REVIEW

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Vaping and subsequent comorbidities potentially associated with increased mortality and more severe illness in COVID-19: a narrative review

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Abstract

Introduction: COVID-19 (or COVID) is a highly virulent viral disease which more frequently presents severe infection in specific populations, such as the elderly, patients with hypertension, patients with respiratory disease, and patients who smoke. The effects vaping (i.e., an electronic cigarette or JUUL device) has on COVID progression remains unclear, because there is an information paucity correlating e-cigarette use and COVID. This review sought to identify links between vape use and COVID severity via literature review. Additionally, because there is more widespread information about cigarette smoking than about vaping, this review sought to illustrate commonalities between smoking and vaping. If smoking and vaping are deemed near-identical practices, then it is possible the effects of smoking on human health and on COVID disease could be comparable in vaping.
Methods: Several searches were performed on PubMed with MeSH headings and JSTOR between 17 December 2020 and 22 December 2020. Search results were excluded if they were not trials or controlled clinical trials, if the articles were not about COVID, if the articles were about smoking behaviors or habits, or if the articles were not related to vaping or smoking. Key findings were summarized and tabled based on relevance, substantiability, and applicability to COVID.
Results: Multiple sources viewed smoking and vaping as equal risk factors for COVID disease, whereas other sources viewed the two as unique risk factors. Because of this controversy, it is challenging to view the two practices as similar enough to pose equivalent risks for COVID. Both practices pose significant health risks to its users, but these health risks are unique to each practice.
Discussion: There are several limitations which exacerbate ambiguity—(1) it is unclear how harmful smoking is for COVID patients, because several publications found smoking may have protective effects; (2) few older patients vape, but yet most severe COVID cases occur in older populations; (3) older patients and impoverished patients show a statistically significant risk for severe COVID disease independent of other factors; (4) vaping is a relatively new practice, and there are few patients who self-report long-term e-cigarette use or long-term adverse effects as a result thereof.
Conclusion: Although vaping may present serious health risks, clinically, it is uncertain how significantly vaping affects COVID disease, especially when compared against cigarette smoking. More research is needed on both the effects of vaping on COVID and the likeness of vaping versus smoking.

Keywords

COVID; Vaping; Vaping and COVID; Vaping and smoking; COVID mortality; COVID hospitalizations; EVALI; Nicotine exposure; Angiotensin converting enzyme-2

1. Introduction

SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2), the cause of coronavirus disease 2019 (COVID-19 or COVID), has—as of 13 May 2021—infected >160 million people worldwide and has contributed to >3.3 million deaths [1]. COVID has multiple distinguishing features which contribute to its virulence including, but not limited to asymptomatic transmission via respiratory droplets, an unpredictable incubation period ranging from 2–14 days,

multiorgan failure [2], cytokine storm, hemophagocytic lymphohistiocytosis, respiratory failure/acute respiratory distress syndrome [3], and neurological symptoms [4]. These factors considered, COVID has been declared as of 13 May 2021 to have a case-fatality ratio ranging from 0.1% (Singapore) to 19.7% (Yemen) depending on country, with a median case-fatality ratio of 1.7% based on data from 179 countries [5]. The most common symptoms seen in COVID patients are relatively mild and include fever, dry cough, fatigue, and myalgia, among others [3]. In some cases, COVID can progress to a more severe illness with symptoms such as pneumonia, venous thromboembolism, and hemodynamic instability which could lead to severe morbidity or mortality [3, 6]. Certain populations are at higher risk for developing severe symptoms or for mortality [2, 6, 7]. This report will focus on the effects vaping has on COVID severe disease development and mortality, dependent and independent of other risk factors.

Vaping is an act of inhaling nicotine or other aerosolized products via an electronic device [8] such as an e-cigarette or JUUL device. While vaping may be anecdotally regarded safer than smoking tobacco, vaping still presents potential health hazards. In February 2020, the Centers for Disease Control and Prevention (CDC) attributed 2807 hospitalizations [9] and 68 deaths to e-cigarette or vaping product use-associated lung injury [8, 9]. The chemical composition of vape vapor is still not fully elucidated, and the risks associated with vaping continue emerging [8]. Osei *et al*. [8] reported chronic vaping increases chances for developing any of the following disease states by 75% compared to non-smokers: emphysema, chronic bronchitis, or chronic obstructive pulmonary disease (odds ratio = 1.8, 95% CI = 1.3, 2.5). Other potential long-term complications from e-cigarette use include cancer, pneumonia, asthma, and systemic inflammation [10].

Because vaping is a more recent trend, introduced into the US market in 2006 with multiple brands by 2010 [11], its effects on human health are still being determined. As such, one of the primary objectives of this report is to contrast smoking and vaping. In this report, "smoking" refers exclusively to tobacco products, primarily cigarettes. Identifying commonalities may answer a transitive question: if vaping can cause or worsen comorbidities as seen in smoking, and COVID is statistically more severe in patients with said comorbidities, then is vaping a risk factor for severe disease and mortality in patients diagnosed with COVID?

