Systematic review of electronic cigarette use (vaping) and mental health comorbidity among adolescents and young adults

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Funding

This research was not supported by external funding.

Conflicts of Interest

The authors declare no conflicts of interest.

Abstract

Background: The prevalence of electronic cigarette (EC) use has risen dramatically among adolescents and young adults (AYA, ages 12-26) over the past decade. Despite extensive established relationships between combustible cigarette (CC) use and mental health problems, the mental health comorbidities of EC use remain unclear.

Objective: To provide a systematic review of existing literature on mental health co-morbidities of EC use among AYA.

Methods: Database searches using search terms related to EC, AYA, and mental health identified 1168 unique articles, 87 of which prompted full-text screening. Multiple authors extracted data, applied the Effective Public Health Practice Project Quality Assessment Tool to evaluate the evidence, and synthesized findings.

Results: Forty articles met eligibility criteria (n=24 predominantly adolescent and 16 predominantly young adult). Analyses yielded three main categories of focus: internalizing disorders (including depression, anxiety, suicidality, eating disorders, PTSD), externalizing disorders (ADHD and conduct disorder), and transdiagnostic concepts (impulsivity and perceived stress). Significant methodological limitations were noted.

Conclusions: Youth EC use is associated with greater mental health problems (compared to non-use) across several domains, particularly among adolescents. Since many existing studies are cross-sectional, directionality remains uncertain. Well-designed longitudinal studies to investigate long-term mental health sequalae of EC use remain needed.

Keywords: adolescents, young adults, e-cigarettes, ENDS, vaping, mental health, systematic review

Implications & Contribution

- Forty recent studies demonstrate a variety of mental health comorbidities with AYA EC use, particularly among adolescents
- Mental health comorbidities of EC use generally parallel those of CC use, with a few exceptions
- Future EC prevention and treatment strategies may be enhanced by addressing mental health

INTRODUCTION

The use of electronic cigarettes (EC) has risen dramatically among adolescents and young adults (AYA, youth aged 12-26) over the past decade in countries around the world [1]. A nationwide survey of United States (US) high school students found that current use of EC increased from 1.5% in 2011 to 20.8% in 2018, despite a decrease in combustible cigarette (CC) use during this period [2]. In 2019, lifetime EC use among high school-age youth exceeded 40% in the US and Canada [3].

ECs are battery-powered devices that heat a liquid to produce an inhalable aerosol that creates sensations mimicking CC smoking [4]. The devices are alternatively referred to as vaporizers, vape-pens, vape pod systems, JUULs (a popular North American brand), and electronic nicotine delivery systems (ENDS); inhalation may be described as vaping or blowing smoke [5]. The increasing popularity of ECs among youth has been attributed to aggressive marketing [6], enticing flavors [7], perceptions of lower harm [8,9], social media influences [10], and discreet designs that enable furtive use [9].

EC liquids can contain mixtures of solvents (e.g, propylene glycol), nicotine, tetrahydrocannabinol (THC) or hash oil, hundreds of flavoring compounds, and trace heavy metals [11–13]. Some ECs (e.g., JUUL) use nicotine salts, enabling consumption of very high doses of nicotine [14,15] that have been associated with high rates of continued use [5]. EC are a vehicle for nicotine use, but do not always contain nicotine. In a national survey of US high school students, a majority reported vaping only flavoring (59-63%), followed by nicotine (13-20%), and cannabis compounds (6%) [12]; however, actual nicotine use may be higher than reported, because subsequent studies have indicated that youth misperceive nicotine content of products they use [5].

Leading health organizations initially supported ECs as a possible smoking cessation aid for adults [4,16]. Though initially presumed less toxic than CC, EC use can cause carcinogen exposure [17],

respiratory toxicity [18], declining oral health [19], and other adverse effects [11]. Among AYA, EC use may act as a gateway to use of CCs [20,21] and to alcohol and illicit substances [22,23]. Some youth may be more susceptible to harmful effects than others.

AYA with mental illness are a population of specific concern. Adults with mental illness use tobacco products at high rates and die prematurely from tobacco-related illnesses [24], a disparity attracting calls for further study [25]. Adolescence is a vulnerable developmental period for the onset of nicotine use and mental illness [26], warranting special attention. Yet, to date, no article has yet to systematically review the evidence base concerning EC use and mental illness in youth.

CC use among adolescents is associated with externalizing (e.g., attention-deficit/hyperactivity disorder (ADHD), oppositional defiant disorder, conduct disorder), internalizing (e.g., depression, anxiety), and substance use disorders [26–28]. AYA with mental illness use nicotine at higher rates than peers without mental illness [29]. This may occur due to 1) attempts to self-medicate symptoms, such as cognitive deficits in ADHD or low mood [30], 2) efforts to counteract sedating side effects of psychotropic medications [30], 3) common underlying genetic or environmental risk factors for smoking and mental illness [31,32], or 4) neurotoxic impacts of nicotine on mental health [33]. A combination of individual-specific factors likely contributes.

