Supplement (B)
Studies description

1. ENDS toxicity (Domain 1)

First Author, Year, country	(1) Bjurlin 2020, USA
Title	Carcinogen Biomarkers in the Urine of Electronic Cigarette Users and Implications for the Development of Bladder Cancer: A Systematic Review.
Target population (youth, young adults, adults, lab/in vitro; Gender)	• An overall sample size of 1259 study participants, where individual sample study sizes ranged from 6 to 280. • The median age of those reported was 36 yr.
Objective/s (only those who are related to the domain)	• Bladder cancer biomarkers in the urine/ urine biomarkers/ carcinogen and toxicant urinary biomarkers
Number of included articles	• 22 articles.
Reported outcomes (name each outcome + results)	• The 22 included studies demonstrate differences in biomarker levels among nontobacco and EC users, as well as persistent presence of worrisome biomarkers in patients who have "switched" from combustible cigarettes to EC. • Most studies, however, did not report or differentiate between older and newer devices that have variable user-controlled heat settings. • Metabolites of carcinogens in urine may be directly related to the intensity of EC usage, including time to last use prior to obtaining the urine specimen, although few studies controlled for this variable. • Several studies found biomarkers indicative of combustible cigarette use in the e-cigarette–only groups, suggesting some study participants were undisclosed dual users or exposed to second-hand cigarette smoke. • Of the parent compounds and urinary biomarkers found in the included studies, six have a strong link to bladder cancer (pyrene, naphthalene, fluorene, phenanthrene, otoluidine, and 2-naphthylamine), six have a limited link (four tobacco-specific nitrosamines, lead, and chromium), and two have a strong link to cancer that was unspecified (1,3-butadiene and acrylamide). • Several of the bladder cancer–linked carcinogens were detected at higher urinary levels in EC users than in controls. • Compared with never-user controls, EC users had significantly higher levels of both 3-hydroxyfluorene and 1-hydroxypyrene present in their urine. • Both o-toluidine and 2-naphthylamine, which are known to produce bladder cancer in human and animal studies, were found in urine at 2.3- and 1.3-fold higher levels, respectively, than in non–EC user controls. • Very low levels of such carcinogenic compounds are usually found in human urine samples resulting from environmental or endogenous (e.g., food) exposure. • In most of the reviewed studies, the intensity of EC use among those reporting exclusive EC use was not high. • The levels of PAH 1- hydroxypyrene (1-OHP) were found to be significantly higher in EC users than in never users and were not significantly different after combustible cigarette smokers switched to EC. • Several (six) urinary compounds that are noted to be carcinogenic to humans (IARC group 1) and found in urine of EC users have no associated link to bladder cancer (benzene, 1,3-butadiene, ethylene oxide, formaldehyde, trichloroethylene, and cadmium).
Main conclusion	• There is evidence from several studies that urine from EC users contains carcinogens. • Several of the carcinogenic urinary biomarkers have a strong link to bladder cancer. • Long-term implications of chronic urothelial exposure to urinary carcinogens of EC users are unknown and will require long-term follow-up. However, the current analysis provides a useful scientific rationale to consider the carcinogenic-specific aspects of using EC. • Although the malignant potential of EC for bladder cancer remains unknown and is likely less than that of combustible cigarettes, the mere presence of these urinary biomarkers strongly associated with carcinogenesis is highly concerning.

Funding (source; related to tobacco industry – Yes/No)	• The project described was supported by the National Center for Advancing Translational Sciences (NCATS), National Institutes of Health, through Grant Award Number UL1TR002489 (MAB), and a New York State ECRIP's award. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH. • Not related to tobacco industry.

First Author, Year, country	**(2) Salam 2020, USA**
Title	Flavor-Toxicant Correlation in EC: A Meta-Analysis.
Target population (youth, young adults, adults, lab/in vitro; Gender)	• Chemical composition of EC in laboratory (no human involved).
Objective/s (only those who are related to the domain)	• To categorize the compounds found in flavored EC liquids into a few chemical classes. • To predict their possible chemical transformations upon EC liquid aerosolization.
Number of included articles	• 11 articles.
Reported outcomes (name each outcome + results)	• Analysis of the structures of these chemical compounds allowed their classification into 22 chemical classes: alcohol, aldehyde, alkene, amide, amine, aryl (or aromatics), diketone, epoxide, ester, ether, furan, hydrazone, imidazole, ketone, lactone, phenol, pyrazine, pyrazole, pyridine, pyrimidine, pyrrole, and thiazole. • Some chemical compounds are common among the tested flavored ECIG liquids, like ethyl maltol (n = 89, 47%), vanillin (n = 69, 37%), menthol (n = 54, 29%), ethyl vanillin (n = 43, 23%), linalool (n = 43, 23%), benzaldehyde (n = 41, 22%), benzyl alcohol (n = 39, 21%), maltol (n = 38, 20%), cinnamaldehyde (n = 37, 20%), ethyl butanoate (n = 35, 19%), and hydroxyacetone (n = 31, 16%).
Main conclusion	• This report highlights the importance of categorizing flavor ingredients into a few chemical classes and correlating their chemical reactivity with the toxicant formation in the aerosols. • This work can be used to construct a conceptual framework that may help in enhancing knowledge on how flavor compounds in ECIG liquids contribute to toxicant emissions in ECIG aerosols.
Funding (related to tobacco industry; Yes/No)	• National Institute on Drug Abuse of the National Institutes of Health and the Center for Tobacco Products of the US Food and Drug Administration • Not related to tobacco industry.

First Author, Year, country	**(3) Lee 2020, USA**
Title	Youth and Young Adult Use of Pod-Based Electronic Cigarettes From 2015 to 2019 A Systematic Review.
Target population (youth, young adults, adults, lab/in vitro; Gender)	• Eighteen studies (51.4%) were youth or young adult focused. • Two studies (5.7%) also included older adult populations.
Objective/s (only those who are related to the domain)	• Nicotine delivery and exposure in JULL compared with other EC. • Toxicants in JULL compared with other EC.
Number of included articles	• 35 articles (28 JUUL only, 7 on JUUL and other brands of pod-based EC.
Reported outcomes (name each outcome + results)	• JUUL ECs have a very low fraction of free nicotine in the pod liquid and aerosol compared with other types of ECs (about 5%-6% free nicotine compared with 13%-95%, respectively) but a high total nicotine content in the form of benzoate salt. • The level of nicotine exposure in 38 adolescents (as measured by urinary cotinine) using pod-based ECs was higher (245 μg/L [to convert to nanomoles per liter, multiply by 5.675]) than levels detected in adolescent regular cigarette smokers (155 μg/mL). • Adolescents using pod-based ECs were more likely than other EC users to vape daily and show greater nicotine dependence symptoms. • An analysis of aerosol emissions found that, compared with other forms of ECs and cigarettes, JUUL had lower levels of certain harmful constituents, such as benzene, volatile organic compounds, free radicals, carbonyls, formaldehyde, and total aldehydes. • One study found that JUUL e-liquids had a cytotoxic association with human lung epithelial cells examined in vitro.
Main conclusion	• While JULL may contain less harmful constituents than other types of ECs and cigarettes, there is no evidence that the levels found are safe among youth.

	• There is evidence for higher nicotine dependence associated with their use. • Further studies with longitudinal designs will be able to answer important questions about the health risks of long-term exposure to harmful constituents, albeit at lower levels than in cigarettes, among youth. • The available data do not allow conclusions as to whether pod-based ECs have the potential to produce serious lung injuries that have been reported in the US in recent months. • Early indications suggest that these injuries are associated with a history of using modifiable EC products that contain tetrahydrocannabinol or cannabidiol oils. Further research will be needed to understand whether this risk applies also to pod-based nicotine ECs.
Funding (source; related to tobacco industry – Yes/No)	• National Cancer Institute of the National Institutes of Health. • Not related to tobacco industry.

First Author, Year, country	**(4) Bozier 2020, Australia**
Title	The Evolving Landscape of EC: A Systematic Review of Recent Evidence.
Target population (youth, young adults, adults, lab/in vitro; Gender)	• Animal • In vitro • In vivo from human samples of all ages.
Objective/s (only those who are related to the domain)	• Evaluates the most recent data (early 2017 to mid-2019) regarding the potential health effects of EC in smokers and nonsmokers.
Number of included articles	• 225 articles
Reported outcomes (name each outcome + results)	• Recent research has highlighted the potential toxicity of flavor additives. Chemical compounds are generated during the vaporization process, and studies suggest adducts may form over time. One of the biggest flaws to date with studies into flavorings is the lack of clarity regarding the components of each e-liquid. • Some e-liquid contain nicotine while some do not. Nicotine has been shown to have adverse effects outside of the other ingredients in ECs. • Flavor-specific findings highlight the need for human studies to consider whether varied flavor use among EC users may unwittingly conceal outcomes.
Main conclusion	• Recent research has highlighted the potential toxicity of flavor additives. • Flavor-specific findings highlight the need for human studies to consider whether varied flavor use among EC users may unwittingly conceal outcomes.
Funding (related to tobacco industry; Yes/No)	• Funding source was not reported. • Not related to tobacco industry.

First Author, Year, country	**(5) Zhao 2020, USA**
Title	Metal/Metalloid Levels in Electronic Cigarette Liquids, Aerosols, and Human Bio samples: A Systematic Review.
Target population (youth, young adults, adults, lab/in vitro; Gender)	**Not applicable**
Objective/s (only those who are related to the domain)	• Metal/metalloid levels in EC liquid (e-liquid), aerosols, and biosamples of EC users across EC device systems • To evaluate metal/metalloid exposure levels for EC users and the potential implications on health outcomes
Number of included articles	**24**
Reported outcomes (name each outcome + results)	• Among those 24 studies, 12 reported data on metals/metalloids in e-liquids [9 from bottle, 4 from cartridges (3 from cig-a-likes and 1 from pod), 1 from an open wick, 1 from both bottles and cartridges, and 1 from the tank after heating]. • Twelve reported data on metals/metalloids in EC aerosols (8 from ciga-likes, 3 from tank devices, and 1 from both cig-a-like and tank devices), and 4 reported data on metals/metalloids in human biosamples of EC users. • Among these metals/metalloids, Cd and Pb were the most commonly determined in e-liquids, and Cu and Ni were the most commonly determined in aerosols. **Metal/Metalloid Levels in e-Liquids:** • The studies assessed between 1 and 10 e-liquid brands and between 1 and 9 flavors. The reported nicotine levels ranged from 0 to 24 mg/ml. The number of different e-liquid

	samples in individual containers of different brand, flavor, or nicotine content ranged from 1 to 56, and the total number of samples analyzed for metal concentrations including replicates ranged from 3 to 132. • Metal/metalloid levels in e-liquid samples not in contact with the heating coil (bottle) were generally lower than levels in most e-liquid samples collected from cartridges or from open wicks/tanks, which had already been in contact with the coil; however, for most metals, mean levels varied between 1 and 3 orders of magnitude across studies even within similar types of e-liquid samples **Metal/Metalloid Levels in Aerosols of ECs:** • The e-liquids assessed included between 1 and 7 flavors, with nicotine levels ranging from 0 to 45 mg/ml. • The puffing protocols to collect the aerosols were widely different, although seven studies used the same puff duration (4 s per puff). The total number of puffs ranged from 4 to 150. • The number of different devices evaluated ranged from 1 to 56, and the total number of aerosol samples ranged from 3 to 108 • Studies of aerosol samples showed generally higher metal/metalloid levels in samples from tank devices in comparison with levels in cig-a-likes. • Al, Fe, Ni, and Zn were found in studies looking at e-liquids and aerosols, whereas Cr, Cu, and Pb were more consistently found in aerosols. Cd levels were low and even undetectable in both e-liquid and aerosol samples in several studies. • With the exception of one study, where metal/metalloid levels in the aerosol were comparable with those of the e-liquid samples, studies found markedly higher levels in the aerosol than in the e-liquid samples. • One study detected Zn only in the e-liquid formulation but found Al, Cu, Fe, Mn, Ni, Pb, and Zn in aerosols. • Another study found higher Al, As, Ni, and Zn in aerosols in comparison with the liquids before aerosolization. • Another study reported markedly higher metal/metalloid levels in the aerosols, with Pb and Zn aerosol levels 25 times higher, and Cr, Ni, and Sn levels 6 times higher than levels in the bottle samples. Still higher metal/metalloid levels were found in the remaining e-liquids from the tank after vaping, with Cr, Cu, Ni, Pb, and Zn aerosol levels being more than 35 times higher than levels in the bottles • In PATH and NHANES, no statistically significant differences were found in the urinary Ba, Be, Co, Mo, Mn, Sb, Sn, and Tl levels of EC users and cigarette smokers, except urinary Sr levels, which were higher among EC users in comparison with cigarette smokers and cigar users, and urinary Cd levels, which were significantly lower in EC users. Neither PATH nor NHANES has measured Ni or Cr. • Some studies reported Cu, Se, and Zn in the serum of EC users. • In NHANES, serum Cu and Se were higher in EC users in comparison with both cigar and cigarette users in adjusted models, even though the results were not statistically significant. • In EC users from Romania, levels of Ag, Se, and V were higher among EC users in comparison with levels found among nonusers and cigarette smokers. • One study reported Cr and Ni in urine, saliva, and exhaled breath condensate (EBC) (micrograms per liter) of EC users. • In comparison with the lowest tertile, participants in the two highest tertiles of aerosol Ni showed 16% and 72% higher urinary Ni, and 202% and 321% higher saliva Ni, whereas no association was found with EBC (adjusted for sociodemographic). • For aerosol Cr, the corresponding comparison showed 98% and 193% higher saliva Cr, with no association with EBC. • In NHANES, EC users had significantly higher blood Mn levels in comparison with levels in cigar users in adjusted models. • EC use behaviors may influence metal/metalloid exposure because ECusers who changed their heating coils more frequently and consumed more e-liquid per week were associated with higher urinary Ni levels, and being a "daily" ECuser (vs. being a "some days" user) was associated with having significantly higher urinary Pb and Sr levels.
Main conclusion	• Numerous metals/metalloids--Al, Sb, As, Cd, Co, Cr, Cu, Fe, Pb, Mn, Ni, Se, Sn, and Zn--were present in EC samples in the studies reviewed. • For most metals/metalloids, levels were heterogeneous according to sample (e-liquid, aerosol), source of the sample (bottle, cartridge, open wick tank), and device type (cig-a-likes and tank). Studies of biosamples support the hypothesis that EC are a source of

	metals/metalloids because most metal/metalloid biosample levels, with the exception of Cd, were similar or even higher in EC users in comparison with conventional cigarette users, and higher in comparison with cigar users. • The direct comparison of metal/metalloid aerosol levels to human biosample levels also provides direct support for the hypothesis that aerosol metals/metalloids are inhaled and absorbed by the EC user. • In comparison with conventional cigarettes, EC aerosols may result in less exposure to Cd but not to other toxic metals/metalloids found in tobacco. • Most e-liquids sampled from cartridges or from tanks or open wicks that were in contact with the coil had higher metal/metalloid levels in comparison with levels in e-liquids sampled from the bottle. • Overall, the evidence available consistently supports that EC are a major concern for exposure to toxic metals/metalloids. • Substantial heterogeneity exists across products and, in particular, across e-liquids that are in contact with the heating coil. • There is also evidence that aerosols have higher metal/metalloid levels than the unused e-liquids have. These findings indicate that higher metal/metalloid levels in aerosol samples are, at least in part, due to the metal/metalloid components of the devices. • Although the studies included in this review found lower Cd levels in human biosamples of ECusers than those found in conventional cigarette and cigar users, most other metal/metalloid levels were similar or even higher in ECusers. • Manufacturing procedures could constitute a major contribution to potential metal impurities and could influence metal/metalloid release during vaping.
Funding (related to tobacco industry; Yes/No)	• NIEHS/FDA grants R21ES029777 and R01ES030025, NIEHS grant P30ES009089, and a Johns Hopkins University Technology Transfer Seed Award. • Not related to tobacco industry.

First Author, Year, country	**(6) Ward 2020 USA**
Title	Electronic nicotine delivery system design and aerosol toxicants: A systematic review.
Target population (youth, young adults, adults, lab/in vitro; Gender)	• Not applicable
Objective/s (only those who are related to the domain)	• Toxicants in EC aerosols
Number of included articles	• 92
Reported outcomes (name each outcome + results)	• Studies were grouped into 6 major chemical groups. • Five were included based on their designation as “harmful and potentially harmful constituents” in tobacco products by the US Food & Drug Administration (FDA): carbonyls, VOCs, trace elements, PAHs, and TSNAs. • Free radicals and reactive oxygen species (ROS) category were added **<u>Carbonyls/VOCs:</u>** • The available literature suggests a similar relationship between voltage and the amount of carbonyls in EC aerosol. • An increase in voltage has been observed to be associated with increased carbonyls in aerosol at a fixed resistance. • Suboptimal EC operating conditions result in what is commonly referred to as a “dry puff”, during which coil heating occurs in the absence of sufficient e-liquid to produce aerosol. • Suboptimal EC operation can result in higher concentrations of carbonyls in aerosol. • Available evidence seems to suggest that maintenance of optimal operation conditions (e.g., adequate wick saturation and avoiding excessive coil heating) is associated with lower levels of carbonyls. • Coil location, orientation, and resistance may also affect carbonyl production. • Top-coil horizontal atomizers have the potential to generate more carbonyls compared to bottom-coil horizontal atomizers, while vertical coils produced fewer carbonyls than horizontal coils. • Several studies, but not all, have observed that carbonyl and VOC production varies by device type. • Device type has been shown to potentially impact carbonyl and VOC output.

	• Numerous articles have reported that e-liquid constituents impact carbonyl aerosol concentrations. • Available evidence suggests that the chemical constituency of aerosol is dependent upon the matrix of the e-liquid as carbonyl compounds are present in the aerosol as both flavoring agents (i.e., diacetyl) and products of thermal degradation (i.e., aldehydes). • The concentration of toxicants in aerosol can be influenced by the bulk e-liquid solution • Various EC operating parameters increase the concentrations of hemiacetals in aerosol. • Power and voltage have been demonstrated to increase formaldehyde hemiacetals in aerosol which can be further influenced by e-liquid composition. **Trace elements:** • Important relationships have been observed between trace elements in EC aerosols and variations in power, device, air-flow, coil material, and e-liquid. • One study found that when power was increased on an open-system device from 20 W to 40 W, median arsenic (As), chromium (Cr), Cu, iron (Fe), manganese (Mn), nickel (Ni), Pb, antimony (Sb), tin (Sn), and Zn concentrations increased 14, 54, 17, 30, 41, 96, 14, 81, 631, and 7-fold, respectively. • Open-system EC with kanthal (Fe, Cr, and aluminum [Al] alloy) and stainless-steel coils had consistently higher Fe and Ni levels. • Not all published articles have detected trace elements. • One study did not detect As and cadmium (Cd) in EC aerosol across 4 commercial EC non-refillable closed-system products. • The ten most examined elements in descending order were Cu, Ni, Zn, Pb, Cd, As, Fe, Cr, Sn, and Al **ROS and free radicals:** • The concentration of free radicals in aerosol has been reported to vary by power and associated coil temperature. The concentration of free radicals in aerosol has been reported to vary by power and associated coil temperature. • No clear relationship between free radicals and device design has been observed. • The composition of e-liquid affects the concentrations of free radicals in aerosol. • Overall, ROS and free radicals in EC aerosol vary by e-liquid composition, but the precise relationship has yet to be determined. **PAHs:** • PAH concentrations in aerosol vary with device and e-liquid but are generally low if detected • Available evidence suggests that PAH concentrations are low which is consistent with the knowledge that PAHs are primarily products of combustion and EC operate at lower temperatures than combusted tobacco products. **TSNAs:** • Studies of different EC products have observed low or undetectable levels of TSNAs • Though TSNAs are carcinogenic and their concentrations eclipse many other carcinogenic compounds in conventional cigarettes, they are less prevalent in EC
Main conclusion	• Device characteristics relevant to the current review of EC are power, voltage, resistance, temperature, coil material, device, and e-liquid. • The major chemical constituents were differentiated into carbonyls, VOCs, trace elements, ROS and free radicals, PAHs, and TSNA • 1- The risk associated with inhaling EC aerosol is associated with “unintentional” contaminants (i.e., impurities), “intentional” constituents (i.e., PG, VG, and flavorings), and the conversion of unintentional and intentional constituents into new chemical species during aerosolization. • The literature suggests that numerous new chemicals are created during aerosolization that are not present in the native e-liquid • Part of the complexity of aerosol and e-liquid composition analysis arises from the addition of flavoring compounds • 2- The relationship between power, resistance, and voltage (power = voltage2/resistance) affects the potential risk associated with the use of EC. • Aerosol toxicants generally increase with increased power and voltage applied to the metal coil for heating. Power per surface area of coil may be a stronger predictor of toxicant production in aerosol than power alone.

	• 3- Atomizer design, specifically as it relates to the adequate supply of e-liquid to a heating coil, is critical to avoid the observed phenomenon of higher toxicant production from coil overheating caused by a deficiency of e-liquid for aerosolization (i.e., dry puff). • This appears to be more common among top-coil designs due to inadequate wicking and could be mitigated with improved wicking to the top coil or the use of bottom, vertically oriented coils. • 4- Atomizer heating elements are an identified source of aerosol metals, and metals used for construction of coils and other components (i.e., clamps, wicks, and soldering) should be selected to minimize metal breakdown and leaching. • Commonly identified metals were Cu, Pb, Ni, Sn, and Zn.
Funding (related to tobacco industry; Yes/No)	• HH Sheikh Hamed Bin Zayed Al Nahyan. • Not related to tobacco industry.

First Author, Year, country	**(7) Wang 2019, China**
Title	Toxicity assessment of electronic cigarettes
Target population (youth, young adults, adults, lab/in vitro; Gender)	• Adolescent/adult animals • In vitro
Objective/s (only those who are related to the domain)	• Toxicology profile of EC, summarizing evidence from in vitro and in vivo studies
Number of included articles	• 47
Reported outcomes (name each outcome + results)	• Toxicity assessments of EC: in vitro studies: • The vaporization process may play a crucial role to the toxicity owing to some toxicants being generated when heating • E-liquids: • Although 9 of 10 existing studies suggested that e-liquids caused cytotoxicity, correlations among which ingredient (nicotine, flavorings, and solvents) in e-liquids was responsible for the adverse effects were inconsistent. • Only one study concluded that e-liquids did not contribute to any toxicological effects, which was supported by a tobacco company. • The toxicity caused by e-liquids depends on many factors, including the exposed doses, exposure duration, the cell types exposed or the composition of e-liquids. • ECaerosol extract: • 7 of 10 studies reported that ECE may induce significant toxicity. • ECaerosol: • 11 of 12 studies reported that ECaerosol may induce adverse effects. • High-throughput in vitro toxicity screening studies: • Data suggested that apoptosis-dependent cellular death occurred in primary normal human bronchial epithelial (NHBE) cells following incubation with 4% of the propylene glycol and glycerol mixture with nicotine, and the occurrence of apoptosis was associated with aforementioned indictors. • Activation of NF-jB pathway could be associated with propylene glycol and glycerol mixture with or without nicotine aerosol exposure • Toxicity assessments of EC: in vivo studies: • Pulmonary effects: • In one study adult rats were exposed to EC aerosols via whole-body inhalation for 1 h/day for 4 weeks: there was no difference in epithelial distribution or inflammation between the exposure group and control group. • Another study: Mice exposed to EC aerosols via whole-body inhalation for 5 h/day for 3 days: found that EC indeed induced the increase of proinflammatory cytokines in bronchoalveolar lavage fluid (BALF) and reduced glutathione levels in the lung. • EC are considered to have deleterious effects on the respiratory system. • E-liquids can exacerbate the allergy-induced asthma symptom. • 5 of 6 studies supported that EC can cause adverse effects on pulmonary system • Extrapulmonary effects • 9 studies of EC aerosols exposure have also been shown to induce toxicity at more distant systems/other bodily systems.

	• Researchers detected the effects on adult rat livers and kidneys after intra-peritoneal injection with e-liquid daily for 4 weeks; both the liver and kidney showed oxidative stress injuries. • Inflammatory cell infiltration and cell death were identified in rat livers, and majority of the cells with reduced and dark nuclei were exclusively located in the renal collecting ducts based on histological inspection. • E-liquids appeared to alter the anti-oxidant defense and promoted changes in renal and liver function parameters. • Authors suggested that EC may be a substantial threat to the developing central nervous system if exposure occurs during prenatal, childhood, and adolescent stages. • One study found that solvents used in eliquids have a deleterious impact when inhaled • Another study found that both nicotine and the common solvent propylene glycol were the major elements causing adverse health effects • The present data is still limited and inconsistent to elucidate which components of EC cause toxicity.
Main conclusion	• • Some in vitro studies showed that nicotine is not associated with cytotoxicity, rather the flavorings or solvents are responsible for causing the detrimental effects. • Other groups either suggested that the adverse effects observed in cells are nicotine-dependent rather than solvents-dependent or suggested that both nicotine and solvents are harmful to cells • Thus, a standardized universal method for evaluation of EC toxicity is urgently required. • The majority of EC toxicity profiles support that EC induce some adverse effects based on in vitro and in vivo researches, although most of them agreed that EC are less toxic than tobacco cigarettes. However, evidence of long-term effects is lacking. • All 14 of 15 in vivo studies of EC showed a certain degree of harmful effects. Toxicology data collecting from animals were used to speculate human health effects. • Comprehensive toxicity evaluation of EC to provide evidence for human health requires further investigation. • It is inconclusive as to which components in the e-liquids or EC aerosols induce adverse effects in model organisms. • Taking all reviewed articles into consideration, the majority of studies claimed that EC can induce adverse effects on cells or animal models, although most of those mentioned that EC may be less toxic than tobacco cigarettes.
Funding (related to tobacco industry; Yes/No)	• National Natural Science Foundation of China [grant number 81502778], and by Startup Fund for Youngman Research at SJTU [SFYR at SJTU, grant number 19X100040040] and the Health and Family Planning Commission of Heilongjiang Province [grant number, 2014-426] • Not related to tobacco industry.

First Author, Year, country	**(8) Gaur 2019, India**
Title	Health Effects of Trace Metals in Electronic Cigarette Aerosols-a Systematic Review.
Target population (youth, young adults, adults, lab/in vitro; Gender)	• Not reported
Objective/s (only those who are related to the domain)	• Provide an overview of the ECs followed by an insight into the plausible adverse health effects of trace metals released in their aerosol
Number of included articles	• 12 (experimental studies)
Reported outcomes (name each outcome + results)	**Metals in EC aerosols:** The ECs are a source of hazardous trace metals, Ranging from potentially toxic heavy metals like Ni, Cd, Cr, Mn, Pb, As, B, Sn, Ba, Al, Zr, Ti, Ag, and Li to metals which may not have adverse health effects in low concentrations like Ca, K, Zn, Fe, Na, Mg, and Cu. Additionally, Si was also identified in a study. Unlike the conventional tobacco smoking, studies reporting the direct health effects of trace metals in EC aerosols are negligible. Therefore, general evidence related to the influence of some of these heavy metals (Ni, Cr, Cd, Pb, Cu, Al, Sn, and Mn), on systemic health and oral health were informed. **Sources of metal in EC:** Filament, E-liquid, Solder joints, Cartridge fluid and outer fibers, thick wire, Brass clamp, Filters, Wick and sheath, Core assembly. **Nickel:** Exposure to high levels of nickel

	• Lung, nasal, and paranasal cancers • Kidney toxicity, genotoxicity, hematoxocity, neurotoxicity, reproductive toxicity • Changes in heart rate • Oxidative stress • Nickel dermatitis **Chromium:** Short-term effects on • Respiratory system • Gastrointestinal system **Lead:** Neurological impact (child and adult) **Aluminum:** • Slow bone growth • Mental impairments
Main conclusion	• ECs are a source of hazardous trace metals. The exposure limits to these metals may be easily exceeded due to prolonged indoor vaping in poorly ventilated rooms or through passive inhalation. • As EC aerosols are a major source of toxic heavy metals, marketing the ECs as a safe alternative to CCs is debatable. It is imperative to reconsider their design characteristics and composition of e-liquids to minimize the associated health hazards.
Funding (related to tobacco industry; Yes/No)	• Not reported

First Author, Year, country	**(9) Armendáriz-Castillo, 2019, Ecuador**
Title	Genotoxic and Carcinogenic Potential of Compounds Associated with Electronic Cigarettes: A Systematic Review.
Target population (youth, young adults, adults, lab/in vitro; Gender)	• Target population characteristic not reported. • It studied chemical composition of EC and health effect in human.
Objective/s (only those who are related to the domain)	• Review chemical compounds found in EC and describe their toxic effects.
Number of included articles	• 10 articles
Reported outcomes (name each outcome + results)	• The research found 50 (24.2%) of total chemical compound are exclusive to EC. These compounds include (+)-aromadendrene, (Z)-3-Hexen-1-ol, 1-Methyl phenanthrene, 1,3-Butanediol, 1,3-Propanediol, 2-Acetylpyrrole, 2,3-Dimethylpyrazine, 2,3-Pentanedione, 2,3,5-Trimethylpyrazine, 3-Methyl-1-butanol, Acetic acid, Benzyl acetate, Benzyl alcohol, Butyl butyrate, Camphor, Cinnamaldehyde, Cinnamyl alcohol, Coumarin, Methyl cyclopentenolone, Diacetyl, Diethylene glycol, Ethyl butyrate, Ethyl maltol, Ethyl vanillin, Ethylene glycol, Glycerin, Hydroxyacetone, Isobutyl acetate, Isoamyl acetate, Isopentyl isovalerate, L-Menthyl acetate, Limonene, Maltol, Cytotoxic, Menthone, Methyl anthranilate, Methyl cinnamate, Methyl salicylate, Myosmine, n-Hexanol, Nicotyrine, o-Tolualdehyde, p-Cymene, Propylene Glycol, Safrole, Thujone (sum of α- and β-diastereomers), Trans-2-hexen-1-ol, Vanillin, β–Damascone and γ–Decalactone
Main conclusion	• There are many cytotoxic and genotoxic effects still unknown related to different compounds of ECs, especially the ones included in e-liquids, which can be potentially toxic and carcinogenic to humans
Funding (related to tobacco industry; Yes/No)	• Funding source was not reported. • Not sure if it is related to tobacco industry.