2. Methods

Evaluating the effects vaping has on COVID disease progression will be accomplished by the following: (1) analyzing literature for research which portray a direct correlation between vaping and COVID, (2) characterizing physiological changes induced by vaping, (3) specifying comorbid/lifestyle conditions which place patients at risk for COVID severe disease, and (4) comparing physiological similarities and differences between smokers and vapers. It is important to distinguish physiological similarities and dissimilarities between traditional smokers and e-cigarette users, as this type of information for vaping is not as abundant as for smoking [12].

A search was performed on PubMed on 17 December 2020 using the following filter: "published within 1 year". The following MeSH headings were applied: "Vaping/adverse effects" OR "Vaping/analysis" OR "Vaping/mortality" OR "Vaping/pathology" OR "Vaping/physiopathology" OR "Vaping/statistics and numerical data" AND "coronavirus". Search results on 17 December 2020 were inspected for quantitative and qualitative evidence which showed connections between vaping and COVID mortality/symptomology or the lack thereof. After completion of the search, results were narrowed by applying additional filters: "clinical trials", "randomized clinical trials," and "reviews".

Another search was performed on 18 December 2020 on PubMed using the following MeSH headings: "Electronic Nicotine Delivery Systems/adverse effects" OR "Electronic Nicotine Delivery Systems/pharmacology" OR "Electronic Nicotine Delivery Systems/statistics and numerical data" AND "Vaping/adverse effects" OR "Vaping/genetics" OR "Vaping/mortality" OR "Vaping/pharmacology" OR "Vaping/physiopathology" OR "Vaping/statistics and numerical data" AND "COVID-19", with a filter: "published within 5 years". Search results on 18 December 2020 sought to illustrate vaping effects on human health or the lack thereof. After completion of the search, results were narrowed by applying additional filters: "clinical trials", "randomized clinical trials", and "reviews".

Additional intermittent searches were performed on PubMed and Journal Storage (JSTOR) between 17 December 2020 and 22 December 2020. The following searches were completed on PubMed with the "published within 1 year" filter and without MeSH headings: "vaping and covid", "smoking and covid", "covid and COPD", "covid and nicotine", and "e-cigarettes and covid". Two searches were performed on JSTOR without filters: "effects of smoking on covid" and "effects of vaping on covid". After two searches, JSTOR was excluded from this review, as the results were random and mostly unrelated to the subject. Searches were also performed via the National Center for Biotechnology Information (NCBI), but all searches rerouted back to PubMed. Thus, only PubMed results are included in this review. The results from PubMed found between 18 December 2020 and 22 December 2020 as mentioned in this paragraph were narrowed down by applying additional filters: "clinical trials", and "randomized clinical trials".

The inclusion criteria for these searches—as illustrated in Fig. 1—is as follows: only clinical trials or randomized clinical trials, reviews of "vaping and COVID", and keywords "vaping, smoking, COPD, nicotine, e-cigarettes, covid". The exclusion criteria are articles that were not clinical trials, randomized clinical trials, or reviews of "vaping and COVID", and articles not about COVID or not relating to keywords.

Other references were corralled by looking over bibliographies within the acquired results. Sporadic searches were conducted on PubMed without filters or keywords until 6 February 2021 as needed for information which would support claims made in Results Section 3.5 and the Discussion. Please note the information surrounding COVID is rapidly evolving and is subject to change at a later date.