Nicotine adversely impacts adolescent neurodevelopment [34] and increases the risk of cognitive and psychiatric disorders [35]. While much of the available evidence derives from animal and pre-clinical research, we can nonetheless mobilize this knowledge while awaiting further clinical youth studies. During adolescence, brain regions that underlie executive functions undergo significant reorganization [36,37], regulated in part by nicotinic acetylcholine receptors [33]. Evidence from animal models suggests that prolonged nicotine exposure may also induce epigenetic changes [33] and increase vulnerability to stress sensitivity [38,39]. These biological changes may, in part, underlie associations

between adolescent nicotine use and subsequent development of mood disorders [39,40], schizophrenia [41], and substance use disorders [33]. Furthermore, reliance on nicotine to overcome challenges interferes with the development of adaptive coping skills [42].

While nicotine remains the most commonly vaped substance, a substantial proportion of youth EC users vape cannabis [12] and nicotine vaping is highly co-morbid with cannabis use among adolescents [43]. Vaped cannabis often comes in high-potency concentrates, leading to greater amounts consumed by vaping than other modes [44]. Like nicotine, cannabis use is associated with adverse mental health outcomes, including psychotic disorders, depression, worse symptoms of mania/hypomania in individuals with bipolar disorder, and suicidality [45].

We aim to assess the current evidence describing mental health comorbidities of EC use among AYA. While prior reviews have assessed the mental health correlates of EC use among adults [46], the evidence concerning relationships between EC use and AYA with mental illness remains unreviewed. As 99% of tobacco users initiate use before age 26, effective prevention and treatment efforts depend on understanding risks for use among AYA [47].

METHODS

The research protocol was developed in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [48] and registered with the International Prospective Register of Systematic Reviews (PROSPERO) (Registration ID CRD42020177159).

Data Sources and Searches

A search of studies that evaluated psychiatric comorbidities associated with EC use among adolescents and young adults was conducted on March 23, 2020 within MEDLINE, EMBASE, PsycINFO, Web of Science Core Collection, and Scopus. The search strategy included appropriate controlled vocabulary and keywords for 1) mental illness, 2) AYA (ages 12-26), and 3) EC use (See **Appendix A**). Publication date was limited from January 2011 to present, and no language or article-type restrictions were included in the search strategy. Reference lists of included studies were reviewed by hand to identify any additional studies.

Study Selection

Search results were uploaded into Covidence [49], a systematic review software package. Two authors independently assessed articles based on title and abstract using screening criteria, with a third author resolving eligibility disagreements. We chose wide eligibility criteria (**Table 1**), since research on mental health among EC users is just emerging. Full texts of selected articles were screened to finalize decisions on eligibility. (**Figure 1**).

Data Extraction

The authors developed and piloted a standardized data extraction tool including first author and year of publication, study aim, participants and setting, study design, response and follow-up rates, EC measurements, mental health measures, prevalence of EC use, findings related to mental health, and covariates adjusted for in analyses. Aspects pertaining to the methods were extracted by a single author and reviewed by a second author. Results were extracted independently by two authors, who discussed each article, including additional team members as needed.

Following extraction of key data, two authors independently rated the quality of each article using the Effective Public Health Practice Project (EPHPP) Quality Assessment Tool, a valid and reliable method for assessing a diversity of research designs [50]. Studies were rated across five domains, including selection bias, study design, confounders, data collection methods, and withdrawals and dropouts (**Table 2, Supplemental Table 1**). Last, a global quality rating inclusive of data in all domains was assigned.

Following data extraction and discussion of included studies, findings were qualitatively synthesized by mental illness categories. Substantial methodological heterogeneity precluded quantitative meta-analysis. Key statistics are reported.

RESULTS

Searches identified 1706 articles, 1167 of which were unique, and one article was identified by hand search. Of the 1168 articles screened, 87 met eligibility by title and abstract, of which 40 were ultimately included for qualitative synthesis (**Figure 1**).

The included articles were published from 2015 through 2020 and pertained to 29 unique cohorts (**Supplemental Table 1**). Most articles report on data collected between 2013-2017. Six cohorts were described by 17 articles, while the remaining 23 cohorts were described by single articles. More articles studied predominantly adolescents (n=24 studies, representing 16 cohorts) than young adults (n=16 studies, representing 13 cohorts).

Most studies were conducted in the US (n=23 cohorts); others included South Korea (n=3 cohorts), the United Kingdom (UK) (n=2 cohorts), and Taiwan (n=1 cohort). A minority of cohorts were nationally representative (n=7/16, 44% of adolescent cohorts, n=2/13, 15% of YA cohorts), two were

clinical samples [51,52], two focused on youth at high-risk for substance use [53,54], and most others were school- or university-based samples.

More than half utilized cross-sectional designs (n=23 articles), although a substantial number were longitudinal (n=16 articles, representing 11 unique cohorts), and one reported a case series [52]. All studies used self-report measures of EC use, none of which were reported to have been established as reliable and valid. EC measures varied in assessing lifetime use, current use, age of use onset, and frequency of use. Most studies (n=37) referred to nicotine use in EC, while three explicitly investigated vaporizing other substances [51,55,56].

Mental health outcomes were sub-grouped by syndrome (e.g., depression, anxiety, ADHD) and age under three main categories: internalizing disorders, externalizing disorders, transdiagnostic concepts. Several additional findings that did not fit the main categories are briefly presented in **Table 3** [51,52,55–59].

