.36-1.49)	.39
Source of THC-containing e-cigarette, or vaped, THC								
Shop or store, formal[d]	593	7 (6.7)	48 (19.8)	81 (32.9)	0.34 (0.16-0.73)	.006	0.20 (0.10-0.43)	<.001
Medical dispensary[d]		0	5 (2.1)	17 (6.9)	NA	NA	NA	NA
Recreational dispensary, vape or smoke shop, or pop-up shop		7 (6.7)	36 (14.9)	69 (28.1)	0.44 (0.20-0.97)	.04	0.24 (0.11-0.51)	<.001
Grocery, drug, or convenience store		0	9 (3.7)	2 (0.8)	NA	NA	NA	NA
In-person or online, informal	622	109 (96.5)	219 (86.9)	193 (75.1)	1.11 (1.05-1.18)	<.001	1.29 (1.19-1.40)	<.001
Family or friend	594	64 (61.0)	102 (42.2)	100 (40.5)	1.41 (1.14-1.75)	<.001	1.52 (1.22-1.88)	<.001
Illicit dealer	595	43 (41.0)	106 (43.6)	86 (34.8)	0.96 (0.73-1.26)	.76	1.18 (0.88-1.56)	.27
Online[d]	593	8 (7.6)	17 (7.0)	14 (5.7)	1.18 (0.53-2.63)	.69	1.34 (0.57-3.10)	.50

Abbreviations: aPR, adjusted prevalence ratio; NA, not applicable; THC, tetrahydrocannabinol.

[a] Data are from national e-cigarette, or vaping, product use–associated lung injury surveillance reports to the Centers for Disease Control and Prevention as of December 17, 2019. Adolescents were aged 13 to 17 years, young adults were aged 18 to 24 years, and adults were aged 25 to 49 years. The percentages cannot be calculated directly from the information in the table.

[b] The sample sizes represent the total number of EVALI cases included in this analysis that had data reported for each variable of interest. For example, 2141 of the 2155 hospitalized or deceased patients with EVALI with known age between 13 and 49 years had data provided to the Centers for Disease Control and Prevention on patient sex. These sample sizes have been provided so that the readers can better understand the completeness of data per variable in relation to the overall sample (N = 2155). Of note, not all estimates may sum to 100% given that some values may not be mutually exclusive or fully complete data may not have been provided. The percentages cannot be calculated directly from the information in the table because missing data on each variable by age stratum are not presented.

[c] Adjusted for sex.

[d] Estimates are based on small sample sizes; therefore, precision in estimates is limited. These models and percentages should be interpreted with caution.

analysis (range, 41.5%-51.0%). Specifically, attention-deficit/hyperactivity disorder (ADHD) was more commonly reported among adolescents with EVALI (18.1%) compared with young adults (7.9%) (aPR, 2.31; 95% CI, 1.27-4.20) and adults (4.9%) (aPR, 3.74; 95% CI, 1.92-7.26). Adolescents more commonly reported a history of asthma (43.6%) compared with adults (28.3%) (aPR, 1.53; 95% CI, 1.14-2.05); there were no statistically significant differences in having a reported history of asthma between adolescents and young adults (41.1%) ($P > .05$) (**Table 2**).

Respiratory symptoms at initial clinical presentation for EVALI were reported by almost all patients with EVALI regardless of age (range, 95.8%-96.7%). Adolescents more commonly reported gastrointestinal symptoms associated with EVALI (90.9%) compared with adults (75.3%) (aPR, 1.20; 95% CI, 1.13-1.28) (Table 2). Adolescents also more frequently reported constitutional symptoms (eg, fever, chills, and malaise) associated with EVALI (97.3%) compared with adults (94.5%) (aPR, 1.03; 95% CI, 1.00-1.06). No difference was noted between adolescents and young adults for report of respiratory, gastrointestinal, or constitutional symptoms. There were no statistically significant differences between age groups for duration between symptom onset and first hospitalization (**Figure 2**A). Adolescents less often reported their first EVALI clinical encounter was a hospitalization (80.4%) compared with adults (85.2%) (aPR, 0.95; 95% CI, 0.89-1.00). Adolescents were more commonly admitted to the intensive care unit (46.9%) than young adults (37.6%) (aPR, 1.24; 95% CI, 1.05-1.48). Intubation was less common among adolescents (12.4%) compared with adults (23.1%) (aPR, 0.54; 95% CI, 0.31-0.94). Percentage intubated was similar for adolescents and young adults. There were no statistically significant differences among age groups in whether corticosteroids were administered (Table 2). No statistically significant differences were found between age groups for duration of first hospitalization (Figure 2B).