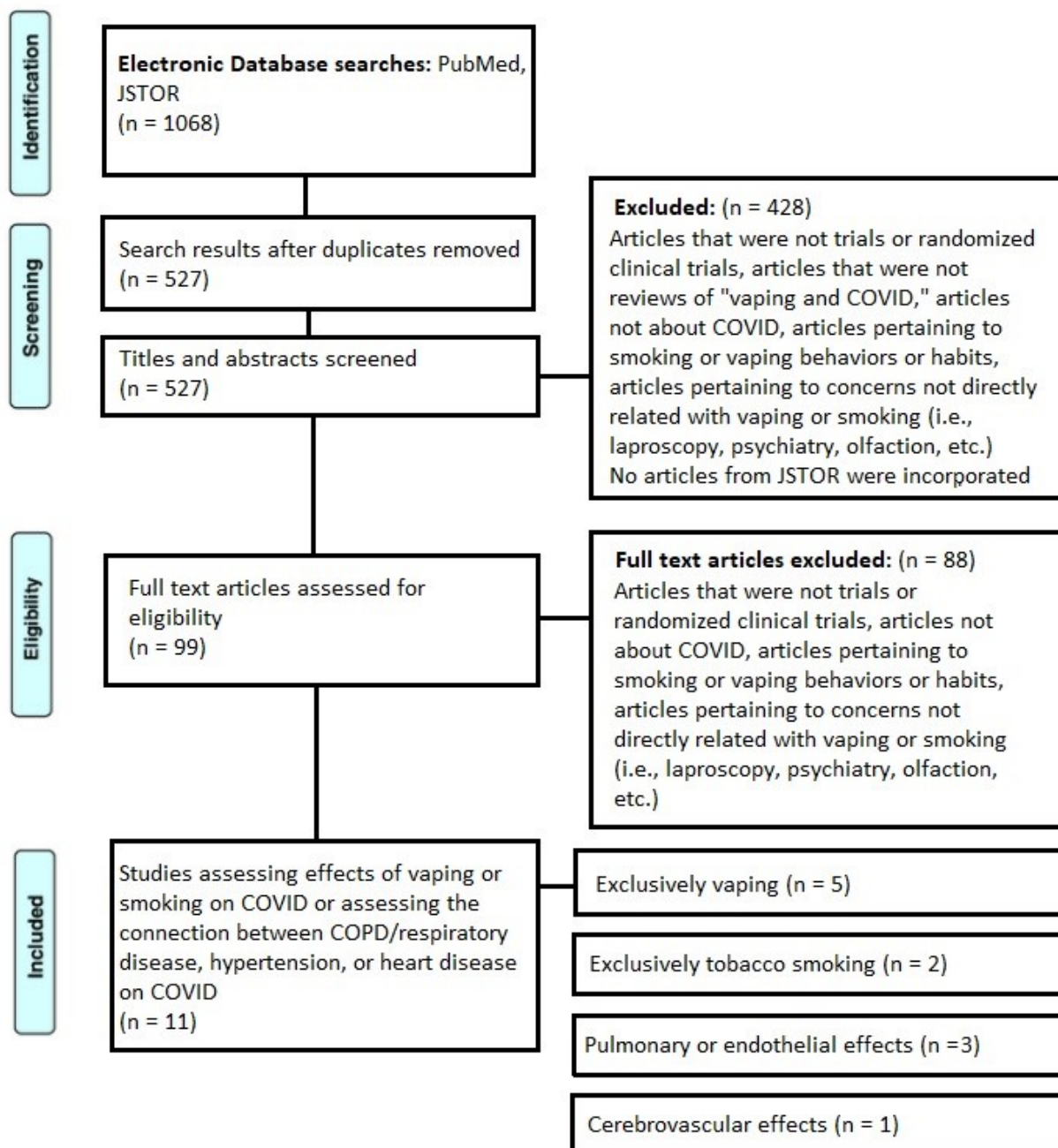PRISMA Diagram Illustrating Search Results Methodology and Inclusion/Exclusion

Identification

Electronic Database searches: PubMed, JSTOR
(n = 1068)

Screening

Search results after duplicates removed
(n = 527)

Titles and abstracts screened
(n = 527)

Excluded: (n = 428)
Articles that were not trials or randomized clinical trials, articles that were not reviews of "vaping and COVID," articles not about COVID, articles pertaining to smoking or vaping behaviors or habits, articles pertaining to concerns not directly related with vaping or smoking (i.e., laproscopy, psychiatry, olfaction, etc.)
No articles from JSTOR were incorporated

Eligibility

Full text articles assessed for eligibility
(n = 99)

Full text articles excluded: (n = 88)
Articles that were not trials or randomized clinical trials, articles not about COVID, articles pertaining to smoking or vaping behaviors or habits, articles pertaining to concerns not directly related with vaping or smoking (i.e., laproscopy, psychiatry, olfaction, etc.)

Included

Studies assessing effects of vaping or smoking on COVID or assessing the connection between COPD/respiratory disease, hypertension, or heart disease on COVID
(n = 11)

Exclusively vaping (n = 5)

Exclusively tobacco smoking (n = 2)

Pulmonary or endothelial effects (n = 3)

Cerebrovascular effects (n = 1)

F I G U R E 1. PRISMA diagram which shows the search methods to narrow down searches in PubMed and JSTOR between 17 December 2020 and 22 December 2020.

Search results were selected for thorough review based on titles and/or abstracts which suggested the publication contained pertinent information. References featured in Tables 1,2,3 were included based on recent publication date, relevance, data presence, distinctiveness (containing unique information not already written in another journal entry), and/or diagrams and tables. Key findings for Tables 1,2,3 were extracted from references—and then later summarized—based on substantiality (backed by other sources or verifiable rationale), relevance to vaping, and applicability to COVID.

3. Results

3.1 Literature review of e-cigarette use and COVID severity and mortality

Table 1 (Ref. [12–19]) illustrates the documented/possible effects of vaping in respect to COVID disease progression. Information which directly correlates vaping to COVID disease progression is sparse. Hence, 6 out of 8 references in Table 1 discuss relevant vaping-related complications which might theoretically increase likelihood for severe disease or death in COVID patients. Only 2 references were studies

T A B L E 1. Pertinent findings which discuss connections between vape use and COVID disease progression, or the lack thereof: effects of e-cigarette use on COVID.