Internalizing Disorders

Internalizing symptoms (composite)

Adolescents: Composite measures of internalizing symptoms were associated with EC use among adolescents in both the Population Assessment of Tobacco and Health (PATH) study [60–64] and a study of at-risk US high school students [54]. Quality of evidence was weak to moderate, with a mix of cross-sectional and longitudinal designs.

Cross-sectional analysis of baseline PATH data revealed that high-severity lifetime internalizing problems were similarly associated with both lifetime EC (aOR=1.6, 95% CI 1.3-1.8, p<0.05) and CC use (aOR=1.7, 95% CI: 1.5-2.0, p<0.05) [61]. In a one-year follow-up longitudinal analysis of baseline

nicotine-naïve adolescents, high past-year internalizing problems were significantly associated with initiation of EC use (aRRR= 1.61, 95% CI: 1.12-2.33, p<0.05), but not initiation of CC-only or dual EC and CC use [60]. In a cross-sectional study of students in alternative high schools (i.e., schools providing nontraditional learning experiences for youth with prior educational and/or behavioral difficulties) internalizing symptoms related significantly to EC use (B=0.100, SE=0.041, OR=1.105, p<0.05) and use frequency (B=0.204, SE=0.095, β =.0128) [54].

Young Adults: Two articles examined and found relationships between internalizing symptoms and EC use among YA respondents in the PATH study [62,65]. Evidence quality was similarly weak to moderate. Similar to the adolescent PATH findings, high-severity past-year internalizing problems (compared to low severity) significantly related to current EC use (aOR=1.97, 95% CI: 1.46-2.65, p<0.001) and CC use (aOR=1.92, 95% CI: 1.64-2.24, p<0.001) in cross-sectional analysis of baseline data [65], and high-severity lifetime internalizing problems predicted onset of EC (aOR=1.4, 95% CI: 1.1-1.8, p<0.05) and CC use (aOR=2.2, 95% CI: 1.5-3.3, p<0.05) among non-users in a one-year longitudinal analysis [62].

Depression

Adolescents: Seven studies, including four distinct national cohorts (US, Taiwan, and Korea) [66–69] and one California-based cohort [70–72] examined associations between EC use and depression among adolescents. Most found positive associations [66–69,71,72] and one suggested a bidirectional relationship [70]. Evidence quality was weak to moderate due to cross-sectional designs, single-item measures, and minimal adjustment for confounders.

In a one-year longitudinal analysis of a California cohort, sustained EC use was associated with the escalation of depressive symptoms over time (b=1.272, SE=0.513, p=0.01), and past-month use frequency was positively associated with depressive symptoms (b=1.611, SE=0.782, p=0.04) among sustained users [70]. The remaining studies were cross-sectional. Three national studies found EC use associated with depressive symptoms [66,68,69], although the Taiwanese study found no relationship for exclusive EC use [67]. In the Taiwan study, depression was associated with exclusive CC use (aOR=2.2, 95% CI: 1.1-5.0) but not EC use [67]; however, in the Korean study depression was associated with both current EC use (current use: aOR=2.21, 95% CI:1.67-2.93) and CC use (current use: aOR=2.04, 95% CI: 1.86-2.24) [69].

Young Adults: Eight studies, among six cohorts, investigated relationships between depression and EC use, with mixed results [21,53,59,73–76]. Most studies were weak, due to cross-sectional designs and risk of selection bias.

A Texas-based cohort provides the strongest evidence (moderate) [59,75,76]. Over 2.5 years of biannual longitudinal follow-up, depressive symptoms were significantly but modestly associated with frequency of past-month use for both EC (adjusted Rate Ratio (aRR)=1.01, 95% CI: 1.00-1.03, p=0.02) and CC (aRR=1.03, 95% CI: 1.02-1.04, p<0.001) [75]. A cross-lagged path analysis of three waves found significant paths from Wave 1 depression to Wave 2 EC use (B=0.06, p<0.01), and Wave 2 depression to Wave 3 EC use (B=0.08, p<0.01), but no paths from EC use to subsequent depressive symptoms [76].

Two cross-sectional studies, among college students [58] and homeless youth smokers [53] found depressive symptoms associated with current EC use (college: aOR=1.04, 95% CI: 1.01-1.08, p=0.022 [58]; homeless: aOR=3.06, 95% CI: 1.68-5.57, p<0.05 [53]). In these studies, depression was

also associated with CC use in the student cohort (aOR=1.03, 95% CI: 1.01-1.06, p=0.015) but not the homeless cohort.

Finally, two longitudinal [21,73] and one cross-sectional study [74] found no relationships between EC use and depression. In a two-year follow-up of Georgia college students, depressive symptoms predicted subsequent CC use (aOR=1.05, 95% CI: 1.02-1.09, p=0.001) but not EC use [73]. In study of Virginia college students, baseline depression did not predict EC initiation during one-year of follow-up [21].

Anxiety

Adolescents: One cross-sectional study, with weak quality evidence, assessed anxiety among adolescents, using scales for several anxiety subtypes, finding EC-only use less strongly related with anxiety than CC-only use [71]. Lifetime EC-only users had higher levels of panic disorder than lifetime nicotine abstainers, but lower levels of generalized anxiety, panic, social phobia, OCD, and anxiety sensitivity than CC-only users [71].