Discussion

Adolescents and young adults are disproportionately affected by EVALI. These age groups comprise 19% of the US general population older than 12 years but contribute to just

Table 2. Differences in Clinical Characteristics Between Adolescent and Young Adult or Adult Hospitalized or Deceased Patients With e-Cigarette, or Vaping, Product Use–Associated Lung Injury (EVALI) (N = 2155) in the US in 2019[a]

Variable	No.[b]	Age, No. (%)			Adolescents vs young adults		Adolescents vs adults	
		13-17 y (n = 360)	18-24 y (n = 859)	25-49 y (n = 936)	aPR (95% CI)[c]	*P* value	aPR (95% CI)[c]	*P* value
Medical history								
History of any mental, emotional, or behavioral disorder	1123	94 (50.0)	191 (41.5)	242 (51.0)	1.16 (0.97-1.39)	.09	0.99 (0.84-1.16)	.87
ADHD	633	17 (18.1)	20 (7.9)	14 (4.9)	2.31 (1.27-4.20)	.006	3.74 (1.92-7.26)	<.001
Anxiety	1137	63 (32.1)	127 (27.8)	177 (36.6)	1.13 (0.88-1.44)	.34	0.90 (0.72-1.13)	.36
Depression	1141	58 (29.4)	111 (24.1)	148 (30.6)	1.17 (0.90-1.53)	.24	0.96 (0.75-1.23)	.74
PTSD[d]	633	0	7 (2.8)	6 (2.1)	NA	NA	NA	NA
Substance use or substance use disorder[d]	633	4 (4.3)	10 (4.0)	27 (9.4)	1.08 (0.34-3.47)	.89	0.49 (0.17-1.36)	.17
History of diabetes[d]	633	3 (3.2)	5 (2.0)	19 (6.6)	1.45 (0.36-5.86)	.60	0.47 (0.14-1.54)	.21
History of any heart disease	1172	11 (5.7)	22 (4.6)	51 (10.1)	1.15 (0.53-2.48)	.72	0.44 (0.22-0.88)	.02
History of any chronic respiratory disease	1263	52 (24.0)	123 (24.1)	112 (20.9)	1.00 (0.75-1.32)	.99	1.17 (0.88-1.56)	.29
Asthma	633	41 (43.6)	104 (41.1)	81 (28.3)	1.05 (0.80-1.38)	.73	1.53 (1.14-2.05)	.005
COPD[d]	633	0	2 (0.8)	9 (3.2)	NA	NA	NA	NA
Obstructive sleep apnea[d]	633	0	3 (1.2)	6 (2.1)	NA	NA	NA	NA
EVALI symptoms reported								
Respiratory symptoms	1532	250 (95.8)	606 (96.7)	622 (96.6)	0.99 (0.96-1.02)	.49	0.99 (0.96-1.02)	.58
Gastrointestinal symptoms	1452	231 (90.9)	534 (89.0)	450 (75.3)	1.03 (0.97-1.07)	.36	1.20 (1.13-1.28)	<.001
Constitutional symptoms	1523	251 (97.3)	610 (97.3)	603 (94.5)	1.00 (0.98-1.02)	.98	1.03 (1.00-1.06)	.04
Gastrointestinal or constitutional symptoms but no respiratory symptoms reported[d]	1477	9 (3.6)	16 (2.6)	16 (2.6)	1.44 (0.65-3.19)	.36	1.39 (0.62-3.11)	.42
EVALI clinical course and treatment								
First reported EVALI clinical encounter was hospitalization	2026	271 (80.4)	645 (80.1)	753 (85.2)	1.00 (0.94-1.07)	.93	0.95 (0.89-1.00)	.049
Corticosteroids administered	1203	183 (84.7)	431 (87.3)	439 (89.1)	0.97 (0.91-1.03)	.33	0.95 (0.89-1.02)	.13
Admitted to the intensive care unit	1300	112 (46.9)	198 (37.6)	249 (46.6)	1.24 (1.05-1.48)	.02	0.99 (0.84-1.17)	.91
Intubated[d]	632	13 (12.4)	36 (14.7)	65 (23.1)	0.86 (0.48-1.56)	.62	0.54 (0.31-0.94)	.03