Authors	Study type	Key findings
Kaur, Rahman [13]	Literature review	Elevated COVID susceptibility, elevated risk for pneumonia, elevated risk for cytokine storm, elevated angiotensin converting enzyme-2 (ACE-2) expression.
Liu *et al*. [14]	Cohort study	Elevated risk for severe disease (respiratory failure, respiratory rate >30) and disease progression compared to nonsmokers/non-vapers.
Brake *et al*. [15]	Literature review	Elevated (ACE)-2 expression, heightened risk for developing COVID, lung injury similar to tobacco use.
McAlinden *et al*. [16]	Literature review	Elevated ACE-2 expression, elevated risk for pneumonia or severe pneumonia, elevated inflammatory responses.
Li *et al*. [17]	Ecological study	Increased incidence of COVID cases per 10,000 compared to nonsmokers, impaired immunity, elevated vulnerability, elevated risk for death.
Sifat *et al*. [18]	Literature review	In a table which compared vaping vs COVID studies, only 2/10 references showed statistically significant ($P < 0.05$) increased risk for severe disease or death compared to nonsmokers or former smokers.
		Also, elevated ACE-2 expression, elevated risk for severe disease, elevated risk for contracting COVID, increased central nervous system (CNS) penetration.
Kashyap *et al*. [12]	Literature review	Effects of vaping on COVID disease progression/susceptibility are not clear.
Singh, Chaturvedi [19]	Literature review	Increased risk for developing COVID pneumonia 14 times greater than nonsmokers, risk for e-cigarette or vaping product use-associated lung injury.

which sought to find a statistical relationship.

3.2 Literature review of pathophysiological effects of e-cigarette use

Table 2 (Ref. [16, 19–26]) shows findings which detail the physiological effects of vaping. Incidence, duration, and/or symptom severity were frequently not discussed. For example, references do not specify how long vaping-induced inflammation persists after vaping cessation nor do they specify the magnitude or clinical significance of said inflammation. Effects that were thought to be exceedingly rare or irrelevant were not included in the results' summaries (i.e., popcorn lung caused by a flavor that is now discontinued [20], enhanced expression of irrelevant biomarkers, hyperglycemia in rats, teratogenicity, etc.) Multiple consulted sources noted data on the effects of vaping—especially long-term effects—are limited.

3.3 Relevant risk factors for COVID severity and morality

The list below—which is information from the CDC—describes comorbidities and/or lifestyle factors which place patients at increased risk for severe COVID disease (Fig. 2). The CDC emphasized the list is not comprehensive. For the purpose of this report, only factors with relevance to smoking, vaping, and smoking- and vaping-associated comorbidities have been included. The CDC defined severe COVID as illness which requires hospitalization, ventilation, and/or intensive care unit (ICU) admission or that causes death [27].

(1) Comorbid/lifestyle factors which undoubtedly place patients at an increased risk for severe COVID illness include smoking, heart conditions (i.e., heart failure, coronary artery disease etc.), chronic obstructive pulmonary disease, and cancer [27] As of 18 April 2021:

a. 45.7% of deceased COVID patients contracted influenza and/or pneumonia while sick with COVID.

b. 19.7% of deceased COVID patients had comorbid hypertensive disease which contributed to death.

c. 18.3% of deceased COVID patients had comorbid ischemic heart disease and/or heart failure.

d. 12.7% of deceased COVID patients had comorbid chronic lower respiratory disease or other diseases of the respiratory system.

e. 7.3% of deceased COVID patients had comorbid cardiac arrhythmia [28].

(2) Comorbid/lifestyle factors which possibly place patients at an increased risk for severe COVID sickness include asthma, cerebrovascular disease, hypertension, being immunocompromised, and pulmonary fibrosis [27]. 20.8% of deceased COVID patients had hypertension at time of death, and 5.1% of deceased COVID patients had cerebrovascular disease [28].

(3) There is a positive correlation between age and COVID death independent of other comorbid factors in the United States of America. As of 21 April 2021:

a. ages 0–39 made up only 1.5% of all COVID-related deaths.

b. 2.9% of deaths were between ages 40–49.

c. 15.3% of deaths were between ages 50–64.

d. 22.1% of deaths were between ages 65–74.

e. 58.2% of deaths were seen in those aged 75 or older [28].

(4) As of February 2021, seniors aged 85 or older were 8700 times more likely to die from COVID than those 5–17 years old

Associations between vape use and COVID outcomes and COVID risks
Vape duration unknown

Direct links between vape use and COVID	**Direct links between vape use and COVID risk**	**High-risk health conditions associated with vaping**
- Elevated COVID susceptibility	- Elevated ACE-2 expression	- Decreased immunocompetency
- Increased risk for cytokine storm	- Potential for lung injury	- Possible nephro- and neurotoxicity
- Increased risk for severe COVID	- Elevated inflammatory markers	- Respiratory disease (asthma, COPD)
- Increased risk for COVID pneumonia	- Possible respiratory function impariment	- Pulmonary fibrosis
- Higher incidence of COVID	- Elevations in blood pressure or heart rate	- Heightened risk of stroke and blood coagulation
- Increased risk for COVID-related death	- Pulmonary inflammation	- Atherosclerosis
	- Oxidative stress	- Reduced ejection fraction
	- Decreased blood brain barrier integrity	

F I G U R E 2. Illustration summarizing the risks associated with vaping respective to COVID outcomes and COVID risks. Some associations are direct as seen in the left two columns, but some associations are more implied as seen in the right column. All information listed in this figure was pulled from Tables 1,2,3 and from Results Section 3.3.

