

# Lung and Airway Disease Caused by E-Cigarette (Vape): A Systematic Review

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## ABSTRACT

Vape use is increasing among the youth and there is a catchphrase that vape is the solution to conventional tobacco smoking. Some case reports show the impact of vape use in the form of lung injury. However, there are no studies that definitively determine how many cases and what kind of problems in the lungs and airways can be caused by the use of vape and this is the purpose of our research. This systematic review article used several databases with the keywords «Vape OR E-cigarette» and «Disease.» We screened and eliminated articles based on the PEOS framework. The included articles were analyzed for risk of bias using the JBI critical appraisal tool. A total of 16 articles were included and involved 313 patients in this review. Several case reports show the incidence of pulmonary infections in vape users, lung damage (EVALI), respiratory failure, burning throat, and various other events associated with vape use. The duration of vape use also varies before the appearance of the disease and the earliest use duration is six months and the longest is up to years. Vape use poses a risk of lung and airway disease and requires further study to accurately determine the degree of risk of the impact of vape use on lung and airway health. In conclusion, vape circulation vigilance needs to be considered because the impacts can cause health issues and interfere with the achievement of health goals for all.

**Keywords:** Lung disease; e-cigarette; vape (Siriraj Med J 2024; 76: 325-332)

## INTRODUCTION

Electronic cigarettes (e-cigarettes), often known as vapes, are gadgets that allow users to vaporize flavors and nicotine solutions instead of burning tobacco leaves as is done with traditional cigarettes.<sup>1</sup> E-cigarettes are now readily available, and their use has skyrocketed all across the world. A 2019 study by Cullen et al.<sup>2</sup> evaluated the prevalence of e-cigarette usage among teenagers in the United States and found that high school and middle school students were the most likely to report using them; 10.5% of middle school students (from 8837) and an estimated 27.5% of high school students (from

10.097) presently use e-cigarettes. According to a 2020 study by Habib et al., 12.2% (49/401) of medical students reported using e-cigarettes, with men three times more likely to do so than women. The most common reasons in this research for using e-cigarettes were to enjoy the variability in flavors (61.4%), to reduce or quit tobacco smoking (29.5%), and to avert the public smoking ban (13.6%).<sup>3</sup>

E-cigarettes are actively marketed as a cheaper, healthier, more socially acceptable option, and a tool for quitting smoking.<sup>4</sup> This may lead to an increase in vape usage, particularly among young individuals. However,

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several studies are starting to demonstrate the negative impacts of vaping on health. In-vitro analysis by Shi et al.<sup>3</sup> in 2022 demonstrated that vaping led to a buildup of inflammatory cells in the alveolar space, surrounding the pleura, and in the bronchial lumen. According to this, inhaling vape for four hours may result in respiratory tract irritation. Although reports of cases involving the effects of e-cigarette use on people are starting to rise, there are still few studies that demonstrate the effects on other aspects of health, leaving the public with a low level of knowledge. A systematic review is required to be able to assess the effect of vaping on health comprehensively. This study examined the effects of vaping on health with a particular emphasis on pulmonary and airway conditions. This study is meant to increase public awareness of the negative effects that vaping can have on health.

## MATERIALS AND METHODS

### Data sources and search strategy

For reporting in systematic reviews, we used Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and synthesis without meta-

analysis. PubMed, Science Direct, Epistemonikos, and Google Scholar were all databases we used to search for articles. We used keywords such as “E-Cigarette OR Vape OR Vaping” AND “Pulmonary OR Disease OR Injury”. We incorporate all research: (1) Full text, (2) English or Indonesian Language, (3) last 10 years and we exclude review articles. The search strategies are described in full in Fig 1. Unpublished data and duplicate research were disregarded. This systematic review is registered at PROSPERO with number ID: CRD42023434514.

### Study Selection

Four researchers (AMS, MERP, NAP, and AH) independently evaluated eligibility based on titles and abstracts using the PEOS framework (Population = Human; Exposure = E-Cigarette OR Vape; Outcome = Pulmonary OR Airway Disease; Study = Case Report OR Observational Study OR Clinical Trial). The consensus was reached between investigators to resolve disagreements, or supervisors (SS, IES) were involved when consensus could not be reached.