Young Adults: Four studies among three cohorts have examined anxiety among YA, yielding mostly negative results [21,73,74,77]. Quality of evidence was weak to moderate with risks of selection bias across studies. Studies of two longitudinal cohorts of college students, in Georgia and Virginia, followed over one to two years found no relationship between anxiety and subsequent EC use [21,73]. Among the Georgia [73] but not the Virginia cohort [21], anxiety predicted CC use (aOR=1.02, 95% CI: 1.00-1.04, p=0.02). On a smaller scale, an ecological momentary analysis among a currently-smoking subset of the Georgia cohort found no relationship between anxiety and EC use [77]. A cross-sectional study found EC

use associated with generalized anxiety (LR X^2=14.0, p=0.001, Cramer's V= 0.066) in a primary unadjusted analysis that resolved with secondary analysis controlling for covariates [74].

Suicidality

Adolescents: Four national cross-sectional studies in the US [66] and Korea [68,69,78] investigated suicidality, consistently finding current EC use associated with suicidal ideation, plans, and attempts. Evidence quality is again weak and is limited by cross-sectional designs, possible confounding, and single-item measures.

In an analysis of the US Youth Risk Behavior Survey (2015-2017), current EC-only use associated with past-year suicidal ideation (aOR=1.23, 95% CI: 1.03-1.47) [66]. Analyses across three years (2015-2017) of the Korean Youth Risk Behavior Survey found similar associations [68,69,78]. The 2016 Korean survey found significant associations between current EC use (versus non-use) and past-year suicidal ideation (aOR=1.58, 95% CI: 1.31-1.89, p<0.05), plans (aOR=2.44, 95% CI: 1.94-3.08, p<0.05), attempts (aOR=2.44, 95% CI: 1.85-3.22, p<0.05), and serious attempts (aOR=3.09, 95% CI: 1.51-6.32, p<0.05) [78]. In the 2017 Korean survey, lifetime and current CC use, EC use, and dual CC and EC use (versus never use) were all associated with suicidal ideation, planning, and attempts, although the magnitude of associations for CC-only users seemed consistently lower than those for EC and dual users—with greater OR, but wide CIs, limiting some comparisons between groups. Furthermore, associations between suicidality and EC use were consistently stronger among women than men [69].

Young adults: No studies identified.

Eating disorders

Adolescents: One South Korean study examined the comorbidity between EC use and past-month report of unhealthy weight control behaviors, including one-food dieting, fasting, diet pill use, and purging, and found significant relationships among both young men and women [79]. Although the study included a large nationally representative sample, overall quality was weak, due to a cross-sectional design, possible confounding, and single-item measures. Female lifetime and current EC adolescent users (compared to lifetime EC abstainers) had significantly higher rates of all unhealthy weight control behaviors (Lifetime EC use: aORs 1.87-2.40, Current EC use: aORs 2.32-3.76), while male current EC users, but not lifetime users had significantly higher rates of all unhealthy weight control behaviors (aORs 2.05-3.18). Similar associations were found for CC use.

Young adults: In one weak quality US university-based sample, EC use was not associated with binge-eating disorder [74].

Post-traumatic stress disorder (PTSD)

Adolescents: No studies identified.

Young adults: Two studies were found examining relationships between aspects of PTSD and EC use [74,80]. Findings were mixed and quality of evidence was weak, both studies used cross-sectional designs, and there was risk of sampling bias and potential confounding**.** Among college students, EC use significantly related to PTSD (Likelihood Ratio (LR) X^2=13.0, p=0.002, Cramer's V= 0.064) in the primary unadjusted analysis, but not after controlling for covariates [74]. In a small sample of YA, self-reported history of childhood mistreatment directly related to lifetime EC use ($\beta = 0.19$, p=0.02), but

not current use, a relationship that subsequent analysis found fully mediated by negative urgency, a dimension of impulsivity reflecting the tendency to act rashly while distressed ($\beta = 0.11$, p=0.04) [80].

Externalizing Disorders

Externalizing disorders (composite)

Adolescents: Analyses of adolescents in the PATH study found externalizing symptoms significantly associated with EC use [60–64]. Evidence quality was weak-to-moderate. In cross-sectional analysis of baseline data, high-severity lifetime externalizing problems were similarly associated with lifetime EC (aOR=1.5, 95% CI 1.3-1.7, p<0.05) and CC use (aOR=1.5, 95% CI: 1.3-1.7, p<0.05) [61]. In a one-year longitudinal analysis of baseline nicotine-naïve adolescents, high past-year externalizing problems were significantly associated with initiation of EC use (aRRR= 2.78, 95% CI: 1.76-4.40, p<0.05), with relative risk ratios not significantly different from initiation of dual use (aRRR= 2.23, 95% CI: 1.15-4.31, p<0.05) and CC use (aRRR= 5.59, 95% CI: 2.63-11.90, p<0.05) [60].

Young adults: One longitudinal analysis of baseline nicotine-naïve YA participants in the PATH study (moderate quality evidence) similarly found that high-severity lifetime externalizing symptoms predicted EC onset (aOR=1.4, 95% CI: 1.1-1.7, p<0.05) at one-year follow-up [62]. The relationship between externalizing symptoms and CC onset was not significant among these YAs.