[29].

(5) There is a positive correlation between age and COVID hospitalizations independent of other comorbidities. Patients aged 50–64, 65–74, 75–84, and >85 years old were 25, 40, 65, and 85 times more likely to be hospitalized for COVID, respectively, than those in the 5–17 age group [29].

(6) Lastly, certain comorbidities place patients at an increased risk for COVID hospitalizations. The following comorbidities were most prevalent in hospitalized COVID patients: hypertension (59.5%), metabolic disease (44.2%), cardiovascular disease (36.8%), neurologic disease (20.6%), chronic lung disease (20.1%), asthma (13% in pediatrics, 11.8% in adults), and immunocompromised state (10.1%) [30].

3.4 Literature review comparing pathophysiological changes between smokers and vapers

The CDC established that smoking is a risk factor for developing severe COVID infection [27] Table 3 (Ref. [16, 20, 22, 25, 31–33]) and 4 (Ref. [34–39]) aim to actively compare the pathophysiological effects of smoking and vaping. Similar pathophysiological effects between both groups might suggest similar possible COVID outcomes. However, this inference does not take into account the average age of e-cigarette users vs smokers nor the duration of use of e-cigarettes vs cigarettes.

Interestingly, there is a disparity in how vaping is perceived in comparison to smoking across references. To clarify, 33.3% of cited entries in Tables 1 and 2 [13, 14, 17, 18, 24] amalgamated smoking and vaping together when assessing pathophysiological problems caused by smoking. For example, a reference may have used terminology like "smoking and/or vaping", implying the two were considered equal risk for the physical problem discussed thereafter. On the contrary, 66.7% of cited entries in Tables 1 and 2 [13, 15, 16, 19–23, 25, 26] considered vaping to be an independent risk for various physical changes, albeit inconsistently. The primary

objective of Tables 1 and 2 was not to identify similarities and differences between smoking and vaping—that is the focus of Tables 3 and 4—but rather to identify how vaping directly affects the body and COVID disease progression. The fact remains that multiple references considered smoking and vaping as equivalent risk factors.

3.5 Vaping/smoking demographics

There is a positive correlation between age and COVID mortality and hospitalization. The CDC recognized a statistically significant association between vape use and age ($P < 0.05$), with vaping being most prevalent in ages 18–24 and least prevalent in ages ≥65 [40]. These data could potentially contradict the thesis that COVID outcomes are worse among people who vape. This is because most COVID deaths and hospitalizations are seen in the older populations, but the majority of vape users are seen in younger populations. Thus, it is more difficult to assess the effects of vaping on this vulnerable population because so few older people vape. In addition, because older individuals are statistically at heightened risk for severe COVID disease independent of other factors, it is especially challenging to gauge if vaping or the absence thereof might have any effect on COVID-related healthcare outcomes in the first place.

A curious observation by the CDC is a larger proportion of vape users are categorized as socioeconomically disadvantaged, being "poor" or "near poor" versus "not poor" ($P < 0.05$) [40]. The CDC considers an individual "poor" if their family income fell below the federal poverty line and "near poor" if their family income was between 100% and 200% of the federal poverty line. There are medically accepted inverse relationships between (1) poverty and obesity [41], (2) poverty and health illiteracy [42], and (3) poverty and adverse health outcomes (i.e., diabetes, hypertension, infectious diseases). Therefore, this observation by the CDC may or may not contribute to the claim that vaping is associated with worse healthcare outcomes, depending on viewpoint.

T A B L E 2. Pertinent findings which describe pathophysiological effects of vaping.