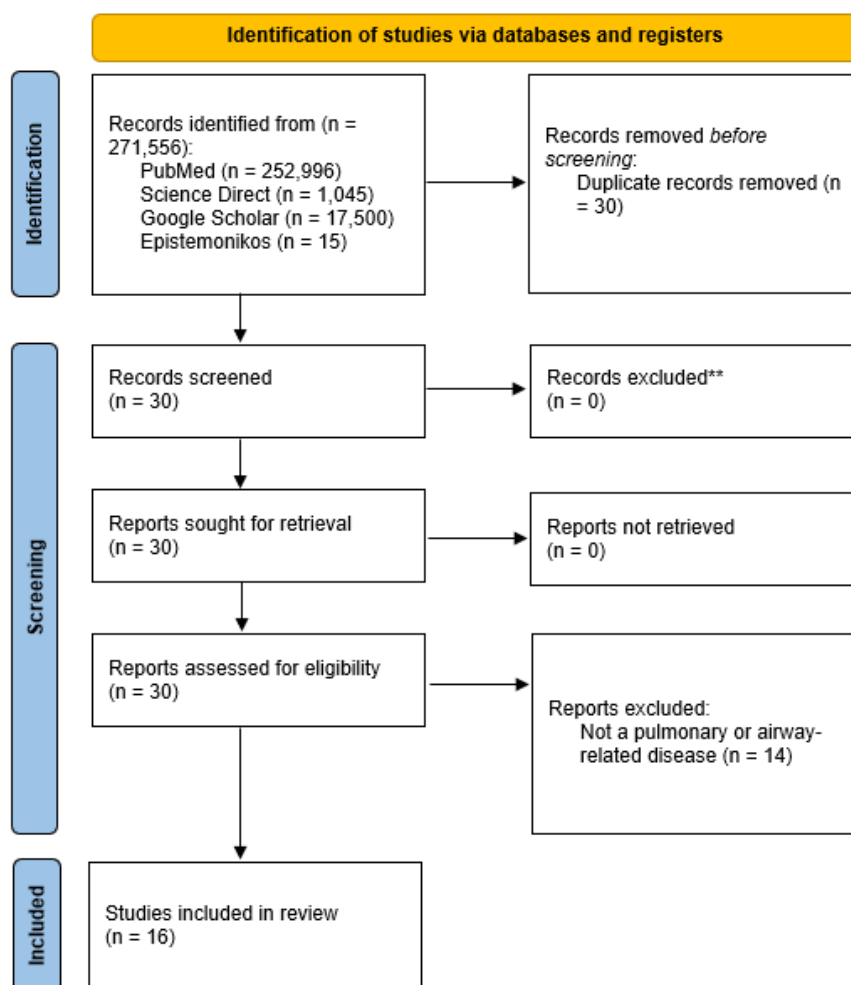


Fig 1. Flow Diagram of Included Studies Based on PRISMA Flow Chart

### Data Extraction and Risk of Bias

From each included study, data were taken on : (1) First author's name, (2) Year of study, (3) Study design, (4) Country, (5) Sample size, (6) Age, (7) Gender, (8) Historical disease, (9) Dual/Single User, (10) Ingredients of E-liquid, (11) Imaging/Radiology, and (12) Diagnosis. A dual user is someone who smokes conventional cigarettes and also vapes and a single user is a vape user only without smoking other conventional cigarettes. The primary outcome was to determine pulmonary and airway diseases caused by e-cigarettes (Vape) and categorize the diagnosis we received from articles.

According to the type of articles received, AMS, MERP, NAP, and AH examined full-text articles using the Joanna Briggs Institute Critical Appraisal Tool (jbi.global/critical-appraisal-tools). We count each "yes" from the tools and make it in the form of a score. If the score for each article is below 75% it is considered a "high risk of bias," Consensus was reached to resolve the disagreements, or when consensus could not be established, supervisors (SS, IES) were involved.

## RESULTS

### Study selection

A total of 271.556 articles were identified from the research database (Fig 1). After removing the duplicate

articles, 30 articles were screened and assessed for eligibility. A total of 16 studies were included in the review, after excluding 14 studies due to out-of-scope based on inclusion criteria.

### Characteristics of included studies

Table 1 shows a resume of the characteristics of the articles we included. Of the articles we included, most had a case report design and some were RCTs. The articles we received were mostly from the US and a few from Belgium, Italy, and Canada. In the case of a disease caused by vape, this was suffered by a variety of ages from 17 years old at the youngest and 54 years old at the oldest found in this data compilation. The effects were gender agnostic and some were reported to have a diverse medical history, which was collected in this review to see if there was any influence of this medical history on e-cigarette-related illnesses.