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; aPR, adjusted prevalence ratio; COPD, chronic obstructive pulmonary disease; NA, not applicable; PTSD, posttraumatic stress disorder.

[a] Data are from e-cigarette, or vaping, product use–associated lung injury surveillence reports to the Centers for Disease Control and Prevention as of December 17, 2019. Adolescents were aged 13 to 17 years, young adults were aged 18 to 24 years, and adults were aged 25 to 49 years. The percentages cannot be calculated directly from the information in the table.

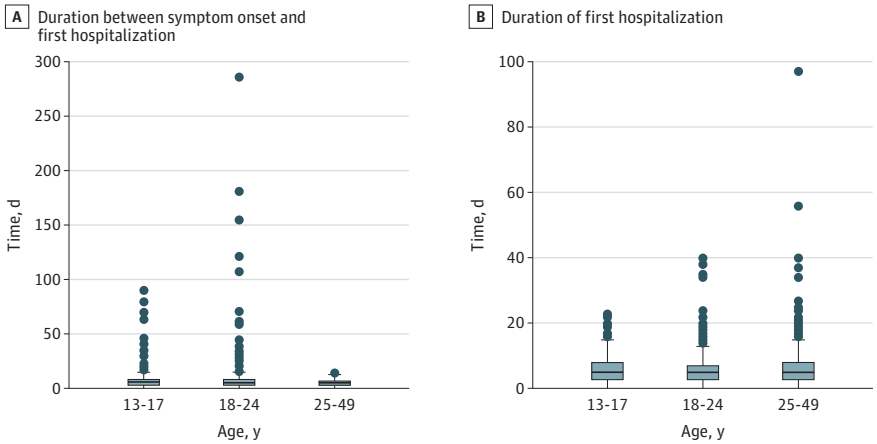
[b] The sample sizes represent the total number of EVALI cases included in this analysis that had data reported for each variable of interest. For example, 1123 of the 2155 hospitalized or deceased patients with EVALI with known age between 13 and 49 years had data provided to the Centers for Disease Control and Prevention on patient history of any mental, emotional, or behavioral disorder. These sample sizes have been provided so that the readers can better understand the completeness of data per variable in relation to the overall sample (N = 2155). Of note, not all estimates may sum to 100% given that some values may not be mutually exclusive or fully complete data may not have been provided. The percentages cannot be calculated directly from the information in the table because missing data on each variable by age stratum are not presented.

[c] Adjusted for sex.

[d] Estimates are based on small sample sizes; therefore, precision in estimates is limited. These models and percentages should be interpreted with caution.

over 50% of reported EVALI cases. Furthermore, among persons with EVALI, important differences exist in substance use behaviors and clinical characteristics of adolescents compared with young adults and adults. Most adolescents with EVALI reported the use of THC-containing products and more frequently reported obtaining these THC-containing products from informal sources (ie, family, friends, and in-person or online dealers) than young adults

Figure 2. Duration Between Symptom Onset and First Hospitalization and Duration of First Hospitalization for Hospitalized or Deceased Patients With e-Cigarette, or Vaping, Product Use–Associated Lung Injury in the US in 2019 (N = 2155), Stratified by Age