First Author, Year, country	**(10) Zulkifli 2018, Malaysia**
Title	Electronic cigarettes: a systematic review of available studies on health risk assessment.
Target population (youth, young adults, adults, lab/in vitro; Gender)	Human
Objective/s (only those who are related to the domain)	To provide a concise conclusion of health risk assessment (HRA) studies on EC and e-liquid contents.
Number of included articles	4

Reported outcomes (name each outcome + results)	• Out of four, three of the papers focused on specific chemicals namely nicotine, propylene glycol (PG), glycerol, and 1,2-propanediol, while one article evaluated the health risks posed by heavy metals contained in EC. • Hazard quotient of the six chemicals, i.e. nicotine, PG, glycerol, cadmium, ethylene glycol, nickel, aluminum and titanium, were found to have the potential to contribute to non-carcinogenic health risks. • None of the lifetime cancer risks calculated had risks exceeding the acceptable limit.
Main conclusion	• It was a Narrative synthesis. • From the further analysis of estimating the health risks of all measured chemicals, there were six types of EC constituents namely nicotine, PG, glycerol, cadmium, ethylene glycol, nickel, aluminum and titanium, which were found to have the potential to contribute to the non-carcinogenic health risks to its users. • There is a need to perform more studies on HRA of EC by using uniformed and comprehensive steps and similar reference threshold levels of exposures. • Furthermore, findings of HRA was more relevant to a particular population of interest based on the specific usage patterns of ECrather than integrating findings from other studies which did not reflect the actual pattern of EC usage. • Sufficient scientific conclusions of EC will assist to provide a reason or act as a force for many countries to regulate EC usage.
Funding (related to tobacco industry; Yes/No)	• This review paper was made possible because of the financial support from the Fundamental Research Grant Scheme (FRGS) Ministry of Education Malaysia, under the Vote 5524532 and Ministry of Higher Education Malaysia (MyBrain). • Not related to tobacco industry

First Author, Year, country	**(11) Farsalinos 2018, Greece & USA**
Title	Carbonyl emissions in e-cigarette aerosol: A systematic review and methodological considerations
Target population (youth, young adults, adults, lab/in vitro; Gender)	Not reported
Objective/s (only those who are related to the domain)	To perform a systematic review of the literature on carbonyl emissions from EC
Number of included articles	32 (Puff volume, puff duration, and inter-puff interval used in studies measuring carbonyl emissions from EC.)
Reported outcomes (name each outcome + results)	**Vape Smoke Toxicants: Carbonyl emissions from EC compared to conventional cigarettes:** • Whenever realistic use conditions were ensured, carbonyl emissions from EC were substantially lower than tobacco cigarette smoke, while newer generation (bottom-coil, cotton wick) atomizers appeared to emit minimal levels of carbonyls with questionable clinical significance in terms of health risk • Extremely high levels of carbonyl emissions were reported in some studies, and all these studies need to be replicated because of potentially important health implications
Main conclusion	• The present review identified different methodologies used in the laboratory assessment of carbonyl emissions. The large diversity of puffing patterns made the comparisons difficult while in some cases the puffing regime was unrealistic. The choice of puffing regimes was not based on ECdevice performance and functional characteristics. • The variability of reported units of carbonyl emissions is difficult to interpret. A reasonable recommendation would be to report values per amount of liquid consumption. • Analytical methods need to be accurately validated since the possibility of false positive and false negative results is of concern due to the complexity of ingredients in flavored liquids.

	• Finally, it is particularly important that laboratory studies ensure that no dry puffs are generated under laboratory conditions; otherwise testing realistic conditions relevant to true human exposure cannot be ensured and the findings could be misleading and misinformative for consumers and regulators. • A result of these research discrepancies is that the reported carbonyl emissions varied from extremely low (lower not only compared to tobacco cigarette but also compared to environmental levels) to extremely high (up to orders of magnitude higher than tobacco cigarettes. • Further research should consider all these concerns in order to improve research quality and find ways to reduce thermal degradation and carbonyl emissions from EC.
Funding (related to tobacco industry; Yes/No)	• In the past 3 years, KF has published 2 studies funded by the non-profit association AEMSA and 1 study funded by the non-profit association Tennessee Smoke-Free Association. Enthalpy Analytical is a for-profit CRO involved in analytical testing of tobacco and EC products. The other author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

First Author, Year, country	**(12) Kaur 2018, USA**
Title	Immunological and toxicological risk assessment of e-cigarettes.
Target population (youth, young adults, adults, lab/in vitro; Gender)	• Human studies • Animal studies • Vivo studies
Objective/s (only those who are related to the domain)	• Cardiovascular, gastrointestinal and neurological risks • Pulmonary atrial fibrillation and acute myocardial infarction • Immunological effects of EC use
Number of included articles	• 104 studies ➢ 56 evaluated the clinical, immunological and toxicological effects of EC vapours, aerosols and liquids, chemical content of EC vapours and aerosols, reports on adverse events and human and animal studies, along with current EC policies and recommendations. ➢ 48 evaluated the immunological, toxicological and chemical composition of conventional cigarettes that may not have been specifically evaluated but are related to ECs.
Reported outcomes (name each outcome + results)	• The adverse health effects of conventional cigarette smoking are well known; however, the immunological responses to e-liquid vaping remain elusive. Few reports have been published, but the results seem to be contradictory. • Transcriptome sequencing of human bronchial epithelial cells following exposure to EC vapours and traditional cigarette smoke demonstrated the induction of distinct gene expression profiles. The results demonstrate that compared to tobacco smoke, the use of EC vapours elicits subdued cellular toxic responses. • Furthermore, researchers observed that exposure to EC vapours results in increased virulence of methicillin-resistant Staphylococcus aureus and concluded that e-liquids can boost drug resistance in bacteria by promoting biofilm formation and causing alterations in surface charge. • While many reports certainly point towards harmful health effects of e-liquids, examining their impact on inflammatory responses is highly challenging due to the wide variety of flavours, which themselves may pose substantial threats to human health. • Currently, there is limited understanding of the full health impacts of EC usage, and only scant reports associating EC use with cardiovascular, gastrointestinal and neurological risks are available. • Compared to other associated health risks, it is more apparent that there are considerable pulmonary health risks associated with continued EC usage. • Overall, the currently available clinical data do not associate serious health risks with EC use, but it should be noted that the current studies have not assessed the long-term effects of EC use and lack the proper study design required to gather conclusive outcomes.
Main conclusion	• Although the amounts of harmful chemicals found in EC aerosols are far lower than conventional cigarettes, individual exposure depends on many factors such as device voltage, temperature, e-liquid flavour, nicotine content and smoking behaviour of the vaper.

	• The results demonstrate that compared to tobacco smoke, the use of EC vapours elicits subdued cellular toxic responses. • Excessive vaping has been reported to induce inflammatory responses including mitogen-activated protein kinase, Janus tyrosine kinase/signal transducer and activator of transcription and nuclear factor-κB signalling, similar to that induced by tobacco smoke.
Funding (related to tobacco industry; Yes/No)	• This work was supported by a Young Clinical Scientist Award from the Flight Attendant Medical Research Institute (FAMRI; 123253_YCSA_Faculty); National Institutes of Health R15 (7 R15 ES023151 02); a Southern University Foundation Grant (FY2017-017); and a Louisiana Biomedical Research Network Startup Grant (2P20GM103424-14 Subaward No. 100011) to S. Batra. Funding information for this article has been deposited with the Crossref Funder Registry. • Not related to tobacco industry.

First Author, Year, country	**(13) Zainol Abidin 2017, Malaysia**
Title	Electronic cigarettes and indoor air quality: a review of studies using human volunteers.
Target population (youth, young adults, adults, lab/in vitro; Gender)	• Human volunteers including male and female gender.
Objective/s (only those who are related to the domain)	• Examined available studies focusing on indoor air quality (IAQ) due to the use of ECs that were carried out using human volunteers that were asked to vape in natural settings (vapers used their ECs in their home) or mimics the actual vaping scenario (vapers were asked to vape in a specified room)
Number of included articles	• 4 articles
Reported outcomes (name each outcome + results)	• Indoor air quality (IAQ) parameters measured PM, PNC, VOCs, PAHs, carbonyls, metals, Nicotine, Low molecular weight carbonyls, TSNAs, Airborne nicotine • Physiological/ biomarkers measured eCO, FeNO, urinary nicotine, salivary cotinine and Urinary cotinine. • Nicotine, propylene glycols and PAHs were consistently found ECs
Main conclusion	• There is a potential exposure towards the known and still unknown contents of the EC vapors. • Thus, the claims made by the manufacturers and retailers as well as the mind-set of the users that ECs only release harmless water vapors have been shown as fallible
Funding (related to tobacco industry; Yes/No)	• Funding source was not reported. • Not sure if it is related to tobacco industry.

First Author, Year, country	**(14) Fernández 2015, Spain**
Title	Particulate Matter from Electronic Cigarettes and Conventional Cigarettes: a Systematic Review and Observational Study
Target population (youth, young adults, adults, lab/in vitro; Gender)	• Environmental human study
Objective/s (only those who are related to the domain)	• Review the literature on the composition of aerosols from ECs originated by human vaping and to describe the emission of particulate matter ≤2.5 μm in diameter (PM2.5) from conventional and ECs at home in real-use conditions.
Number of included articles	• 8 articles
Reported outcomes (name each outcome + results)	• Emissions from ECs do contain potential toxic compounds such as nicotine, carbonyls, metals, and organic volatile compounds, besides particulate matter. • The number of studies available and the types of ECs assessed is relatively small, and it is thus unknown if the chemicals and their concentrations vary markedly or not across different EC types. • In an experimental study of secondhand aerosol exhaled by three volunteers, the median of the droplet size exhaled by the EC users were 0.34μm in ECs with nicotine and 0.29μm in the ECs without nicotine indicating no difference in the particle diameter of the ECs with or without nicotine. • In the investigation of emissions of particulate matter and ultrafine particles generated by ECs under mimicking real-life conditions in a 50-m3 room furnished as an office where a volunteer used an EC with and without nicotine, total suspended particles emissions were

	systematically higher in vapor from ECs without nicotine(11.6µg/m3) than from ECs with nicotine (1.2µg/m3), but ultrafine particle concentrations were similar (641particles/cm3among ECs without nicotine and 566particles/cm3among ECs with nicotine. • The real-time plots (moving average of 60s) of PM2.5 concentrations for 1 h in the four homes shows that the PM2.5 median concentration was 572.52µg/m3in the conventional cigarettes smoker's home (interquartile range (IQR) 431.08–747.24). This concentration was significantly higher than the concentrations in the home of the EC user and the non-smoker homes. • The concentration in the home of the EC user (9.88µg/m3, IQR 8.84–11.96) was similar to those in the non-smoker's homes (9.53µg/m3, IQR8.32–10.50, and 9.36µg/m3, IQR 8.84–10.40). While the PM2.5medians in the EC user home and non-smokers smoke-free homes were similar, we noticed PM2.5peaks con-current with the EC puffs.
Main conclusion	• Results support that EC use in real conditions emit PM2.5, although these are notably lower than those from conventional cigarettes as also shown in previous studies. • These results add new information to characterize secondhand exposure to EC emissions and warrant further research using sensitive particle monitors to assess longer period of time. • Additional research is needed assessing these relevant chemicals and potential new ones across a variety of EC devices as well as measuring personal biological markers among exposed people.
Funding (related to tobacco industry; Yes/No)	• This project was co-funded by the Instituto de Salud CarlosIII, Subdirección General de Evaluación, Government of Spain and European Regional Development Fund (RTICC RD12/0036/0053, PI/081436, PI12/01114). The literature review is part of a comprehensive report prepared for (and supported by) the World Health Organization Tobacco Free Initiative (contract HQPND1409799). • Not related to tobacco industry.

First Author, Year, country	**(15) Cheng 2014, USA**
Title	Chemical evaluation of electronic cigarettes
Target population (youth, young adults, adults, lab/in vitro; Gender)	• Lab study
Objective/s (only those who are related to the domain)	• To review the available evidence evaluating the chemicals in refill solutions, cartridges, aerosols, and environmental emissions of ECs.
Number of included articles	• 29 articles
Reported outcomes (name each outcome + results)	• The levels of nicotine, tobacco-specific nitrosamines (TSNAs), aldehydes, metals, volatile organic compounds (VOCs), flavors, solvent carriers and tobacco alkaloids in EC refill solutions, cartridges, aerosols, and environmental emissions vary considerably. • Aerosols generated from 15 EC brands (16 products) show that nicotine in aerosol varied by brand from 0.5 to 15.4 mg per 300 puffs (20 series of 15 puffs, 70 mL/puff, triplicate tests of each product) and that the nicotine in aerosol varied from 21% to 85% of the nicotine present in the cartridge). • Repeated test of three individual cartridges with the same label showed results varying from 26.8 to 43.2µg nicotine per 100 mL puff (estimated to be 8.04–13.0 mg nicotine per 300 puffs). • Other chemical substance (tobacco-specific nitrosamines (TSNAs), aldehydes, metals, volatile organic compounds (VOCs), flavors, solvent carriers, and tobacco alkaloids). For example, the acrolein level in the aerosol generated from two different product models within the same brand is reported to be 4.4±2.5µg/150 puffs for one model and 16.6±2.5µg/150puffs for the other model. • The relative standard deviations (SDs) reported for all measurements range from 0% to 100% of the mean values, indicating inconsistencies in the release of these chemicals across product.
Main conclusion	• Various chemical substances and ultrafine particles known to be toxic, carcinogenic and/or to cause respiratory and heart distress have been identified in EC aerosols, cartridges, refill liquids and environmental emissions. • In addition to the uniqueness of the liquid compositions in each brand, inconsistency of both the device performance properties and the data collection methodologies used by researchers

	contribute to the observed variation in constituent levels and to the range of particle size distributions among pro-ducts. • Moreover, few of these methods are well validated. In addition, EC use behaviors have only been taken into account for aerosol generation in two publications. Therefore, additional studies based on scientifically validated aerosol generation methods, aerosol physical property measurement methods and chemical analysis methods would be helpful in generating reliable estimates of chemical quantities and, thus, the toxic potential of ECs.
Funding (related to tobacco industry; Yes/No)	• Not reported.

First Author, Year, country	**(16) Callahan-Lyon 2014, USA**
Title	Electronic cigarettes: human health effects
Target population (youth, young adults, adults, lab/in vitro; Gender)	• Both male and female population.
Objective/s (only those who are related to the domain)	• This is a review of published data on the health effects associated with exposure to ECs with a focus on individual harm.
Number of included articles	• 44
Reported outcomes (name each outcome + results)	• EC aerosols may contain propylene glycol, glycerol, flavorings, nicotine, tobacco-specific nitrosamines (TSNA) and diethylene glycol. • Particulate matter (PM) evaluations of other EC components have not found serious health effects, but findings must be interpreted with caution due to limited data and lack of standardized testing methods.
Main conclusion	• Although ECs have potential advantages over traditional cigarettes, there are many deficiencies in the available data. • Differences in product engineering, components and potential toxicities make it difficult to discuss ECs as a single device. • ECs may be useful in facilitating smoking cessation, but definitive data is lacking. • ECs may provide a less harmful source of nicotine than traditional cigarettes, but evidence of decreased harm with long-term use is not available. • It is encouraging that few serious adverse events have been reported related to EC use during the years the products have been available, but without a specific reporting mechanism, adverse event data may not be comprehensive.
Funding (related to tobacco industry; Yes/No)	• Not reported.

First Author, Year, country	**(17) Farsalinos 2014, Greece**
Title	Safety evaluation and risk assessment of electronic cigarettes as tobacco cigarette substitutes: a systematic review.
Target population (youth, young adults, adults, lab/in vitro; Gender)	• Lab study.
Objective/s (only those who are related to the domain)	• This systematic review appraises existing laboratory and clinical research on the potential risks from EC use, compared with the well-established devastating effects of smoking tobacco cigarettes.
Number of included articles	• 114

Reported outcomes (name each outcome + results)	***Liquid*** • tobacco-specific nitrosamines (TSNAs) levels in in the range of 500- to 1400-fold lower than those in conventional cigarettes and similar to those in NRTs. Other chemicals found very low levels, which are not expected to result in significant harm. ***Vapor*** • Carbonyl compounds (formaldehyde, acetaldehyde and acrolein), VOCs (toluene and trace levels of xylene), trace levels of TSNAs (NNN and NNK) and very low levels of metals (cadmium, nickel and lead) were found in almost all examined EC vapors. • Trace amounts of formaldehyde, acetaldehyde, cadmium, nickel and lead were also detected from the Nicorette inhalator. • Compared with conventional cigarette, formaldehyde, acetaldehyde and acrolein were 9–450 times lower; toluene levels 120 times lower; and NNN and NNK levels 380 and 40 times lower respectively.
Main conclusion	• Existing evidence indicates that EC use is by far a less harmful alternative to smoking. • There is no tobacco and no combustion involved in EC use; therefore, regular vapers may avoid several harmful toxic chemicals that are typically present in the smoke of tobacco cigarettes. • Indeed, some toxic chemicals are released in the EC vapor as well, but their levels are substantially lower compared with tobacco smoke, and in some cases (such as nitrosamines) are comparable with the amounts found in pharmaceutical nicotine product.
Funding (related to tobacco industry; Yes/No)	• This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors. • Not related to tobacco industry.

First Author, Year, country	**(18) Burstyn 2014, USA**
Title	Peering through the mist: systematic review of what the chemistry of contaminants in electronic cigarettes tells us about health risks.
Target population (youth, young adults, adults, lab/in vitro; Gender)	• Not applicable
Objective/s (only those who are related to the domain)	• Chemistry of liquids and aerosols of EC, with particular emphasis on the contaminants • Estimate potential exposures from aerosols produced by EC and compare those potential exposures to occupational exposure standards • Estimate potential exposures from aerosols produced by EC and compare those potential exposures to occupational exposure standards
Number of included articles	• 59 studies
Reported outcomes (name each outcome + results)	• In excess of 9,000 determinations of single chemicals (and rarely, mixtures) were reported in reviewed articles and reports, typically with multiple compounds per EC cigarette tested **Propylene glycol and glycerin:** • Assuming extreme consumption of the liquid per day via vaping (5, to 25 ml/day and 50-95% propylene glycol in the liquid), levels of propylene glycol in inhaled air can reach 1–6 mg/m3. • It has been suggested that propylene glycol is very rapidly absorbed during inhalation • When consuming low-nicotine or nicotine-free liquids, the chance to consume larger volumes of liquid increases, leading to the upper end of propylene glycol and glycerin exposure. • Estimated levels of exposure to propylene glycol and glycerin are close enough to Threshold Limit Values (TLV) to warrant concern. **Nicotine:** • Nicotine is present in most EC liquids and has TLV of 0.5 mg/m3 for average exposure intensity over 8 hours. If approximately 4 m3 of air is inhaled in 8 hours, the consumption of 2 mg nicotine from ECs in 8 hours would place the vaper at the occupational exposure limit. • For a liquid that contains 18 mg nicotine/ml, TLV would be reached upon vaping ~0.1-0.2 ml of liquid in a day, and so is achieved for most anyone vaping nicotine-containing ECs. **Polycyclic aromatic hydrocarbons:** • Polycyclic aromatic hydrocarbons (PAH) were quantified in aerosols and liquids

	• For PAH, only non-carcinogenic pyrene that is abundant in the general environment was detected at 36 ng/cartridge in 5 samples of liquid; PAHs were not detected in most of the analyses of aerosols, except for chrysene in the analysis of the aerosol of one EC. **Tobacco-specific nitrosamines:** • As expected, because the TSNAs are contaminants of nicotine from tobacco leaf, there is also evidence of association between nicotine content of the liquid and TSNA concentrations, with reported concentrations <5 ng/cartridge tested. • Smaller studies of TSNA content in liquids are variable, with some not reporting any detectable levels and others clearly identifying these compounds in the liquids when controlling for background contamination. • Analyses of aerosols indicate that TSNAs are present in amounts that can results in doses of < ng/day to µg/day (assuming 150 puffs/day). • The most comprehensive survey of TSNA content of 105 samples of liquids from 11 manufactures indicates that >90% of tested liquids contained TSNAs in µg/L quantities **Volatile organic compounds:** • Total volatile organic compounds (VOC) were determined in aerosol to be non-detectable except in one sample that appeared to barely exceed the background concentration of 1 mg/m3 by 0.73 mg/m3. • For most VOC and aldehydes, one can predict the concentration in air inhaled by a vaper to be < <1% of TLV. The only exceptions to this generalization are: • Acrolein: ~1% of TLV (average of 12 measurements) • and measurements at a mean of 2% of TLV (average of 150 measurements) and • Formaldehyde: between 0 and 3% of TLV based on18 tests (average of 12 measurements at 2% of TLV, the most reliable test) and an average of results at 4% of TLV • In summary, these results do not indicate that VOC generated by vaping are of concern by standards used in occupational hygiene. • Even the quantities detected in the single FDA result were of little concern, amounting to less than 1% of TLV. **Inorganic compounds:** • One study that attempted to quantify metals in the liquid found none above 0.1- 0.2 ppm levels or above unspecified threshold. • Most metals that were detected were present at <1% of TLV even if we assume that the analytical results imply the presence of the most hazardous molecules containing these elements that can occur in aqueous solution • It can be inferred that there is no evidence of contamination of the aerosol with metals that warrants a health concern. **Consideration of exposure to a mixture of contaminants:** • The examined reports detected no more than 5–10 compounds in the aerosol, and the calculation does not place any of them out of compliance with TLV for mixture.
Main conclusion	• The exposures from using ECs fall well below the threshold for concern for compounds with known toxicity. • Expressed concerns about nicotine only apply to vapers who do not wish to consume it • There is no serious concern about the contaminants such as volatile organic compounds (formaldehyde, acrolein, etc.) in the liquid or produced by heating • The frequently stated concern about contamination of the liquid by a nontrivial quantity of ethylene glycol or diethylene glycol remains based on a single sample of an early-technology product and has not been replicated. • Tobacco-specific nitrosamines (TSNA) are present in trace quantities and pose no more (likely much less) threat to health than TSNAs from modern smokeless tobacco products, which cause no measurable risk for cancer. • Contamination by metals is shown to be at similarly trivial levels that pose no health risk, and the alarmist claims about such contamination are based on unrealistic assumptions about the molecular form of these elements. • The existing literature tends to overestimate the exposures and exaggerate their implications. • The most important is confusion of the concentration in aerosol, which on its own tells us little about risk to heath, with the relevant and much smaller total exposure to compounds in the aerosol averaged across all air inhaled in the course of a day. • There is also clear bias in previous reports in favor of isolated instances of highest level of chemical detected across multiple studies, such that average exposure that can be calculated are higher than true value because they are “missing” all true zeros.

	• The only unintentional exposures (i.e., not the nicotine) that seem to rise to the level that they are worth further research are the carrier chemicals themselves, propylene glycol and glycerin. This exposure is not known to cause health problems, but the magnitude of the exposure is novel and thus is at the levels for concern based on the lack of reassuring data.
Funding (related to tobacco industry; Yes/No)	• The Consumer Advocates for Smokefree Alternatives Association (CASAA) Research Fund • Not related to tobacco industry.

First Author, Year, country	**(19) Pisinger, 2014, Denmark**
Title	A systematic review of health effects of electronic cigarettes.
Target population (youth, young adults, adults, lab/in vitro; Gender)	• Human and animal lab studies
Objective/s (only those who are related to the domain)	• To give a systematic and critical review of the existing literature on the health consequences of vaping of ECs and discuss the implications of our findings for public health.
Number of included articles	• 76 articles • 34 studies investigating content/effect of e-fluid or -vapor • 20 studies reporting adverse events • 21 human experimental studies • one animal experimental study
Reported outcomes (name each outcome + results)	• Most studies used CCs as reference and investigated concentrations of several substances known to be toxic/carcinogenic in CCs. Many studies found that the product labels did not show the concentrations of solvents and flavorings. • High amounts of propylene glycol (also called 1,2-propandiol) and glycerin were found in studies testing for these substances. • Several studies found a large variability in nicotine concentrations across brands, labels and cartridges, others found smaller variability. • Some studies found that ECs and CCs produce aerosols with comparable particle sizes with fine and ultrafine particles in vapor, but one study found particles from ECs much smaller and another much bigger than in tobacco smoke. • One study found that several samples were highly cytotoxic to human embryonic and mouse neural stem cells, and cytotoxicity was due to flavors. • A study found that concentrations of lead and chromium in vapor were within the range of CCs, while nickel was up to 100 times higher than in CCs. • Some studies found high maximum concentrations of total TSNAs in the vapor of most, or almost all fluids. • In one study the potential human carcinogens formaldehyde, acetaldehyde and acrolein were detected in the vapors of almost all ECs. • Studies found either no PAHs in fluid, or that most PAHs were below detection level or as traces, only. • The researchers found that cells exposed to high-nicotine vapor showed a similar pattern of gene expression to those exposed to tobacco smoke.
Main conclusion	• Due to the many methodological problems, the relatively few and often small studies, the inconsistencies and contradictions in results and the lack of long-term results, no firm conclusions can be drawn on the safety of ECs. • Based on 76 studies, ECs cannot be regarded as safe, even though they probably are less harmful than CCs. • The “harm reduction” strategy might be a gain for smokers reluctant to quit but ex- and never-smokers probably have an increased risk by using ECs.
Funding (source; related to tobacco industry – Yes/No)	• This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors. CP is partly funded by a Danish fund, Health Foundation (Helsefonden) (2012B233) that had no influence on choice of research topic, study conduct, analyses or interpretation of results. • The authors have no conflict of interest • In 26 studies (34%) the authors had a conflict of interest. Most studies were funded or otherwise supported/influenced by manufacturers of ECs, but several authors had also been consultants for manufacturers of medicinal smoking cessation therapy.

First Author, Year, country	(20) Schroeder, 2014, USA
Title	Electronic cigarettes and nicotine clinical pharmacology.
Target population (youth, young adults, adults, lab/in vitro; Gender)	• 91 inexperienced EC users. • 52 experienced EC users. • Including male and female adults aged 18 years and older.
Objective/s (only those who are related to the domain)	• Nicotine clinical pharmacology in EC use compared to cigarette smokers.
Number of included articles	• 16 articles were deemed relevant for this review. • 9 articles are eligible. • 5 studies measured nicotine or cotinine exposure in participants with no EC experience. • 4 clinical studies have been conducted in current experienced EC users.
Reported outcomes (name each outcome + results)	*5 studies measured nicotine or cotinine exposure in participants with no EC experience* • Bullen et al showed for e-cigarette: 5 min; inhaler: 10 min; cigarette: 5 min, plasma nicotine (venous): Cmax 1.3 ng/ mL, Tmax 19.6 min and Nicorette inhaler (10 mg nicotine): Cmax 2.1 ng/mL, Tmax 32 min; own brand cigarette: Cmax 13.4 ng/mL; Tmax 14.3 min. • Eissenberg showed for 2 bouts of 10 puffs, 30 s interpuff interval, 1 hr between bouts, plasma nicotine: after 5 min, 2.5 ng/mL (NJOY), 3.5 ng/mL (Crown 7); plasma nicotine: after 5 min, 2.5 ng/mL (NJOY), 3.5 ng/mL (Crown 7) and no increases in HR. • Vansickel et al (2010) showed for 2 bouts of 10 puffs, 30 s interpuff interval, 1 h between bouts, no significant changes to plasma nicotine; own brand cigarette: within 5 min, 2.1–18.8 ng/mL and no increases in HR. • Vansickel et al (2012) showed for 6 bouts of 10 puffs, 20 s interpuff interval, 30 min between bouts, plasma nicotine: 5 min after final bout, 2.2– 7.4 ng/mL and 5 min after first bout, HR increased from 67.5 to 75 bpm. • Flouris et al showed for equivalent puffs to approximate nicotine delivery with two own brand cigarettes, based on 1.5 cigarette/EC nicotine absorption ratio, serum cotinine: significant increases immediately following and 1 h after use and serum cotinine: significant increases immediately following and 1 h after use. *4 clinical studies have been conducted in current experienced EC users* • Etter and Bullen found for ad libitum, in the 30 EC users who reported no tobacco or NRT use in the previous 48 h, median salivary cotinine levels were 322 ng/mL. • Vansickel and Eissenberg found study participants used their preferred EC for a 10-puff bout (to approximate a single cigarette) and a 1 h ad libitum period. Five minutes after the bout, plasma nicotine concentrations were significantly increased; after 1 h of ad libitum use (4–76 puffs), peak plasma levels measured 16.3 ng/mL, suggesting that EC are capable of reliable and significant nicotine delivery. • Dawkins et al found that for 10 puffs within 5 mins, plasma nicotine: after 10 min, 0.74–6.77 ng/mL; for 1 h ad libitum, plasma nicotine: 13.91 ng/mL (range: 4.35 to 25.6 ng/mL). • Caponnetto et al found that for 7.2 mg for 12 weeks, salivary cotinine: 6 weeks, 42.5 ng/mL; 12 weeks, 91 ng/mL; for 7.2 mg for 6 weeks, 5.4 mg for another 6 weeks, salivary cotinine: 6 weeks, 67.8 ng/mL; 12 weeks, 69.8 ng/mL.
Main conclusion	• Knowledge about EC nicotine pharmacology remains limited. • Because a user's EC experience may significantly impact nicotine delivery, future nicotine pharmacokinetic and pharmacodynamic studies should be conducted in experienced users to accurately assess the products' impact on public health. • These studies highlight several important research areas, including: (1) measuring effective pH and other characteristics of EC aerosol that influence nicotine absorption, (2) development of a standardized EC smoking regimen based on experienced EC use behaviours and standard reporting units, (3) clinical nicotine pharmacokinetic and pharmacodynamic studies conducted in current and experienced EC users and (4) evaluating differences in EC effects between populations (e.g., gender, former and current cigarette smokers, and daily vs non-daily EC users).
Funding (source; related to tobacco industry – Yes/No)	• No funding resources were declared. • None competing interests were reported. • Not related to tobacco industry.

2. ENDS Health Effects (Domain 2)

1. Respiratory disease

First Author, Year, Country	(1) Bravo-Gutiérrez 2021, Mexico
Title	Lung Damage Caused by Heated Tobacco Products and Electronic Nicotine Delivery Systems: A Systematic Review
Target population (youth, young adults, adults, lab/in vitro; Gender)	• Animal, in vitro • Human, in vitro
Objective/s (only those who are related to the domain)	• Describe the adverse effects of EC and heated tobacco products (HTP) on the respiratory system in consumers.
Number of included articles	• 79 articles
Reported outcomes (name each outcome + results)	• Damage produced by using EC is involved in pathways related to pulmonary diseases, involving mechanisms previously reported in conventional cigarettes as well as new mechanisms particular to this device, which challenges that the tobacco industry's claims. ***In Vitro Models***: • Cytotoxicity: EC flavors and substances in the e-liquid cause cytotoxicity Inflammation: Exposure to EC causes increased levels of pro-inflammatory biomarkers. Airway infections: Inhalation of contaminants increases airway bacterial infection risk; in vitro, exposure to EC vapor extract increases platelet-activating factor receptor (PAFR) expression and increases pneumococcal adhesion and infection cells. ***Animal models:*** • Alterations in pro-inflammatory and inflammatory mechanisms, DNA damage, and impaired repair mechanisms by EC exposure. ***Human studies:*** • Damage in Human Lungs: Proteomic analysis of induced sputum of EC consumers showed significant increases of MMP-9, myeloperoxidase, and protein-arginine deaminase 4 as well as an elevated concentration of MUC5AC; these results indicate an altered innate defense and lung structure • Pulmonary Pathology: Patients with EC or vaping-associated lung injury (EVALI) presented leukocytosis, elevated erythrocyte sedimentation rate, and high C-reactive protein levels in peripheral blood. The BALF showed a predominance of macrophages and neutrophils; chest radiography revealed multifocal, multi-lobar opacities, variable in extent and distribution, consistent with foci of alveolar consolidation
Main conclusion	• EC and HTPs use is involved in damage related to the development of pulmonary diseases. The evidence available so far is significant enough for physicians, researchers, and public health policymakers to address these devices as an emerging public health problem that needs regulation.
Funding (related to tobacco industry; Yes/No)	• Instituto Nacional de Enfermedades Respiratorias Ismael Cosío Villegas (INER). • Not related to tobacco industry.