### Pulmonary and Airways Disease Caused by E-Cigarette (Vape)

Table 2 shows a collection of lung and airway diseases caused by e-cigarettes (vaping). This table is grouped according to agreed disease categories such as airway infection, E-Vaping Acute Lung Injury (EVALI), respiratory failure, and others that have various diseases.

**TABLE 1.** Characteristics of included studies.

Study, Year	Design	Country	N	Age (year)	Gender	Historical Disease
Savage, 2023 <sup>7</sup>	Case Report	America	1	17	M	CAP
Kooragayalu, 2020 <sup>23</sup>	Case Report	America	1	26	F	Scizoaffective
Massey, 2021 <sup>24</sup>	Case Report	America	1	33	M	Dental Infection
Chen, 2021 <sup>8</sup>	Case Report	America	3	18,19,34	1F,2M	Asthma
Chaumont, 2019 <sup>25</sup>	RCT	Belgium	25	23±0.4*	7F, 18M	NA
Roman, 2021 <sup>9</sup>	Case Report	America	1	31	M	Paroxysmal Atrial Fibrillation
Aftab, 2019 <sup>26</sup>	Case Report	America	1	26	F	Asthma
Drabkin, 2020 <sup>6</sup>	Case Report	America	1	19	M	NA
Fryman, 2020 <sup>10</sup>	Case Report	America	5	29,34,24,54,27	2F, 3M	NA
Lin, 2020 <sup>27</sup>	Case Report	America	1	34	F	Low-Grade Carcinoid Tumor
Edmonds, 2020 <sup>28</sup>	Case Report	America	1	31	F	Untreated Hepatitis C
Grech, 2022 <sup>29</sup>	Case Report	America	1	52	F	Obesity
Lucchiari, 2019 <sup>30</sup>	RCT	Italy	210	62.8±4.58*	98F, 132M	NA
Chaumont, 2019 <sup>31</sup>	RCT	Belgium	30	38±2*	M	NA

**Abbreviations:** CAP: Community-Acquired Pneumonia, F: Female, M: Male, NA: Not Available

\*: Mean±SD

**TABLE 2.** Pulmonary and airway disease caused by E-Cigarette (Vape).

Study, Year	Dual/Single User	Ingredients of E-Liquid	Duration of Vaping	Imaging	Result	Diagnosis
<b>Lung Physiology Impairment</b>						
Chaumont, 2019 <sup>25</sup>	S	Nicotine	During Experiment	CT-Scan	Extensive Bilateral Alveolar Infiltrates	Lung Inflammation
<b>Pulmonary Infection</b>						
Savage, 2023 <sup>7</sup>	S	Nicotine	Every day for 5 years	X-Ray	Right lung pleural effusion	Empyema (Streptococcus)
Kooragayalu, 2020 <sup>23</sup>	S	Tobacco and Marijuana	NA	X-Ray	Bilateral Patchy Opacities	EVALI + Pneumonia ( <i>Mycoplasma pneumoniae</i> )
Massey, 2021 <sup>24</sup>	D	Marijuana	1 – 2x/day (1 year)	X-Ray	Bilateral Pulmonary Vascular Congestion	<i>Actinomyces odontolyticus</i> infection
Chen, 2021 <sup>8</sup>	D/S	Nicotine, THC, dabbing, and Cannabinoid	6 months	CT-Scan	5x9cm Cavity	Non-Tuberculous Mycobacteria
<b>EVALI</b>						
Roman, 2021 <sup>9</sup>	D	Cannabis Oil	3-5x/day	CT-Scan	Bilateral Alveolar Opacities	EVALI
Aftab, 2019 <sup>26</sup>	S	Nicotine and Marijuana	NA	CT-Scan	Consolidation and ground-glass opacity	EVALI
Drabkin, 2020 <sup>6</sup>	S	Nicotine and Marijuana	NA	CT-Scan	Bilateral ground-glass opacities	EVALI
Fryman, 2020 <sup>10</sup>	S	Nicotine and Marijuana	NA	CT-Scan	Ground glass opacities	Acute Respiratory Failure
	S	Marijuana	Several years	CT-Scan	Consolidation	Acute Respiratory Failure
	S	Marijuana	NA	CT-Scan	Bilateral diffuse nodular opacities	Acute Respiratory Failure
	S	Marijuana	2x/week	CT-Scan	Patchy, bilateral ground glass opacities	Acute Respiratory Failure
	S	Marijuana	2 months	CT-Scan	Reticulonodular opacities	Acute Respiratory Failure
<b>Others</b>						
Lin, 2020 <sup>27</sup>	D	NA	Everyday	CT-Scan	Nodular Ground Glass Opacities	Pulmonary Granulomatous
Edmonds, 2020 <sup>28</sup>	S	Cinnamon and Nicotine	Every day	CT-Scan	Consolidation	Diffuse alveolar Hemorrhage
Grech, 2022 <sup>29</sup>	D	Nicotine	1 year	NA		Extreme Carboxyhaemoglobinemia
Lucchiari, 2019 <sup>30</sup>	S	Nicotine	6 months			Burning Throat