ADHD

Adolescents: Two studies examined longitudinal relationships between ADHD symptoms and EC use among US high school students [72,81]. Both were moderate in quality, utilizing longitudinal designs with minimal attrition over 12-18 months while adjusting for covariates. Both studies found that ADHD symptoms predicted subsequent EC but not CC use. In a California-based cohort, overall ADHD symptoms (aOR=1.22, 95% CI: 1.04-1.42) and hyperactivity-impulsivity subscale symptoms (aOR=1.26, 95% CI: 1.09-1.47) but not inattentive subscale symptoms predicted initiation of EC over 18-month follow-up [72]. Similarly, in a small study of college-bound seniors, using a cross-lagged path model, ADHD symptoms at Time 1 (T1) predicted EC use at Time 2 (β=0.206, p<0.001) and ADHD symptoms at Time 2 predicted EC use at Time 3 (β =0.350, p<0.001), but EC use frequency was not associated with subsequent ADHD symptoms [81].

Young adults: In contrast to the findings of adolescent samples, two studies examined ADHD symptoms and EC use among college students, both finding no associations when controlling for covariates [73,74]. The quality of evidence was weak-moderate in strength, due to only one longitudinal design and self-report measures. In a cross-sectional study, ADHD symptoms were significantly associated with EC use status (LR X^2=16.778, p<0.001, Cramer's V= 0.073) in the primary unadjusted analysis, but there was no significant association when controlling for covariates [74]. In a two-year longitudinal study, neither ADHD nor any other psychological factors measured predicted EC use after controlling for covariates [73].

Conduct disorder and delinquency

Adolescents: Three articles examined conduct disorder symptoms and found significant relationships with subsequent EC use [64,72,82]. All were moderate-quality longitudinal studies, and two were nationally representative (US, UK). An analysis of baseline nicotine-naïve adolescents in the PATH study found that baseline rule-breaking tendency independently predicted EC use in the subsequent year (aOR=1.93, 95% CI: 1.58-2.34) [64]. Similarly, past 6-month delinquent behavior was associated with later EC use (aOR=1.32, p<0.001) and CC use (aOR=1.41, p<0.05) among a cohort of nicotine-naïve US high school students [72]. Reports of various delinquent behaviors (e.g., theft, vandalism, graffiti) were significantly higher for lifetime EC-only users (versus never users) (aORs range 3.9-6.0, p<0.001) but to less extent than among CC users and dual-EC and CC users (aORs range 5.7-11.9, p<0.001) [82].

Young adults: No studies identified.

Transdiagnostic constructs

Impulsivity & Executive Function

Impulsivity describes a predisposition toward rapid, unplanned actions without regard for long-term consequences and has been implicated in ADHD, conduct disorder, bipolar disorder, and personality disorders [83]. Executive function (EF) describes closely related capacities for planning, working memory, self-control, and attention shifting.

Adolescent: Three studies examined impulsivity and EC use [71,84,85] and two studies among one cohort examined executive function [86,87]. These studies consistently found EC use related to impulsivity and EF deficits. Overall, quality of evidence was weak, with non-probability samples and cross-sectional designs.

In a cross-sectional analysis of California high school students, impulsivity was elevated similarly among EC and CC users [71]. In longitudinal analysis of British high school students, baseline impulsivity predicted onset of EC use (aOR=1.263, 95% CI: 1.183-1.349), and CC use (aOR=1.452, 95% CI: 1.286-1.638) at 24-month follow-up [84]. In a cross-sectional study using a mediation model, impulsivity was associated with more frequent EC use through an early age of EC initiation [85].

In a cross-sectional study of 12-year-old children in California, lifetime EC use was strongly associated with EF deficits (aOR=4.99, 95% CI: 1.80-13.96, p<0.01) [86]; with subsequent analysis finding the relationship between low inhibitory control and EC use most applicable among low SES respondents [87].

Young Adult: Four studies, also weak in overall quality, investigating EC use and various subcomponents of impulsivity (e.g., sensation seeking, negative urgency, lack of premeditation, and perseverance) have had mixed results, with studies most consistently supporting a relationship between sensation seeking and EC use [21,80,88,89]. Two longitudinal studies [88,89] found relationships between sensation seeking and subsequent EC use, (e.g. ever JUUL use: aOR=1.76, 95% CI 1.52-2.05, p<0.01; current use: aOR=2.16, 95% CI 1.81-2.58, p<0.01) [89], and one cross-sectional study [80] found a correlation between sensation seeking and EC use, although relationships with other subcomponents of impulsivity were generally not significant (one small study found significance for negative urgency [80]). One study found lack of perseverance predicted CC use (aOR=1.52, 95% CI: 1.11-2.07, p<0.05) but not EC use at one-year follow-up [21]. Additionally, in a cross-sectional study assessing impulse control disorders, EC use was related to gambling disorder (LR X^2=37.2, p=0.000, Cramer's V= 0.081) but not other impulse control disorders [74].

Perceived Stress

Perceived stress describes a heritable tendency to deem negative events as unpredictable and uncontrollable and has been implicated in anhedonic depression, anxious dysthymia, psychosis, post-traumatic stress, and various personality disorders [90].

Adolescent: One moderate quality study assessed perceived stress in adolescents [90]. In a four-year longitudinal follow-up of California teenagers, baseline (age 13) perceived stress was associated with lifetime and past-month EC use (aOR= 1.25, 95% CI: 1.07-1.47, p<0.01) at age 17, as well as lifetime and past-month CC use (aOR=1.32, 95% CI=1.08-1.61, p<0.01).