First Author, Year, country	(2) Wills 2021, USA
Title	• Electronic cigarette use and respiratory disorders: an integrative review of converging evidence from epidemiological and laboratory studies.
Target population (youth, young adults, adults, lab/in vitro, gender)	• Adolescents – Mostly 15-18 years • Adults – 18-80 years
Objective/s (only those who are related to the domain)	• Provide a comprehensive review and meta-analysis of evidence from epidemiological studies about the association of EC use with asthma and COPD in human populations and to discuss this evidence in relation to findings from controlled laboratory studies of biological processes affected by EC use
Number of included articles	• Asthma/Bronchitis: 15 articles • COPD: 9 articles

Reported outcomes (name each outcome + results)	**Epidemiological studies** • A significant association of EC use with respiratory disorder (Asthma/Bronchitis, and COPD) was found across 23 of the 24 studies reviewed, and EC use typically added independently to risk derived from cigarette smoking. **Laboratory studies** • Laboratory studies have shown ECs to have effects on four biological processes (cytotoxic effects, oxidative stress and inflammation, linkage to immune function and susceptibility to infection, and genetic effects) that are relevant for respiratory disease. • Asthma (n =15 studies). The pooled aOR was 1.39 (95% CI 1.28–1.51) • COPD (n = 9 studies). The pooled aOR was 1.49 (95% CI 1.36–1.65).
Main conclusion	• Hill's criteria have been adequately satisfied and the evidence supports the conclusion of a real relationship between ECs and respiratory disorders.
Funding (related to tobacco industry; Yes/No)	• National Cancer Institute. • Not related to tobacco industry.

First Author, Year, country	**(3) Xian 2021, China**
Title	Electronic cigarette users are associated with asthma disease: a meta-analysis.
Target population (youth, young adults, adults, lab/in vitro; Gender)	• Human • Male and female • Adolescents and adults
Objective/s (only those who are related to the domain)	• Explore the relationship between ECs and asthma.
Number of included articles	• 11 articles
Reported outcomes (name each outcome + results)	• Current or former use of ECs are associated with the prevalence of asthma. • This meta found the association of EC use with asthma, and the combined OR value was 1.27 (95% CI = 1.17–1.37). • A significant association of current EC usage with asthma (OR = 1.30, 95% CI = 1.17–1.45), and the former use of ECs also had an association with asthma (OR = 1.22, 95% CI = 1.08–1.39). • When ECs were used in combination with traditional cigarettes, the association odds with asthma was 1.47 (95% CI = 1.13–1.91), which was higher than that of users who used traditional cigarettes (OR = 1.33, 95% CI = 1.19–1.49). • In subgroup analysis, adult and female EC users were more closely associated with asthma. Age group • Teenager OR = 1.24 (CI = 1.08–1.42) • Adult OR = 1.46 (CI = 1.21–1.76) Gender • Male OR = 1.09 (CI = 0.97–1.22) • Female OR = 1.38 (CI = 1.15–1.65) • Both OR = 1.39 (CI = 1.24–1.55)
Main conclusion	• The study found that current or previous EC use are associated with an increased prevalence of asthma. Traditional cigarettes combined with EC users may further increase the risk of asthma.
Funding (related to tobacco industry; Yes/No)	• Funding source was not reported. • Not sure if it is related to tobacco industry.

First Author, Year, country	**(4) Gonsalves 2021, Canada**
Title	Diagnosis and Acute Management of Electronic Cigarette or Vaping Product Use–Associated Lung Injury in the Pediatric Population: A Systematic Review.
Target population (youth, young adults, adults, lab/in vitro; Gender)	• 13-18 years; Both male and female.
Objective/s (only those who are related to the domain)	• To assess EC or vaping-associated lung injury (EVALI) in the pediatric population.
Number of included articles	• 23

Reported outcomes (name each outcome + results)	• 10 patterns of lung injury were identified: acute lung injury/diffuse alveolar damage pattern, pneumonitis (hypersensitivity and acute), cryptogenic organizing pneumonia, eosinophilic pneumonia (acute and chronic), spontaneous pneumothorax, spontaneous pneumomediastinum, status asthmaticus, acute exogenous lipoid pneumonia, acute fibrinous organizing pneumonia, and bronchiolitis obliterans. ***Among the 61 patients:*** • Acute lung injury/diffuse alveolar damage pattern were reported for 15 patients. • Thirteen patients were reported to have confirmed cases of EVALI as defined by CDC (CDC-EVALI). • Of the remaining 33 patients, the most commonly described patterns of lung injury included 7 cases of cryptogenic organizing pneumonia, 7 cases of hypersensitivity pneumonitis and 4 cases of acute eosinophilic pneumonia. • Other more frequent presentations included spontaneous pneumothorax (n = 3), spontaneous pneumomediastinum (n = 2) and status asthmaticus (n =2).
Main conclusion	• Cases of EVALI in the pediatric population have been reported in patients as young as 13 years and often present with respiratory, constitutional, abdominal, and cardiovascular signs and symptoms. Diagnostic findings vary based on the underlying lung injury pattern. However, typical patterns of common findings were identified, including the presence of ground-glass opacities on computed tomography scan and leukocytosis.
Funding (related to tobacco industry; Yes/No)	• Not reported.

First Author, Year, country	**(5) Xantus 2021, UK**
Title	The role of vitamin E acetate (VEA) and its derivatives in the vaping associated lung injury: systematic review of evidence.
Target population (youth, young adults, adults, lab/in vitro; Gender)	• Randomized control trials • Human articles • Aged over 18 years old • Intervention vs. placebo-controlled group
Objective/s (only those who are related to the domain)	• Is the administration of VEA or any of its derivatives via any route associated with any harm (defined by increased mortality and/or length of hospital stay – LOS) in adults with any respiratory conditions? • To investigate the effect of Vitamin E acetate and/or its derivatives administered via any route (oral/parenteral/aerosolised)
Number of included articles	• 7 articles
Reported outcomes (name each outcome + results)	• Case reports of harmful exposure of VE and VEA • There was one case report of a fatal fat embolism following a gluteal injection of excessive amount of VE by an untrained professional and a case series of 3 patients with contact dermatitis linked to aerosolized tocopherol. • No lung illness has been reported in connection with aerosoled VE or VEA exposure in either the food/cosmetic industry or through the literature search. <u>Summary of the qualifying articles</u> • (2004, UK) Dietary supplementation with vitamin E adds no benefit to current standard treatment in adults with mild to moderate asthma. • (2008, India) An 8 wk supplementation of standard treatment with vitamin E, 400 IU twice a day, provided no additional clinical benefit although it might be augmented by certain endogenous antioxidants. • (2009, Iran) From the results of this study, it seems that the use of vitamin E antioxidant along with other supportive measures is beneficial in decreasing APACHE II score in ARDS patients. • (2011, Iran) From the results of this study, it seems that supplementation of vitamin E as a potent antioxidant, along with other supportive measures, can be beneficial in decreasing SOD total activity, ROM production and risk of organ failure in critically ill patients. • (2011, Brazil) These findings suggest that antioxidant supplementation might help to decrease the lung injury response of runners when exercising in adverse conditions but has little effect on performance.

	• (2016 USA) a-Tocopherol may aid the recovery of pulmonary function in subjects with EIA. • (2017, USA) Significant differences in mucociliary clearance and neutrophil influx. No meaningful change in FEV1.
Main conclusion	• Present review found no evidence of either harm associated with the administration of any Vitamin E isomers (including Vitamin E acetate) via any route, or significant clinical improvement in human asthma/COPD and/or ARDS/ALI. • Minor ventilatory parameters might be improved however, the methodological flaws and the heterogeneity may compromise the validity of the data. • Further studies are needed to explore the role of VE in respiratory medicine.
Funding (source; related to tobacco industry – Yes/No)	• This paper had no financial support to be prepared, designed, provided and reviewed. The authors declare no conflict of interest in this study. • Not related to tobacco industry.

First Author, Year, country	**(6) Prasetyo 2020, Indonesia**
Title	Nasal Mucociliary Clearance in Smokers: A Systematic Review
Target population (youth, young adults, adults, lab/in vitro; Gender)	• 6-65 years; Both male and female.
Objective/s (only those who are related to the domain)	• To look systematically into the current literature and carefully collect and analyze results to explore nasal mucociliary clearance (NMC) in smokers.
Number of included articles	• 16 articles
Reported outcomes (name each outcome + results)	• Nasal mucociliary clearance in electronic EC was explained in only one study. • Nasal mucociliary clearance in EC smokers was impaired by oxidative stress induced by nicotine exposure via transient receptor potential ankyrin 1 (TRPA 1) receptors. • Other studies also reported that formaldehyde in ECIG-generated aerosols related to DNA strand breaks and cell death and propylene glycol thicken the respiratory epithelium by increasing the number of goblet cells and increasing the content of mucin within the goblet cell.
Main conclusion	• Findings suggest that there is an impairment of NMC in EC smokers. • The impairment of NMC in chronic exposure to smoking is caused by the ciliotoxic effect, hypersecretion and viscoelastic change of mucous, airway surface liquid depletion, increased oxidative stress, and deteriorations in the inflammatory and immune systems.
Funding (related to tobacco industry; Yes/No)	• Not reported

First Author, Year, country	**(7) Jonas 2020, USA**
Title	Vaping-Related Acute Parenchymal Lung Injury: A Systematic Review.
Target population (youth, young adults, adults, lab/in vitro; Gender)	• Human • Gender: Male and female • Age range: 19-37.5
Objective/s (only those who are related to the domain)	• Detailed the clinical, radiographic, and pathologic patterns of lung injury that are attributable to vaping and provide an overview of the scientific literature to date on the effects of vaping on respiratory health.
Number of included articles	• 169 articles
Reported outcomes (name each outcome + results)	• 216 patient cases spanning 41articles of parenchymal lung injury attributable to vaping, including 96 cases from the ongoing outbreak of EVALI. • Patients generally present with approximately one week of nonspecific signs and symptoms of cough, dyspnea, respiratory distress, and hypoxia after a few weeks to months of vaping. • Imaging demonstrates a combination of ground glass opacities, consolidations, and nodular opacities in various distribution patterns; no specific radiologic finding is pathognomonic. • Lung biopsy almost always shows a nonspecific acute lung injury pattern, which can be centered around the airways.

	• Lipid-laden macrophages on BAL are favored to reflect a marker of exposure to vape aerosols, and these patients do not meet the diagnostic criteria for lipoid pneumonia on radiologic or histopathologic evaluation.
Main conclusion	• Review of the scientific literature revealed 216 patient cases that spanned 41 reports of parenchymal lung injury attributed to vaping.
Funding (related to tobacco industry; Yes/No)	• Funding source was not reported. • Not sure if it is related to tobacco industry.

First Author, Year, country	**(8) Goniewicz, 2020, USA and Sweden**
Title	How effective are electronic cigarettes for reducing respiratory and cardiovascular risk in smokers? A systematic review.
Target population (youth, young adults, adults, lab/in vitro; Gender)	• Human (18+ years age) • Both male and female • 19,475 to 161,529 sample • Self-reported health outcomes
Objective/s (only those who are related to the domain)	• To review estimated odds of respiratory and cardiovascular outcomes among former smokers who use ECs compared to current smokers.
Number of included articles	• 6 studies (5 in USA, 1 in Sweden; 5 cross-sectional, 1 longitudinal studies)
Reported outcomes (name each outcome + results)	• Respiratory risk: compared with current exclusive cigarette smokers and never vapers • Former smokers who transitioned to ECs showed~40% lower odds of respiratory outcomes compared to current exclusive smokers. • ORs of respiratory outcomes (including chronic obstructive pulmonary disease, chronic bronchitis, emphysema, asthma, and wheezing) in former smokers who transitioned to ECs versus current exclusive smokers were below 1.0, ranging from 0.58 (95%CI 0.36–0.94) to 0.66 (95%CI 0.50–0.87; all $p<0.05$).
Main conclusion	• The estimates of relative risk of vaping compared to smoking are primarily based on a limited number of epidemiological studies with several important limitations • Both randomized controlled trials and prospective cohort studies are needed to better evaluate contributions of ECs as harm reduction tools for smokers.
Funding (related to tobacco industry; Yes/No)	• This work was supported by the US Food and Drug Administration and National Cancer Institute under grant award U54CA238110. The content is solely the responsibility of the authors and does not necessarily represent the offcial views of the National Institutes of Health or the US Food and Drug Association. • Not related to tobacco industry

First Author, Year, country	**(9) Cedano 2020, USA**
Title	Confirmed electronic cigarette or vaping product use associated lung injury (EVALI) with lung biopsy; A case report and literature review.
Target population (youth, young adults, adults, lab/in vitro; Gender)	• Age 21-52 • Both male and female.
Objective/s (only those who are related to the domain)	• To coalesce the updated literature regarding cases of confirmed EVALI (EC or Vaping Product Use Associated Lung Injury) with lung biopsy for better understanding of the physiopathology of this condition.
Number of included articles	• 7 articles
Reported outcomes (name each outcome + results)	• A total of 27 confirmed cases of EVALI with lung biopsy were reported. • Regarding chest CT findings, 89% (n=24) of cases had diffuse bilateral ground glass opacities (DB GGO); rest of the patients reported bilateral reticulonodular opacities in 3.7% (n=1), bilateral nodules in 3.7% (n=1) and one had a CXR showing bilateral infiltrates without chest CT scan results. • Pathology results of the cases showed that 48% (n=13) had organizing pneumonia (OP), 26% (n=7) diffuse alveolar damage (DAD), 15% (n=4) a combination of Acute Fibrinous Pneumonitis (AFP) with OP, and the rest of them showed AFP in 3.7% (n=1), lipoid pneumonia (LP) in 3.7% (n=1) and in 3.7% (n=1) it was not clear between OP or early DAD.

	• Finally, 63% (n=17) of patients had complete resolution of symptoms and imaging findings. • There was no outcome reported in 22% (n=6) of the cases and 15% (n=4) of patients died. DAD was present in all patients who died.
Main conclusion	• Advances in the understanding of the clinical findings and histopathology of EVALI have been made and continue to evolve. • Currently, the chest imaging patterns are clear and current studies agree that DB GGO is the classic finding in this pathology. • Additionally, we must continue with the idea that EVALI is likely a result of direct lung damage by inhaled agents causing acute lung injury as highlighted by the most common pattern in the histopathology of this review.
Funding (related to tobacco industry; Yes/No)	• Not reported.

First Author, Year, country	**(10) Tzortzi 2020, Greece**
Title	A Systematic Literature Review of Electronic Cigarette Related Illness and Injury: Not Just for the Respirologist.
Target population (youth, young adults, adults, lab/in vitro; Gender)	• Human • Male and female • Age range: 23 (19-33)
Objective/s (only those who are related to the domain)	• To collect all related clinical cases for study and analysis and provide a critical synopsis of the proposed injury mechanism.
Number of included articles	• 159 • Individual case reports: 131 • Aggregate cases: 26 • Individual case reports and aggregate: 2 • Majority of publications (63%) pertained to cases in the US while the remaining 37% were from the UK, Australia, Canada, China, Denmark, France, Germany, Ireland, Italy, Japan, Korea, Malaysia, the Netherlands, Poland, Portugal, Scotland, South Korea, Switzerland, and Turkey
Reported outcomes (name each outcome + results)	***Illness and injury*** • 238 individual cases were identified: • 53% traumatic injuries due to EC explosion or self-combustion, • 24% respiratory cases, and • 12%poisonings. • Additional cases pertained to oral, cardiovascular, immunologic, hematologic, allergic reactions, infant complications, and altered medication levels. • Case reports were mainly published between 2016–2019 (78%). • The oldest case, a lipoid pneumonia, was published in 2012. • The current review showed that EC-related health effects extend beyond the acute lung injury syndrome, including traumatic, thermal injuries and acute intoxications.
Main conclusion	• It was a narrative synthesis • Showed the full range of the EC-related injury beyond the plausible respiratory disorder • To protect and promote public health, regulators and public health authorities such as the European Commission, CDC, FDA, and WHO should address the regulatory gap regarding EC and novel tobacco products, aiming to protectively cover the global population.
Funding (related to tobacco industry; Yes/No)	• This research received no external funding • Not related to tobacco industry

First Author, Year, country	**(11) Chaaban 2020, USA**
Title	Acute eosinophilic pneumonia associated with non-cigarette smoking products: a systematic review.
Target population (youth, young adults, adults, lab/in vitro; Gender)	• Age 15-60 years old • Both male and female.

Objective/s (only those who are related to the domain)	• To review the reported cases of Acute eosinophilic pneumonia (AEP) in association with non-cigarette smoking such as EC, marijuana, and waterpipe smoking.
Number of included articles	• 12 articles
Reported outcomes (name each outcome + results)	• Patients presented with dyspnea (91.6%), cough (66.6%), fever (66.6%) and chest pain (25%). • Lung auscultation findings were reported in 9 out of 12 patients and findings included crackles (55.5%) and wheezing (22.2%. • Only 2 patients (16.6) had peripheral eosinophilia on presentation. • Three additional patients (25%) developed peripheral eosinophilia during their hospitalization ***Treatment:*** • Two patients (16.6%) did not require respiratory support, two patients (16.6%) required supplemental oxygen therapy, 1 patient (8.3%) was treated with noninvasive positive pressure ventilation, and 5 patients (41.6%) required invasive mechanical ventilation. • One patient required extracorporeal membrane oxygenation (ECMO) and another patient was transferred for ECMO to another institution. • Ten patients (83.3%) were treated in an intensive care unit. All patients received corticosteroids with varying regimens with five of them (41.6%) receiving oral cortico-steroids.
Main conclusion	• AEP is reported with smoking outside of traditional cigarette smoking including vaping, waterpipe smoking, marijuana and (heat-not-burn cigarettes) HNBCs. The disease has a similar presentation and clinical course to AEP associated with cigarette smoking and other exposures.
Funding (related to tobacco industry; Yes/No)	• Not reported.

First Author, Year, country	**(12) Sharma 2020, India**
Title	'Vaping'- a trojan horse against fight toward tobacco use and cancer: A systematic review of the existing evidence.
Target population (youth, young adults, adults, lab/in vitro; Gender)	• Youth and young adults
Objective/s (only those who are related to the domain)	• Health consequences using ECs
Number of included articles	• 36 articles
Reported outcomes (name each outcome + results)	• Long-term use may have a detrimental effect on brain health due to cerebral oxidative stress, which is very similar to smoking-related oxidative stress. • Even in small quantities, inhalation of nicotine results in local and systemic release of catecholamine, which leads to increased heart rate, blood pressure, and heart contraction. • Potentially hazardous Vitamin E acetate were found from bronchoscopy and bronchoalveolar lavage (BAL) of all patients suffering from EC, or vaping, product use-associated lung injury (EVALI), which may be a potential additive related to the injury • Many of the EVALI patients reported having respiratory symptoms such as cough, chest pain, and shortness of breath, while some reported gastrointestinal symptoms such as abdominal pain, nausea, vomiting, and diarrhea with constitutional symptoms such as fever chills and weight loss. • Since EVALI patients may have symptoms similar to those associated with influenza or other respiratory infections, it may be difficult to distinguish EVALI from influenza or community-acquired pneumonia upon initial assessment, and EVALI may co-occur with respiratory infections, thus making it difficult to identify and treat
Main conclusion	• Vaping may be linked with significant health issues, including respiratory diseases such as asthma, very severe forms of bronchitis such as popcorn lung, or EC, or vaping, product use-associated lung injury, and cardiovascular illnesses such as atherosclerotic plaque and myocardial ischemia. • No long-term toxicological and health studies have been carried out in humans using these vaping products and their constituents to date.

Funding (related to tobacco industry; Yes/No)	• None

First Author, Year, country	**(13) Kaur 2018, USA**
Title	Immunological and toxicological risk assessment of electronic cigarettes.
Target population (youth, young adults, adults, lab/in vitro; Gender)	• Human studies • Animal studies • Vivo studies
Objective/s (only those who are related to the domain)	• Cardiovascular, gastrointestinal and neurological risks • Pulmonary atrial fibrillation and acute myocardial infarction • Immunological effects of EC use
Number of included articles	• 104 articles ➢ 56 evaluated the clinical, immunological and toxicological effects of EC vapours, aerosols and liquids, chemical content of EC vapours and aerosols, reports on adverse events and human and animal studies, along with current EC policies and recommendations. ➢ 48 evaluated the immunological, toxicological and chemical composition of conventional cigarettes that may not have been specifically evaluated but are related to ECs.
Reported outcomes (name each outcome + results)	• The adverse health effects of conventional cigarette smoking are well known; however, the immunological responses to e-liquid vaping remain elusive. Few reports have been published, but the results seem to be contradictory. • Transcriptome sequencing of human bronchial epithelial cells following exposure to EC vapours and traditional cigarette smoke demonstrated the induction of distinct gene expression profiles. The results demonstrate that compared to tobacco smoke, the use of EC vapours elicits subdued cellular toxic responses. • Furthermore, researchers observed that exposure to EC vapours results in increased virulence of methicillin-resistant Staphylococcus aureus and concluded that e-liquids can boost drug resistance in bacteria by promoting biofilm formation and causing alterations in surface charge. • While many reports certainly point towards harmful health effects of e-liquids, examining their impact on inflammatory responses is highly challenging due to the wide variety of flavours, which themselves may pose substantial threats to human health. • Currently, there is limited understanding of the full health impacts of EC usage, and only scant reports associating EC use with cardiovascular, gastrointestinal and neurological risks are available. • Compared to other associated health risks, it is more apparent that there are considerable pulmonary health risks associated with continued EC usage. • Overall, the currently available clinical data do not associate serious health risks with EC use, but it should be noted that the current studies have not assessed the long-term effects of EC use and lack the proper study design required to gather conclusive outcomes.
Main conclusion	• Excessive vaping has been reported to induce inflammatory responses including mitogen-activated protein kinase, Janus tyrosine kinase/signal transducer and activator of transcription and nuclear factor-κB signalling, similar to that induced by tobacco smoke. • Based on recent evidence, prolonged exposure to some constituents of EC aerosols might result in respiratory complications such as asthma, chronic obstructive pulmonary disease, and inflammation.
Funding (related to tobacco industry; Yes/No)	• This work was supported by a Young Clinical Scientist Award from the Flight Attendant Medical Research Institute (FAMRI; 123253_YCSA_Faculty); National Institutes of Health R15 (7 R15 ES023151 02); a Southern University Foundation Grant (FY2017-017); and a Louisiana Biomedical Research Network Startup Grant (2P20GM103424-14 Subaward No. 100011) to S. Batra. Funding information for this article has been deposited with the Crossref Funder Registry. • Not related to tobacco industry.

2. Cardiovascular diseases

First Author, Year, country	(1) Martinez-Morata 2021, USA
Title	Electronic Cigarette Use and Blood Pressure Endpoints: a Systematic Review
Target population (youth, young adults, adults, lab/in vitro; Gender)	• Adults: age range 20 to 58 years old (men and women) • Sample size ranged from 15 to 76 • Nonsmokers and current cigarette smokers
Objective/s (only those who are related to the domain)	• Association of EC use with BP endpoints
Number of included articles	• 13 trials (12 cross-over designs; 1 observational study)
Reported outcomes (name each outcome + results)	**<u>3 experimental studies were conducted in non-tobacco smokers:</u>** • EC with nicotine arm: SBP and DBP increased compared to baseline in all studies. • Comparing SBP and DBP changes happening in less than an hour post-intervention vs. pre-intervention: the mean SBP/DBP change was + 5/+ 4 mmHg in one study and + 2/+ 4 mmHg in another study. • No nicotine EC arm: the corresponding changes were + 3/+ 2 mmHg in one study and a nonsignificant decline in the other. • Another study did not provide the baseline SBP/DBP data but reported a significant increase at 40 min after the intervention with a nicotine EC arm and no significant changes in either SBP or DBP with the no nicotine EC arm. • A study reported that between 1 and 2 h of the intervention, SBP/DBP declined, but they were still higher compared to baseline both in the nicotine and non-nicotine EC arms. **<u>Ten experimental studies were conducted in smokers:</u>** • All of them included an EC arm with nicotine that experience elevations of SBP and DBP after the intervention compared to baseline. ➢ Comparing the SBP and DBP change from baseline vs. after the intervention: immediately after the intervention, the mean SBP/DBP change was + 12/+ 10 mmHg in one study (and at 10 min, the mean SBP/DBP change was + 8.0/+ 7.4 mmHg) and + 9.9/+ 8.6 mmHg in another. ➢ At 10 min, the mean SBP/DBP change were + 8.9/+ 6.2 mmHg, + 6.6/+ 3.0 mmHg, no change/+ 1.9 mmHg [18], and − 1/no change in different studies respectively. ➢ At 20 min, the mean SBP/DBP change was + 5.8/+ 6.8 mmHg. • Another study graphically reported an increase of SBP and DBP at 40 min. • A study reported a non-significant mean change of + 2 mmHg for SBP and a significant mean change of + 4.9 mmHg for DBP 2 h after the intervention. • Another study also reported an increase of SBP and DBP at 2 h that was significant for DBP. **<u>3 studies conducted in smokers included a no nicotine EC arm, and all 3 studies found increases in SBP during the intervention:</u>** The findings for DBP were variable. • The mean SBP/DBP change immediately after the intervention compared to baseline was + 5.2/+ 4.3 mmHg in one study (and at 10 min, the mean SBP/DBP change was + 2.0/+ 2.5 mmHg) and + 7/+ 5 mmHg in another study. • A study reported a significant mean change of + 2 mmHg for DBP 2 h after the intervention. • Another study graphically reported increases of SBP and DBP compared to baseline for 2 h after the intervention. This study included a placebo arm that experienced no significant changes in BP levels. • Another study graphically reported an increase in SBP at 60 min vs baseline that was not statistically significant, and a significant decrease in DBP at 10 and 30 min. • All the studies that included a traditional cigarette arm found elevations of SBP and DBP for this group. **<u>One observational study</u>** reporting the association between EC use and blood pressure endpoints. • Prospective 3.5 years follow-up study with a cohort of 9 daily exclusively EC users for more than 3 months and a control group of 12 people naïve to any tobacco products. • A discrete increase in SBP and a discrete decrease of DBP at the end of the follow up period (3.5 years) were reported for the EC group. • The mean change for SBP/DBP at 3 years was + 3/− 3 mmHg for the EC group and + 1/− 1 mmHg for the control group.

	• None of the changes was significant during the follow-up period
Main conclusion	• Intervention studies on the short-term effects of EC use on blood pressure endpoints showed: ➢ a consistent increase of blood pressure immediately to several hours after exposure to ECs containing nicotine ➢ variable changes after exposure to non-nicotine ECs, including significant increases of SBP and/or DBP, ➢ no changes when using a placebo device. • The study populations were heterogeneous including tobacco smokers, nonsmokers, or EC users. • The intervention arms, protocols, and EC devices, including their nicotine content and other e-liquid and coil components, varied among studies, representing potential limitations for their comparability. • This systematic review supports that the use of EC with and without nicotine results in short-term elevations of both SBP and DBP
Funding (source; related to tobacco industry – Yes/No)	• This work is supported by R01ES029967 and P30ES009089 • Not related to tobacco industry

First Author, Year, country	**(2) Garcia 2020, USA**
Title	Cardiovascular autonomic effects of electronic cigarettes use: a systematic review
Target population (youth, young adults, adults, lab/in vitro; Gender)	• Humans (age not specified)
Objective/s (only those who are related to the domain)	• To collect and synthesize available studies that have investigated the autonomic cardiovascular effects of EC use in humans. • Acute and chronic effects of ECs, the relative contributions of the nicotine versus non-nicotine constituents in EC emissions and the relative effects of ECs compared to tobacco cigarettes (TCs)
Number of included articles	• 19 articles
Reported outcomes (name each outcome + results)	• Acute autonomic cardiovascular effects of TC smoking versus EC vaping: The effects of TC smoking on acute cardiovascular autonomic functions are greater than those of EC vaping (mean differences between for HR was3.06 bpm; 95% CI 2.01–4.10; p=0.00001). • Most studies did not confirm comparable TC and EC exposures, as estimated by acute increases in plasma nicotine levels. • Acute autonomic cardiovascular effects of ECN versus EC0 vaping: nicotine in the EC aerosol was responsible for the acute sympathomimetic effects of EC vaping. The overall mean differences between the ECN and EC0 studies across all studies was 6.44 bpm; 95% CI 3.52–9.36 (p<0.00001) for HR. • Chronic autonomic cardiovascular effects of ECs: EC smokers have chronically elevated cardiac sympathetic activation compared to non-vapers, as measured by HRV, but that this cardiac sympathetic activation does not translate into clinically detectable higher HR or BP • Chronic autonomic cardiovascular effects of switching from chronic TC smoking to EC vaping: most, but not all of the TC to EC switch studies involving chronic TC smokers tended to show a small decrease in BP, but not HR, over time.
Main conclusion	• EC use has acute effects on the autonomic cardiovascular system as estimated by acute increases in HRV, HR and BP. • The sympathoexcitatory effects of acute EC use are largely attributable to nicotine, and are less than those of acute TC smoking, as estimated by HR and BP. • Chronic EC use is associated with sympathetic activation, even in the absence of acute nicotine inhalation.
Funding (related to tobacco industry; Yes/No)	• This work was supported by the Tobacco-Related Disease Research Program (TRDRP) under the contract numbers: 25IR-0024 (HRM), and TRDRP 28IR-0065 (HRM) • Not related to tobacco industry

First Author, Year, country	(3) Goniewicz 2020, USA and Sweden
Title	How effective are electronic cigarettes for reducing respiratory and cardiovascular risk in smokers? A systematic review.
Target population (youth, young adults, adults, lab/in vitro; Gender)	• Human (18+ years age) • Both male and female • 19,475 to 161,529 sample • Self-reported health outcomes
Objective/s (only those who are related to the domain)	• To review estimated odds of respiratory and cardiovascular outcomes among former smokers who use ECs compared to current smokers.
Number of included articles	• 6 studies (5 in USA, 1 in Sweden; 5 cross-sectional, 1 longitudinal studies)
Reported outcomes (name each outcome + results)	• Cardiovascular risk compared with current exclusive cigarette smokers and never vapers • Cardiovascular: stroke, myocardial infarction, coronary heart disease • Switching from smoking to EC does not appear to significantly lower odds of cardiovascular outcomes. • All ORs for cardiovascular outcomes (including stroke, myocardial infarction, and coronary heart disease) did not differ significantly from 1.0
Main conclusion	• The estimates of relative risk of vaping compared to smoking are primarily based on a limited number of epidemiological studies with several important limitations • Both randomized controlled trials and prospective cohort studies are needed to better evaluate contributions of ECs as harm reduction tools for smokers.
Funding (related to tobacco industry; Yes/No)	• This work was supported by the US Food and Drug Administration and National Cancer Institute under grant award U54CA238110. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health or the US Food and Drug Association. • Not related to tobacco industry

First Author, Year, country	(4) Sharma 2020, India
Title	'Vaping'- a trojan horse against fight toward tobacco use and cancer: A systematic review of the existing evidence.
Target population (youth, young adults, adults, lab/in vitro; Gender)	• Youth and young adults
Objective/s (only those who are related to the domain)	• Health consequences using ECs
Number of included articles	• 36 articles
Reported outcomes (name each outcome + results)	• Long-term use may have a detrimental effect on brain health due to cerebral oxidative stress, which is very similar to smoking-related oxidative stress. • Even in small quantities, inhalation of nicotine results in local and systemic release of catecholamine, which leads to increased heart rate, blood pressure, and heart contraction. • Potentially hazardous Vitamin E acetate were found from bronchoscopy and bronchoalveolar lavage (BAL) of all patients suffering from EC, or vaping, product use-associated lung injury (EVALI), which may be a potential additive related to the injury • Many of the EVALI patients reported having respiratory symptoms such as cough, chest pain, and shortness of breath, while some reported gastrointestinal symptoms such as abdominal pain, nausea, vomiting, and diarrhea with constitutional symptoms such as fever chills and weight loss. • Since EVALI patients may have symptoms similar to those associated with influenza or other respiratory infections, it may be difficult to distinguish EVALI from influenza or community-acquired pneumonia upon initial assessment, and EVALI may co-occur with respiratory infections, thus making it difficult to identify and treat
Main conclusion	• Vaping may be linked with significant health issues, including respiratory diseases such as asthma, very severe forms of bronchitis such as popcorn lung, or EC, or vaping, product use-associated lung injury, and cardiovascular illnesses such as atherosclerotic plaque and myocardial ischemia. • No long-term toxicological and health studies have been carried out in humans using these vaping products and their constituents to date.