Authors	Study type	Key findings
Singh *et al*. [20]	Literature review and case study	Carcinogenesis, possible retinoblastoma, possible nephrotoxicity, possible neurotoxicity, possible hemotoxicity, possible alveolar basal epithelial cell toxicity, decreases immune defense in mice, increased inflammatory markers in mice, risk for bronchiolitis obliterans, oxidative stress.
Callahan-Lyon [21]	Literature review	Dry cough, possible respiratory function impairment, elevated cotinine levels.
		Limited data on long-term effects.
Singh, Chaturvedi [19]	Literature review	E-cigarette or vaping product use-associated lung injury most common in ages 18–24; acute respiratory illness.
Stoebner *et al*. [22]	Literature review	Pulmonary opacity, digestive symptoms, elevated inflammatory markers, respiratory disease symptoms.
		THC-containing e-cigarettes considered highest risk.
Blagev *et al*. [23]	Cohort study	Lung injury requiring hospitalization, antibiotics, and steroids; respiratory and gastrointestinal symptoms, chest abnormalities on radiograph after e-cigarette or vaping product use-associated lung injury recovery, impaired pulmonary function tests after lung injury recovery.
Archie, Cucullo [24]	Literature review	Increased incidence of chronic obstructive pulmonary disease and pulmonary fibrosis, decreased blood-brain barrier integrity, elevated vascular inflammation, facilitation of stroke, elevated risk for ischemic brain injury, blood coagulation.
Laucks, Salzman [25]	Literature review	Medical dangers not fully known, possible elevated lifetime risk for any cancer, possible cardiovascular effects, possible lung mucosal damage, elevated expression of inflammatory cytokines, nicotine addiction that is more severe than that seen from smoking tobacco, withdrawal effects similar to that of heroin when discontinuing THC-containing electronic-delivery systems.
McAlinden *et al*. [16]	Literature review	Asthma, decreased lung function, carcinogenesis, increased platelet activating factor expression, pneumonia or "walking" pneumonia risk, epithelial cell inflammation, higher risk for bronchitis, emphysema or chronic obstructive pulmonary disease, angiogenesis in mouse cardiac tissue, oxidative stress, vaping-associated lung injury.
Buchanan *et al*. [26]	Meta-analysis	Possible cardiomyoblast cytotoxicity (preclinical), altered vascular function, mild to significant elevations in blood pressure and heart rate, vasoconstriction, systemic oxidative stress (use >1 year), elevated sympathetic activity (use >1 year), risk for myocardial infarction 1.8 × higher than nonsmokers (chronic), possible arrhythmias, possible myocardial remodeling, possible thrombogenesis, atherosclerosis, coronary heart disease, pulmonary inflammation, reduced ejection fraction in mice.
		In some studies, both heart rate and blood pressure dropped after switching to e-cigarettes from tobacco, but in other studies, only BP dropped.

The effects included would either unequivocally influence COVID outcomes or hypothetically influence COVID outcomes. Abbreviations: THC, Tetrahydrocannabinol.

T A B L E 3. Pertinent findings which highlight similarities and dissimilarities between traditional smoking and novel e-cigarette use in an attempt to find parallels in how they affect physiology.

Authors	Study type	Key findings
Kopa, Pawliczak [31]	Systematic review	Vaping emits lower levels of tar, carbon monoxide, free radicals, and carbonyls compared to cigarettes, but does not eliminate the risk for tobacco-related disease or addiction.
Herr *et al*. [32]	Literature review	E-cigarette vapor had no effect on host defense and barrier integrity. Tobacco vapor negatively impacted host defense and significantly reduced barrier integrity.
Arastoo *et al*. [33]	Comparative study	Similar increase in plasma nicotine seen in both electronic cigarette and cigarette groups, acute elevated hemodynamic outcomes in both groups compared to control (nicotine-free vape), baseline hemodynamics were not statistically different between chronic vapers and chronic smokers, hemodynamics were elevated statistically higher in cigarette smokers vs vapers.
McAlinden *et al*. [16]	Literature review	Both e-cigarette vapor and cigarette smoke demonstrated toxicity to human bronchial epithelial cells and human airway smooth muscle cells, increased release of inflammatory mediators in both groups.
		E-cigarettes are not an effective aid for smoking cessation, as 80% of smokers who switched to vaping still vaped after 1 year, but only 9% of smokers who used nicotine replacement still smoked after 1 year.
Singh *et al*. [20]	Literature review and case study	E-cigarettes are safer than cigarettes due to absence of toxins, but they are not risk-free; cell blood counts unaffected by vapes but affected by cigarettes, nicotine in vape aerosol 85% lower than cigarettes, plasma nicotine following vape use only 10% of plasma nicotine from cigarettes, decreased carbonyl exposure from vapes, decreased exposure to acrolein and formaldehyde from vapes, blood pressure and heart rate not as high following vape us vs cigarette use.
Stoebner *et al*. [22]	Literature review	Unlike cigarettes, vapes do not expose users to carbon monoxide.
Laucks, Salzman [25]	Literature review	Addiction is more severe in vapers than in cigarettes smokers, electronic devices may deliver more nicotine per puff than cigarettes because the drugs are concentrated.
		Flavoring additives in vapes are approved for oral consumption only; the effects of edible additives are not known when vaporized at high temperatures and inhaled. This is unlike cigarettes where the inhaled chemicals have been better studied.

T A B L E 4. Studies which compare the physiological effects of both cigarettes and e-cigarettes.