Young Adult: One study, weak, limited by cross-sectional design, assessed past-week perceived stress among college students, finding perceived stress associated with past 30-day EC use (aOR=1.03, 95% CI: 1.00-1.05, p=0.03) and CC use (aOR=1.02, 95% CI: 1.00-1.04, p=0.04).

DISCUSSION

Forty existing studies assess mental health comorbidities of EC use among AYA. This review of the current evidence, the first on this topic, summarizes our current knowledge base and facilitates future investigation.

Among adolescent studies, EC use is associated with internalizing problems, depression, suicidality, disordered eating, externalizing problems, ADHD, conduct disorder, impulsivity, and perceived stress, with additional limited evidence for an association with anxiety. These findings largely

align with prior findings regarding mental health and CC use [26,27,91–93]. Among YA specifically, EC use has been associated with internalizing problems, externalizing problems, depression, sensation seeking, and perceived stress, while existing evidence does not support relationships with ADHD or anxiety.

The finding that ADHD was associated with EC use among adolescents but not YA may reflect methodological differences. Alternatively, ADHD may represent a risk factor for EC initiation among adolescents that becomes attenuated by young adulthood, due to neurobiological and psychosocial factors. Given well-established risks for substance use among AYA with untreated ADHD [94], adolescents may gravitate toward ECs, influenced by social media [95] and availability [96], while YA tend toward other substances (e.g., alcohol). Brain maturation and resulting improvements in self-regulation, may also contribute to the observed difference.

Most adolescent cohorts (6/7), but only half of YA cohorts (3/6) found relationships between EC use and depression. Most of the adolescent studies were national cohorts, versus university-based samples in YA studies, and some adolescent studies used single-item measures for past-year depressive episodes [66,69]. These methodological differences may underly the difference in findings. Alternatively, the clear association in adults between depression and alcohol and substance use [97] again supports the hypothesis that depressed adolescents may turn to ECs whereas YAs access other substances.

Findings were similar for both EC and CC with a few notable exceptions. ADHD predicted onset of EC use but not CC use among adolescents [72,81]. This difference may reflect the role of sensation seeking in EC use, as youth with ADHD may be particularly attracted to their novel flavors. Although minimal associations were found between EC use and anxiety, associations were somewhat stronger for CC use and anxiety among adolescents and YA [71,73]. Externalizing symptoms were more strongly

associated with onset of CC use than EC use among adolescents [60], but not YA [65]. Adolescents with conduct problems may view CC use as a greater act of rebellion and risk-taking, given longstanding regulations against CC use, which have only recently begun for EC. Among YA, many high externalizing respondents were likely excluded for prior nicotine use [62], so the negative finding may reflect that high externalizing youth had an earlier age of onset.

Implications for Practice

Clinicians should have a low threshold for providing mental health screening and referrals when treating youth using EC, as EC use may be an indicator of behavioral health risk. At this time, it seems reasonable to counsel AYA with depression and other mental health problems against vaping, warning that vaping and other substance use may exacerbate their mental illness. Although the longitudinal evidence linking vaping to subsequent psychopathology remains limited, there is some evidence of a relationship [70], which would be consistent with relationships between CC use and mental illness [98], and with existing models of nicotine and neurodevelopment (as described in the introduction). Additionally, it is important to emphasize vaping cessation in AYA with mental illness to prevent potential progression to CC and other substance use [20–23] and associated long-term health sequelae [24], which disproportionately affect adults with mental illness.

Further research is needed to better understand how co-morbid mental illness influences uptake, use patterns, and cessation among AYA with mental illness to appropriately counsel and treat this population. There are no known effective treatments for youth EC cessation. While EC manufacturers have created “curricula” to reduce underage abuse, these have many limitations [99]. Parents and school administrators struggle in implementing restrictions to curb use [100,101]. While there exists a need for additional studies to enlarge the evidence base for adolescent CC smoking

cessation, existing evidence best supports group-based behavioral interventions [102]. Adapting these programs to EC use may be effective alongside policies targeting specific problematic practices in EC marketing [103]. However, in developing interventions to mitigate EC use, it will also be important to monitor for the possible unintended consequence of diverting youth toward other, potentially riskier, substances. The results of this review highlight the importance of interventions to take into account AYA with mental illness as a special vulnerable population which may benefit from tailored practices on both the intervention and public health policy levels.

Limitations of Evidence & Directions for Further Research

The quality of evidence among included studies varied, with several consistent limitations. The young adult studies were largely among college-based samples, raising the risk of selection bias. Given high prevalence of EC use among other groups of YA [53], further study of high-risk YAs remains warranted. Additionally, few studies have adjusted for use of other substances (See Supplemental Table 1), despite high comorbidity between vaping and other substance use [43] and the potential impacts of other substance use on mental health. Most studies that included substance use as a covariate still found significant relationships between EC use and mental health comorbidities [57,60,70,78,82].

Most studies were cross-sectional, or longitudinal studies with short-term follow-up. As a result, important questions about the impact of EC use on the trajectory of mental health symptoms remain unanswered. One study presented data to support a bidirectional relationship [70], while two found no evidence for EC affecting subsequent mental health [76,81]. Given that EC use may alter cognitive and emotional health through multiple pathways [13], further longitudinal studies remain important.