**Abbreviations:** D: Dual, D/S: few participants dual users, few are single users, EVALI: E-Vaping causing Acute Lung Injury, Gly: Glycerol, NA: Not Available, PG: Propylene glycol, S: Single, THC: Tetrahydrocannabinol

It was found that the diversity of users in the data was dual users and single users and was dominated by single users. The content of E-liquid is very difficult to know for sure because vape users can use various liquids with a variety of different contents. Some liquids contain nicotine and some that do not contain nicotine. In Table 2, the E-liquid content reported in the study has been compiled and it can be seen that there is a diversity of liquid content. Some E-liquids only contain nicotine, some contain mixed marijuana content, and others do.<sup>6-9</sup>

Table 2 also collected data on the duration of e-cigarette use. What is different between tobacco smoking and e-cigarette is the Brinkman Index which can determine the severity of smoking that correlates with disease (number of cigarettes per day x duration of smoking (years)). As e-cigarettes do not have such an index, the data collected are the reported duration and have their diversity. From this study, some durations that can be said to be very short can cause a lung problem with a duration of six months, and even some during the experimental period in the RCT have problems due to the use of e-cigarettes. The results of lung imaging also varied, such as diffuse ground-glass infiltrates, pleural effusion, pulmonary congestion, and others. Diagnostically, there was diversity such as non-tuberculous mycobacteria, empyema, and a combination of EVALI with pneumonia. The incidence of EVALI is well-known but Fryman's study showed that it lasted until respiratory failure. Other uncategorized events include asthma, burning throat, and carboxyhemoglobinemia.<sup>10</sup>

### Risk of Bias

Fig 2 displays the risk of bias score of each article included using the JBI Critical Appraisal tool. The average

JBI score for all articles was 83.63% with the lowest score being 75%. No article was found to have a score below 75%.

## DISCUSSION

### Summary and interpretation of findings

The use of e-cigarettes that are predicted to be safe and not cause harm to health can be questioned. This review found various incidents of pulmonary and airway diseases that could potentially be caused by vape. There are several events such as lung infections, burning throat, asthma, and EVALI related to respiratory failure. This is certainly dangerous and has the potential to injure human health. No studies have been found regarding the impact on a person exposed to smoke from e-cigarettes, and this study only focused on direct users of these devices. The potential health problems caused to people who are around e-cigarette users are very possible but there are no studies that show this. This review can be interpreted as the use of e-cigarettes can cause various lung and respiratory diseases and related research is also still very minimal so the use of e-cigarettes must be monitored for its impact on health and also its circulation.

### Potential damaging content and mechanism of lung and airway damage caused by E-cigarette (VAPE)

Electronic cigarettes are very different from traditional cigarettes in terms of their chemical makeup. The chemical-filled liquid is heated in electronic cigarettes and turned into vapor. When you take into account the chemical makeup and how it affects the body of the user, it's not hard to say that electronic cigarettes are just as toxic as traditional cigarettes.