A and B, Adolescents (age, 13-17 years) had similar duration between symptom onset and first hospitalization compared with young adults (age, 18 to 24 years) (β = −0.12; 95% CI, −2.33 to 2.09; *P* = .91) and adults (age, 25-49 years) (β = 0.19; 95% CI, −1.63 to 2.01; *P* = .84). Adolescents also had similar duration of first hospitalization compared with young adults (β = 0.64; 95% CI, −0.28 to 1.55; *P* = .17) and adults (β = −0.41; 95% CI, −1.43 to 0.61; *P* = .43). The horizontal lines within the boxes represent the median, with the lower and upper line of the box representing the first and third quartiles. The outliers represent individual patients whose data points were greater than 1.5 times the interquartile range.

or adults with EVALI. Moreover, a history of ADHD was more commonly reported among adolescents with EVALI than among young adults or adults with EVALI; a history of asthma was more commonly reported among adolescents with EVALI than among adults with EVALI. Gastrointestinal and constitutional symptoms were more common for adolescents at clinical presentation, which may complicate the clinical picture and could delay EVALI diagnosis and treatment. These findings can inform public health and clinical professionals' response to EVALI among adolescents.

Most adolescents with EVALI (81.7%) reported THC-containing e-cigarette or vaping product use, and almost all adolescents with EVALI (96.5%) reported obtaining THC-containing products from informal sources (ie, family, friends, and in-person, or online dealers). Informal sources were more commonly reported by adolescents with EVALI than by young adults or adults with EVALI. Many adolescents (57.9%) reported daily THC-containing product use. The finding of frequent informally sourced THC-containing product use is consistent with previous national results and with data suggesting that THC-containing e-cigarette or vaping products are associated with most of the EVALI cases and played a major role in the 2019 EVALI outbreak.[1,2,4,5,18] Informally sourced THC-containing e-cigarette or vaping products obtained from geographically diverse states have been found to contain vitamin E acetate, a chemical associated with EVALI.[7,19] The finding of vitamin E acetate in bronchoalveolar lavage fluid of patients with EVALI but not in the lung fluid of people who do not have EVALI further supports the association between vitamin E acetate and EVALI.[8] However, evidence is not sufficient to rule out other chemicals of concern, including those in THC or non-THC products; product sources remain under investigation. There may be more than 1 cause of EVALI.[1]

The common occurrence of several specific comorbidities in adolescents with EVALI may inform clinical evaluation and intervention. The prevalence of ADHD among adolescents with EVALI in our study was higher than the prevalence among adolescents in the US general population (18.1% vs 10.5%),[25] and adolescents with EVALI reported a history of ADHD between 2 to 4 times more often than young adults or adults with EVALI (18.1% vs 7.9% and 4.9%, respectively). Furthermore, ADHD is associated with risk-taking behaviors, including e-cigarette use[26] and other substance use.[27-29] Half of adolescents with EVALI reported a history of any co-occurring behavioral health condition; these conditions are common in the overall population of patients with EVALI and are important to consider to optimize clinical care and appropriate referral to behavioral health services.[20,21] Addressing these needs in adolescent patients may reduce risk of subsequent substance use disorder.[16] Similar to the general population,[30] adolescents with EVALI more commonly reported a history of asthma than adult patients with EVALI. Notably, the prevalence of asthma among adolescents with EVALI appears to be higher than that among the general adolescent population (43.6% vs 18.2%),[30] which reflects previous reports of higher prevalence of asthma among all patients with EVALI[31,32] and may indicate that adolescents with asthma and EVALI more frequently seek hospital care. Our findings support the importance of asking adolescents who are seen with asthma symptoms about e-cigarette or vaping product use and consideration of EVALI in differential diagnoses.

Adolescents with EVALI were more likely to report experiencing gastrointestinal or constitutional symptoms compared with adults with EVALI. Prior evidence supports a high frequency of gastrointestinal symptoms in patients with EVALI, which are sometimes reported as the reason for obtaining medi-

cal care.[32] Although the reason is unclear, it is possible that differing patterns of product use by adolescents might play a role. For example, adolescents might be inexperienced e-cigarette users compared with adults and inhale less deeply, leading to increased swallowing of the e-cigarette aerosol and a higher exposure of aerosol constituents to the gastrointestinal system. Additional research is needed to test this hypothesis.[33,34] The occurrence of nonspecific gastrointestinal and constitutional symptoms may delay clinical recognition of EVALI given that it is a diagnosis of exclusion. A confidential, accurate substance use history paired with appropriate patient education, including about e-cigarette or vaping product use, is needed to ensure timely diagnosis of EVALI.