Comparative acute physiological effects of vaping and tobacco smoking [21]

Reference	Sample details	Study groups	Results
Vansicket *et al.* [34]	32 smokers, e-cig naïve	Own cigarette (10 puffs)	Increased HR, plasma nicotine, plasma CO
		E-cig (10 puffs)	No increase in HR, nicotine, or CO
Flouris *et al.* [35, 36]	15 smokers	Passive or active e-cig use	No change in CBC indices, FEV1/FVC unchanged, plasma cotinine increased
		Passive cigarette	Increase in WBCs, lymphocytes, granulocytes, elevated plasma cotinine, FEV1/FVC unchanged
		Passive cigarette	Increased plasma cotinine and CO
Chorti *et al.* [37]	15 smokers	Active cigarette, smoked two cigs	Decreased FEV1 and FEV1/FVC, decreased FeNO, increased plasma cotinine and CO
		Active e-cig, one e-cig	Lung function unchanged, cotinine increased
		Passive e-cig, one e-cig	Increased cotinine, decreased FEV1/FVC
Farsalinos *et al.* [38]	22 e-cig users, quit tobacco	Cardiac echo before and after one cig or e-cig	No change in cardiac echo
	20 cigarette smokers		Decreased LV function
Tzatzarakis *et al.* [39]	10 smokers with brief active session	Active cigarette	Increased interleukins and epidermal growth factor
		Active e-cig	No change in inflammatory markers
	10 nonsmokers, passively exposed for 1 h	Passive cigarette	Increase in TNF-alpha
		Passive e-cig	No change in inflammatory markers

Credit: Callahan-Lyon. Abbreviations: HR, heart rate; CO, carbon monoxide; CBC, complete blood count; FEV1, forced expiratory volume at 1 second; FVC, forced vital capacity; WBC, white blood cell; FeNO, fractional exhaled nitric oxide; LV, left ventricle; TNF, tumor necrosis factor.

From one viewpoint, vaping may cause or worsen untreated or undertreated comorbid conditions which are left unmanaged due to health illiteracy and/or inadequate access to care [42]. From another perspective, it is plausible poverty and the health problems associated with poverty are the principal contributing factors to unfavorable COVID-related outcomes, with some patients coincidentally being vape users.

Demographics on cigarette smoking may be relevant to this report depending on how vaping is defined. If vaping is deemed the same or comparable to smoking, then the information on smoking is relevant. Like vaping, smoking is seen at higher rates in impoverished and less educated populations, both of which are susceptible to adverse health outcomes [42]. Salah, Sharma, and Mehta found the COVID mortality rate for smokers was nearly double that of non-smokers (29.4% vs. 17.0%, respectively [$P < 0.0001$]) [43]. However, the mortality rate of smokers against former smokers was not statistically different ($P = 0.34$) [43].

As of 2018, 39.1% of seniors older than 65 were former smokers and 8.4% were current smokers [44]. One-half of former smokers older than 65 had smoked for 25 years or longer [44]. It has already been recognized that smoking is a risk factor for developing severe COVID disease. Seniors are more vulnerable to the effects of smoking than patients under 65 [44], even if smoking has ceased [43].

Interestingly, 18.8% more men have died of COVID in the United States than women as of 3 February 2021 [28]. The CDC reported the case-fatality ratio for men is 2.4 times higher than the case-fatality ratio for women [45]. Griffith *et al.* hypothesized multiple significant contributing factors—two of which are relevant to this topic—which could explain why males are dying from COVID at higher rates than females. For one, men have higher endogenous plasma ACE-2 levels than women, an enzyme which is expressed at higher rates following nicotine exposure [13, 15, 16, 18]. The second is men partake in more careless/risky behaviors than women, such as not handwashing and not social distancing, despite having comorbid conditions which would place them at elevated risk for severe COVID disease. Suggestions by Griffith *et al.* [45] to improve healthcare outcomes for men included patient education—especially in undereducated patients—and strict management of hypertension/other high-risk comorbid conditions.

Worldwide, 80% of approximately one billion smokers are males, whereas 20% are females [46]. This sex-smoking link is also seen in vaping, with more men vaping than women ($P < 0.05$) [40]. Whether the significantly higher rates of smoking/vaping in part explain higher COVID mortality rates in men versus women is still uncertain.

4. Discussion

Five out of fifteen referenced sources in Tables 1 and 2 classified smoking and vaping as equivalent behaviors when discussing risks associated with smoking. Since both activities involve inhaling a hot, noxious aerosol into one's lungs, and both cigarettes and e-cigarettes contain nicotine and other exogenous substances, this may be reasonable. Based on the data in Table 2, there is evidence which supports the notion that vaping can be harmful to its users, much like cigarettes. However, because the data for vaping are less abundant than for smoking, reported information on vaping must be considered not comprehensive. Moreover, the incidence of adverse events for vaping is often unknown, and the duration of e-cigarette use is often unspecified. Vaping is a relatively new phenomenon, whereas cigarette smokers sometimes self-report smoking for >25 years [44].

Ignoring the paucity of information for vaping and its effects on health, vaping appears to conserve some core detriments of smoking, including, but not limited to nicotine exposure, addiction, elevations in hemodynamics, airway inflammation, bronchial cell injury, increased risk for major adverse cardiovascular events, risk for chronic lung disease, and risk for cancer. The prevalence of vaping-related health problems in the general population is not established. Furthermore, the severity of symptoms associated with vape use is not entirely clear. The information attained in this narrative review has inconsistencies which make it problematic to clearly describe the association of vaping on human health and, consequently, COVID outcomes. Of course, the effects of vaping on COVID are at most implied and suggestive at this point.