Future studies should develop more nuanced measures of EC use, and establish their validity and reliability. Most studies measured either lifetime use or current use by self-report. Factors such as frequency and patterns of use, dose of nicotine (which varies considerably among products), and nicotine dependence remain relatively uninvestigated and will be important to identifying factors of youth most at risk of adverse outcomes. Additionally, most studies relied on mental health screening measures, which were not designed to be diagnostic.

We expect EC use to remain an active area of investigation, given evolving legal restrictions on EC use and changing youth behavioral trends. Although youth vape numerous substances, we only found a few studies assessing vaping of cannabis and illicit drugs. In the US, the rise of ECs over the past decade has coincided with loosening of restrictions on cannabis use [104]. Although studies indicate nicotine remains the main psychoactive substance inhaled by AYA EC users, use of cannabis in ECs is not inconsequential [12]. Like nicotine, cannabis use during adolescence influences development of depression and psychosis [105,106].

Although we found studies examining EC use across a range of psychopathology, we found no studies assessing psychosis. Given high rates of nicotine-associated long-term mortality and the potential etiologic role of nicotine in development of psychosis [41], this subgroup may be most at risk of long-term adverse outcomes from EC addiction, and thus most in need of early intervention.

Limitations of Review

We acknowledge several limitations of this review. We defined inclusion criteria broadly to permit a wider view of the existing literature, but one which precluded quantitative meta-analysis, since each subcategory of results ultimately includes only a few studies, using a variety of mental health measures and covariates (See Supplemental Table 1). We anticipate this review will provide a horizon to permit future systematic studies to evaluate narrower questions. We excluded studies focused only on

substance use disorder comorbidities, an important topic needing a dedicated review. While we included all internalizing and externalizing mental health conditions and transdiagnostic concepts reported in this literature, we did not include search terms for transdiagnostic concepts. Our review yielded mostly US-based studies, which may in part reflect our exclusion of non-English studies, thus it is not clear to what extent results generalize to other settings.

Conclusions

We identified forty recent articles investigating the relationship between mental health and EC use among AYA. EC use correlates with several domains of AYA mental health problems. Much remains unknown about the particular use patterns of high-risk youth and the long-term neuropsychiatric sequelae of EC use during AYA development. Given the elevated rates of EC use among AYA with mental health problems, further research remains warranted.

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Table 1: Inclusion and Exclusion Criteria

Inclusion (must meet all four):	**Exclusion (meets any single criterion):**
1.) Quantitative or mixed-methods studies, including cross-sectional and longitudinal observational studies, experimental studies, case series, and meta-analyses **2.)** A majority of the sample (or a clearly defined subgroup) fit within the **AYA age range (i.e., 12-26 years)** **3.) Mental health assessed** via: a.) psychometric assessments of mental health conditions (e.g., depression, anxiety, ADHD), or transdiagnostic concepts associated with AYA psychopathology (e.g., impulsivity, executive function, reward responsiveness) b.) self-reported mental illness diagnoses, c.) participants engaged in mental health treatment **4.) Assesses EC use** (containing any substance).	**1.) Focused on non-human subjects** **2.) Commentaries** or expert statements **3.) Case studies** with n=1 **4.) Not written in English** **5.) Non-peer reviewed**, (e.g., dissertations, conference abstracts) **6.)** Psychiatric outcomes **focused on substance use disorders exclusively** (e.g., binge drinking, cannabis dependence) 7.) Studies in which EC use and psychiatric **mental health comorbidities were measured but were not outcomes of interest in the analyses reported** (e.g., studies in which EC use and depression were covariates to analyses investigating other substance use patterns)*****

* The authors agreed to add this criterion during full-text screening, because the analyses presented in these papers did not contribute significantly to answering the main research question of this review.

Table 2: Quality Rating of Included Studies (n= 40)

	n	%
Selection bias		
Weak: All other responses or not stated	12	30%
Moderate: Somewhat likely to be representative of the target population, 60-79% participation rate	16	40%
Strong: Very likely to be representative of the target population, >80% participation rate	12	30%
Study design		
Weak: All other designs or not stated	25	63%
Moderate: Cohort analytic, case-control, cohort, or interrupted time series	15	38%
Strong: Randomized control trial or controlled clinical trials	0	0%
Confounders		
Weak: Confounders not controlled for or not stated	15	38%
Moderate: Controlled for 60-79% of confounders	21	53%
Strong: Controlled for at least 80% of confounders	14	35%
Data collection methods		
Weak: Data collection tools have not been shown to be valid or both reliability and validity are not described	40	100%
Moderate: Data collection tools have been shown to be valid and have not been shown to be reliable (or reliability not described)	0	0%
Strong: Data collection tools have been shown to be valid and reliable	0	0%
Withdrawals and dropouts		
Weak: Follow-up rate <60% of participants or withdrawals and dropouts not described	3	19%

Moderate: Follow-up rate of 60-79% of participants	7	44%
Strong: Follow-up rate of >80% of participants	6	38%
Not applicable: One-time surveys or interviews	24	
Global rating		
Weak: Two or more weak ratings	29	73%
Moderate: One weak rating	11	28%
Strong: No weak ratings	0	0%