Funding (related to tobacco industry; Yes/No)	• None

First Author, Year, country	**(5) Kennedy 2019, Denmark**
Title	• The cardiovascular effects of electronic cigarette: A systematic review of experimental studies
Target population (youth, young adults, adults, lab/in vitro; Gender)	• Humans (age not specified) • Animals • In vitro (humans)
Objective/s (only those who are related to the domain)	• Physiological and pathophysiological cardiovascular effects after direct exposure to ECs and the implications for cardiovascular disease
Number of included articles	• 38 studies (6 in animals, 24 in humans, and 8 in human cardiovascular cells in vitro)
Reported outcomes (name each outcome + results)	**<u>In vitro studies:</u>** **Oxidative stress:** • 3 studies found statistically significant increases in reactive oxygen species (ROS) associated with endothelial injury • Another study did not however find significant upregulation in expression of genes involved in the oxidative stress pathway **Endothelial cellular function:** • 4 studies reported statistically significant reductions in endothelial • cell viability when exposed to certain eCAE • A study identified significant impairment in endothelial cell viability after exposure to serum from EC and cigarette smokers compared to non-smokers. This study also identified increased endothelial cell tube formation, reflective of increased angiogenesis. • Other cardiotoxic effects identified included DNA damage, cell morphological changes and reduced cell metabolic activity • Statistically significant reductions in endothelial cell density and proliferation (recognized indicators of endothelial injury and dysfunction) were detected in eCAE exposures in one study each. • A study found significant inhibition of endothelial cell migration while another found no significant inhibition after eCAE exposure. **Endothelial-complement interactions:** • All eCAE exposures were associated with statistically significant increases in C1q and C4d complement deposition and expression of gC1qR and cC1qR cellular proteins, with some extracts causing statistically significant complement inhibitor expression. • Endothelial C1q deposition did not increase when cells were exposed to smoke extract from conventional cigarettes. **Platelet function:** • A study reported significant increases in platelet aggregation, • adhesion, activation and complement deposition after exposure to eCAE **<u>Animal studies:</u>** **Cardiac function:** • A study reported statistically significant increases in two mutagens (O6-methyldeoxyguanosines and γ-hydroxy-1,N2-propano-deoxyguanosine) in cardiac tissue of mice exposed to eCAE. • Another study identified cardiomyocyte mitochondrial nuclear damage and cytoplasmic abnormalities; as well as intramyocardial lipid accumulation and reduced expression of a cardioprotective gene after exposure to eCAE. • Another study reported statistically significant increases in left ventricular mass of mice after chronic exposure to EC vapour but not those exposed to cigarette smoke • Another study however observed no significant change • A study observed no significant decreases in fractional shortening and ejection fraction in mice exposed to EC vapour whilst another study observed both of these findings • A study found no significant effects of vaping on cardiac contractility, fibrosis or geometric properties. **Vascular function:** • Vascular inflammation (PECAM-1, VCAM-1, ICAM-1) after EC vapour inhalation.

	• A study reported significant increases in pulse wave velocity (a measure of arterial stiffness associated with endothelial dysfunction in mice after long-term EC vapour inhalation. • No significant difference in aortic vasodilation was identified however in response to (the vasodilator) nitroprusside between mice exposed to EC vapour and filtered air. • Urine cotinine level in mice exposed to EC vapour was approximately half that of those exposed to cigarette smoke, yet vascular damage was similar, suggesting a role for mechanisms other than those involving nicotine • A study identified statistically significant increases in atherosclerotic plaque formation in mice exposed to eCAE compared to aerosol control. **Platelet function and haemostasis:** • A study reported statistically significant increases in platelet aggregation, alpha particle secretion, dense particle secretion, platelet integrin activation and platelet resistance to inhibition by prostacyclin but not platelet count following eCAE exposure. The study also identified significant decreases in bleeding time (indicative of increased haemostasis) and occlusion time (indicative of increased thrombogenesis) • Another study reported statistically significant decreases in circulating thrombomodulin in mice - a molecule protective against thrombosis. **<u>Human studies:</u>** **Sympathetic nerve activation (18 studies):** • 18 studies measured heart rate as a biomarker of high sympathetic nerve activation – a state associated with increased cardiovascular risk • Most studies reported increases (n=14) and some decreases (n=2) after EC use. 7 of these studies reported statistically insignificant changes and one reported clinically insignificant changes. • 17 studies investigated resting blood pressure as a proxy for sympathetic nerve activation. These found both increases (n=10) and decreases (n=4) in systolic pressure and increases (n=9) and decreases (n=3) in diastolic pressure, with differing degrees of significance. • A study assessed the effect of EC use on exercising peripheral blood pressure, identifying significant increases in systolic pressure compared to nicotine-free ECs • Another study investigated the microcirculation of the hand following EC use, identifying statistically significant decreases in both superficial and deep flow, potentially associated with worse microvascular surgical outcomes. • A study found a statistically significant decrease in cardiac vagal tone and an increase in sympathetic tone after EC use whilst another identified significant increases in exercising HRV after vaping compared to the control group • Another identified no significant effect of vaping on myocardial function after very brief exposure. **Oxidative stress:** • Two studies found significant increases in two ROS (sNOx2-dp and iso-PGF2a) and a significant decrease in vitamin E levels and nitrogen oxide bioavailability, which are protective against ROS • A study found significant increases in the ROS hydrogen peroxide (H2O2) and significant decreases in HBA% (protective H2O2 breakdown activity) • A study found significant oxidative stress after EC use, as measured by malondialdehyde (MDA) • A study did not find any significant acute effect of EC use on oxidative stress burden, as measured by paraoxonase-1 (PON-1) activity • A study identified significant increases in plasma concentrations of myeloperoxidase, an enzyme involved in oxidative stress pathways which has been associated with increased cardiovascular risk. No significant increases were identified in the oxidative stress-associated protein-bound 3-chlorotyrosine or homocitrulline • 2 studies found significant increases in circulating CD40L after EC use, which leads to endothelial cell activation and the production of ROS • A study found significant increases in ROS generation and C-reactive protein (a biomarker of inflammatory processes including atherothrombosis), as well as significant decreases in (protective) NO metabolites after vaping. **Endothelial function:** • A study measured arterial flow-mediated dilatation (FMD) finding significant impairment

	• A study reported insignificant changes in arterial stiffness index (SI) and reflection index (RI) after EC use • 4 studies identified significant increases in augmentation index normalised to a heart rate of 75 beats per minute (AIx75) whilst 5 studies reported significant increases in pulse wave velocity (PWV) after EC use. • A study found an increase in reactive hyperaemia index, an indicator of endothelial dysfunction whilst another found significant increases in circulating reparative endothelial progenitor cells (EPCs) - suggesting vascular injury from vaping. • A study found significant increases in soluble and endothelial ICAM-1 (an adhesion molecule involved in endothelial activation and dysfunction), however another study did not. • Finally, a study identified significantly reduced vasodilatory responses to the endothelial-dependent vasodilator acetylcholine but no significant reduction in vasodilatory response to the endothelial-independent vasodilator sodium nitroprusside after vaping, suggestive of endothelial dysfunction. **Platelet activation:** • A study found significant increases in platelet microparticle secretion whilst another found significant increases in platelet aggregation after EC use • 2 studies found significant increases in soluble Platelet (P-) selectin whilst another found a significant decrease in P-selectin **21.1% of studies included in this review were deemed to have a potential COI (n=8)** ***Quality assessment:*** • 34.2% of included studies were deemed to have a moderate- • High risk of bias (n=13). • 11 of these studies formed conclusions on the implications of ECs use for health, with 6 (54.5%) having conclusions that were supportive of EC use.
Main conclusion	• 90% of studies deemed to be without COI found potentially harmful effects on the cardiovascular system. • Only 2 of 8 studies deemed to have a potential COI reported a potentially harmful cardiovascular effect, whilst 6 of 11 studies with moderate-high risk of bias had conclusions that were supportive of EC use. • Human studies largely showed increases in heart rate and blood pressure as well as abnormalities in HRV, suggestive of sympathetic nerve activation. • Both in vitro and in vivo studies showed an increase in ROS production and a reduction in antioxidants after EC exposure, constituting an atherosclerotic risk. This was evidenced in one murine study which found significantly greater atherosclerotic plaque development in mice exposed to EC vapour. • In vitro studies identified disordered endothelial cellular structure, function and interactions; murine studies identified vascular inflammatory markers and angiogenesis, whilst human studies identified increased arterial stiffness - all suggestive of endothelial dysfunction. • Platelet haemostatic processes were reported across murine, human in vitro and human in vivo studies, suggestive of an increased thrombotic risk. • Vaping but not smoking increased endothelial (c)1q deposition, reactive hyperaemia and murine left ventricular mass. • These changes may be suggestive of endothelial dysfunction and cardiac remodelling. • Primary studies suggest potentially harmful cardiovascular effects from ECs, through inducing sympathetic nerve activation, oxidative stress, endothelial dysfunction and platelet activation. • It is concerning that COI status and median-high risk of bias were both significantly associated with the identification of no harmful cardiovascular effects. • Further research is required to assess effects of ECs in subjects with primary cardiovascular disease, and to distinguish effects of nicotine-containing and nicotine-free ECs.
Funding (related to tobacco industry; Yes/No)	• Not specified

First Author, Year, country	(6) Skotsimara 2019, Greece
Title	• Cardiovascular effects of electronic cigarette: A systematic review and meta-analysis.
Target population (youth, young adults, adults, lab/in vitro; Gender)	• Human (male and female)
Objective/s (only those who are related to the domain)	• Cardiovascular effects: heart rate, diastolic, systolic/diastolic blood pressure were compared with conventional cigarette smoking participants
Number of included articles	• 14 (meta-analysis) • 26 (systematic review)
Reported outcomes (name each outcome + results)	• Evidence suggests that the ECs negatively affects endothelial function, arterial stiffness and the long-term risk for coronary events, but these findings are from single study reports and have not been confirmed in additional studies. • Conflicting evidence exists on the effects of the ECs on heart rate and blood pressure, which is mainly based on non-randomized clinical studies of moderate quality. • The meta-analysis of 14 studies (N=441 participants) suggested that despite the negative acute effects of the ECs on heart rate (pooled mean difference (MD)=2.27, 95% confidence interval (CI): 1.64 to 2.89, p<0.001), diastolic (pooled MD=2.01 mmHg, 95%CI: 0.62 to 3.39, p=0.004) and systolic blood pressure (pooled MD=2.02 mmHg, 95% CI: 0.07 to 3.97, p=0.042), benefits may be observed in terms of blood pressure regulation when switching from tobacco smoking to chronic ECs use (systolic blood pressure pooled MD=-7.00,95% CI:-9.63 to-4.37,p<0.001; diastolic blood pressure pooled MD=-3.65, 95% CI:-5.71 to-1.59,p=0.001).
Main conclusion	• The existing evidence on the cardiovascular effects of the ECs is concerning, with several unexplored issues. • Given the existing concerning evidence in this field, ECs should not be labelled as cardiovascular safe products. Future studies should delineate whether ECs use is less hazardous to cardiovascular health than conventional cigarette smoking.
Funding (related to tobacco industry; Yes/No)	• The author(s) received no financial support for the research, authorship, and/or publication of this article. • Not related to tobacco industry

3. Cancer

First Author, Year, country	(1) Flach 2019, Germany and UK
Title	Electronic cigarettes and head and neck cancers: A systematic review of the current literature.
Target population (youth, young adults, adults, lab/in vitro; Gender)	• Human (male/female): Adolescents and adults • Lab
Objective/s (only those who are related to the domain)	• The aim of this systematic review was to evaluate the effects of ECs on the pathogenesis of head and neck cancers as reported in the literature
Number of included articles	• 18 studies (laboratory-based studies, Cohort and case studies) • 4 E-liquids; 1 Liquid nicotine; 13 EC aerosol
Reported outcomes (name each outcome + results)	***Head and neck cancers:*** • This is the first systematic review to explore the association between e-cigarettes and HN cancer pathogenesis. • Only low-quality evidence from laboratory research, cohort studies and case studies was identified. • There is evidence that e-cigarettes can cause in vitro damage, including increased DNA double-strand breaks and oxidative stress. • E-cigarettes have only been on the European market for a bit longer than a decade, and only recently evidence has appeared about their potentially harmful effects. Thus, not enough time has passed for long-term studies with larger cohorts and well-designed controls to emerge in the literature, or to draw a conclusion whether e-cigarettes play a relevant role in the pathogenesis of HN cancers
Main conclusion	• There is limited evidence that ECs are harmful and potentially carcinogenic for the head and neck, with some reports stating that ECs can lead to in vitro damage and that flavoured e-liquids are particularly damaging.

	• There is currently no good quality evidence to conclude that ECs are less harmful than conventional cigarettes
Funding (related to tobacco industry; Yes/No)	• Not reported • Not related to tobacco industry

4. Passive exposure to ENDS aerosol

First Author, Year, country	**Hess 2016, Australia**
Title	A systematic review of the health risks from passive exposure to electronic cigarettes vapour.
Target population (youth, young adults, adults, lab/in vitro; Gender)	• Human volunteers • Animal models • No human volunteers (air quality model/smoking machine)
Objective/s (only those who are related to the domain)	• Compared volunteers passively exposed to EC vapour with non-exposed volunteers • Measured chemical and toxicological compounds in the vapour produced by human volunteers using ECs
Number of included articles	• 16 studies • Direct passive exposure studies with human volunteers (n = 4) • Direct passive exposure studies in animal models (n = 1) • Indirect exposure with human volunteers (± smoking machine) using ECs (n = 7) • Indirect exposure studies with no human volunteers (n = 4)
Reported outcomes (name each outcome + results)	• Epidemiological evidence from environmental studies has demonstrated adverse health effects from short-term and long-term exposures to PM, especially the smaller fraction of PM2.5, even at very low concentrations. • Adverse health effects from exposure to PM2.5 include an increase in cardiovascular and respiratory diseases, as well as an increase in mortality from all causes. • Nicotine has also been shown to have adverse health effects from short-term and long-term exposure. • A recent review examined the effect of nicotine on the developing human and concluded that nicotine exposure during vulnerable periods of brain and lung development, such as during pregnancy, childhood and adolescence, can have detrimental effects. • Since EC vapour has been shown to contain PM as well as nicotine (when e-liquid with nicotine is used), passive exposure to EC vapour has the potential to cause adverse health effects. • Exposure to carbonyl compounds such as formaldehyde can cause irritation in acute settings and has been shown to cause nasopharyngeal cancers in humans with chronic exposure. • Exposure to some heavy metals can cause organ toxicity, and exposure to VOCs can cause irritation or cause cancer in long-term exposure settings.
Main conclusion	• Adverse health effects from exposure to nicotine and PM have been widely discussed in the literature. • Adverse health effects have also been observed from exposure to some of the other chemicals that have been identified in e-liquids and vapour. • Although more research is required, current evidence regarding passive exposure to EC vapours shows the potential for health impacts. • Those passively exposed to the vapours of EC users are exposed to numerous pollutants at levels above background and at concentrations that are associated with potential adverse health effects.
Funding (related to tobacco industry; Yes/No)	• No funding resources were declared. • Competing interest was not declared but 3 of the internal articles involved in employee of tobacco company, one is funded by employee of tobacco company and one is funded by National Vapers Club

First Author, Year, country	**(13) Zainol Abidin 2017, Malaysia**
Title	Electronic cigarettes and indoor air quality: a review of studies using human volunteers.

Target population (youth, young adults, adults, lab/in vitro; Gender)	• Human volunteers including male and female gender.
Objective/s (only those who are related to the domain)	• Examined available studies focusing on indoor air quality (IAQ) due to the use of ECs that were carried out using human volunteers that were asked to vape in natural settings (vapers used their ECs in their home) or mimics the actual vaping scenario (vapers were asked to vape in a specified room)
Number of included articles	• 4 articles
Reported outcomes (name each outcome + results)	• Indoor air quality (IAQ) parameters measured PM, PNC, VOCs, PAHs, carbonyls, metals, Nicotine, Low molecular weight carbonyls, TSNAs, Airborne nicotine • Physiological/ biomarkers measured eCO, FeNO, urinary nicotine, salivary cotinine and Urinary cotinine. • Nicotine, propylene glycols and PAHs were consistently found ECs
Main conclusion	• There is a potential exposure towards the known and still unknown contents of the EC vapors. • Thus, the claims made by the manufacturers and retailers as well as the mind-set of the users that ECs only release harmless water vapors have been shown as fallible
Funding (related to tobacco industry; Yes/No)	• Funding source was not reported. • Not sure if it is related to tobacco industry.

5. Ear diseases

First Author, Year, country	**Patel 2020, UK**
Title	A systematic review of the impact of cigarettes and electronic cigarettes in otology.
Target population (youth, young adults, adults, lab/in vitro; Gender)	• Human • Gender and age range bot specified
Objective/s (only those who are related to the domain)	• Provide an up-to-date overview of the latest data on evidence on ECs use and its effects on middle-ear disease, hearing loss and surgical outcomes.
Number of included articles	• 43 articles
Reported outcomes (name each outcome + results)	• Early studies on ECs have demonstrated respiratory irritation and reduced lung cell viability, which poses concern for middle-ear health due to the shared ciliated columnar epithelial lining. • One in vitro investigation of ECs liquid solution on human middle-ear epithelial cells has been conducted. In this study, electronic liquids were found to induce cytotoxic effects on these cells and reduce their viability from 100 per cent to 32–62 per cent. Moreover, increased cytotoxicity was seen with menthol and fruit flavoured electronic liquid.
Main conclusion	• The effects of ECs in otology are largely unknown.
Funding (related to tobacco industry; Yes/No)	• Rowlands Library, Worcestershire Acute NHS Foundation Trust • Not related to tobacco industry.

6. Ocular diseases

First Author, Year, country	**Martheswaran, 2021, USA**
Title	The impact of vaping on ocular health: a literature review
Target population (youth, young adults, adults, lab/in vitro; Gender)	• Not specified
Objective/s (only those who are related to the domain)	• This review compiles the most recent studies performed regarding implications on ocular health caused by EC use
Number of included articles	• 38 articles
Reported outcomes (name each outcome + results)	General effects: • Nicotine induces nystagmus and reduced staccadic latency period. • Aldehydes (Formaldehydes, acetyl aldehydes, etc) are carcinogenic substances. Tear Film:

	• Aldehydes and free radicals cause tear film instability, irritation and severe eye dryness. • Propylene Glycol and vape flavorings damage lipid layer through peroxidation. Cornea: • Minor Corneal Staining. • Nicotine and Acrolein may reduce ion conductance in epithelial cells and induce inflammatory response. Choroid: • Nicotine reduces choroid thickness • Nicotine-induced vasoconstriction may reduce ocular blood flow. Traumatic injury (explosive batteries or accidental eye contamination) • Burn injuries, Corneal Lacerations • Decreased Visual Acuity • Ocular Tissue Damage (e.g, Prolapsed Iris) • Hyphema Retina: • Nicotine may interfere with retinal light-adapted vision. • Responses to circadian cycle may be altered.
Main conclusion	• EC may induce dry eye, reduce tear film stability, or reduce ocular blood flow, among other effects. • These effects, along with tissue damage sustained from EC explosions, present both short-term and long-term health risks that may impair visual acuity and may interfere with proper visual correction in the future, such as the wearing of contact lenses or undergoing LASIK.
Funding (source; related to tobacco industry – Yes/No)	• This study was funded by an unrestricted grant from Research to Prevent Blindness (RPB), 360 Lexington Avenue, 22nd Floor New York, NY 10017. • Not related to tobacco industry.

7. Pregnancy outcomes

First Author, Year, country	(1) Romer, 2021, Germany
Title	Effects of Prenatal Electronic Cigarette Exposure On Foetal Development: a Review of the Literature
Target population (youth, young adults, adults, lab/in vitro; Gender)	• Fetus • Animal and in vitro studies
Objective/s (only those who are related to the domain)	• This paper aims to provide an overview of the current research on the effects of prenatal EC exposure on the fetus.
Number of included articles	• 17 articles
Reported outcomes (name each outcome + results)	Comparison with effects of traditional cigarettes: • Possible sequelae resulting from prenatal exposure to traditional cigarettes were also seen in prenatal exposure to EC. Fetal development: • Aerosols and their chemical constituents appear to affect cerebral metabolic processes. • In mice, prenatal EC exposure greatly reduced the cell vitality of neural and stem cells and increased cell death. • Prenatal EC exposure was found to be associated with increased DNA methylation overall, resulting in lower gene expression. This could adversely impact the development of affected children, especially in case of those genes relevant to their development. • Prenatal exposure to EC resulted in numerous developmental disorders, such as malformations of facial morphology and lower birth weight. • In animal models the animals suffered from a deterioration of their short-term memory. Activity and cognitive flexibility increased, while anxiety behavior decreased.
Main conclusion	• Nicotine exposure is a major cause of a wide range of adverse and pathological birth outcomes such as low birth weight, miscarriage and stillbirth.
Funding (source; related to tobacco industry – Yes/No)	• This study was funded by the German Federal Ministry of Education and Research under grant number 01NV1601C.

	• Not related to tobacco industry.

First Author, Year, country	(2) Calder 2021, UK
Title	Vaping in Pregnancy: A Systematic Review
Target population (youth, young adults, adults, lab/in vitro; Gender)	• Female in pregnancy
Objective/s (only those who are related to the domain)	• What is the prevalence of vaping during pregnancy and postpartum? • Among people who vape during pregnancy, what patterns of use are identified? • Among people who vape during pregnancy, what reasons for use are identified? • What are the effects of vaping on smoking cessation or reduction during pregnancy and postpartum? • Which health outcomes have been reported in studies of vaping in pregnancy and what findings have been reported for these outcomes?
Number of included articles	• 23 relevant studies
Reported outcomes (name each outcome + results)	• A study found that the mean birth weight of babies born to mothers who vaped (n = 218) in the last trimester of their pregnancy was very similar (within 1 g) to those born to nonsmoking mothers who neither smoked or vaped (n = 108; 3470 ± 555 g and 3471 ± 504 g respectively; p = .97) and was significantly higher than that birthweight of babies born to mothers who smoked (n = 99; 3166 ± 504 g; p< .001). • The birth centile of babies born to mothers who vaped and to mothers who did not smoke or vape were similar, and both were significantly higher than those born to mothers who smoked. • At discharge, 27.2% of babies born to mothers who smoked were breastfed compared with 48.6% of babies born to mothers who vaped (p < .001) and 61.1% for babies born to mothers who neither smoked nor vaped. • For mothers who both vaped and smoked (dual users), the outcomes for birthweight, birth centile, and breastfeeding rates at discharge were similar to those for smokers. • Two further articles reported data from one US cohort study of 248 pregnant women, of whom 6 were exclusive vapers, 17 were dual users, 56 were current smokers, and 64 were unexposed (including secondhand exposure). Compared with those not exposed to vaping or smoking, babies born to dual users had a relative risk for smallness for gestational age of 2.5 (95% confidence interval [CI]: 0.7–8.8), similar to the relative risk of those born to smokers (2.6, 95% CI: 0.9–7.2).
Main conclusion	• The data reviewed here are insufficient to draw any firm conclusions for practice or policy. • It appears that vaping has less of a detrimental effect on birthweight outcomes than smoking, so pregnant smokers struggling with smoking cessation could benefit from using vaping products in attempts to quit smoking.
Funding (related to tobacco industry; Yes/No)	• RC's post is part funded by a grant from Public Health England (ECM_7125). DR is supported by the National Institute for Health Research (NIHR) Applied Research Collaboration South London (NIHR ARC South London) at King's College Hospital NHS Foundation Trust. The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care. • Not related to tobacco industry.

First Author, Year, country	(3) Cardenas 2019, USA
Title	The use of electronic nicotine delivery systems during pregnancy and the reproductive outcomes: A systematic review of the literature.
Target population (youth, young adults, adults, lab/in vitro; Gender)	• Women during pregnancy. • Human, animals or animal/tissue models.
Objective/s (only those who are related to the domain)	• The effects of EC use during pregnancy on the health of the fetus.
Number of included articles	• 96 articles. • One-third of the publications (n=34) consisted of reviews, with only 11 specifically addressing EC use during pregnancy or on the potential effects of EC use during pregnancy.

	• There were 21 reports of studies of fetal outcomes from pregnant animals or animal/tissue models, and 9 of these were designed to address EC prenatal exposure and its reproductive effects. • There was only one population-based study that estimated the prevalence of current EC use among pregnant women. • Other studies were conducted in prenatal clinics and failed to specify a case-definition of current use or excluded persons unfamiliar with EC.
Reported outcomes (name each outcome + results)	• No studies of pregnant women exposed to EC use and its effect on their fetus or neonates. • There is a growing body of experimental studies in animals that suggest that nicotine in EC alters DNA methylation, induces birth defects, reduces the birth weight, and affects the development of the heart and lungs of their offspring. • A large population-based cohort study in the United States estimated that 5% of pregnant women were current EC users in 2014; most of them also smoked cigarettes. • Surveys conducted among practitioners indicate that there is a need to screen and counsel pregnant women. • Systematic reviews and meta-analysis of studies of women who used smokeless tobacco during pregnancy suggest that prenatal nicotine alone is a risk factor for low birth weight, premature delivery, and stillbirth.
Main conclusion	• Since there are no current studies on the effects that EC use has on pregnancy outcomes, one can only hypothesize, based on existing studies on the reproductive effects of smokeless tobacco, that EC use by pregnant women is not safe for their fetuses. • Given the need for studies of pregnant women who use EC, funding is urgently needed in support of studies on the health effects of EC use on birth outcomes. • Pregnancy cohort studies are not only feasible, but they also have a limited follow-up period, are less likely therefore to be affected by follow-up bias. • Further, with relatively common outcomes such as smallness for gestational age and preterm delivery, only a relatively small study sample size is required, and could serve as the baseline for longer follow-up studies to assess child and adult health.
Funding (source; related to tobacco industry – Yes/No)	• This work was supported in part by a grant from the Arkansas Department of Health (ADH) to the University of Arkansas at Pine Bluff Minority Research Center (MRC) on Tobacco and Addictions, sub-awarded to V.M. Cardenas. This study was also supported by the UAMS Translational Research Institute (grant: UL1TR000039) through the National Institutes of Health (NIH) National Center for Research Resources and National Center for Advancing Translational Sciences. • Not related to tobacco industry.

First Author, Year, country	**(4) Riley 2016, USA**
Title	Hormonal contraception among electronic cigarettes users and cardiovascular risk: a systematic review.
Target population (youth, young adults, adults, lab/in vitro; Gender)	• Human • Gender: Male and female • Age range: 17 – 63
Objective/s (only those who are related to the domain)	• To determine whether women who use hormonal contraceptives (HC) and ECss (ECs) also have an increased risk
Number of included articles	• 14 articles
Reported outcomes (name each outcome + results)	• No evidence on cardiovascular (CV) outcomes among EC users using HC. • Limited data reporting mostly acute outcomes suggested that CV events are rare among EC users in the general population and that EC may affect heart rate and blood pressure less than conventional cigarettes.
Main conclusion	• Limited data reporting mostly acute outcomes suggested that CV events are rare among EC users in the general population and that EC may affect heart rate and blood pressure less than conventional cigarettes.
Funding (related to tobacco industry; Yes/No)	• Funding source was not reported. • Not sure if it is related to tobacco industry.

8. Oral health

First Author, Year, country	(1) Figuered 2020, Canada
Title	The impact of vaping on periodontitis: A systematic review
Target population (youth, young adults, adults, lab/in vitro; Gender)	• Human • Gender: Male and female • Age range: 24 – 45
Objective/s (only those who are related to the domain)	• Systematically review the literature about the impact of vaping on periodontitis.
Number of included articles	• 8 articles
Reported outcomes (name each outcome + results)	• Presence of periodontal disease as indicated by increased probing depth, attachment loss, gingival recession, and bone resorption. Subjects who vaped consistently showed more loss of clinical attachment compared to non-smokers. • Estimate of fixed effect of vapers compared to controls for BOP was 13.73% ($p < .0001$) less, for PI was 13.32% ($p < .015$) more, for CAL was 0.2 mm more ($p < .5$), for PD in % greater than 4 mm was 3.26% more ($p < .2$), PD in mm was 1.18 mm more ($p < .03$) for MBL mesial was 0.19 mm more ($p < .4$) and MBL distal was 0.12 mm more ($p < .7$).
Main conclusion	• Evidence not enough to fully characterize the impacts of vaping on periodontitis. • The available results point to increased destruction of the periodontium leading to the development of the disease.
Funding (related to tobacco industry; Yes/No)	• Funding source was not reported. • Not sure if it is related to tobacco industry.