These findings highlight the importance of clinicians working with adolescents to provide education and access to services. Teaching should (1) emphasize the association between THC-containing e-cigarette or vaping product use and EVALI; (2) reinforce that there may be other chemicals of concern aside from vitamin E acetate, including those in products not containing THC, associated with EVALI; and (3) counsel adolescents that any e-cigarette or vaping product use is unsafe.[1,35] The identification of common comorbidities, including ADHD and asthma, can inform clinical evaluation and intervention; our findings support the critical need to make tobacco use cessation, substance use screening, and mental health services easily accessible to all youth.[20,36,37] Clinician awareness that adolescents commonly report nonspecific gastrointestinal and constitutional symptoms may hasten timely recognition of EVALI.

When addressing EVALI among youth, it is important for clinicians and public health professionals to distinguish between the 2019 EVALI outbreak and the ongoing US epidemic of youth e-cigarette use. Primarily, EVALI is associated with the use of THC-containing products from informal sources (ie, family, friends, and in-person or online dealers), whereas the youth e-cigarette use epidemic has primarily been associated with the use of nicotine-containing products from formal sources (eg, legal retail establishments). However, each of these epidemics (ie, EVALI and youth e-cigarette use) disproportionately influences young people and is complicated by a multifactorial causation.[38] These 2 events (EVALI and youth e-cigarette use) represent opportunities for public health and clinical communities to prevent and reduce the use of e-cigarette or vaping products among adolescent and young adult populations. In 2016, the FDA asserted regulatory authority over e-cigarettes, which required that all e-cigarettes on the market at that time needed to have an authorization from the FDA to be legally marketed. However, the agency subsequently deferred enforcement of the premarket authorization requirements, which means that all e-cigarettes now on the US market are considered illegally marketed and are subject to enforcement. Regardless of whether nicotine, THC, or any other substance is used in an e-cigarette or vaping product, these products are not safe for youth or young adults because of known negative health influences.[13-15,35,39]

Limitations

This study has limitations. Data collection methods varied across jurisdictions, which may have resulted in reporting inconsistencies that could not be accounted for in this analysis. Information was obtained from medical records and patient or proxy interviews, which may be incomplete or subject to social desirability or recall bias. In addition, comparisons with national prevalence data (eg, for asthma) may be inexact given the variability in question framing or the time frame of data collection. This analysis only includes hospitalized or deceased EVALI cases; it is possible that many more adolescents may be affected but not severely enough to require hospitalization. Proxies may not have had complete knowledge about the patient's exposure history. For medical history, indicators of some conditions (any mental, emotional, or behavioral disorder, including ADHD, posttraumatic stress disorder, and substance use, as well as a history of diabetes, asthma, chronic obstructive pulmonary disease, and obstructive sleep apnea) were created using responses to free-text fields and may not have been reported systematically. Finally, some estimates are based on small sample sizes, and precision in estimates is thus limited; these models should be interpreted with caution.

Conclusions

It is important for public health and clinical professionals to continue providing information to adolescents about the association between EVALI and THC-containing e-cigarette or vaping product use, in particular those from informal sources, and that any e-cigarette or vaping product use is unsafe.[35] The high prevalence of ADHD, other mental or behavioral health conditions, and asthma among adolescents with EVALI may complicate care and follow-up. Youth should be referred to appropriate treatment for co-occurring conditions and substance use cessation services.[20,37] The high proportion of adolescents seen with nonspecific gastrointestinal and constitutional symptoms may delay EVALI diagnosis. It is essential that clinicians caring for adolescents obtain a confidential substance use history that includes e-cigarette or vaping product use.[37,40,41] Ultimately, the need for programs and policies to limit youth exposure to e-cigarette products, regardless of nicotine or THC content, is a public health imperative.[42]