Gonzalez-Rubio *et al.* published research which suggested smoking has protective effects in COVID disease. Gonzalez-Rubio *et al.* [47] wrote smokers were less likely to be hospitalized than nonsmokers. Garufi *et al.* [48] supported this idea by writing: "smoking could attenuate the normal defensive function of the immune system, which becomes tolerant of a continuous inflammatory insult, while the immune system of never smokers may be more suitable for a cytokine release syndrome". However, Berlin and Thomas emphasized extreme caution with this viewpoint, writing that the research performed by Gonzalez-Rubio *et al.* [47, 49] is concerning and potentially biased due to obscure data collection [49]. To clarify, the notion that smoking is protective is concerning because it may convince patients to continue, resume, or start smoking for "protective" effects when protection from smoking remains uncertain. Additionally, Berlin and Thomas described a recent report which directly contradicted the research published by Gonzalez-Rubio *et al.* [47, 49] This is a disputed point in the research which needs further investigation.

Other noteworthy inconsistencies met in this research were vape liquid composition, and the effects of vaping on the cardiopulmonary system. Singh *et al.* [20] wrote the nicotine content in e-cigarettes is 85% lower than that found in cigarettes, and measured plasma concentrations of nicotine following vape use was 10% of plasma nicotine following cigarette use. Notwithstanding, Singh *et al.* [20] stated vaping is not safer than smoking even though product delivery is safer in the former. Laucks and Salzman, however, wrote vaping delivers a greater, more concentrated amount of nicotine than cigarette smoking, and vapes are more addicting than cigarettes [25]. McAlinden *et al.* [16] indicated vaping is not an effective method for smoking cessation, but the US Surgeon General published vapes are an effective tool for smoking cessation [50]. The US Surgeon General also emphasized that although vaping is less harmful than smoking, it does not mean vaping is harmless [50]. This is somewhat conflicting to a statement by Singh *et al.* [20]—"[vapes are] poisonous, some moderately

and some highly toxic to lung cells".

Information on the effects of vaping on the cardiopulmonary system was equivocal. For example, in a meta-analysis, Buchanan *et al*. [26] found some studies which suggested both heart rate and blood pressure dropped after cigarette users switched to vapes, but other studies suggested only blood pressure dropped. Table 4 contains only one study which suggests e-cigarette use decreases lung function, but the other studies in Table 4 suggested e-cigarette use has no effect on the cardiopulmonary system. This is inconsistent with the idea that nicotine, which is found in e-cigarettes, raises blood pressure and heart rate, and ultimately increases the risk for cardiovascular disease. Some studies found that vaping increased heart rate and blood pressure—perhaps not to the extent of cigarettes—while others, as shown, wrote vaping does not affect hemodynamics.

In order to better understand the effects vaping has on COVID, and all disease states for that matter, more research is needed on the outcomes of vapers who contracted COVID versus non-vapers. Additionally, more research is needed on the pathophysiological effects of chronic e-cigarette users, especially in comparison to chronic cigarette users. If it is determined that vaping is the same or like cigarette smoking, then it can be assumed that vaping would present similar health consequences as smoking for COVID patients and for disease states like diabetes, chronic obstructive pulmonary disease, or other infectious diseases.

This review has several limitations. It is a narrative review of the literature, and the literature contains only a paucity of sources which distinctly differentiate vaping and smoking. In some cases, as noted, sources equated vaping with cigarette smoking, making it difficult to characterize the two practices apart from one another. Vaping is a relatively new phenomenon, and there are no identified lifelong vapers in the population who might compare to lifelong smokers. Finally, while most cigarettes are relatively similar to each other, there are numerous different vapes available, and it is not clear if some are potentially more hazardous to health than others.

5. Conclusions

It is difficult to definitively evaluate the effects of vaping on COVID disease progression, particularly when many researchers view vaping and smoking as equivalent practices. It may be possible to describe vaping as a less risky—but not risk-free—alternative to cigarette smoking, with potential undesirable implications to health which can affect COVID outcomes. More research is needed on the effects of vaping on COVID health outcomes and of vaping on outcomes in other disease states. Additionally, more research is needed on the effects of smoking vs vaping to get a better understanding of how vaping affects its users, which predominantly consist of youth and males.

AUTHOR CONTRIBUTIONS

KB performed the searches, collected pertinent information, designed the figures and tables, and drafted the manuscript. FB, GV, PM, and JP helped review and edit the manuscript. FB provided mentorship and helped with intergroup correspondence. GV helped with implantation of new ideas and approval of the final draft to be published. PM helped with formatting. JP helped provide concept and content.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest. Joseph Pergolizzi and Giustino Varrassi are members of the Editorial Board of this journal.

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