First Author, Year, country	(2) Yang 2020, USA
Title	The oral health impact of electronic cigarettes use: a systematic review
Target population (youth, young adults, adults, lab/in vitro; Gender)	• Human • Gender: Male and female • Age range: Not reported
Objective/s (only those who are related to the domain)	• Systematically review the available research evidence on the oral health impact of EC use.
Number of included articles	• 99 articles
Reported outcomes (name each outcome + results)	• The majority of mouth and throat symptoms experienced by ECusers were relatively minor and temporary, with some evidence that conventional smokers who switched to ECs experienced mitigation of these symptoms. • EC exposure increased the risk for deteriorating periodontal, dental and gingival health as well as changes to the oral microbiome. Extensive dental damage as a result of EC explosions were described in case reports. • Components of EC vapor have known cytotoxic, genotoxic, and carcinogenic properties. • Commonly reported mouth symptoms related to EC use or direct e-liquid exposure included dryness, burning, irritation, bad taste, bad breath and pain/discomfort. Studies noted that oral symptomatology was decreased in EC users compared to conventional smokers and that EC users had significantly less adverse complaints and more positive symptoms compared to conventional cigarette users. EC users were less likely to report mouth irritation. Former smokers who used ECs, regardless of nicotine concentration, experienced a decrease in mouth irritation. Researcher reported improved taste and mouth odor for conventional smokers who switched to ECs
Main conclusion	• Although switching to e-cigarettes may mitigate oral symptomatology for conventional smokers, findings from this review suggest that a wide range of oral health sequelae may be associated with e-cigarette use.
Funding (related to tobacco industry; Yes/No)	• This review did not receive funding.

First Author, Year, country	(3) Ralho 2019, Portugal
Title	Effects of ECss on oral cavity: A systematic review.

Target population (youth, young adults, adults, lab/in vitro; Gender)	• 18-47 years, Both male and female.
Objective/s (only those who are related to the domain)	• To evaluate the adverse effects of EC on the oral health.
Number of included articles	• 8 articles
Reported outcomes (name each outcome + results)	• Periodontal and peri-implant clinical and radiographic parameters (plaque index, clinical attachment loss, probing depth, peri-implant bone loss, and radiographic bone level) are worse, and proinflammatory cytokine levels are higher among EC and conventional cigarette smokers than among nonsmokers. • Bleeding on probing was higher in nonsmokers than in conventional cigarette smokers and EC users. • Nine different lesions of the oral mucosa were detected, with nicotinic stomatitis, hairy tongue, and angular cheilitis being more prevalent in EC consumers.
Main conclusion	• The results suggest that EC are less harmful than conventional cigarettes. • There is also a greater susceptibility of EC consumers to developing alterations in oral biological tissues than ex-smokers or nonsmokers. • There is still a clear need for the development of new studies.
Funding (related to tobacco industry; Yes/No)	• This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. • Not related to tobacco industry

9. Injuries

First Author, Year, country	**(1) Vyncke 2020, Belgium**
Title	Injuries associated with electronic nicotine delivery systems: A systematic review.
Target population (youth, young adults, adults, lab/in vitro; Gender)	• Age 17-59 years old • Both male and female.
Objective/s (only those who are related to the domain)	• To provide an overview of all relevant studies concerning EC-related traumatic injuries of all kinds: burn injuries (flame and chemical) and traumatic injuries of the skin, soft tissue, and/or bone (e.g., fractures), to estimate the implications on immediate management with a particular focus on surgical versus conservative treatment.
Number of included articles	• 41 articles
Reported outcomes (name each outcome + results)	***Direct injury:*** • Type 1: Hand injuries while ECs were being held or kept in the patient's pocket. Severe hand burns can result in the patient's inability to work or care for himself/herself if the functionalities of their hands are lost. • Type 2: Face injury while ECs were being held or used. These injuries may cause concern for upper airway injury and may warrant an admission for airway observation. • Type 3: Waist/groin injuries. These injuries are seen when the EC explodes/ignites while being stored in the individual's pocket. • Type 5a: Upper airway injuries that occur from the direct flash or explosion of the EC. ***Indirect injury:*** • Type 4: House or car fire injuries after an EC ignites, resulting in a house or car fire. These injuries are sustained during attempts to contain or extinguish the fire that was set off by the device. • Type 5b: Chemical, subglottic inhalation injuries that occur after inhaling smoke within a closed space (house or car), from a fire that set off following explosion of the EC.
Main conclusion	• Injuries from overheating, ignition, or explosion of ECs are an emerging, strongly underestimated and under researched topic. There is growing evidence that ECs are in fact a public safety concern, which demands increased regulation and design changes to improve their safety.
Funding (related to tobacco industry; Yes/No)	• Not reported.

First Author, Year, country	**(2) Tzortzi 2020, Greece**

Title	A Systematic Literature Review of EC-Related Illness and Injury: Not Just for the Respirologist.
Target population (youth, young adults, adults, lab/in vitro; Gender)	• Human • Male and female • Age range: 23 (19-33)
Objective/s (only those who are related to the domain)	• To collect all related clinical cases for study and analysis and provide a critical synopsis of the proposed injury mechanism.
Number of included articles	• 159 • Individual case reports: 131 • Aggregate cases: 26 • Individual case reports and aggregate: 2 • Majority of publications (63%) pertained to cases in the US while the remaining 37% were from the UK, Australia, Canada, China, Denmark, France, Germany, Ireland, Italy, Japan, Korea, Malaysia, the Netherlands, Poland, Portugal, Scotland, South Korea, Switzerland, and Turkey
Reported outcomes (name each outcome + results)	***Illness and injury*** • 238 individual cases were identified: • 53% traumatic injuries due to EC explosion or self-combustion, • 24% respiratory cases, and • 12%poisonings. • Additional cases pertained to oral, cardiovascular, immunologic, hematologic, allergic reactions, infant complications, and altered medication levels. • Case reports were mainly published between 2016–2019 (78%). • The oldest case, a lipoid pneumonia, was published in 2012. • The current review showed that EC-related health effects extend beyond the acute lung injury syndrome, including traumatic, thermal injuries and acute intoxications.
Main conclusion	• It was a narrative synthesis • Showed the full range of the EC-related injury beyond the plausible respiratory disorder • To protect and promote public health, regulators and public health authorities such as the European Commission, CDC, FDA, and WHO should address the regulatory gap regarding EC and novel tobacco products, aiming to protectively cover the global population.
Funding (related to tobacco industry; Yes/No)	• This research received no external funding • Not related to tobacco industry

First Author, Year, country	**Scarpino, 2020, Italy**
Title	• Severe neurological nicotine intoxication by e-cigarette liquids: Systematic literature review.
Target population (youth, young adults, adults, lab/in vitro; Gender)	• Human (male/female) • Average age: 19 – 67
Objective/s (only those who are related to the domain)	• To collect all e-liquid-related case reports • To understand the multifactorial process and possible mechanisms implicated in the pathogenesis of e-cigarette-related severe neurological complications that often result in a fatal outcome
Number of included articles	• 33
Reported outcomes (name each outcome + results)	• Despite nicotine being currently considered the main cause of toxicity both at the central and peripheral nervous system (CNS and PNS) levels, it is not clear whether the solvents composing the e-liquid may all contribute to the toxic effect or the mechanisms of neurological damage. • It is thought that propylene glycol (PG) may determine metabolic acidosis due to its degradation into lactic acid, and increase blood osmolarity, with further multi-organ involvement such as the heart and kidney. • Other components of e-liquid could contribute to clinical deterioration, by synergic effects: potentially toxic elements including formaldehyde, diethylene glycol, ethylene glycol and tobacco alkaloids, have been found in the available e-cigarette liquids, along with the noted ingredients.

	• High percentage of fatal cases were reported
Main conclusion	• Several cases of e-liquid intoxication have been reported in the literature in the last 10 years. • Data from the literature are still conflicting, showing a lack of agreement about the minimum lethal dose of nicotine and regarding the pathogenesis of the neurological damage.
Funding (source; related to tobacco industry – Yes/No)	• Not reported

First Author, Year, country	**(3) Seitz 2018, USA & UK**
Title	Burn injuries caused by EC explosions: A systematic review of published cases
Target population (youth, young adults, adults, lab/in vitro; Gender)	• Male and female (age range: 16 to 63 years)
Objective/s (only those who are related to the domain)	• Burn injuries caused by EC explosions
Number of included articles	• 31
Reported outcomes (name each outcome + results)	• A total of 31 studies reporting 164 patients were included in this systematic review, finding that EC explosions happened most often in pants pockets and among young men. • The burn injuries were usually on the thighs and hands and ranged in severity. • The majority of patients (90%) were male and were young (20 to 29 years) • In the majority of cases (65%), ECs exploded in people's pockets. • The most common injured body areas included the thigh, hand, genitals, and face • Burn severity was typically second-degree (35%) and a combination of second-degree and third-degree burns (20%). • Reports described 84 patients' total body surface area (TBSA) burns, which ranged from 0.5% to 27.25% (M=4.9, Mdn=4, SD=4.3). • In all, 48 patients required skin grafting. • Of the articles that described 19 patients' length of stay in the hospital for treatment, the number of days ranged from 1 to 31 days (M=7.4, Mdn=5, SD=6.9). • Explosions happened while ECs were being used or stored in users' pockets.
Main conclusion	• The severity of burns and the commonly injured locations (e.g. thigh, hands, genitals, face) strongly indicate a need for improved EC construction and for health professionals to advocate regulation of EC batteries, as well as insist on improved dissemination of information on explosions, for safety purposes.
Funding (related to tobacco industry; Yes/No)	• No source of funding

First Author, Year, country	**(4) Yang 2014, USA**
Title	EC: incorporating human factors engineering into risk assessments
Target population (youth, young adults, adults, lab/in vitro; Gender)	• Humans
Objective/s (only those who are related to the domain)	• Adverse events (AEs) associated with EC use
Number of included articles	• 12
Reported outcomes (name each outcome + results)	• Events related to EC product exposure reported to the American Association of Poison Control Centers (AAPCC) increased 42% from 2011 (n=256) to 2012 (n=438). • More than 30% of cases involved children younger than 5 years (n=84 in 2011; n=172 in 2012) and intentional misuse increased 56% (n=12 in 2011 and n=27 in 2012). • Approximately 15% of the exposures were allergic or idiosyncratic responses and 25% required medical treatment. • Intentional misuse cases included a completed suicide by injecting e-liquid (serum nicotine level was 2000 ng/mL) and a suicide attempt with ingestion and dermal application of e-liquid.

	• There were 14 EC ignition events injuring 8 individuals, including at least 2 non-users; 13 were explosions of rechargeable devices. • 2 explosions occurred during use, resulting in burns, oral disfigurement and unilateral blindness. • One disposable EC exploded while being removed from the package, resulting in sensory impairments and property damage. • 11 explosions during device charging have caused burns (n=2), smoke inhalation injuries (n=2) and property damage (n=8). *Analysis of product complaints and AEs voluntarily reported to the FDA*: • Of the 20 reports containing AEs: • 8 were serious including an infant death from choking on a flavour cartridge • 4 explosions causing burn injuries of three adults and one child • 2 confirmed nicotine overdoses (one with cartridge overheating and one with intentional dual use of traditional cigarettes) • 1 possible nicotine overdose with psychotic symptoms reported after e-liquid ingestion. • 12 non-serious AE reports included: • non-specific physical complaints pertaining to advertisement, labelling or website issues (n=4) • leakage of e-liquid resulting in oral or hand irritation (n=3) • oral burns due to overheating or explosion (n=2) • noxious smell and taste causing respiratory, gastrointestinal and constitutional symptoms (n=1) • persistent after taste associated with difficulty using the charger (n=1); • possible product adulteration with marijuana (n=1).
Main conclusion	• The impact of HFE on the hazards associated with ECs is not adequately characterized. • AEs reported for ECs: explosions, burn injuries, poisonings, choking deaths and nicotine overdoses
Funding (related to tobacco industry; Yes/No)	• Not specified

10. Mental health

First Author, Year, country	(1) Becker 2020, USA
Title	Systematic Review of ECs Use (Vaping) and Mental Health Comorbidity Among Adolescents and Young Adults
Target population (youth, young adults, adults, lab/in vitro; Gender)	• Adolescents and young adults (ages 12–26)
Objective/s (only those who are related to the domain)	• Mental health comorbidities of EC use among adolescents and young adults (AYA)
Number of included articles	• 40 articles (n = 24 predominantly adolescent and 16 predominantly young adult) • United States United States (n = 23 cohorts); Korea (n = 3 cohorts), the United Kingdom (n = 2 cohorts), and Taiwan
Reported outcomes (name each outcome + results)	**a. Internalizing Disorders Internalizing Symptoms (Composite):** <u>Adolescents:</u> • Composite measures of internalizing symptoms were associated with EC use among adolescents in both the Population Assessment of Tobacco and Health (PATH) study and a study of at-risk US high school students. • 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 (adjusted odds ratio [aOR] = 1.6, 95% confidence interval [CI]: 1.3–1.8, $p < .05$) and CC use (aOR = 1.7, 95% CI: 1.5–2.0, $p < .05$). • In a 1-year follow-up longitudinal analysis of baseline nicotine-naive adolescents, high past-year internalizing problems were significantly associated with initiation of EC use (adjusted relative risk ratio [aRRR] = 1.61, 95% CI: 1.12–2.33, $p < .05$), but not initiation of CC-only or dual EC and CC use.

	• In a cross-sectional study of students in alternative high schools (ie, schools providing nontraditional learning experiences for youth with prior educational and/or behavioral difficulties) internalizing symptoms related significantly to EC use (B = 0.100, standard error [SE] = 0.041, OR = 1.105, p < .05) and use frequency (B = 0.204, SE = 0.095, β = 0.0128) <u>Young Adults:</u> • 2 articles examined and found relationships between internalizing symptoms and EC use among YA respondents in the PATH study. • Evidence quality was similarly weak to moderate. • Similar to the adolescent PATH findings, high-severity past-year internalizing problems (compared with low severity) significantly related to current EC use (aOR = 1.97, 95% CI: 1.46– 2.65, p < .001) and CC use (aOR = 1.92, 95% CI: 1.64–2.24, p < .001) in cross-sectional analysis of baseline data, and high-severity lifetime internalizing problems predicted onset of EC (aOR = 1.4, 95% CI: 1.1–1.8, p < .05) and CC use (aOR = 2.2, 95% CI: 1.5–3.3, p < .05) among nonusers in a 1-year longitudinal analysis. **b. Depression:** <u>Adolescents:</u> • 7 studies, including 4 distinct national cohorts (United States, Taiwan, and Korea) and 1 California-based cohort examined associations between EC use and depression among adolescents. Most found positive associations and 1 suggested a bidirectional relationship. • Evidence quality was weak to moderate due to cross-sectional designs, single-item measures, and minimal adjustment for confounders. • In a 1-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 = .01), and past-month use frequency was positively associated with depressive symptoms (b = 1.611, SE = 0.782, p = .04) among sustained users. • The remaining studies were cross-sectional. • Three national studies found EC use associated with depressive symptoms, although the Taiwanese study found no relationship for exclusive EC use. • In the Taiwan study, depression was associated with exclusive CC use (aOR = 2.2, 95% CI: 1.1–5.0) but not EC use; 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). <u>Young Adults:</u> • 8 studies, among 6 cohorts, investigated relationships between depression and EC use, with mixed results. • Most studies were weak, due to cross-sectional designs and risk of selection bias. • A Texas-based cohort provides the strongest evidence (moderate). • 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 = .02) and CC (aRR = 1.03, 95% CI: 1.02–1.04, p < .001). • A cross-lagged path analysis of three waves found significant paths from Wave 1 depression to Wave 2 EC use (B = 0.06, p< .01) and Wave 2 depression to Wave 3 EC use (B = 0.08, p < .01), but no paths from EC use to subsequent depressive symptoms • 2 cross-sectional studies, among college students and homeless youth smokers found depressive symptoms associated with current EC use (college: aOR = 1.04, 95% CI: 1.01–1.08, p= .02258; homeless: aOR = 3.06, 95% CI: 1.68–5.57, p < .0553). • In these studies, depression was also associated with CC use in the student cohort (aOR = 1.03, 95% CI: 1.01–1.06, p = .015), but not the homeless cohort. • 2 longitudinal and 1 cross-sectional study found no relationships between EC use and depression. In a 2-year follow-up of Georgia college students, depressive symptoms predicted subsequent CC use (aOR = 1.05, 95% CI: 1.02–1.09, p = .001) but not EC use. • In study of Virginia college students, baseline depression did not predict EC initiation during 1-year of follow-up **c. Anxiety** <u>Adolescents:</u> • 1 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.

	• 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. Young Adults: • 4 studies among 3 cohorts have examined anxiety among YA, yielding mostly negative results • Quality of evidence was weak to moderate with risks of selection bias across studies. • Studies of 2 longitudinal cohorts of college students, in Georgia and Virginia, followed over 1–2 years found no relationship between anxiety and subsequent EC use. • Among the Georgia but not the Virginia cohort, anxiety predicted CC use (aOR = 1.02, 95% CI: 1.00–1.04, p = .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. • A cross-sectional study found EC use associated with generalized anxiety (likelihood ratio χ 2 = 14.0, p = .001, Cramer's V = 0.066) in a primary unadjusted analysis that resolved with secondary analysis controlling for covariates **d. Suicidality** Adolescents: • 4 national cross-sectional studies in the United States and Korea 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) • Analyses across 3 years (2015–2017) of the Korean Youth Risk Behavior Survey found similar associations. • The 2016 Korean survey found significant associations between current EC use (vs. nonuse) and past-year suicidal ideation (aOR = 1.58, 95% CI: 1.31–1.89, p < .05), plans (aOR = 2.44, 95% CI: 1.94–3.08, p < .05), attempts (aOR = 2.44, 95% CI: 1.85–3.22, p < .05), and serious attempts (aOR = 3.09, 95% CI: 1.51–6.32, p < .05). • In the 2017 Korean survey, lifetime and current CC use, EC use, and dual CC and EC use (vs. 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. Young Adults: No studies identified **e. Eating Disorders** Adolescents: • 1 South Korean study: • Female lifetime and current EC adolescent users (compared with 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), whereas 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 Young Adults: • In one weak-quality US university-based sample, EC use was not associated with binge-eating disorder. **f. Post-traumatic Stress Disorder** Adolescents: No studies identified. Young Adults: • 2 studies were found examining relationships between aspects of post-traumatic stress disorder and EC use. • 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 post-traumatic stress disorder (likelihood ratio χ 2 = 13.0, p = .002, Cramer's V = 0.064) in the primary unadjusted analysis, but not after controlling for covariates.

	• In a small sample of YA, self-reported history of childhood mistreatment directly related to lifetime EC use (β = 0.19, p = .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 (β = 0.11, p = .04 **g. Externalizing Disorders Externalizing Disorders (Composite):** <u>Adolescents:</u> • Analyses of adolescents in the PATH study found externalizing symptoms significantly associated with EC use. • 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 < .05) and CC use (aOR = 1.5, 95% CI: 1.3–1.7, p < .05). • In a 1-year longitudinal analysis of baseline nicotine-naive adolescents, high past-year externalizing problems were significantly associated with initiation of EC use (aRRR = 2.78, 95% CI: 1.76–4.40, p < .05), with relative risk ratios not significantly different from initiation of dual use (aRRR = 2.23, 95% CI: 1.15–4.31, p < .05) and CC use (aRRR = 5.59, 95% CI: 2.63–11.90, p < .05). <u>Young Adults:</u> • One longitudinal analysis of baseline nicotine-naive 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 < .05) at 1-year follow-up. • The relationship between externalizing symptoms and CC onset was not significant among these Ya. **h. Attention-Deficit/Hyperactivity Disorder** <u>Adolescents:</u> • 2 studies examined longitudinal relationships between ADHD symptoms and EC use among US high school students. • 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 use, 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. • 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 < .001) and ADHD symptoms at Time 2 predicted EC use at Time 3 (β = 0.350, p < .001), but EC use frequency was not associated with subsequent ADHD symptoms <u>Young Adults:</u> • In contrast to the findings of adolescent samples, 2 studies examined ADHD symptoms and EC use among college students, both finding no associations when controlling for covariates. • The quality of evidence was weak-moderate in strength, due to only 1 longitudinal design and self-report measures. • In a cross-sectional study, ADHD symptoms were significantly associated with EC use status (likelihood ratio $\chi 2 = 16.778$, p < .001, Cramer's V = 0.073) in the primary unadjusted analysis, but there was no significant association when controlling for covariates. • In a 2-year longitudinal study, neither ADHD nor any other psychological factors measured predicted EC use after controlling for covariates. **i. Conduct Disorder and Delinquency** <u>Adolescents:</u> • 3 articles examined conduct disorder symptoms and found significant relationships with subsequent EC use. • All were moderate-quality longitudinal studies, and 2 were nationally representative (United States, United Kingdom). • An analysis of baseline nicotine-naive 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).

	• Similarly, past 6-month delinquent behavior was associated with later EC use (aOR = 1.32, p < .001) and CC use (aOR = 1.41, p < .05) among a cohort of nicotine-naive US high school students. • Reports of various delinquent behaviors (eg, theft, vandalism, graffiti) were significantly higher for lifetime EC-only users (vs. never users) (aORs range 3.9–6.0, p < .001) but to less extent than among CC users and dual-EC and CC users (aORs range 5.7–11.9, p < .001). Young Adults: **No studies identified** **j. Transdiagnostic Constructs** **Impulsivity and Executive Function** Adolescent: • 3 studies examined impulsivity and EC use and 2 studies among 1 cohort examined executive function. • These studies consistently found EC use related to impulsivity and executive function deficits. • Overall, quality of evidence was weak, with nonprobability samples and cross-sectional designs. In a cross-sectional analysis of California high school students, impulsivity was elevated similarly among EC and CC users. • 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. • In a cross-sectional study using a mediation model, impulsivity was associated with more frequent EC use through an early age of EC initiation. • In a cross-sectional study of 12-year-old children in California, lifetime EC use was strongly associated with executive function deficits (aOR = 4.99, 95% CI: 1.80–13.96, p < .01), with subsequent analysis finding the relationship between low inhibitory control and EC use most applicable among low-socioeconomic status respondents Young Adults: • 4 studies, also weak in overall quality, investigating EC use and various subcomponents of impulsivity have had mixed results, with studies most consistently supporting a relationship between sensation seeking and EC use. • 2 longitudinal studies found relationships between sensation seeking and subsequent EC use (eg, ever JUUL use: aOR = 1.76, 95% CI: 1.52–2.05, p < .01; current use: aOR = 2.16, 95% CI: 1.81–2.58, p < .01), and 1 cross-sectional study found a correlation between sensation seeking and EC use, although relationships with other subcomponents of impulsivity were generally not significant (1 small study found significance for negative urgency). • 1 study found lack of perseverance predicted CC use (aOR = 1.52, 95% CI: 1.11–2.07, p < .05), but not EC use at 1-year follow-up. • In addition, in a cross-sectional study assessing impulse control disorders, EC use was related to gambling disorder (likelihood ratio $\chi 2 = 37.2$, p = .000, Cramer's V = 0.081), but not other impulse control disorders. **Perceived Stress:** Adolescent: • One moderate-quality study assessed perceived stress in adolescents. • In a 4-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 < .01) at age 17 as well as lifetime and past-month CC use (aOR = 1.32, 95% CI = 1.08–1.61, p < .01). Young Adults: • 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 = .03) and CC use (aOR = 1.02, 95% CI: 1.00–1.04, p = .04)
Main conclusion	• Analyses yielded 3 main categories of focus: internalizing disorders (including depression, anxiety, suicidality, eating disorders, post-traumatic stress disorder), externalizing disorders (attention-deficit/hyperactivity disorder and conduct disorder), and transdiagnostic concepts (impulsivity and perceived stress). • Significant methodological limitations were noted. • Youth EC use is associated with greater mental health problems (compared with nonuse) across several domains, particularly among adolescents.

	• 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. • Among young adults, EC use has been associated with internalizing problems, externalizing problems, depression, sensation seeking, and perceived stress, whereas existing evidence does not support relationships with ADHD or anxiety. • Because many existing studies are cross-sectional, directionality remains uncertain. • Well-designed longitudinal studies to investigate long-term mental health sequelae of EC use remain needed.
Funding (related to tobacco industry; Yes/No)	• No source of funding

First Author, Year, country	**(2) Sharma 2020, India**
Title	'Vaping'- a trojan horse against fight toward tobacco use and cancer: A systematic review of the existing evidence.
Target population (youth, young adults, adults, lab/in vitro; Gender)	• Youth and young adults
Objective/s (only those who are related to the domain)	• Health consequences using ECs
Number of included articles	• 36 articles
Reported outcomes (name each outcome + results)	• Long-term use may have a detrimental effect on brain health due to cerebral oxidative stress, which is very similar to smoking-related oxidative stress. • Even in small quantities, inhalation of nicotine results in local and systemic release of catecholamine, which leads to increased heart rate, blood pressure, and heart contraction. • Potentially hazardous Vitamin E acetate were found from bronchoscopy and bronchoalveolar lavage (BAL) of all patients suffering from EC, or vaping, product use-associated lung injury (EVALI), which may be a potential additive related to the injury • Many of the EVALI patients reported having respiratory symptoms such as cough, chest pain, and shortness of breath, while some reported gastrointestinal symptoms such as abdominal pain, nausea, vomiting, and diarrhea with constitutional symptoms such as fever chills and weight loss. • Since EVALI patients may have symptoms similar to those associated with influenza or other respiratory infections, it may be difficult to distinguish EVALI from influenza or community-acquired pneumonia upon initial assessment, and EVALI may co-occur with respiratory infections, thus making it difficult to identify and treat
Main conclusion	• Vaping may be linked with significant health issues, including respiratory diseases such as asthma, very severe forms of bronchitis such as popcorn lung, or EC, or vaping, product use-associated lung injury, and cardiovascular illnesses such as atherosclerotic plaque and myocardial ischemia. • No long-term toxicological and health studies have been carried out in humans using these vaping products and their constituents to date.
Funding (related to tobacco industry; Yes/No)	• None

11. Addiction

First Author, Year, country	**(1) Bozier 2020, Australia**
Title	The Evolving Landscape of E-cigarettes: A Systematic Review of Recent Evidence
Target population (youth, young adults, adults, lab/in vitro; Gender)	• Human, animal, in vitro, ex vivo from human samples; Gender not specified.
Objective/s (only those who are related to the domain)	• To provide a comprehensive update of data on the potential health effects of e-cigarettes since the National Academies of Sciences, Engineering and • Medicine (NASEM) report.

Number of included articles	• 225
Reported outcomes (name each outcome + results)	• There is evidence that smokers do not "quit" with e-cigarettes but rather "switch" to e-cigarette use.
Main conclusion	• This review did find evidence suggesting that smokers who switch to e-cigarettes may experience harm reduction, particularly in relation to cardiopulmonary health, but we were unable to find evidence suggesting that these clinical measures returned to the levels of a nonsmoker • Much remains unknown about the effects of e-cigarette use, in the long term. • There is evidence that smokers do not "quit" with e-cigarettes but rather "switch" to e-cigarette use. • The latest studies which show that dual use of e-cigarettes and tobacco cigarettes may put users at increased cardiovascular disease risk over smoking or e-cigarette use alone.
Funding (related to tobacco industry; Yes/No)	• None. • Not related to tobacco industry.

First Author, Year, country	**(9) Armendáriz-Castillo, 2019, Ecuador**
Title	Genotoxic and Carcinogenic Potential of Compounds Associated with Electronic Cigarettes: A Systematic Review.
Target population (youth, young adults, adults, lab/in vitro; Gender)	• Target population characteristic not reported. • It studied chemical composition of EC and health effect in human.
Objective/s (only those who are related to the domain)	• Review chemical compounds found in EC and describe their toxic effects.
Number of included articles	• 10 articles
Reported outcomes (name each outcome + results)	• The research found 50 (24.2%) of total chemical compound are exclusive to EC. These compounds include (+)-aromadendrene, (Z)-3-Hexen-1-ol, 1-Methyl phenanthrene, 1,3-Butanediol, 1,3-Propanediol, 2-Acetylpyrrole, 2,3-Dimethylpyrazine, 2,3-Pentanedione, 2,3,5-Trimethylpyrazine, 3-Methyl-1-butanol, Acetic acid, Benzyl acetate, Benzyl alcohol, Butyl butyrate, Camphor, Cinnamaldehyde, Cinnamyl alcohol, Coumarin, Methyl cyclopentenolone, Diacetyl, Diethylene glycol, Ethyl butyrate, Ethyl maltol, Ethyl vanillin, Ethylene glycol, Glycerin, Hydroxyacetone, Isobutyl acetate, Isoamyl acetate, Isopentyl isovalerate, L-Menthyl acetate, Limonene, Maltol, Cytotoxic, Menthone, Methyl anthranilate, Methyl cinnamate, Methyl salicylate, Myosmine, n-Hexanol, Nicotyrine, o-Tolualdehyde, p-Cymene, Propylene Glycol, Safrole, Thujone (sum of α- and β-diastereomers), Trans-2-hexen-1-ol, Vanillin, β–Damascone and γ–Decalactone
Main conclusion	• There are many cytotoxic and genotoxic effects still unknown related to different compounds of ECs, especially the ones included in e-liquids, which can be potentially toxic and carcinogenic to humans
Funding (related to tobacco industry; Yes/No)	• Funding source was not reported. • Not sure if it is related to tobacco industry.

12. Substances use

First Author, Year, country	**(1) Rothrock, 2020**
Title	Association of E-cigarettes with adolescent alcohol use and binge drinking-drunkenness: A systematic review and meta-analysis.
Target population (youth, young adults, adults, lab/in vitro; Gender)	• Human. • Male and female • Children: 6-12 and Adolescents
Objective/s (only those who are related to the domain)	• Evaluate the association of e-cigarettes (ECIGs) with alcohol use in adolescents.
Number of included articles	• 28 articles
Reported outcomes (name each outcome + results)	• Pooling of data showed that ECIG users had a higher risk for any alcohol use compared to NON-ECIG users (Odds Ratio/OR 6.62, 95% confidence interval/CI 5.67–7.72) and a higher rate of binge drinking/drunkenness compared to NON-ECIG users (OR 6.73, 95% CI 4.5 − 10.07).