Table 3: Additional Findings

1. **Prevalence of EC use among AYA with mental illness:** Since few studies used categorical variables for psychiatric diagnoses, EC use prevalence among AYA with mental illness could not be determined, but rates appear higher among AYA with mental illness. One study among adolescent psychiatric inpatients reported a lifetime use prevalence of 58% [51]. Three non-probability samples of YA reported higher rates of lifetime use (34% among AYA with mental illness, 22% overall) [57] and current use (8% versus 5.3% overall [58], 20.9% in youth with high depression scores versus 17% overall [59]).
2. **Vaping non-nicotine psychoactive substances:** Although ECs can be used to inhale a range of substances, we identified only three studies that explicitly investigated vaping psychoactive substances other than nicotine, with mixed findings about relationships with mental health problems [51,55,56].
    a. ***Adolescents:*** Among a sample of hospitalized adolescents, 12.4% reported illicit substance use via EC, including cannabis, methamphetamines, PCP, and cough syrup [51]. In a 2015 cross-sectional survey among California high schoolers, 4.9% of youth reported current cannabis vaping (compared to 8.7% current EC use), which was associated with all psychiatric symptoms and traits measured (including conduct problems, ADHD, impulsivity subtypes, anhedonia, and depression) with ORs ranging from 1.09-1.82 [56]. Compared to other cannabis subtypes, vaporized cannabis was less associated with conduct disorder and more strongly related to lack of premeditation.
    b. ***Young adults:*** A small sample of US college students found a 10.7% lifetime use rate of cannabis vape-pens, and no significant relationship between vaporized cannabis and mental health outcomes assessed (impulsivity and social anxiety) [55].
3. **EC use and seizures:** A series of 123 cases of seizures among AYA EC users in the US [52] reported mental health conditions were the most commonly documented comorbidity and 43% of reports with medication information showed concurrent use of medications associated with seizures, including sertraline (n=7, 8.5%), escitalopram (n=6, 7.3%), bupropion (n=5, 6.1%).

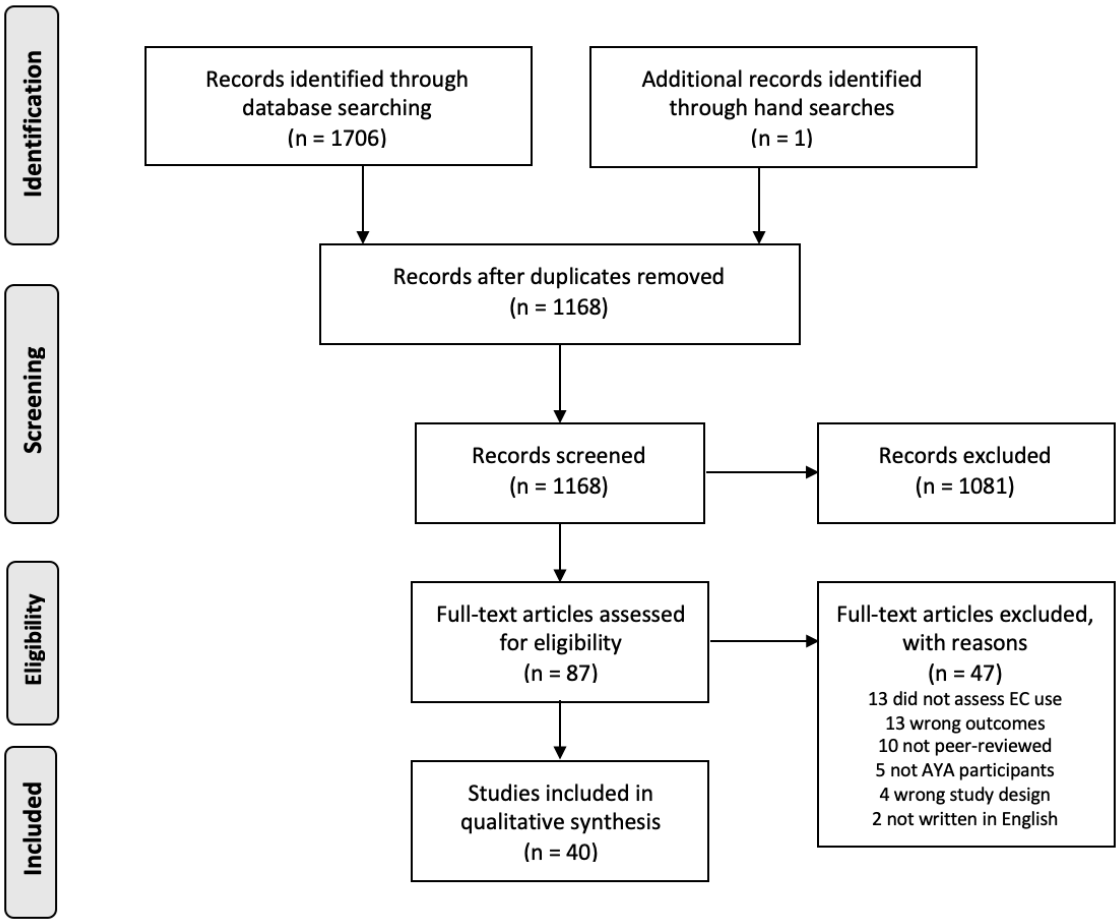

Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) Flow Diagram