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REFERENCES

1. Centers for Disease Control and Prevention. Outbreak of lung injury associated with the use of e-cigarette, or vaping, products. Accessed December 15, 2019. https://www.cdc.gov/tobacco/basic_information/e-cigarettes/severe-lung-disease.html#latest-outbreak-information

2. Navon L, Jones CM, Ghinai I, et al. Risk factors for e-cigarette, or vaping, product use–associated lung injury (EVALI) among adults who use e-cigarette, or vaping, products: Illinois, July-October 2019. *MMWR Morb Mortal Wkly Rep*. 2019;68(45):1034-1039. doi:10.15585/mmwr.mm6845e1

3. Lewis N, McCaffrey K, Sage K, et al. e-Cigarette use, or vaping, practices and characteristics among persons with associated lung injury: Utah, April-October 2019. *MMWR Morb Mortal Wkly Rep*. 2019;68(42):953-956. doi:10.15585/mmwr.mm6842e1

4. Lozier MJ, Wallace B, Anderson K, et al; Lung Injury Response Epidemiology/Surveillance Task Force. Update: demographic, product, and substance-use characteristics of hospitalized patients in a nationwide outbreak of e-cigarette, or vaping, product use–associated lung injuries: United States, December 2019. *MMWR Morb Mortal Wkly Rep*. 2019;68(49):1142-1148. doi:10.15585/mmwr.mm6849e1

5. Ghinai I, Pray IW, Navon L, et al. e-Cigarette product use, or vaping, among persons with associated lung injury: Illinois and Wisconsin, April-September 2019. *MMWR Morb Mortal Wkly Rep*. 2019;68(39):865-869. doi:10.15585/mmwr.mm6839e2

6. Ellington S, Salvatore PP, Ko J, et al; Lung Injury Response Epidemiology/Surveillance Task Force. Update: product, substance-use, and demographic characteristics of hospitalized patients in a nationwide outbreak of e-cigarette, or vaping, product use–associated lung injury: United States, August 2019-January 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69(2):44-49. doi:10.15585/mmwr.mm6902e2

7. US Food and Drug Administration. Lung illnesses associated with use of vaping products. Accessed December 2019. https://www.fda.gov/news-events/public-health-focus/lung-illnesses-associated-use-vaping-products

8. Blount BC, Karwowski MP, Morel-Espinosa M, et al. Evaluation of bronchoalveolar lavage fluid from patients in an outbreak of e-cigarette, or vaping, product use–associated lung injury: 10 states, August-October 2019. *MMWR Morb Mortal Wkly Rep*. 2019;68(45):1040-1041. doi:10.15585/mmwr.mm6845e2

9. US Department of Health and Human Services. *e-Cigarette Use Among Youth and Young Adults: A Report of the Surgeon General*. US Dept of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2016.

10. Wang TW, Gentzke AS, Creamer MR, et al. Tobacco product use and associated factors among middle and high school students: United States, 2019. *MMWR Surveill Summ*. 2019;68(12):1-22. doi:10.15585/mmwr.ss6812a1

11. Trivers KF, Phillips E, Gentzke AS, Tynan MA, Neff LJ. Prevalence of cannabis use in electronic cigarettes among US youth. *JAMA Pediatr*. 2018;172(11):1097-1099. doi:10.1001/jamapediatrics.2018.1920

12. National Institute on Drug Abuse; National Institutes of Health; US Department of Health and Human Services. Monitoring the Future 2019 survey results: overall findings. Accessed December 22, 2019. https://www.drugabuse.gov/related-topics/trends-statistics/infographics/monitoring-future-2019-survey-results-overall-findings

13. Yuan M, Cross SJ, Loughlin SE, Leslie FM. Nicotine and the adolescent brain. *J Physiol*. 2015;593(16):3397-3412. doi:10.1113/JP270492

14. Miguez MJ, Chan W, Espinoza L, Tarter R, Perez C. Marijuana use among adolescents is associated with deleterious alterations in mature BDNF. *AIMS Public Health*. 2019;6(1):4-14. doi:10.3934/publichealth.2019.1.4