	• The subset of high school ECIG users had higher rates of alcohol use (OR 8.17, 95% CI 5.95–11.2) and binge drinking/drunkenness (OR 7.98, 95% CI 5.98–10.63) compared to NON-ECIG users. • ECIG users had a higher risk of alcohol use and binge drinking/drunkenness compared to NON-ECIG users.
Main conclusion	• There is a strong association between ECIG use and alcohol use plus binge drinking/drunkenness in adolescents.
Funding (related to tobacco industry; Yes/No)	• None reported • Cannot ascertain if it is related to tobacco industry.

First Author, Year, country	**(2) Chadi 2019, USA**
Title	Association Between Electronic Cigarette Use and Marijuana Use Among Adolescents and Young Adults: A Systematic Review and Meta-analysis.
Target population (youth, young adults, adults, lab/in vitro; Gender)	• Youth aged 10 to 24 years
Objective/s (only those who are related to the domain)	• To characterize and quantify the association between e-cigarette and marijuana use among youth using a meta-analysis
Number of included articles	• 21 studies: 3 longitudinal and 18 cross-sectional studies (128,227 participants)
Reported outcomes (name each outcome + results)	• Pooling of data from all studies suggested that ENDS use is associated with an increased risk of marijuana use (AOR, 3.47 [95% CI, 2.63-4.59]; I 2, 94%). • Subgroup analysis by study type revealed significantly increased odds of marijuana use in both longitudinal (3 studies; AOR, 2.43 [95% CI, 1.51-3.90]; I 2, 73.8%) and cross-sectional studies (18 studies; AOR, 3.70 [95% CI, 2.76-4.96]; I 2, 94%). • Subgroup analyses by age showed a stronger association between EC use and marijuana use in studies with participants with a mean or median age younger than 18 years (4 studies; AOR, 4.29 [95% CI, 3.14-5.87]; I^2, 93.5%) vs studies with participants with a mean or median age 18 years and older (7 studies; AOR, 2.30 [95% CI, 1.40-3.79]; I^2, 91%). • Subgroup analysis by single use of EC vs dual use of both END and cigarettes or other tobacco products revealed a stronger association between EC and marijuana use in studies with youths with dual use (4 studies; AOR, 5.39 [95% CI, 3.53- 8.24]; I 2 , 87.6%) than in studies with youths with single use (17 studies; AOR, 3.10 [95% CI, 2.22-4.34]; I^2, 94.6%). ***By region:*** • The pooled AOR for the association between EC use and marijuana use was higher for North American studies (15 studies; AOR, 4.03 [95% CI, 2.97-5.49]) than for European studies (4 studies; AOR, 2.12 [95% CI, 1.70- 2.65]). • There were only 2 non-European, non–North American studies (from Australia and New Zealand; 2 studies; AOR, 2.84 [95% CI, 1.41-5.76]), and they had a pooled AOR with a 95% CI that overlaps with the 95% CIs of the pooled AOR for the North American and European studies. ***By date of publication:*** • Studies published in 2017 or later (12 studies; AOR, 4.57 [95% CI, 3.47- 6.03]) revealed a stronger association between EC use and marijuana use than studies that were published before 2017 (9 studies; AOR, 2.39 [95% CI, 1.67-3.40]). • Quality ratings ranged from 3 to 5 points (of 6 points) for cross-sectional studies and 6 to 8 points (of 9 points) for longitudinal studies. The Egger test was nonsignificant, suggesting that a small study effect was unlikely.
Main conclusion	• The odds of past or current marijuana use among youth who used e-cigarettes were 3.5 times higher than for those who denied e-cigarette use; this association was significant in both cross-sectional and longitudinal studies. • Studies conducted in adolescents aged 12 to 17 years (vs young adults aged 18 to 24 years) showed a stronger association between e-cigarette and marijuana use. • Subgroup analyses revealed that the association was stronger in youths who were younger and who combined EC and cigarette or tobacco use. • The analyses also revealed regional and temporal variations: North American studies and studies published since 2017 showed stronger associations between EC use and marijuana use than European studies and studies published before 2017 did.

Funding (source; related to tobacco industry – Yes/No)	• None reported

First Author, Year, country	**(3) Breitbarth 2018, Australia**
Title	E-cigarettes: An unintended illicit drug delivery system
Target population (youth, young adults, adults, lab/in vitro; Gender)	• Youth and adults
Objective/s (only those who are related to the domain)	• The use of electronic cigarettes or other vaping devices to vape illicit drugs
Number of included articles	• 38 studies: Cannabis use in e-cigarette: 28, other illicit drug use in e-cigarette: 10
Reported outcomes (name each outcome + results)	***Cannabis:*** • Vaping is a highly prevalent mode of use among medical marijuana patients, with 39% of survey respondents having vaped in the past month. However, it is rarely an explicit route of administration, often combined with others including smoking, oral and topical. ***Synthetic cannabinoids:*** • A report found that around 15% of individuals who vaped cannabis have also vaped synthetic cannabinoids • In a survey study by the same group 7.8% of electronic vaping device users admitted to vaping synthetic cannabinoids. • A National Early Warning System Report out of Atlanta stated that the use of vaporization techniques involving e-cigarettes is becoming a popular method of use for administration of synthetic cannabinoids. ***Methamphetamine:*** • Literature indicates that an increasing number of individuals are using drug vaporization, such as e-cigarettes, as a new method of administration for methamphetamin. • Researchers have recently shown that methamphetamine is present at reasonable concentrations in vapor from e-cigarettes. • 3-4-Methylenedioxymethamphetamine (MDMA): • There is evidence on internet drug forums of users employing vaporization techniques, such as e-cigarettes and table-top vaporizers, to vape MDMA. • A survey determined that 11.7% of electronic vaping device users have vaped MDMA. ***Synthetic cathinones:*** • There is evidence of e-cigarette use of a variety of synthetic cathinones (including derivatives) on illicit drug forums, including the user's perceived importance of the ability to consume drugs via stealth in public. • There is literature evidence that MDPV has been administered by vaporization and that e-cigarettes are being used to vaporize drugs such as methamphetamine and α-PVP as vaporization has a more rapid onset of effects and a shorter duration of action when compared to nasal inhalation. • One study provided additional evidence of the use of electronic vaping devices to vape synthetic cathinones with a convenience survey suggesting that 8.5% of electronic vaping device users had vaped mephedrone and 7.1% had vaped α-PVP. ***Cocaine:*** • Illicit drug forums suggest that cocaine in its free base form (crack cocaine) is being used in electronic cigarette style devices. • Survey data found that 10.9% of electronic vaping device users had vaped cocaine powder and 8.4% had vaped crack cocaine. • The majority of the respondents to this survey used e-cigarettes as their preferred vaping device (74.2%). ***Heroin:*** • Illicit drug forums suggest that the freebase form of heroin is being used in personal electronic devices such as e-cigarettes • A convenience survey found that 7.1% of responding electronic vaping device users had vaped heroin • There is also evidence on illicit drug forums of other opioids including oxycodone and morphine being used in e-cigarettes. • Fentanyl and derivatives:

	• A survey study found that 7.3% of electronic vaping device users had vaped fentanyl (2.5% of all survey respondents). ***Other drugs:*** • A sample of resin submitted for testing by a concerned parent was found to be a concentrated resin from the blue lotus flower (N. caerulea) for suspected use in an e-cigarette 'dripper-style' device. • The confiscated resin was shown to contain a very high concentration of Nuciferine (4300 ng/ml), an alkaloid associated with dopamine receptor blockade. • Subsequent investigation led to the identification of a number of blue lotus flower e-liquids and resins on sale for use in e-cigarettes. • Recent survey of e-cigarette users also self-reported use of tryptamines (7.0%), NBOMe (2,5-dimethoxy-4- bromophenethylamine) (6.9%) and ketamine (6.7%). • Of all the drugs analyzed in this study only gamma-hydroxybutyric acid (GHB) and 3,4-methylenedioxyamphetamine (MDA) were found to have no evidence of use in e-cigarettes in either the literature or on illicit drug forums. • This may be due to the well-established oral dosing behaviors of GHB, and the less frequent present-day abuse of MDA.
Main conclusion	• The review found evidence of current use of e-cigarettes to vape almost all illicit drug types analyzed.
Funding (related to tobacco industry; Yes/No)	• Nothing declared

First Author, Year, country	**(4) Hershberger 2017, USA**
Title	Electronic nicotine delivery system use is related to higher odds of alcohol and marijuana use in adolescents: Meta-analytic evidence
Target population (youth, young adults, adults, lab/in vitro; Gender)	• Human (male/Female) • 11+ (Adolescents and adults) • Sample: 150,299 for alcohol, 89,962 for marijuana
Objective/s (only those who are related to the domain)	• To quantify the extent to which EC use is associated with alcohol and marijuana use among adolescents and to compare the odds across adolescent samples and a comparison group of adult samples
Number of included articles	• 32 (as outcome 17 for marijuana, 32 for alcohol) • Cross-sectional • Longitudinal studies • Dissertations • Conference abstracts
Reported outcomes (name each outcome + results)	• Marijuana and alcohol use compared to non- • e-cigarette users: • Adolescents who use EC had greater odds of reporting co-occurring alcohol use (OR= 4.50, p< .001), particularly binge drinking (OR= 4.51), and marijuana use (OR= 6.04, p< .001) than adolescent who did not use EC. • Adults who use EC were also more likely to use alcohol (OR= 1.57, p< .001) and marijuana (OR= 2.04, p< .001) than those who did not use EC. • EC use was associated with significantly greater odds of alcohol use (log odds ratio; LOR= 0.96 (OR = 2.61), p< .001) and a trend of greater marijuana use (LOR =0.93 (OR = 2.53), p= 0.08) in adolescents than in adults. • Effects were large in adolescents and small in adults.
Main conclusion	• Findings suggest that EC use should be assessed in adolescents in both re-search and clinical settings • EC use is strongly associated with co-occurring alcohol or marijuana use in adolescents.
Funding (related to tobacco industry; Yes/No)	• F31 grant awarded by the National Institute of Alcohol Abuse and Alcoholism (NIAAA) to Alexandra Hershberger (F31 AA024682) under the mentorship of Melissa A. Cyders. • Not related to tobacco industry

3. Effect ENDS on improving smoking cessation (Domain 3)

First Author, Year, country	(1) Chan 2021, Australia
Title	A systematic review of randomized controlled trials and network meta-analysis of e-cigarettes for smoking cessation
Target population (youth, young adults, adults, lab/in vitro; Gender)	• Human.
Objective/s (only those who are related to the domain)	• Compare the effectiveness of nicotine e-cigarettes for smoking cessation with licensed nicotine replacement therapies (NRT) and nicotine-free based control conditions
Number of included articles	• 16 articles
Reported outcomes (name each outcome + results)	• Results from NMA without pilot studies indicated that participants in the nicotine e-cigarette condition were more likely to remain abstinent than those in the control condition (pooled RR = 2.13, 95% CI = [1.46, 3.11]), and those in an NRT condition (pooled RR = 1.48, 95% CI = [1.06, 2.06]) after adjusting for multiple comparisons. • Results from NMA with additional NRT studies from between 2010 and 2013 indicated that participants in the nicotine e-cigarette condition were more likely to remain abstinent than those in the control condition (pooled RR = 2.27, 95% CI = [1.55, 3.32]), and those in an NRT condition (pooled RR = 1.45, 95% CI = [1.03, 2.05]) after adjusting for multiple comparisons. • Results from NMA without studies that have less than 6 months of follow-up indicated that participants in the nicotine e-cigarette condition were more likely to remain abstinent than those in the control condition (pooled RR = 2.63, 95% CI = [1.70, 4.08]), and those in an NRT condition (pooled RR = 1.72, 95% CI = [1.16, 2.56]) after adjusting for multiple comparisons.
Main conclusion	• Study found that nicotine e-cigarettes are effective in helping smokers quit smoking.
Funding (related to tobacco industry; Yes/No)	• National Health and Medical Research Council, Australia. • Not related to tobacco industry.

First Author, Year, country	(2) Grabovac 2021, Austria
Title	Effectiveness of Electronic Cigarettes in Smoking Cessation: A Systematic Review and Meta-analysis.
Target population (youth, young adults, adults, lab/in vitro; Gender)	• Human.
Objective/s (only those who are related to the domain)	• Provide a summary of the current evidence landscape and to assess the strength and quality of evidence of e-cigarette effectiveness in smoking cessation in placebo trials and compared with other nicotine replacement products.
Number of included articles	• 9 articles
Reported outcomes (name each outcome + results)	• Comparing achieved smoking abstinence of participants who received nicotine e-cigarettes with participants who received non-nicotine placebo e-cigarettes, evidence in favor of nicotine e-cigarettes was modest. • In contrast, compared to nicotine replacement therapy and counseling alone, our meta-analysis showed evidence that nicotine e-cigarettes helped in smoking cessation. However, the evidence is not conclusive. Thus, offering clear recommendations may be too early. • Given the small number of included studies and their heterogeneous designs, the overall quality of evidence is moderate to low. More comparable data are needed to strengthen confidence in the quality of evidence. • RR= 1.71 [1.02.2.84]: RR for abstinence in nicotine e-cigarettes vs. placebo e-cigarettes- each study's last follow-up • RR= 1.41 [0.87,2,28]: RR for abstinence in nicotine e-cigarettes vs. placebo e-cigarettes- similar follow-up • RR= 1.73[1.31,2.28]: RR for abstinence in nicotine e-cigarettes vs. NRT and/or counseling- each study's last follow-up • RR= 1.49[1.24,1.78]: RR for abstinence in nicotine e-cigarettes vs. NRT and/or counseling- similar follow-up

Main conclusion	• Study found that there is modest evidence that nicotine e-cigarette is more effective in smoking cessation than non-nicotine placebo e-cigarettes.
Funding (related to tobacco industry; Yes/No)	• Health Insurance Group of Styria (Steiermärkische ebietskrankenkasse) • Not related to tobacco industry.

First Author, Year, country	**(3) Ibrahim 2021, Qatar**
Title	Efficacy of Electronic Cigarettes for Smoking Cessation: A Systematic Review and Meta-Analysis.
Target population (youth, young adults, adults, lab/in vitro; Gender)	• Human
Objective/s (only those who are related to the domain)	• To synthesize available evidence to assess the efficacy as well as safety of e-cigarettes versus different forms of NRT and placebo to quit smoking.
Number of included articles	• 12 articles
Reported outcomes (name each outcome + results)	***Sustained abstinence*** • CO- validated continuous abstinence rate did not differ significantly between comparison groups whether NRT or placebo along different follow up periods. • Biochemically validated 1-month continuous abstinence rate was borderline significant in the e-cigarettes group than control (5 studies, 32.6 vs 23.1%, N = 1970, RR 1.335, 95 % CI 1.068: 1.667). • 3-month and 6-month abstinence rate didn't differ significantly between E-cigarettes and control groups (3 Studies, 12.1 vs 12.8%, N = 1099, RR 1.52, 95% CI 0.348; 6.701) and (7studies, N = 5435, 10.2 vs 6.6%, RR 1.347, 95%CI 0.953; 1.903) respectively (Figure 4). • E-cigarettes didn't significantly improve 12-month abstinence than the control group (2 studies, N = 1184, RR 2.52, 95 % CI 0.00; 1444.26). ***Sustained reduction.*** • Sustained reduction of 50% or greater in baseline cigarette consumption was assessed in 5 studies across 1,2,3,6, and 12 months. Proportion of participants with sustained reduction didn't differ significantly between E-cigarette's arm and control arm either NRT or Placebo • at 1 month (3 studies, 50.9 vs 33.2%, N = 955, RR 1.29, 95 % CI 0.59; 2.82), • at 2 months (2 studies, 26.4 vs 21.9%, N = 330, RR 1.27, 95 % CI 0.08; 19.41), • at 3 Month (3 studies, 43.2 vs 25.3%, N = 1067, RR 1.36, 95 % CI 0.66; 2.79), • at 6 month (5 studies, 27.1 vs 13.4%, N = 1981, RR 1.38, 95 % CI 0.90; 2.11) or • at 12 months (1 study, 14.5 vs 12%, N = 300, RR 1.21, 95 % CI 0.64; 2.27) ***Seven-day point prevalence abstinence*** • There is insignificant difference between E-cigarettes and control group regarding 7-day point abstinence • at 1 month (3 studies, 37.4 vs 23.7%, N = 2166, RR 1.59, 95 % CI 0.84; 2.98), • at 3 months (3 studies, 31.6 vs 23%, N = 1424, RR 1.31, 95 % CI 0.56; 3.06), • at 4 month (1 study, 6.5 vs 4.5%, N = 68, RR 1.43, 95 % CI 0.16; 13.02) or • at 6 months (4 studies, 27.1 vs 21.1%, N = 2308, RR 1.30, 95 % CI 0.71; 2.38) (Figure 8). • However, only one study of 884 participants displayed improved point abstinence by 46% (improvement range 17-82%) in E-cigarettes group relative to control at 12 months (1study, 32.7 vs 22.3%, N = 884, RR 1.46, 95 % CI 1.17; 1.82). ***Adverse effects.*** • Four studies assessed adverse effects at 6- month follow-up and 2 studies at 12-month follow-up. While insignificant difference was detected between E-cigarettes and control groups in the proportion of serious adverse effects at 6- and 12-month follow-up • Nature of non-serious adverse effects reported at 6 months was dry mouth, mouth irritation, breath shortness, throat irritation, headache in 3 studies.
Main conclusion	• There is low certainty evidence that e-cigarettes improve short term (1-month) continuous abstinence rate. We are uncertain whether improvement involves 12-month long-term follow up period given very serious imprecise results from only 2 clinical trials. We are uncertain if e-cigarettes compared to control whether NRT or placebo influence 7-day point prevalence abstinence rate at 1,3 and 6-month follow up.

	Moderate certainty evidence suggests that e-cigarettes are likely to improve 7-day point abstinence rate at 1-year as evidenced from only one clinical trial. There is very low certainty evidence of effect of e-cigarettes compared to control whether NRT or placebo on sustained reduction. The proportion of serious adverse effect at 6 and 12 months follow up may not differ between e-cigarettes and control groups. There is not enough evidence to determine if e-cigarettes are a safe and efficacious means of smoking cessation in the long term (12þ months)
Funding (related to tobacco industry; Yes/No)	• No financial support • Not related to tobacco industry.

First Author, Year, country	**(4) Barufaldi 2021, Brazil**
Title	Risk of smoking relapse with the use of electronic cigarettes: A systematic review with meta-analysis of longitudinal studies.
Target population (youth, young adults, adults, lab/in vitro; Gender)	• Human. • Male and female • Age: 43–48
Objective/s (only those who are related to the domain)	• To synthesize the risk of smoking relapse with the use of e-cigarettes by former smokers.
Number of included articles	• 6 articles
Reported outcomes (name each outcome + results)	• Risk of relapse was 2.03 (95% CI: 1.39–2.96) among former smoker users than non-users of e-cigarettes, and 1.38 (95% CI: 1.11–1.65) when pooling the adjusted association measures. Long-term former smokers were the main contributors for the higher relapse risk, while the impact of frequency of exposure to e-cigarettes (past, non-daily, daily) was uncertain.
Main conclusion	• There is an increased risk of smoking relapse among users of e-cigarettes. Results point to their great potential to increase the frequency of relapse to conventional smoking, besides moving to the regular use of e-cigarettes.
Funding (related to tobacco industry; Yes/No)	• Institutional Development Program of the National Cancer Institute José Alencar Gomes da Silva (INCA). • Foundation for Research Support in the State of Rio de Janeiro (FAPERJ) • Not related to tobacco industry.

First Author, Year, country	**(5) Zhang 2021, China**
Title	The effect of e-cigarettes on smoking cessation and cigarette smoking initiation: An evidence-based rapid review and meta-analysis.
Target population (youth, young adults, adults, lab/in vitro; Gender)	• Human. • Male and female • Youth and adults (14 – 85)
Objective/s (only those who are related to the domain)	• Evaluate the effects of e-cigarettes on smoking cessation among smokers and the risks for smoking initiation among non-smoking adolescents, and their safety
Number of included articles	• Qualitative synthesis: 35 articles • Quantitative synthesis: 29 articles
Reported outcomes (name each outcome + results)	5 meta-analysis: • 8.2% smokers achieved cessation in the EC group versus 5.6% in the control group (RR=1.55; 95% CI: 1.00–2.40; I2 =57.6%; low certainty; 5 trials, n=4025). 9 cohort studies: • EC use was not associated with smoking cessation (AOR=1.16; 95% CI: 0.88–1.54; I2=69.0%; 9 trials; n=22220). • Intensive EC use was more effective in achieving cessation than non-EC use (AOR= 2.03; 95% CI: 1.35–3.05; I2=37.8%; 4 trials, n=1144)
Main conclusion	• Low certainty evidence suggests that e-cigarettes appear to be potentially effective for smoking cessation.
Funding (related to tobacco industry; Yes/No)	• National Natural Science Foundation of China (No.81830115). • Overseas Expertise Project, Ministry of Education of China • Not related to tobacco industry.

First Author, Year, country	(6) Calder, 2021, 17 studies from the US, 3 from the UK, 1 from Ireland, 2 not restricted to a specific country
Title	**Vaping in pregnancy: A systematic review**
Target population (youth, young adults, adults, lab/in vitro; Gender)	• Pregnant women
Objective/s (only those who are related to the domain)	• What are the effects of vaping on smoking cessation or reduction during pregnancy and postpartum? • Which health outcomes have been reported in studies of vaping in pregnancy and what findings have been reported for these outcomes?
Number of included articles	• 23 studies (11 survey, 7 qualitative, 3 cohort, and 2 secondary analyses of RCT) • 3 studies reported health-related outcomes
Reported outcomes (name each outcome + results)	***Smoking cessation:*** • 5 quantitative studies of poor, fair, and good quality and 1 qualitative study that scored 16 of 32 on the COREQ checklist were included for this outcome • 1 good-quality longitudinal study of 428 pregnant women (36 women had vaped in the past 7 days and 392 women had not). • At 1-month follow-up, those who vaped had similar odds as those who did not vape, of having quit smoking for 7 d and of having attempted to quit smoking • Made quit attempt of at least one day: Vaped at baseline: 69.4% (25); did not vape at baseline: 67.6% (265); OR (95% CI): 1.09 (0.52 to 2.28); adjusted OR (95% CI): 1.20 (0.56 to 2.55). • Reduction in cigarettes per day, mean (standard deviation): Vaped at baseline: 3.39 (5.5), Did not vape at baseline: 3.4 (5.0). • 1 study analyzing the content of online forums reported posts from women saying that: • They had quit smoking when pregnant using vaping products • Had then continued to vape to remain abstinent from cigarettes postpartum ***Health Outcomes:*** • 3 articles of fair and good quality published data on pregnancy and birth health outcomes • 1 study conducted in Ireland found that: • Mean birthweight of babies born to mothers who vaped (n = 218) in the last trimester of their pregnancy was very similar (within 1 g) to those born to nonsmoking mothers who neither smoked or vaped (n = 108; 3470 ± 555 g and 3471 ± 504 g respectively; p = .97) and was significantly higher than that birthweight of babies born to mothers who smoked (n = 99; 3166 ± 504 g; p < .001) • The birth centile of babies born to mothers who vaped and to mothers who did not smoke or vape were similar, and both were significantly higher than those born to mothers who smoked. • For mothers who both vaped and smoked (dual users), the outcomes for birthweight, birth centile, and breastfeeding rates at discharge were similar to those for smokers • 2 articles reported data from 1 US cohort study of 248 pregnant women, of whom 6 were exclusive vapers, 17 were dual users, 56 were current smokers, and 64 were unexposed (including secondhand exposure): ***Risk of smallness for gestational age:*** • Unexposed, including to second-hand exposure (n=97): 11.3%, referent • Dual (vapes and cigarettes) users (n=17): 23.5%; RR (95% CI) = 2.1 (0.7-5.8) • Vapes only (n=6): 33.3%; RR (95% CI) = 2.9 (0.8-10.4) • Current smokers only (n=56): 23.1% RR (95% CI) = 2.0 (1.0-4.3) • After removing inconsistent self-report for 'unexposed group' and adjusting for maternal age and race/ethnicity: • Unexposed, incl to second-hand exposure (n=64): 7.8%, referent • Dual (vapes and cigarettes) users (n=17): 23.5%; RR (95% CI) = 2.5 (0.7-8.8) • Vapes only (n=6): 33.3%; RR (95% CI) = 5.1 (1.2-22.2) • Current smokers only (n=56): 23.1% RR (95% CI) = 2.6 (0.9-7.2) • Raw levels of cotinine and the tobacco-specific nitrosamines NNK and NNAL were higher among dual users than among those not exposed to smoking or vaping, but these differences were nonsignificant (small sample sizes) • When splitting the sample by nicotine level, those with higher nicotine levels (smokers and dual users) had an increased risk of babies that were small for gestational age.

Main conclusion	• There were insufficient data available to assess the efficacy of vaping for smoking cessation in pregnant women. • Other findings highlighted no difference between vapers and non-vapers in smoking cessation, although 1 study indicated that cessation effects from vaping might have been obscured by heightened motivation to quit smoking among all pregnant women • The small literature on birth outcomes of vaping in pregnancy suggest that birthweight and birth centile outcomes from mothers who vape during pregnancy may be similar to those for babies born to mothers who neither smoke or vape, and better than for babies born to mothers who smoke • The data reviewed here are insufficient to draw any firm conclusions for practice or policy. • It appears that vaping has less of a detrimental effect on birthweight outcomes than smoking, so pregnant smokers struggling with smoking cessation could benefit from using vaping products in attempts to quit smoking. • However, more research would increase the confidence of this recommendation.
Funding (source; related to tobacco industry – Yes/No)	• Robert Calder post is part funded by a grant from Public Health England (ECM_7125). • Not related to tobacco industry

First Author, Year, country	**(7) Wang 2021, USA**
Title	E-Cigarette Use and Adult Cigarette Smoking Cessation: A Meta-Analysis
Target population (youth, young adults, adults, lab/in vitro; Gender)	• Human (both male and female)
Objective/s (only those who are related to the domain)	• To determine the association between e-cigarette use and smoking cessation.
Number of included articles	• 64 papers (55 observational studies and 9 randomized clinical trials [RCTs])
Reported outcomes (name each outcome + results)	• In observational studies of all adult smokers (odds ratio [OR] = 0.947; 95% confidence interval [CI] = 0.772, 1.160) and smokers motivated to quit smoking (OR = 0.851; 95% CI = 0.684, 1.057), e-cigarette consumer product use was not associated with quitting. • Daily e-cigarette use was associated with more quitting (OR = 1.529; 95% CI = 1.158, 2.019) • Less-than-daily use was associated with less quitting (OR = 0.514; 95% CI = 0.402, 0.665). • The RCTs that compared quitting among smokers who were provided e-cigarettes to smokers with conventional therapy found e-cigarette use was associated with more quitting (relative risk = 1.555; 95% CI = 1.173, 2.061).
Main conclusion	• E-cigarettes were not associated with increased smoking cessation in the adult population in observational studies. • Provision of free e-cigarettes as a therapeutic intervention was associated with increased smoking cessation in RCTs.
Funding (source; related to tobacco industry – Yes/No)	• This study was supported by National Heart, Lung, and Blood Institute grants F32HL144063 and K12HL143961 (R. J. W.), T32HL007185 (S. B.), and cooperative agreement U54HL147127 from the National Heart, Lung, and Blood Institute and the Food and Drug Administration Center for Tobacco Products (S. A. G.) • Not related to tobacco industry

First Author, Year, country	**(8) Pound,2021, Canada**
Title	Smoking cessation in individuals who use vaping as compared with traditional nicotine replacement therapies: a systematic review and meta-analysis
Target population (youth, young adults, adults, lab/in vitro; Gender)	• Human (both male and female)
Objective/s (only those who are related to the domain)	• To determine the effect of e-cigarette on cigarette smoking cessation, as compared with other types of nicotine replacement therapies (NRT) • All included studies compared ENDS with non-electronic NRT. NRT comprised, but were not limited to, nicotine patch, gum, lozenge, nasal spray, inhalator, mouth spray, mouth strips, microtabs and combination of products

Number of included articles	• 6
Reported outcomes (name each outcome + results)	Pooled results showed no difference between groups in: ➢ Smoking cessation (rate ratio (RR) 1.42, 95% CI 0.97 to 2.09) ➢ Proportion of participants reducing smoking consumption (RR 1.25, 95% CI 0.79 to 1.98) ➢ Mean reduction in cigarettes smoked per day (mean difference 1.11, 95% CI −0.41 to 2.63), or harms (RR 0.96, 95% CI 0.76 to 1.20)
Main conclusion	• No difference in smoking cessation, harms and smoking reduction between e-cigarette and NRT users. • The quality of the evidence was low.
Funding (source; related to tobacco industry – Yes/No)	• The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors. • Not related to tobacco industry

First Author, Year, country	**(9) Hartmann-Boyce, 2020, Not specified**
Title	Electronic cigarettes for smoking cessation.
Target population (youth, young adults, adults, lab/in vitro; Gender)	• Current smokers (18 years and older)
Objective/s (only those who are related to the domain)	• To evaluate the safety and effect of using ECs to help people who smoke achieve long-term smoking abstinence.
Number of included articles	• 24 (3 RCTs, and 21 cohort studies)
Reported outcomes (name each outcome + results)	• Participants using an EC were more likely to have abstained from smoking for at least six months compared with participants using placebo EC (RR 2.29, 95% CI 1.05 to 4.96; placebo 4% versus EC 9%; 2 studies; 662 participants. GRADE: low). **Cessation: Nicotine EC versus placebo EC** assessed with exhaled CO ➢ Follow-up: 6 - 12 months ➢ Control: 40 per 1000 ➢ Electronic cigarettes: 93 per 1000 (42 to 201) ➢ Relative effect: RR 2.29 (1.05 to 4.96) ➢ Total number of participants: 662 (2 studies) • The one study that compared EC to nicotine patch found no significant difference in six-month abstinence rates, but the confidence intervals do not rule out a clinically important difference (RR 1.26, 95% CI 0.68 to 2.34; 584 participants. GRADE: very low). • Cessation: **1 study:** Nicotine EC versus nicotine replacement therapy assessed with exhaled CO ➢ Follow-up: 6 months ➢ Control: 58 per 1000 ➢ Electronic cigarettes: 73 per 1000 (39 to 135) ➢ RR 1.26 (0.68 to 2.34)
Main conclusion	• There is evidence from 2 trials that ECs help smokers to stop smoking in the long term compared with placebo ECs. • The study could not determine if EC was better than a nicotine patch in helping people stop smoking, because the number of participants in the study was low. • More studies are needed to evaluate this effect. • None of the studies found that smokers who used EC short- to mid-term (for two years or less) had an increased health risk compared to smokers who did not use ECs. • However, the small number of trials, low event rates and wide confidence intervals around the estimates mean that the confidence in the result is rated 'low' by GRADE standards
Funding (related to tobacco industry; Yes/No)	***Internal sources*** • Queen Mary University of London, UK: provides salary, office space and library resources for HM and PH • The University of Auckland, New Zealand: provides salary, office space and library resources for CB ***External sources*** • No sources of support supplied • Not related to tobacco industry

First Author, Year, country	(10) Patil 2020, India
Title	Are electronic nicotine delivery systems (ENDs) helping cigarette smokers quit? Current evidence.
Target population (youth, young adults, adults, lab/in vitro; Gender)	• Adults aged 18-65 years. • Clinical trials (randomized controlled trial) and/or observational studies (case-control, cross-sectional or population-based) that recruited patients who used e-cigarettes to stop their tobacco habits were included.
Objective/s (only those who are related to the domain)	• To explore the role of e-cigarettes in tobacco cessation among tobacco users.
Number of included articles	• 13
Reported outcomes (name each outcome + results)	Tobacco cessation • All studies that assessed smoking cessation in e-cigarette users had the outcome compared with those who did not use e-cigarettes. • The majority of studies showed a decreased smoking cessation among e-cigarettes users, five of which indicated statistically significant results. • One study reported a significantly increased smoking cessation among e-cigarette users who smoked e-cigarettes daily for one month. • No significant decrease in smoking cessation was observed among intermittent e-cigarette users.
Main conclusion	• The odds of increased smoking cessation in association with e-cigarette use ranged from onefold to six folds. • No significant increase in smoking cessation was found among e-cigarette users compared with non–e-cigarette users. • Pattern of e-cigarette may have significant effect on smoking cessation capability of e-cigarettes. • Well-designed randomized controlled clinical trials are needed to assess the clinical efficacy of e-cigarettes in comparison with approved smoking cessation therapies.
Funding (source; related to tobacco industry – Yes/No)	• No funding information. • Not related to tobacco industry.