Electronic cigarette liquid can have a variety of



Fig 2. Risk of Bias Score with JBI Critical Appraisal Tools



chemical makeup. Common butter flavoring ingredients in e-cigarette liquids include diethyl and 2, 3-pentanedione, which can harm the respiratory epithelium's cilia activity and impair lung function.<sup>4</sup> Diacetyl in electronic cigarettes is also thought to contribute to fibrosis and destruction of the respiratory epithelium, which results in bronchiolitis obliterans.<sup>5</sup> Formaldehyde displays toxicity that can cause oxidative stress, endoplasmic reticulum stress, mitochondrial malfunction, and inflammation as a result of its interaction with proteins and DNA.<sup>5</sup> The primary components of e-cigarette liquid, propylene glycol, and glycerin, have been shown to disturb the homeostasis of lung immune cells, leading to inflammation. This is one of the many mechanisms that are still not fully understood in terms of the possibility of EVALI occurring in electronic cigarette users.<sup>5</sup>

According to other research, users who inhale the vitamin E included in e-cigarette liquid may experience cytotoxicity that results in acute lung damage.<sup>6</sup> In the meantime, smoking increases the creation of mucus, slows down cell division, and, due to a persistently reduced inflammatory response, raises the risk of respiratory viral infections.<sup>7</sup>

The tastes included in the liquid used in electronic cigarettes are another way they are distinguished. Plethysmography and flexion lung function tests were done in a study employing a mouse model, and the findings revealed that a combination of vegetable glycerin or propylene glycol with vanilla flavoring reduced lung function metrics.<sup>8</sup> The combination of these components also had an impact on immunoglobulin levels, markedly raising IgG1 levels. Additionally, lipid mediator levels were raised by vegetable glycerin or propylene glycol.<sup>8</sup> Some studies suggest that lung disease is not only caused by the liquid content, but also by coil power, coil resistance, coil heat, and even nicotine and PG/Gly levels in the liquid. Differences in levels and settings in electric tokens can change the size of smoke particles that can settle in the alveoli of the lungs.<sup>9</sup>

Several studies have tested vapes and taken samples from the airways of those affected by lung disease. The examination found the presence of Vitamin E Acetate (VEA). This VEA is a thick clear liquid used as an additive in vape products that contain tetrahydrocannabinol (THC).<sup>10</sup> VEA (or vitamin A, retinoic acid) is used as an additive to dissolve/dilute (cutting agent) THC oils alongside minerals, coconut oil, and triglyceride medium chain oils, and is also used as a thickening agent for other non-THC e-liquids. This VEA is safe in food, but harmful when inhaled as it can cause oxidative stress and inflammatory responses.<sup>11</sup> THC itself is one of the

active substances that provide psychic effects due to the content of psychoactive molecules.<sup>12</sup> This mixture of VEA and THC has been used and traded since the spring of 2019. When VEA is heated to a certain temperature, it breaks down into Ketene gas, alkene, and benzene, which are highly toxic.<sup>10,13</sup> When tested in animals, VEA caused acute lung injury when inhaled from e-cigarettes.<sup>10</sup> Vitamin E acetate is attracting increasing attention as a potential culprit in the pathophysiology of EVALI outbreaks. Vitamin E acetate was found in 94% of LAB samples collected from EVALI patients.<sup>13</sup>

In contrast to e-liquid constituents, lipid derivatives from “endogenous” sources such as epithelial lining fluid (ELF) and/or lung surfactant and its constituents, namely phospholipids, including *dipalmitoylphosphatidylcholine* (DPPC), may also be associated with the innate immune cell inflammatory response of Electronic Nicotine Delivery Systems (ENDS) users. Therefore, dysregulation of airway lipids may also contribute to ENDS in the presence of an associated inflammatory response and may also be involved in EVALI. This not only leads to EVALI but also to the development of other comorbid conditions involving cardiomyopathy.<sup>11</sup>

The epithelium is the initial barrier in the lungs, but exposure to e-cigarette aerosols not only sloughs off epithelial cells but also disrupts the integrity of the epithelial barrier. Inhalation of VEA causes pulmonary edema, neutrophilia, epithelial cell death, and lymphocyte-dominant perivascular inflammation, as well as reduced production of surfactant protein A. In addition, vaping also disrupts mucociliary clearance, which is very important for airway protection from toxic substances, making it easier for infection, colonization, and growth of pathogenic bacteria which, coupled with the presence of nicotine contained in the liquid, also reduces phagocytosis and decreases bactericidal activity. Vape also reduces the frequency of ciliary surfaces with decreased ATP production resulting from disorganized mitochondria. Exposure to e-cigarette vapor reduces airway surface fluid hydration and increases mucus viscosity.<sup>14</sup>