15. Levine A, Clemenza K, Rynn M, Lieberman J. Evidence for the risks and consequences of adolescent cannabis exposure. *J Am Acad Child Adolesc Psychiatry*. 2017;56(3):214-225. doi:10.1016/j.jaac.2016.12.014

16. Compton WM, Jones CM, Baldwin GT, Harding FM, Blanco C, Wargo EM. Targeting youth to prevent later substance use disorder: an underutilized response to the US opioid crisis. *Am J Public Health*. 2019;109(S3):S185-S189. doi:10.2105/AJPH.2019.305020

17. Chatham-Stephens K, Roguski K, Jang Y, et al; Lung Injury Response Epidemiology/Surveillance Task Force; Lung Injury Response Clinical Task Force. Characteristics of hospitalized and nonhospitalized patients in a nationwide outbreak of e-cigarette, or vaping, product use–associated lung injury: United States, November 2019. *MMWR Morb Mortal Wkly Rep*. 2019;68(46):1076-1080. doi:10.15585/mmwr.mm6846e1

18. Moritz ED, Zapata LB, Lekiachvili A, et al; Lung Injury Response Epidemiology/Surveillance Group; Lung Injury Response Epidemiology/Surveillance Task Force. Update: characteristics of patients in a national outbreak of e-cigarette, or vaping, product use–associated lung injuries: United States, October 2019. *MMWR Morb Mortal Wkly Rep*. 2019;68(43):985-989. doi:10.15585/mmwr.mm6843e1

19. Taylor J, Wiens T, Peterson J, et al; Lung Injury Response Task Force. Characteristics of e-cigarette, or vaping, products used by patients with associated lung injury and products seized by law enforcement: Minnesota, 2018 and 2019. *MMWR Morb Mortal Wkly Rep*. 2019;68(47):1096-1100. doi:10.15585/mmwr.mm6847e1

20. Evans ME, Twentyman E, Click ES, et al; Lung Injury Response Clinical Task Force; Lung Injury Response Clinical Working Group. Update: interim guidance for health care professionals evaluating and caring for patients with suspected e-cigarette, or vaping, product use–associated lung injury and for reducing the risk for rehospitalization and death following hospital discharge: United States, December 2019. *MMWR Morb Mortal Wkly Rep*. 2020;68(5152):1189-1194. doi:10.15585/mmwr.mm685152e2

21. Mikosz CA, Danielson M, Anderson KN, et al; Lung Injury Response Epidemiology/Surveillance Task Force. Characteristics of patients experiencing rehospitalization or death after hospital discharge in a nationwide outbreak of e-cigarette, or vaping, product use–associated lung injury: United States, 2019. *MMWR Morb Mortal Wkly Rep*. 2020;68(5152):1183-1188. doi:10.15585/mmwr.mm685152e1

22. US Census Bureau. Annual estimates of the resident population by single year of age and sex: April 1, 2010 to July 1, 2018. 2018 Population estimates. Accessed April 2, 2020. https://www.census.gov/data/tables/time-series/demo/popest/2010s-national-detail.html

23. Zou G. A modified Poisson regression approach to prospective studies with binary data. *Am J Epidemiol*. 2004;159(7):702-706. doi:10.1093/aje/kwh090

24. Spiegelman D, Hertzmark E. Easy SAS calculations for risk or prevalence ratios and differences. *Am J Epidemiol*. 2005;162(3):199-200. doi:10.1093/aje/kwi188

25. Ghandour RM, Sherman LJ, Vladutiu CJ, et al. Prevalence and treatment of depression, anxiety, and conduct problems in US children. *J Pediatr*. 2019;206:256-267.e3. doi:10.1016/j.jpeds.2018.09.021

26. Goldenson NI, Khoddam R, Stone MD, Leventhal AM. Associations of ADHD symptoms with smoking and alternative tobacco product use initiation during adolescence. *J Pediatr Psychol*. 2018;43(6):613-624. doi:10.1093/jpepsy/jsx153

27. Lee SS, Humphreys KL, Flory K, Liu R, Glass K. Prospective association of childhood attention-deficit/hyperactivity disorder (ADHD) and substance use and abuse/dependence: a meta-analytic review. *Clin Psychol Rev*. 2011;31(3):328-341. doi:10.1016/j.cpr.2011.01.006