First Author, Year, country	(11) Gentry, 2019, USA, Australia, Italy, New Zealand
Title	Are Electronic Cigarettes an Effective Aid to Smoking Cessation or Reduction Among Vulnerable Groups? A Systematic Review of Quantitative and Qualitative Evidence
Target population (youth, young adults, adults, lab/in vitro; Gender)	• Participants and carers' of any age in any country/setting in at least one of the following vulnerable groups: o Mental illness o Substance misuse o Homeless o Criminal justice system
Objective/s (only those who are related to the domain)	• Are e-cigarettes effective and cost-effective for smoking cessation or reduction for vulnerable groups?
Number of included articles	9 (5 quantitative, 4 qualitative)
Reported outcomes (name each outcome + results)	**Smoking Cessation:** • Study 1: Mean (SD) reduction in cigarettes smoked per day (among those who did not quit) from baseline to follow-up: Total N= 86 (time of follow-up: 26 weeks); P-value o Intervention group 1: 9.9 (7); 0.035 (patch vs. 16 mg e-cig) o Intervention group 2: 4.7 (3.5); 0.068 (16 mg e-cig vs. 0 mg e-cig) o Control: 5.7 (6.3); 0.083 (patch vs. combined e-cig) **Smoking reduction in uncontrolled before and after studies:** **Cigarettes per day:** **Study 1: Total participants: 12; Mean at baseline: 17.8** o Week 3: **Mean**: 5.4, **Mean reduction**: -12.4 (**95% CI**= -15.0; -9.9) o Week 5: 3.0, -14.8 (-17.4; -12.2) o Week 7: 3.9, -13.9 (-16.6;-11.2) o Week 9: 7.0, -10.8 (-13.4;-8.2) **Study 2: Total participants: 14; Mean at baseline: 19**

	○ Week 52: **Mean:** 13, **Mean reduction:** -6 **Study 3: Total participants: 21; Mean at baseline: 27** ○ Week 4: 10, -17 **<u>Cigarettes per week:</u>** **Study 3: Total participants: 21; Mean at baseline: 191.9** ○ Week 4: 66.7 (SD = 76.3), -125.2 **Interpretation:** • Smoking cessation varied from 0.0% to 14.3%. • 3 studies included people with mental illness and 1, people on methadone. • 3 studies were rated as weak on quality appraisal and included fewer than 30 participants, making statistical analyses potentially unreliable. • The 4th was rated moderate and was the only study with a control group. There were no significant differences between nicotine e-cigarette, non-nicotine e-cigarette, and NRT; however, this secondary analysis of an RCT had limited power. • 1 observational study involving people with mental illness found no significant difference between e-cigarette users and nonusers. • Participants were part of an RCT comparing brief, extended, and usual smoking cessation treatment, so may not be representative of wider mental illness populations. **<u>Smoking reduction:</u>** Observation prospective study: Time to follow-up: 18 months **Reduction in cigarettes per day**: • E-cigarette users: -7.1 (SD= 12.5) • Non-e-cigarette users: -6.6 (SD= 11.0) • P-value: 0.730 **Cigarettes per day:** • E-cigarette users: 10 (8.9) • Non-e-cigarette users: 10.1 (9.0) • P-value: 0.915 **≥50% reduction:** • E-cigarette users: 51% • Non-e-cigarette users: 51% • P-value: 0.978 **RCT secondary analysis: outcome: biochemically verified continuous abstinence** • Total participants: 86 (follow-up: 26 weeks) • Intervention group 1: 2 out of 39 (5.1%) • Intervention group 2: 0 out of 12 (0.0%) • Control: 5 out of 35 (14.3%) • P-value: 0.245 (patch vs. 16 mg e-cig)- (16 mg vs. 0 mg e-cig); 0.115 (patch vs. combined e-cig) **Observational studies:** • Outcome: Tobacco abstinence: Total participants: 956, time to follow-up: 18 months; • E-cigarette users: 21% • Non-e-cigarette users: 19% • P-value: 0.726 **Interpretation:** • A moderate quality study of people on medication for mental illness suggested a reduction of 9.9 cigarettes/day among 16 mg nicotine e-cigarette users compared with 5.7 among patch users. • This difference was statistically significant and, if sustained, may lead to clinically significant differences, but the study lasted only 26 weeks and • included only 86 participants. • There was some evidence from 3 weak quality uncontrolled before and after studies of statistically significant smoking reduction from baseline to follow-up for participants with mental illness and substance misuse. • Reduction was confirmed with eCO among those with mental illness. However, as there was no control group, it is unclear if these reductions would have occurred without e-cigarettes.

	• An observational study found no significant reduction in smoking among e-cigarette users
Main conclusion	• Due to the low quality of available evidence, it is uncertain whether e-cigarettes are effective for smoking cessation for vulnerable groups. There was some evidence from a moderate quality study that e-cigarettes were as effective as NRT for smoking cessation. • There was some evidence from 4 studies of statistically and clinically significant smoking reduction, however, 3 were uncontrolled and had sample sizes less than 30. • However, included studies identified no serious adverse events and qualitative studies suggested e-cigarettes could attain to key aspects of smoking addiction, including habit and social connectedness.
Funding (related to tobacco industry; Yes/No)	• Not reported

First Author, Year, country	**(12) Maglia, 2018, Italy**
Title	Dual use of electronic cigarettes and classic cigarettes: a systematic review
Target population (youth, young adults, adults, lab/in vitro; Gender)	• Youths, adults, and special populations (cancer, schizophrenia and asthma patients). • Both male and female.
Objective/s (only those who are related to the domain)	• To summarize the literature focused on dual use of the e-cigarette and classic cigarette.
Number of included articles	• 76
Reported outcomes (name each outcome + results)	***Cessation:*** • 13-48% quit smoking at 1-month follow-up. • 31% quit at 6 months follow-up. • 46% quit at 1 year follow up. ***Reduction:*** • Reduced from 22.4 cig per day at baseline to 3.9 at 6 months. • Reduced 5.3 cigarettes per day at one month and one year.
Main conclusion	• Dual users make use of e-cigarettes for smoking reduction and smoking cessation. • Dual users are more likely to use tobacco cigarettes in hedonistic situations, when there is no restriction of use, or when stressed and/or anxious. Situations such as these might be the most difficult circum-stances to dissuade dual users from classic smoking.
Funding (related to tobacco industry; Yes/No)	• Not reported.

First Author, Year, country	**(13) Liu 2018, China**
Title	Efficiency and adverse events of electronic cigarettes: A systematic review and meta-analysis (PRISMA-compliant article).
Target population (youth, young adults, adults, lab/in vitro; Gender)	• Human (male/female) • Age: Not reported • Sample: 35665
Objective/s (only those who are related to the domain)	To assess the efficiency of e-cigarettes on smoking reduction and smoking cessation together with their adverse events using meta-analysis that scientifically summarized all of the existing studies.
Number of included articles	• 14: • Observational studies (7), • Online surveys (4), • Randomized controlled trials (3) • Adverse events of e-cigarettes found in 11 studies • Nicotine dose in e-cigarettes (mg/mL): • <16: for 6 studies • ≥16: for 7 studies
Reported outcomes (name each outcome + results)	• Smoking cessation: • The pooled efficacy rate of e-cigarettes ranged from 48.3% to 58.7% for smoking reduction and from 13.2% to 22.9% for smoking cessation.

	• Individuals smoked e-cigarettes less than 12 months were easier to cut down their cigarettes use than those who smoked longer than 12 months (pooled rate 67.6% vs 37.1%) (P<.05). • Smokers who smoke ≥3 cartridges/day were easier to quit than those whom smoked 1 to 2 cartridges/day (68.6 vs 50.8) (P=.103). • Individuals who smoked cigarettes less than 20 years were easier to quit than those who smoked cigarettes over 20 years (27.7% vs 12.1%) (P<.05). • Individuals who smoked less than 20 cigarettes/day were easier to quit than those who smoked over 20 cigarettes/day (23.7% vs 19.2%) (P<.05). • No significant difference was observed in smoking cessation between the individuals who smoked longer or less than 12 months (P=.06)
Main conclusion	• E-cigarettes are the promising smoking substitute for cutting down smoking and quitting smoking by potentially diminishing the attractiveness or temptation of nicotine cigarettes smoking • Study findings suggest that e-cigarettes are moderately effective with regard to smoking reduction and smoking cessation
Funding (related to tobacco industry; Yes/No)	• Not reported • Not related to tobacco industry

First Author, Year, country	**(14) El Dib, 2017, Brazil**
Title	Electronic nicotine delivery systems and/or electronic non-nicotine delivery systems for tobacco smoking cessation or reduction: a systematic review and meta-analysis.
Target population (youth, young adults, adults, lab/in vitro; Gender)	• Human (male/female) • Age: 18+ • Sample: • RCT: 1007 • Cohort: 13115
Objective/s (only those who are related to the domain)	Investigate the impact of electronic nicotine delivery systems (ENDS) and/or electronic non-nicotine delivery systems (ENNDS) versus no smoking cessation aid, or alternative smoking cessation aids, in cigarette smokers on long-term tobacco use
Number of included articles	• 12 • Randomized controlled trials (RCTs) (3) • Prospective cohort studies (9)
Reported outcomes (name each outcome + results)	• Smoking cessation compared to no smoking cessation aid, alternative non-electronic smoking cessation aid, including NRT, behavioural and/or pharmacological cessation aids (eg, bupropion and varenicline) and alternative electronic smoking cessation aid (ENDS or ENNDS): • Based on pooled data from two RCT with 481 participants, the study found evidence for a possible increase in tobacco smoking cessation with ENDS in comparison with ENNDS. • Smoking cessation with ENDS in comparison with ENNDS: RR 2.03, 95% CI 0.94 to 4.38; p=0.07; I2=0%, risk difference (RD) • The adjusted OR from primary meta-analysis of eight cohort studies comparing ENDS with no ENDS without reported concomitant interventions failed to show a benefit in cessation smoking: (OR 0.74, 95% CI0.55 to 1.00; p=0.051; I2=56% • Two RCTs results failed to show a difference between ENDS-type cigalikes versus ENNDS group with regards to reduction in cigarettes but with a very wide CI: (RR 0.97, 95% CI 0.57 to 1.66; p=0.92; I2=61%). • The evidence is, however, of low certainty: the 95% CI of the relative risk crossed 1.0 and a plausible worse case sensitivity analysis to assess the risks of bias associated with missing participant data yielded results that were inconsistent with the primary complete case analysis.
Main conclusion	• There is very limited evidence regarding the impact of ENDS or ENNDS on tobacco smoking cessation, reduction or adverse effects: data from RCTs are of low certainty and observational studies of very low certainty. • The limitations of the cohort studies led us to a rating of very low-certainty evidence from which no credible inferences can be drawn. • Lack of usefulness with regard to address the question of e-cigarettes' efficacy on smoking reduction and cessation was largely due to poor reporting.

	• This review underlines the need to conduct well-designed trials measuring biochemically validated outcomes and adverse effects
Funding (related to tobacco industry; Yes/No)	• WHO Grant • Not related to tobacco industry

First Author, Year, country	**(15) Glasser, 2017, USA**
Title	Overview of Electronic Nicotine Delivery Systems: A Systematic Review.
Target population (youth, young adults, adults, lab/in vitro; Gender)	• Human, animal • No information on age, gender, sample • Biomarker used: Nicotine, pulmonary, cardiovascular, cytotoxicity, blood, urine, cell, body weight and motor performance
Objective/s (only those who are related to the domain)	• To report updated findings from a comprehensive review of the published scientific literature on ENDS.
Number of included articles	• 687 • experimental studies, quasi-experimental studies, observational studies (including case control, cohort and cross-sectional studies), case reports, case series, qualitative studies, mixed methods, preclinical/animal studies
Reported outcomes (name each outcome + results)	• Smoking cessation compared to NRT: • ENDS products are highly variable. A standardized method is needed to characterize products with respect to nicotine and toxicant delivery and their potential harms, both relative to smoking and relative to no use (absolute harm). • The field lacks consistent definitions of types of users and patterns of use, which complicates the interpretation of research findings. • Many studies have small sample or cell sizes and employ convenience samples, raising concerns about selection bias, unmeasured confounders, low statistical power, and limited generalizability to draw firm national public health or policy conclusions. • There exist gaps in the current evidence base, including longitudinal data and data on reasons for vaping and use trajectories (including polytobacco use and use of cessation aids) that may help to explain population impacts and changing trends. • Caution must be exercised when drawing conclusions from in vitro, or cellular, studies because effects on cells cannot be readily extrapolated to human harms.
Main conclusion	• More research, especially independent, high-quality RCTs with appropriate measures and control group is needed to further determine whether and how ENDS can be an effective cigarette-cessation or - reduction aids.
Funding (related to tobacco industry; Yes/No)	• Financial support for this study was provided by The Schroeder Institute at Truth Initiative, the Robert Wood Johnson Foundation (Grant ID: 72208 and 72390), and a NIH K01 Career Development Award in Tobacco Control Regulatory Research (Principal Investigator, Pearson; 1K01DA037950-01). The funding agreement ensured the authors are independence in designing the study, interpreting the data, writing, and publishing the report. • Not related to tobacco industry

First Author, Year, country	**(16) Kalkhoran, 2016, USA**
Title	E-cigarettes and smoking cessation in real-world and clinical settings: a systematic review and meta-analysis.
Target population (youth, young adults, adults, lab/in vitro; Gender)	• Human studies • 40,878 in total sample • 15 and above: Considered all study populations that were defined as “adult” by the study authors (youngest age varied from 15 to 30 years)
Objective/s (only those who are related to the domain)	• To assess the association between e-cigarette use and cigarette smoking cessation among adult cigarette smokers, irrespective of their motivation for using e-cigarettes.
Number of included articles	• 38 studies (of 577 studies identified). • 20 studies with control groups (15 cohort studies, three cross-sectional studies, and two clinical trials) were included in random effects meta-analysis and sensitivity analyses.

Reported outcomes (name each outcome + results)	• Point estimates in 13 of the 15 longitudinal studies indicated decreased smoking cessation among those who used e-cigarettes, six of which reported statistically significant results. • 2 of 3 cross-sectional studies showed significantly lower smoking cessation among smokers using e-cigarettes compared with those who did not, and the other study (of smokers who had made a quit attempt in the past year) found significantly higher smoking cessation in those who used e-cigarettes compared with those who used NRT or no smoking cessation aid. • The one randomised controlled trial comparing cigarette quit rates of e-cigarette users with those of NRT users showed a non-significant increase in quitting associated with e-cigarette use. • For trials without control groups (ie, all participants used e-cigarettes), cigarette quit rates ranged from 12·5% to more than 40%. • 19 real-world estimates of the relationship between e-cigarette use and quitting smoking) and the two clinical trials in a random effects meta-analysis (figures 2, 3) indicated that the odds of quitting smoking were 28% lower in those who used e-cigarettes compared with those who did not use e-cigarettes (OR 0·72, 95% CI 0·57–0·91). • Studies that included only smokers interested in quitting cigarettes yielded a pooled OR for quitting of 0·86 (0·60–1·23) for those using e-cigarettes compared with those not using e-cigarettes. Studies of all smokers (irrespective of motivation to quit) yielded a pooled OR of 0·63 (0·45–0·86), which is not significantly different from studies limited to smokers interested in quitting (p=0·94). • All of the observational studies had low risk of selection bias, half (nine of 18) controlled for confounders, and seven of 15 longitudinal studies had follow-up periods of at least 6 months (appendix).
Main conclusion	• Odds of quitting cigarettes were 28% lower in those who used e-cigarettes compared with those who did not use e-cigarettes (odds ratio [OR] 0·72, 95% CI 0·57–0·91). • Association of e-cigarette use with quitting did not significantly diff er among studies of all smokers using e-cigarettes (irrespective of interest in quitting cigarettes) compared with studies of only smokers interested in cigarette cessation (OR 0·63, 95% CI 0·45–0·86 vs 0·86, 0·60–1·23; p=0·94). • Other study characteristics (design, population, comparison group, control variables, time of exposure assessment, biochemical verification of abstinence, and definition of e-cigarette use) were also not associated with the overall effect size (p≥0·77 in all cases).
Funding (related to tobacco industry; Yes/No)	• SK's work was supported by NIH NRSA T32HP19025. SAG's work reported in this publication was supported by grant 1P50CA180890 from the National Cancer Institute and FDA Center for Tobacco Products (CTP). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health or the Food and Drug Administration. • National Institutes of Health, National Cancer Institute, FDA Center for Tobacco Product. • Not related to tobacco industry.

First Author, Year, country	**(17) Khoudigian 2016, Canada**
Title	• The efficacy and short-term effects of electronic cigarettes as a method for smoking cessation: a systematic review and a meta-analysis.
Target population (youth, young adults, adults, lab/in vitro; Gender)	• Human (male/female) • Age: 18 +
Objective/s (only those who are related to the domain)	• Smoking cessation: To assess the efficacy of e-cigarettes for smoking cessation as well as desire to smoke, withdrawal symptoms, and adverse events in adult smokers compared with other nicotine replacement therapies (e.g., nicotine patches, nicotine gums, nicotine inhalers etc.) or placebo-containing e-cigarettes
Number of included articles	• 5 • Randomized controlled trials (RCTs) or comparative observational studies • Follow up (1 day to 9 months)

Reported outcomes (name each outcome + results)	• Study participants were more likely to stop smoking when using nicotine e-cigarettes (43/489, 9 %) versus placebo e-cigarettes (8/173, 5 %); however, this difference was not statistically significant (RR 2.02; 95 % CI 0.97, 4.22). • The pooled effect estimates for the desire to smoke (RR -0.22;95 % CI -0.80, 0.36), irritability (RR -0.03; 95% CI -0.38, 0.31), restlessness (RR -0.03; 95 % CI -0.42, 0.35), poor concentration (RR -0.01; 95 % CI -0.35, 0.32), depression (RR -0.01; 95 % CI -0.22, 0.20), hunger (RR -0.01; 95 % CI -0.32, 0.30), and average number of non-serious adverse events (RR -0.09; 95 % CI -0.28, 0.46) were not statistically significantly different. • Only one study reported serious adverse events with no apparent association with e-cigarette use. • Risk ratio: 2.02 [0.97, 4.22]: Comparison of smoking abstinence between Nicotine e-cigarette and placebo e-cigarette • Mean difference: -0.22 [-1.65, 0.45]: Comparison of desire to smoke between nicotine e-cigarette and placebo e-cigarette
Main conclusion	• This review only included comparative studies and conducted meta-analyses to achieve greater statistical power for more precise estimates of the outcomes of interest. It suggests that the use of nicotine e-cigarette increased the proportion of patients who stopped smoking, although this change was not statistically significant. Importantly, the lower-bound 95 % CI of the estimate of treatment effect, or the most conservative estimate, suggested only a 3 % decrease in smoking abstinence among the intervention group. Thus, the finding of this review does not suggest that e-cigarettes are likely to be counterproductive for smoking abstinence among healthy adult smokers, whether or not they were willing to quit.
Funding (source; related to tobacco industry – Yes/No)	• The author(s) received no financial support for the research, authorship, and/or publication of this article. • Not related to tobacco industry

First Author, Year, country	**(18) Malas 2016, Canada**
Title	• Electronic Cigarettes for Smoking Cessation: A Systematic Review
Target population (youth, young adults, adults, lab/in vitro; Gender)	• Human, both male and female
Objective/s (only those who are related to the domain)	• To examine the effectiveness of e-cigarettes as smoking cessation aids in terms of smoking abstinence and reduction.
Number of included articles	• 62
Reported outcomes (name each outcome + results)	• Smoking Abstinence Abstinence (no duration specified): compared to NRT (AOR=1.63 (1.17-2.27)) compared to no aid (AOR=1.61 (1.19-2.18)) Abstinence at 6-month follow-up or longer: No control (AOR=0.10 (0.05-0.22)-6.07 (1.11-33.18) • Reduction At 6-month follow up or longer: % participants more than 50% reduction No control: 30% Compared to NRT: 57% compared to 41%
Main conclusion	• While the majority of studies demonstrate a positive relationship between e-cigarette use and smoking cessation, the evidence remains inconclusive due to the low quality of the research published to date. Well-designed randomized controlled trials and longitudinal, population studies are needed to further elucidate the role of e-cigarettes in smoking cessation
Funding (source; related to tobacco industry – Yes/No)	• This work was supported by the Ministry of Health and Long-Term Care (Ontario, Canada) through a Health System Research Fund (HSRF) award (grant number 06699). • Not related to tobacco industry

First Author, Year, country	(19) Gualano, 2014, Italy
Title	Electronic cigarettes: assessing the efficacy and the adverse effects through a systematic review of published studies.
Target population (youth, young adults, adults, lab/in vitro; Gender)	• Human studies. • Observational studies and experimental studies.
Objective/s (only those who are related to the domain)	• Smoking reduction. • Smoking cessation.
Number of included articles	• 12 relevant studies
Reported outcomes (name each outcome + results)	***Efficacy (reduction of desire to smoke and/or number of cigarettes smoked)*** • Experimental studies: The authors found that 57% of the e-cigarettes group reduced daily cigarettes by at least half at 6 months than in the patches group (41%; P = 0.0002) and in the placebo e-cigarettes group (45%; P = 0.08). An abstinence at 6 months after quit day of 7.3% in the nicotine e-cigarettes group, followed by the patches group (5.8%), and placebo e-cigarettes group (4.1%; P = 0.44) were observed. Moreover, the median time to relapse in the nicotine e-cigarettes group was 35 days, more than twice as long as in the patches group (14 days, P< 0.0001) or placebo e-cigarettes group (12 days, P = 0.09). • Cohort studies: two cohort studies1,23 reported a reduction in the number of cigarette/day (from 50 to 80%) after the introduction of the EC. ***Efficacy (reduction of nicotine withdrawal symptoms)*** • Experimental studies: Even in prospective cohort studies, the EC seems to reduce the withdrawal symptoms associated with smoking traditional cigarettes. • Cohort studies: Even in prospective cohort studies, the EC seems to reduce the withdrawal symptoms associated with smoking traditional cigarettes.
Main conclusion	• Finally, six experimental studies and six cohort studies were included. In the prospective 12-month, randomized controlled trial, smoking reduction was documented in 22.3 and 10.3% at Weeks 12 and 52, respectively (P< 0.001 versus baseline). • Moreover, two cohort studies reported a reduction in the number of cigarette/day (from 50 to 80%) after the introduction of the EC. 'Mouth and throat irritation', 'nausea', 'headache' and 'dry cough' were the most frequently AEs reported. • The use of the EC can reduce the number of cigarettes smoked and withdrawal symptoms, but the AEs reported are mainly related to a short period of use. Long-term studies are needed to evaluate the effects of the EC usage after a chronic exposure.
Funding (related to tobacco industry; Yes/No)	• Not reported for funding information. • Not related to tobacco industry.

First Author, Year, country	(20) Lam, 2015, Canada
Title	Are electronic nicotine delivery systems an effective smoking cessation tool?
Target population (youth, young adults, adults, lab/in vitro; Gender)	• Human studies. • 1,045 in total sample • Only RCTs
Objective/s (only those who are related to the domain)	• Whether ENDS constitute an effective smoking cessation tool. • Self-reported continuous smoking abstinence over the entire follow-up period.
Number of included articles	• 4 articles
Reported outcomes (name each outcome + results)	• Adriaens et al, 2014 • First laboratory session, after use of EC and previous 4 h of abstinence resulted in reduction in cigarette craving, same magnitude as when cigarette was smoked. • After 2 months, 34% of EC groups had stopped smoking tobacco cigarette versus 0% in control group. • After 5 months, (switch over in place), EC group showed 37% total quit rate, and 38% quit rate in control group after initiating EC usage. • After 8 months, overall 60% reduction in the number of cigarettes smoked per day. • After 8 months, reduction or complete abstinence from tobacco smoking was achieved with the EC in 44% of participants. • Bullen et al, 2010

	• Over 60 min, participants using 16 mg ENDD recorded 0.82 units less desire to smoke than the placebo ENDD (P=0.006). • No change in desire to smoke between 16 mg ENDD versus inhalator. ENDS showed more pleasant to use than inhalator (P=0.016) and produced less irritation of mouth throat (P<0.001). • Bullen et al, 2013 • At 6 months, verified abstinence was 7.3% (21 of 289) with nicotine EC, 5.8% (17 of 295) with patches and 4.1% (3 of 73) with placebo EC. RD for nicotine EC versus patches 1.51 (95% CI –2.49 to 5.510, and for nicotine EC versus placebo EC 3.16 (95% CI –2.29 to 8.61). • 7-day point prevalence abstinence: A difference in favour of nicotine EC; however, was not significant at the 6-month post quit date. Repeated measurement at 1 month showed a benefit of nicotine EC compared with patches. • Caponnetto et al, 2013 • Decrease in tobacco cigarettes/day use and eCO levels were observed at each study visits in all three study groups compared with baseline (P<0.001), no consistent differences among study groups. Complete abstinence from tobacco smoking was documented in 22.3% and 10.3% at week 12 and week 52.
Main conclusion	• Based on the current available literature, ENDS may constitute an effective smoking cessation tool. In the studies included in the present systematic review, smoking cessation was measured through self-reported smoking reduction, complete smoking abstinence, level of desire to smoke and level of withdrawal symptoms. • Based on the four studies included in the present review, ENDS have the potential to eliminate the harmful effects of tobacco smoking. • Areas of investigation that could provide useful understanding on the topic of ENDS in the future include health effects related to longterm use of ENDS, and long-term population studies to discover how ENDS may influence uptake of smoking habits in younger populations and the impact of secondhand exposure to ENDS smoke.
Funding (source; related to tobacco industry – Yes/No)	• The authors have no financial disclosures or conflicts of interest to declare. • ML, via his company Health New Zealand, previously did research funded by Ruyan (an e-cigarette manufacturer). • One of the studies was supported by a grant-in-aid from Lega Italiana AntiFumo.

First Author, Year, country	**(21) Waghel 2015, USA**
Title	Effectiveness of Electronic Cigarettes as a Tool for Smoking Cessation or Reduction.
Target population (youth, young adults, adults, lab/in vitro; Gender)	• N/A
Objective/s (only those who are related to the domain)	• To examine the evidence concerning effectiveness of electronic cigarettes (e-cigarettes) in smoking cessation or reduction and reduction in desire to smoke and withdrawal symptoms.
Number of included articles	• 7 studies were included.
Reported outcomes (name each outcome + results)	• Smoking cessation or reduction. • Of 7 trials, one showed similar 6-month abstinence rates between e-cigarettes and nicotine patches. • Another trial reported 12.5% of participants achieving abstinence at 24 months with e-cigarettes. • Three studies demonstrated significant percentages of patients maintaining ≥50% reduction in cigarettes/day from baseline to 24 or 52 weeks. • Another trial showed significant reductions in cigarette use from baseline through 52 weeks with e-cigarettes; no difference in abstinence rates beyond 12 weeks was found between nicotine and placebo e-cigarettes. • Only 2 trials assessed reduction in desire to smoke or withdrawal symptoms, and results varied.
Main conclusion	• The limited evidence available supports that e-cigarette may be effective as monotherapy for smoking cessation and reduction.

	• However, superiority to nicotine replacement therapy was not proven. • Limited conclusions can be drawn regarding reduction in desire to smoke and withdrawal symptoms. • The unknown long-term safety risk should also be considered.
Funding (source; related to tobacco industry – Yes/No)	• The author(s) received no financial support for the research, authorship, and/or publication of this article. • Not related to tobacco industry.

First Author, Year, country	**(22) Callahan-Lyon, 2014, USA**
Title	Electronic cigarettes: human health effects.
Target population (youth, young adults, adults, lab/in vitro; Gender)	• Human; Both male and female.
Objective/s (only those who are related to the domain)	• To review published data on the human health effects of exposure to e-cigarettes and their components.
Number of included articles	• 44
Reported outcomes (name each outcome + results)	• Studies attempting to show efficacy of e-cigarettes as a cessation therapy have had mixed results, with generally low sustained cessation rates (self-reported or verified).
Main conclusion	• Some evidence suggests that e-cigarette use may facilitate smoking cessation, but definitive data are lacking. No e-cigarette has been approved by FDA as a cessation aid.
Funding (related to tobacco industry; Yes/No)	• Not reported.

First Author, Year, country	**(23) Franck, 2014, Canada**
Title	Electronic Cigarettes in North America-History, Use, and Implications for Smoking Cessation.
Target population (youth, young adults, adults, lab/in vitro; Gender)	• Both male and female.
Objective/s (only those who are related to the domain)	• To review the available data on the efficacy and safety of e-cigarettes for smoking cessation and to consider issues relevant to the context in which they are used, including product awareness and regulatory and ethical concerns.
Number of included articles	• 7
Reported outcomes (name each outcome + results)	• Studies have concluded that e-cigarettes can help reduce the number of cigarettes smoked and may be as effective for smoking cessation as the nicotine patch. Although there is a lack of data concerning the safety and efficacy of e-cigarettes as a smoking cessation therapy, available evidence showed no significant difference in adverse event rates between e-cigarettes and the nicotine patch. E-cigarettes are widely used among smokers attempting to quit. However, significant international variation remains in the regulatory mechanisms governing the sale and distribution of e-cigarettes.
Main conclusion	• Given the limited available evidence on the risks and benefits of e-cigarette use, large, randomized, controlled trials are urgently needed to definitively establish their potential for smoking cessation.
Funding (related to tobacco industry; Yes/No)	• This study was supported by a Knowledge Synthesis grant from the Canadian Institutes of Health Research (CIHR, grant number KRS-134302). • Not related to tobacco industry.