Several physiological mechanisms, including pulmonary surfactant, mucociliary clearance, and phagocytosis of inhaled particulates, are critical in maintaining airway homeostasis. Airway epithelial cells (AEC), including alveolar type I (AT-I) and type II (AT-II) cells, alveolar macrophages (AM), and granulocytes or polymorphonuclear cells (PMN) are the innate immune cells of the airway. This physiological function is one of the first responses after exposure to aerosol/vape ENDS. AMs are resident professional phagocytes that digest and degrade various inhaled irritants, pathogens, and apoptotic cells by

“efferocytosis” to help reduce the inflammatory response in damaged tissues. Vape exposure will cause changes in the phenotype and function of AMs that will suppress their efferocytic activity which helps reduce inflammation.<sup>15</sup>

E-cigarettes cause adverse health effects through direct contact of aerosols with tissues or cells of the oral cavity and lungs or through systemic effects on multiple organs including the heart, brain, eyes, and kidneys. Damage to organs other than the lungs is caused by injury to the lungs. This lung damage can occur because e-cigarette exposure induces the secretion of proinflammatory cytokines, including interleukins (IL-1, IL-6, IL-8) and Tumor Necrotic Factor (TNF- $\alpha$ ) from epithelial cells and immune cells in the upper airway, and lungs. Some studies have also reported the discovery of specific patterns of detectable neutrophil signaling. In the sputum of e-cigarette users, the neutrophilic granule proteins neutrophil elastase, proteinase 3, leukocidin 1, and myeloperoxidase were significantly increased, indicating neutrophil activation through e-cigarette exposure which markedly increased the expression of CD11b and CD66b which play an important role in neutrophil activation. Furthermore, exposure to e-cigarette vapor extract caused an increase in IL-8 and protease activity, including neutrophil elastase and matrix metalloproteinase. Increased proteases can damage the lung basement membrane and extracellular matrix, causing emphysema.<sup>14</sup>

Differences in electronic devices and wattage applied affect the particle size of the vapor that can settle in the pulmonary alveoli and cause changes in many cytokines within the airways and lung parenchyma. Vaping produces an increase in reactive aldehyde species leading to cellular accumulation of 4-hydroxynonenal, which induces apoptosis, mitochondrial dysfunction, and protein inactivation. E-cigarette exposure also directly induces cellular damage by promoting increased oxidative stress and DNA damage, leading to an increased risk of lung cancer.<sup>9,14</sup>

### Limitation, strength, and future research direction

The weakness of this study is that it only collects data on diseases potentially caused by e-cigarettes. This study has not been able to determine exactly whether the disease is caused by vaping directly or whether there are other factors that a health problem to arise in humans. However, the concept is clear that chemical compounds that enter the respiratory tract that are not commonly inhaled by humans have the potential to cause problems in the future. The strength of this study is to gather evidence of current health problems that can be caused by e-cigarette users. Thus, it can invalidate the justification

for using e-cigarettes because it is safer than conventional smoking.

Directions for future research are to find means to determine the severity of vape use such as the Brinkman index for conventional cigarette users. The Brinkman index uses the number of cigarette butts used per day multiplied by how many years the patient smokes. This certainly cannot be used in the case of e-cigarettes because what is used is E-liquid in milliliters (mL). Possibly it could be measured by how many mL of E-liquid are used in one month or how many bottles of E-liquid are used and multiplied by the duration of the year of e-cigarette use. However, this requires further research, especially the limits of mild, moderate, and severe degrees.

For future research, it is also necessary to pay attention if there are health problems in vape users whether the patient is a dual or single user because the use of conventional cigarettes has the potential to react to cause a disease. Other research is also needed to determine the risk of disease directly caused by vape.

### CONCLUSION

The use of e-cigarettes (Vape) has the potential to cause pulmonary and airway diseases, so it is necessary to break the justification that e-cigarettes are safe to use. With its users increasingly angry, especially among teenagers, the circulation of vape needs to be concerned because of its impact on health and interfering with the success of achieving joint health. Today, the use of conventional cigarettes (tobacco smoking and others) has become a global problem because it has health impacts not only on the users but the surroundings of those living with cigarette smoke. The use of e-cigarettes will potentially be the same if uncontrolled circulation and research on the impact on health is carried out as well as minimal education of the dangers of future use of e-cigarettes.

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