28. Molina BS, Hinshaw SP, Eugene Arnold L, et al; MTA Cooperative Group. Adolescent substance use in the Multimodal Treatment Study of Attention-Deficit/Hyperactivity Disorder (ADHD) (MTA) as a function of childhood ADHD, random assignment to childhood treatments, and subsequent medication. *J Am Acad Child Adolesc Psychiatry*. 2013;52(3):250-263. doi:10.1016/j.jaac.2012.12.014

29. Pingault JB, Côté SM, Galéra C, et al. Childhood trajectories of inattention, hyperactivity and oppositional behaviors and prediction of substance abuse/dependence: a 15-year longitudinal population-based study. *Mol Psychiatry*. 2013;18(7):806-812. doi:10.1038/mp.2012.87

30. Centers for Disease Control and Prevention. Most recent national asthma data. Accessed December 15, 2019. https://www.cdc.gov/asthma/most_recent_national_asthma_data.htm

31. Layden JE, Ghinai I, Pray I, et al. Pulmonary illness related to e-cigarette use in Illinois and Wisconsin: final report. *N Engl J Med*. 2020;382(10):903-916. doi:10.1056/NEJMoa1911614

32. Blagev DP, Harris D, Dunn AC, Guidry DW, Grissom CK, Lanspa MJ. Clinical presentation, treatment, and short-term outcomes of lung injury associated with e-cigarettes or vaping: a prospective observational cohort study. *Lancet*. 2019;394(10214):2073-2083. doi:10.1016/S0140-6736(19)32679-0

33. Taylor G, Warren S, Dwivedi S, et al. Gamma scintigraphic pulmonary deposition study of glycopyrronium/formoterol metered dose inhaler formulated using co-suspension delivery technology. *Eur J Pharm Sci*. 2018;111:450-457. doi:10.1016/j.ejps.2017.10.026

34. Carrigy NB, Ruzycki CA, Golshahi L, Finlay WH. Pediatric in vitro and in silico models of deposition via oral and nasal inhalation. *J Aerosol Med Pulm Drug Deliv*. 2014;27(3):149-169. doi:10.1089/jamp.2013.1075

35. Centers for Disease Control and Prevention. Quick facts on the risks of e-cigarettes for kids, teens, and young adults. Accessed December 19, 2019. https://www.cdc.gov/tobacco/basic_information/e-cigarettes/Quick-Facts-on-the-Risks-of-E-cigarettes-for-Kids-Teens-and-Young-Adults.html

36. American Academy of Pediatrics. Supporting youth who are addicted to nicotine: advice for pediatricians. Accessed December 15, 2019. https://downloads.aap.org/RCE/Factsheet_Supporting_Youth_Addicted_to_Nicotine.pdf

37. Levy SJ, Williams JF; Committee on Substance Use and Prevention. Substance use screening, brief intervention, and referral to treatment. *Pediatrics*. 2016;138(1):e20161211. doi:10.1542/peds.2016-1211

38. King BA, Jones CM, Baldwin GT, Briss PA. The EVALI and youth vaping epidemics: implications for public health. *N Engl J Med*. 2020;382(8):689-691. doi:10.1056/NEJMp1916171

39. Volkow ND, Baler RD, Compton WM, Weiss SR. Adverse health effects of marijuana use. *N Engl J Med*. 2014;370(23):2219-2227. doi:10.1056/NEJMra1402309

40. Committee on Adolescence. Achieving quality health services for adolescents. *Pediatrics*. 2016;138(2):e20161347. doi:10.1542/peds.2016-1347

41. Hagan JF Jr, Shaw JS, Duncan PM, eds. *Bright Futures: Guidelines for Health Supervision of Infants, Children, and Adolescents*. 4th ed. American Academy of Pediatrics; 2017.

42. National Center for Chronic Disease Prevention and Health Promotion Office on Smoking and Health. *The Health Consequences of Smoking: 50 Years of Progress: A Report of the Surgeon General*. Centers for Disease Control and Prevention; 2014.