First Author, Year, country	**(24) Rahman 2015, Australia**
Title	• E-Cigarettes and Smoking Cessation: Evidence from a Systematic Review and Meta-Analysis
Target population (youth, young adults, adults, lab/in vitro; Gender)	• Human (both males and females)
Objective/s (only those who are related to the domain)	• To investigate whether the use of e-cigarettes is associated with smoking cessation or reduction, and whether there is any difference in efficacy of e-cigarettes with and without nicotine on smoking cessation

Number of included articles	• 6
Reported outcomes (name each outcome + results)	• Nicotine filled e-cigarettes were more effective for cessation than those without nicotine (pooled Risk Ratio 2.29, 95%CI 1.05-4.97) • Amongst 1,242 smokers, 224 (18%) reported smoking cessation after using nicotine-enriched e-cigarettes for a mum period of six months. • Use of such e-cigarettes was positively associated with smoking cessation with a pooled Effect Size of 0.20 (95%CI 0.11-0.28). • Use of e-cigarettes was also associated with a reduction in the number of cigarettes use • Included studies were heterogeneous, due to different study designs and gender variation.
Main conclusion	• E-cigarettes containing nicotine are more effective at aiding smoking cessation than e-cigarettes without nicotine • E-cigarettes of both types may help ongoing smokers by reducing the number of tobacco cigarettes they use. • The association between the use of e-cigarettes and smoking cessation was consistently observed in all included studies, also seen in different study designs, and abstinence verification method. • Studies that relied on a more objective biochemical abstinence verification method had a lower pooled effect size than the studies that had self-reported information. • Nonetheless, the effect sizes in each verification method remained statistically significant. • Results indicate that nicotine enriched e-cigarettes may prove to be a useful smoking cessation method • More randomized controlled trials are needed to assess effectiveness against other cessation methods
Funding (source; related to tobacco industry – Yes/No)	• The authors have no support or funding to report. • Not related to tobacco industry.

4. The Effect of ENDS on Tobacco Smoking Initiation (Domain 4)

First Author, Year, country	(1) O'Brien 2021, UK
Title	Association between electronic cigarette use and tobacco cigarette smoking initiation in adolescents: a systematic review and meta-analysis
Target population (youth, young adults, adults, lab/in vitro; Gender)	• 13 to 19 years
Objective/s (only those who are related to the domain)	• To determine whether EC use by teenagers who had never smoked conventional tobacco cigarettes (tobacco cigarettes) at baseline was associated with subsequently commencing tobacco cigarette smoking.
Number of included articles	• 12
Reported outcomes (name each outcome + results)	• Meta-analysis calculated a 4.06 (95% confidence interval (CI): 3.00-5.48, I2 68%, 9 primary studies) times higher odds of commencing tobacco cigarette smoking for teenagers who had ever used e-cigarettes at baseline, • The odds ratios were marginally lower (to 3.71 times odds, 95%CI: b2.83–4. 86, I2 35%, 4 primary studies) when only the four high-quality studies were analyzed.
Main conclusion	• EC use was associated with commencement of tobacco cigarette smoking among teenagers in Europe and North America, identifying an important health-related harm.
Funding (related to tobacco industry; Yes/No)	• The systematic review was funded as part of the routine work of the Health Research Board • Not related to tobacco industry.

First Author, Year, country	(2) Baenziger 2021, Australia
Title	E-cigarette use and combustible tobacco cigarette smoking uptake among nonsmokers, including relapse in former smokers: umbrella review, systematic review and meta-analysis
Target population (youth, young adults, adults, lab/in vitro; Gender)	• All ages
Objective/s (only those who are related to the domain)	• To review and summarise the current evidence on the uptake of combustible cigarette smoking following EC use in non-smokers— including never-smokers, people not currently smoking and past smokers
Number of included articles	• 14 studies (9 in Meta-analysis)
Reported outcomes (name each outcome + results)	• On average, non-smokers who used EC have around threefold the odds of either initiating smoking (OR= 3.25, 95% CI 2.61 to 4.05, I2 85.7%) or currently smoking combustible cigarettes (OR= 2.87, 95% CI 1.97 to 4.19, I2 90.1%) compared with non-smokers who have not used EC. • Former smokers who report current e-cigarette use within the previous 30-days have more than twice the odds of relapse and resumption of current smoking compared with former smokers who have not used EC (OR=2.40, 95% CI 1.50 to 3.83, I2 12.3%).
Main conclusion	• Non-smokers who use EC are consistently more likely than those avoiding EC to initiate combustible cigarette smoking and become current smokers. • The magnitude of this risk varied, with an average of around three times the odds. • Former smokers using EC have over twice the odds of relapse as non-EC users.
Funding (related to tobacco industry; Yes/No)	• The Australian Government Department of Health. • Not related to tobacco industry.

First Author, Year, country	(3) Zhang 2021, China
Title	The effect of e-cigarettes on smoking cessation and cigarette smoking initiation: An evidence-based rapid review and meta-analysis.
Target population (youth, young adults, adults, lab/in vitro; Gender)	• Human. • Male and female • Youth and adults (14 – 85)
Objective/s (only those who are related to the domain)	• Evaluate the effects of e-cigarettes on smoking cessation among smokers and the risks for smoking initiation among non-smoking adolescents, and their safety
Number of included articles	• Qualitative synthesis: 35 articles

	• Quantitative synthesis: 29 articles
Reported outcomes (name each outcome + results)	• Finding from one systematic review based on cohort studies involving 17389 young people aged 14–30 years indicated that ever e-cigarette users were more likely to initiate cigarette smoking at follow-up than never users (23.2% vs 7.2%) (AOR=3.5; 95% CI: 2.38–5.16; I2 =56.0%; 7 trials, n=8759). • Another finding from Fifteen cohort studies were included. The pooled results suggested that ever e-cigarette users were more likely to initiate smoking than non-e-cigarette users (AOR=2.91; 95% CI: 2.61–3.23; I2 =61.0%; 15 trials, n=68943)
Main conclusion	• Based on cohort studies involving 17389 adolescents and young adults aged 14-30 years indicated that ever EC users were more likely to initiate cigarette smoking at follow-up than never users, AOR, 3.5; 95% CI 2.38-5.16; I2 =56.0%; 7 trials, n=8759. • The pooled results suggested that ever EC users were more likely to initiate smoking than EC nonusers (AOR, 2.91; 95% CI 2.61-3.23; I2 =61.0%; 15 trials, n=68943).
Funding (related to tobacco industry; Yes/No)	• National Natural Science Foundation of China (No.81830115). • Overseas Expertise Project, Ministry of Education of China • Not related to tobacco industry.

First Author, Year, country	**(4) Bozier 2020, Australia**
Title	The Evolving Landscape of e-Cigarettes: A Systematic Review of Recent Evidence
Target population (youth, young adults, adults, lab/in vitro; Gender)	• Human, animal, in vitro, ex vivo from human samples; Gender not specified.
Objective/s (only those who are related to the domain)	• To provide a comprehensive update of data on the potential health effects of e-cigarettes since the National Academies of Sciences, Engineering and • Medicine (NASEM) report.
Number of included articles	• 225
Reported outcomes (name each outcome + results)	• There is evidence that smokers do not “quit” with e-cigarettes but rather “switch” to e-cigarette use.
Main conclusion	• This review did find evidence suggesting that smokers who switch to e-cigarettes may experience harm reduction, particularly in relation to cardiopulmonary health, but we were unable to find evidence suggesting that these clinical measures returned to the levels of a nonsmoker • Much remains unknown about the effects of e-cigarette use, in the long term. • There is evidence that smokers do not “quit” with e-cigarettes but rather “switch” to e-cigarette use. • The latest studies which show that dual use of e-cigarettes and tobacco cigarettes may put users at increased cardiovascular disease risk over smoking or e-cigarette use alone.
Funding (related to tobacco industry; Yes/No)	• None. • Not related to tobacco industry.

First Author, Year, country	**(5) Chan 2020, Australia**
Title	Gateway or common liability? A systematic review and meta-analysis of studies of adolescent e-cigarette use and future smoking initiation.
Target population (youth, young adults, adults, lab/in vitro; Gender)	• Human; Both male and female.
Objective/s (only those who are related to the domain)	• Systematically review published longitudinal studies of vaping and smoking initiation among adolescents and conduct a meta-analysis to estimate the strength of the association. • Conduct a meta-regression to examine the effects by study quality characteristics including sample size, attrition rate and length of follow-up. • Calculate E-values for each study to evaluate if existing studies are sensitive to unmeasured confounding. • Examine the impact of key confounders and other potential sources of bias, such as sample attrition and publication bias
Number of included articles	• 11

Reported outcomes (name each outcome + results)	• The unadjusted ORs from the 11 included studies ranged from 2.39 to 12.40, with a significant overall pooled OR of 4.31 [95% confidence interval (CI) = 3.33, 5.58, P<0.001]. • The adjusted aORs ranged from 1.60 to 10.57. The overall pooled aOR was 2.93 (95% CI = 2.22, 3.87, P<0.001).
Main conclusion	• Longitudinal studies have consistently reported a positive association between adolescent vaping and subsequent initiation of cigarette smoking. However, it is not clear how much of the relationship is causal (gateway effect) or is due to common liability. Existing evidence is limited by publication bias, high sample attrition and inadequate adjustment for potential confounding variables.
Funding (related to tobacco industry; Yes/No)	• Investigator Grant from the National Health and Medical Research Council, Australia. • Not related to tobacco industry.

First Author, Year, Country	**(6) Khouja 2020, UK**
Title	Is e-cigarette use in non-smoking young adults associated with later smoking? A systematic review and meta-analysis.
Target population (youth, young adults, adults, lab/in vitro; Gender)	• Human; Both male and female.
Objective/s (only those who are related to the domain)	• To investigate whether e-cigarette use compared with non-use in young non-smokers is associated with subsequent cigarette smoking.
Number of included articles	• 24
Reported outcomes (name each outcome + results)	• When pooled in a random-effects meta-analysis, e-cigarette use in non-smoking young people was associated with a four-and-a-half-fold increase in the odds of subsequent smoking (unadjusted; OR: 4.59, 95% CI: 3.60 to 5.85). • Pooling the adjusted estimates, the association was still strong but somewhat weaker (adjusted; OR: 2.92, 95% CI: 2.30 to 3.71).
Main conclusion	• There is a strong consistent association in observational studies between e-cigarette use among non-smokers and later smoking. However, findings from published studies do not provide clear evidence that this is explained by a gateway effect rather than shared common causes of both e-cigarette use and smoking.
Funding (related to tobacco industry; Yes/No)	• This work was supported by the Medical Research Centre Integrative Epidemiology Unit at the University of Bristol [grant number MC_UU_0011/7]. This study was supported by the NIHR Biomedical Research Centre at University Hospitals Bristol NHS Foundation Trust and the University of Bristol. • Not related to tobacco industry.

First Author, Year, country	**(7) Aladeokin 2019, UK**
Title	Is adolescent e-cigarette use associated with smoking in the United Kingdom? A systematic review with meta-analysis.
Target population (youth, young adults, adults, lab/in vitro; Gender)	• Adolescents (aged 10–19 years)
Objective/s (only those who are related to the domain)	• To systematically review the empirical evidence on whether adolescent e-cigarette use is associated with traditional cigarette smoking in the UK
Number of included articles	• Studies included in quantitative synthesis (n = 8) (involving 73076 adolescents): 5 cross-sectional, 3 longitudinal studies • Studies included in meta-analysis n = 3
Reported outcomes (name each outcome + results)	***Smoking initiation:*** • A longitudinal study reported that young e-cigarette users (young never smokers who had tried an e-cigarette) had more than 4 times greater odds of initiating traditional smoking by the following year (OR=4.62, 95% Cl: 3.34–6.38) (Adjusted OR=2.42, 95% CI: 1.63–3.60). • Another longitudinal study investigated whether adolescent e-cigarette use was prospectively associated with initiation of traditional cigarette use; and found that

	baseline ever use of e-cigarettes was strongly associated with subsequent initiation of traditional cigarettes (OR=5.38, 95% Cl: 4.02–7.22) (Adjusted OR=4.06, 95% CI: 2.94–5.60). • A 3rd study examined whether ever use of e-cigarettes by adolescents was associated with traditional cigarette initiation at follow-up and found that the odds of smoking initiation in ever users of e-cigarettes were significantly high (OR=12.31, 95% Cl: 5.06–29.94) (Adjusted OR=10.57, 95% CI: 3.33–33.50). • Meta-analysis based on number of events (unadjusted odds ratios): This meta-analysis showed the odds of smoking traditional cigarettes were increased in non-smoking adolescents who used e-cigarettes (OR=26.01, 95% CI: 5.35–126.44). • Meta-analysis based on adjusted odds ratios: The meta-analysis showed that the odds of smoking traditional cigarettes were increased up to six times in non-smoking adolescents who used e-cigarettes (OR=5.55, 95% Cl: 3.94–7.82). **Intent to smoke:** • A study observed that ever use of e-cigarettes at baseline was statistically significant in predicting weakening smoking intentions (OR=0.7, 95% Cl: 0.52–0.96) and attitudes (OR=0.68, 95% Cl: 0.44–1.04). • Another study demonstrated a statistically significant increased willingness to smoke in the future in participants that had used e-cigarettes compared to those that had not (OR=3.21, 95% Cl: 1.66–6.23). • The highest impact of e-cigarette use was observed in adolescents who expressed low susceptibility to smoking at baseline but had eventually used traditional cigarettes at follow-up ($\chi 2$ =53.93, p<0.001). ***Combined use of electronic and traditional cigarettes:*** • 4 cross-sectional studies found that in adolescents who have ever used e-cigarettes, current regular smokers were more likely to use e-cigarettes than other groups such as light smokers or ex-smokers showing an association of use. • In longitudinal studies: 1 study found that there was as much of a significant likelihood for an adolescent smoker to initiate e-cigarette use as an adolescent e-cigarette user to initiate traditional smoking (OR=3.54, 95% CI: 1.68–7.45). • Other studies found that there was an increase in use of one of either e-cigarettes or traditional cigarettes when the alternate product was initiated, although one study found this became non-significant when covariates (socioeconomic status, sex, age, family smoking, friends' smoking) were controlled for.
Main conclusion	• The meta-analysis, including three longitudinal (prospective) studies, showed that the odds of smoking traditional cigarettes were increased up to 6 times in non-smoking adolescents who used e-cigarettes in the UK. • Longitudinal studies also reported an increase in use of one of either e-cigarettes or traditional cigarettes when the alternate product was initiated. • The remaining included studies employed cross-sectional surveys and therefore were only able to show an association between e-cigarette use and traditional cigarette smoking in British adolescents.
Funding (related to tobacco industry; Yes/No)	• No source of funding for this research.

First Author, Year, country	**(8) Soneji 2017, USA**
Title	Association Between Initial Use of e-Cigarettes and Subsequent Cigarette Smoking Among Adolescents and Young Adults: A Systematic Review and Meta-analysis.
Target population (youth, young adults, adults, lab/in vitro; Gender)	• Human (male/female) • Adolescents and young adults (14-30 years old) • Sample: 17389 • Baseline and follow-up data were collected between 2012 and 2016 for these studies
Objective/s (only those who are related to the domain)	• To perform a systematic review and meta-analysis of longitudinal studies that assessed initial use of e-cigarettes and subsequent cigarette smoking among adolescents and young adults

Number of included articles	• 9 (3 paper-based survey, 5 internet-based survey and 1 was both) • RCT and Observational studies (only longitudinal) • Seven studies examined cigarette smoking initiation between baseline and follow-up and included a total of 8168 participants who were never cigarette smokers at baseline • Two studies examined past 30-day cigarette smoking and included a total of 2084 participants who were not past 30-day cigarette smokers at baseline
Reported outcomes (name each outcome + results)	• Longitudinal studies reporting odds ratios for cigarette smoking initiation associated with ever use of e-cigarettes or past 30-day cigarette smoking associated with past 30-day e-cigarette use: • The pooled probabilities of cigarette smoking initiation were 23.2% for baseline ever e-cigarette users and 7.2% for baseline never e-cigarette users. • The pooled probabilities of past 30-day cigarette smoking at follow-up were 21.5% for baseline past30-day e-cigarette users and 4.6% for baseline non-past 30-day e-cigarette users. • Adjusting for known demographic, psychosocial, and behavioral risk factors for cigarette smoking, the pooled odds ratio for subsequent cigarette smoking initiation was 3.50 (95% CI, 2.38-5.16) for ever vs never e-cigarette users, and the pooled odds ratio for past 30-day cigarette smoking at follow-up was 4.28 (95% CI, 2.52-7.27) for past 30-day e-cigarette vs non-past 30-day e-cigarette users at baseline. • A moderate level of heterogeneity was observed among studies (I2= 56%)
Main conclusion	• E-Cigarette use was associated with greater risk for subsequent cigarette smoking initiation and past 30-day cigarette smoking. • Strong e-cigarette regulation could potentially curb use among youth and possibly limit the future population-level burden of cigarette smoking.
Funding (related to tobacco industry; Yes/No)	• This study was supported by grants R21-CA197912 (Dr Soneji), R01-CA077026(Dr Sargent), R01-CA140150 (Dr Primack), R21-CA185767 (Dr Primack), and R01-CA153154 andP30-CA071789-16S2 (Dr Wills) from the National Cancer Institute (NCI) at the National Institutes of Health (NIH); grants P50-CA180905 (Drs Barrington-Trimis and Unger) and P50-CA179546(Drs Gibson and Hornik) from the NCI and the USFood and Drug Administration Center for Tobacco Products; and grants P50-DA036105 (Mr Spindleand Dr Eissenberg), R01-DA033296 (Dr Leventhal),R01-DA10767 (Dr Andrews), and R01-DA016310 (DrUnger) from the National Institute on Drug Abuse at the NIH. • Not related to tobacco industry

First Author, Year, country	**(9) Zhong 2016, China**
Title	Electronic Cigarettes Use and Intention to Cigarette Smoking among Never-Smoking Adolescents and Young Adults: A Meta-Analysis.
Target population (youth, young adults, adults, lab/in vitro; Gender)	• Human (male/female) • 10-29 years • Sample: 91051
Objective/s (only those who are related to the domain)	• To explore the association between e-cigarettes use and smoking intention among adolescents and young adults to contribute to the much-needed evidence.
Number of included articles	• 6 • Cross-sectional (5) • Longitudinal cohort (6)
Reported outcomes (name each outcome + results)	• Smoking intentions/Willingness to smoking/Openness to smoking compared to those who never used e-cigarettes: • Never-smoking adolescents and young adults who used e-cigarettes have more than 2 times increased odds of intention to cigarette smoking (OR = 2.21, 95% CI: 1.86–2.61) compared to those who never used, with low evidence of between-study heterogeneity (p = 0.28, I2 = 20.1%). • Among never-smoking adolescents and young adults, e cigarettes use was associated with increased smoking intention. • Overall effect size: OR = 2.21, 95% CI: 1.86–2.61

Main conclusion	• cigarettes use by never-smoking adolescents and young adults is associated with cigarette smoking intention have important implications for the debates on the benefits and risks of e-cigarettes. • In order to reduce the smoking intentions of youth and prevent them from initiating the first cigarette, prevention efforts around e-cigarettes restrictions should be enhanced
Funding (related to tobacco industry; Yes/No)	• The study was sponsored by "Medicine and Health Care in Zhejiang Province Science and Technology Plan" (Grant number: 2015KYB084). • Not related to tobacco industry

5. ENDS marketing effects on consumers (Domain 5)

First Author, Year, country	(1) Lee 2020, Republic of Korea
Title	Youth and Young Adult Use of Pod-Based Electronic Cigarettes From 2015 to 2019 A Systematic Review.
Target population (youth, young adults, adults, lab/in vitro; Gender)	• Human studies • 163,378 in total sample • 12-54 years old • Cross-sectional surveys
Objective/s (only those who are related to the domain)	• To conduct a systematic review of recent peer-reviewed scientific literature on pod-based e-cigarettes.
Number of included articles	• 35 studies (of 317 studies identified).
Reported outcomes (name each outcome + results)	***Marketing*** • JUUL annual sales exceeded $650 million in 2017. JUUL spent a relatively modest amount on marketing between 2015 and 2017 ($2.1 million) across television, print, radio, and internet compared with other e-cigarette brands. • With JUUL's success in the market, partly fueled by its high nicotine content, other e-cigarette vendors have increased the nicotine content in e-liquid and JUUL-compatible pods and begun to offer the popular mango flavor and imitation devices (small, elongated, and pod-based). • In April 2018, the FDA requested that eBay remove online sales listings for JUUL. ***Social Media Communication*** • A content analysis on Twitter of approximately 1000 tweets revealed mostly positive sentiments (eg, expressing positive emotions toward JUUL use) among young users about JUUL. • An analysis of 364 Reddit posts showed mixed sentiments, with adult and youth users expressing negative and positive perceptions of youth JUUL use. • The volume of JUUL-associated Twitter tweets increased 17-fold in 2017 compared with 2016 and there were 35 JUUL-associated YouTube videos that exceeded 100 000 views, suggesting the growing popularity of JUUL over time. • The main topics discussed regarding JUUL on social media (Twitter and Reddit) include experiences of using or buying JUUL in college or school contexts, reasons for using JUUL (eg, popularity, getting a buzz), barriers to using JUUL (eg, age restriction, price), and JUUL flavors. • Social media communications rarely addressed the use of JUUL as a cessation strategy, ranging from 0.29% to 16.2% across studies of posts on Twitter and Reddit.
Main conclusion	• Advertising and marketing must be regulated to prevent exposure to youth. • Evidence in this review suggests that social media is being used to market pod-based e-cigarettes with high efficiency and substantial reach. • Social media marketing campaigns5have likely increased favorable perceptions among youth and young adults, which is evident from the rare discussion of health risks and use of these products as a smoking cessation device (JUUL Lab's stated goal).
Funding (related to tobacco industry; Yes/No)	• This research was made possible by a gift from Roslyn and Lisle Payne. This research was also supported by grants R25CA057711 and 2T32CA057711-26 from the National Cancer Institute of the National Institutes of Health. The content is solely the responsibility of the authors. • Not related to tobacco industry.

First Author, Year, country	(2) Collins 2019, USA
Title	E-Cigarette Marketing and Communication: How E-Cigarette Companies Market E-Cigarettes and the Public Engages with E-cigarette Information.
Target population (youth, young adults, adults, lab/in vitro; Gender)	• Human studies. • Experimental studies, quasi-experimental studies, observational studies, case reports, case series, qualitative studies, mixed methods, and preclinical/animal studies.
Objective/s (only those who are related to the domain)	• The objective of this study was to provide a comprehensive review of the published literature on e-cigarette marketing and communication
Number of included articles	• 124 articles (80 marketing, 44 communication)

Reported outcomes (name each outcome + results)	• Marketing • E-cigarettes are marketed as alternatives to combustible cigarettes, with advertisements placed in retail outlets and across various media channels. • Advertisements contain content appealing to youth and are available through channels with youth exposure. • Cross-sectional data suggests that e-cigarette users recall more e-cigarette marketing and are more likely to find the advertisements appealing compared nonusers; however, these studies are subject to recall bias and should be interpreted with caution. • There is also an association between recall of e-cigarette marketing and lower e-cigarette harm perceptions, greater intention to use, and use of e-cigarettes, although most of these studies are cross-sectional, so causality cannot be inferred. • Research is limited and findings are inconclusive as to the effect of e-cigarette marketing on cigarette smoking and cessation. • The majority of e-cigarette products and retailer sites feature warnings, but the content and location of the warnings is inconsistent. • The inclusion of warnings in e-cigarette advertisements may increase e-cigarette harm perceptions and reduce the odds of purchasing e-cigarettes. Future research is needed to determine how best to present modified risk and prevention messages, as well as harmful and potentially harmful constituent information to benefit public health. • Communication • E-cigarette information is widely available across media channels. • Public interest in e-cigarette information has been increasing and is projected to continue to grow. • Content analyses of online media and social media platforms suggest e-cigarettes are primarily discussed in a neutral or positive context, but this may vary by information source and population. • Online portrayals of e-cigarettes are heavily influenced by e-cigarette companies and advertisers, who utilize online media platforms to create a direct link with their consumers.
Main conclusion	• One hundred twenty-four publications on e-cigarette marketing and communication were identified. • They covered topics including e-cigarette advertisement claims/promotions and exposure/ receptivity, the effect of e-cigarette advertisements on e-cigarette and cigarette use, public engagement with e-cigarette information, and the public's portrayal of e-cigarettes. • Studies show increases in e-cigarette marketing expenditures and online engagement through social media over time, that e-cigarettes are often framed as an alternative to combustible cigarettes, and that e-cigarette advertisement exposure may be associated with e-cigarette trial in adolescents and young adults.
Funding (source; related to tobacco industry – Yes/No)	• All authors were supported by Truth Initiative. ACV was also supported by the Centers of Biomedical Research Excellence P20GM103644 award from the National Institute on General Medical Sciences and the Tobacco Centers of Regulatory Science (TCORS) award P50DA036114 from the National Institute on Drug Abuse and Food and Drug Administration (FDA). JLP was also supported by the Office of the Director of the NIH, NIDA/NIH, and the FDA Center for Tobacco Products (K01DA037950). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH or the Food and Drug Administration. • Not related to tobacco industry.

First Author, Year, country	**(3) Lee 2018, USA**
Title	A new form of nicotine retailers: a systematic review of the sales and marketing practices of vape shops.
Target population (youth, young adults, adults, lab/in vitro; Gender)	• Environmental studies.
Objective/s (only those who are related to the domain)	• To identify (a) how vape shops can be identified and (b) sales and marketing practices of vape shops.

Number of included articles	• 22 relevant studies were included.
Reported outcomes (name each outcome + results)	• Promotion • Vape shop promotions show some differences from traditional tobacco retailer promotions, including some promotional activities that are prohibited for other regulated tobacco products. • Product • Product availability mirrors increasing preference away from first-generation devices in vape shops and toward second-generation and third-generation devices that offer the opportunity to refill e-liquids and modify the devices. • Price • In San Francisco, when buying more than one liquid, devices and/or e-liquids were often discounted (96% and 87% of vape shops, respectively). In New Hampshire, over 70% of stores had price promotions on their products, which was more common in vape shops than stores selling both vape and combustible products. • Placement • Studies in Los Angeles and New Hampshire noted rates of e-liquid self-service at 83% and 16%respectively, illustrating a large discrepancy between vape shops. • Density and proximity • Vape shops are more likely to be concentrated near college and university campuses28 and are patterned in opposite ways of conventional tobacco retailers (ie, they are more likely to be present in neighborhoods with a higher proportion of White residents) in New Jersey.
Main conclusion	• Vape shops represent a new type of retailer for tobacco products. • Vape shops have potential to promote e-cigarettes for smoking cessation but also sometimes provide inaccurate information and mislabelled products. • Vape shop owners use innovative marketing strategies that sometimes diverge from those of traditional tobacco retailers. • Vape shop staff believe strongly that their products are effective harm-reduction products. • Vape shops were more common in areas with more White residents.
Funding (related to tobacco industry; Yes/No)	• Research reported in this publication was supported by the National Cancer Institute of the US National Institutes of Health under Award Number U01CA154281. • Not related to tobacco industry.

First Author, Year, country	**(4) Glasser 2017, USA**
Title	Overview of Electronic Nicotine Delivery Systems: A Systematic Review.
Target population (youth, young adults, adults, lab/in vitro; Gender)	• Human and animal studies. • All age groups but mainly focusing on adolescents and young adults.
Objective/s (only those who are related to the domain)	• To identify (a) how vape shops can be identified and (b) sales and marketing practices of vape shops.
Number of included articles	• 687 relevant studies were included. • 74 articles on the marketing and communication of ENDS products. • 30 articles addressing the sales of ENDS products.
Reported outcomes (name each outcome + results)	• Marketing and Communication • Among noncombustible tobacco products, ENDS advertisements are the most widely circulated. • Individuals aware of ENDS report the most common product exposures are through in-person communications, by seeing them at the point of sale, and through online and TV advertisements. • ENDS are promoted heavily online through ENDS company–sponsored advertisements and users' social media profiles,424 with occurrences on YouTube and Twitter. • Exposure to industry and ingredient warnings is associated with lower odds of intent to purchase ENDS. • Several studies have reported the presence of interior and exterior ENDS advertisements at tobacco retail outlet. • Blu eCigs led in total advertisement expenditure until Altria's MarkTen entered the national market in 2014.

	• Commonly marketed as alternatives to cigarettes, ENDS advertisements often make claims, such as being an effective smoking-cessation aid. • Sales • The ENDS market is expanding and accessible to consumers through Internet vendors and in most tobacco outlets. • Field observations of tobacco retail outlets have found that more than half of tobacco retailers sell ENDS. • One study found no significant relationship between retail availability and neighborhood demographics, but another study indicated a greater likelihood of ENDS retailers in communities with higher median incomes. • One cross-sectional survey of adults found that frequent (weekly/daily) vapers were significantly more likely to purchase over the Internet than infrequent (monthly or less) vapers. • Studies assessing online retailers found inadequate age verification methods, with one study reporting a 93.7% rate of successful youth purchases without age verification. • ENDS products can be sold at an estimated 200%–400% markup in vape shops.
Main conclusion	• Studies indicate that ENDS are increasing in use, particularly among current smokers, pose substantially less harm to smokers than cigarettes, are being used to reduce/quit smoking, and are widely available. • The most common claims advertise ENDS as a healthier alternative to cigarettes, and a way to circumvent smoking bans. • Advertisements also highlight celebrity use to appeal to youth • Information is limited on the impact of pricing on ENDS sales, with one study indicating that vapers are two to three times more sensitive to price than smokers,758 and several studies finding that ENDS are substitutes for cigarettes as cigarette prices increase.
Funding (related to tobacco industry; Yes/No)	• Financial support for this study was provided by The Schroeder Institute at Truth Initiative, the Robert Wood Johnson Foundation (Grant ID: 72208 and 72390), and a NIH K01 Career Development Award in Tobacco Control Regulatory Research (Principal Investigator, Pearson; 1K01DA037950-01). The funding agreement ensured the authors' independence in designing the study, interpreting the data, writing, and publishing the report. • Not related to tobacco industry.