SUPPLEMENT

Table 1: Search terms

Electronic cigarette	Vape (smoke) toxicants	ENDS users' exposure to toxicants	Direct health effects	ENDS risk for cigarette initiation and dual-use
"Electronic Cigarette*" OR E-Cig* OR E-Cigarette* OR "Electronic Nicotine Delivery System" OR vaping OR "electronic nicotine devices"	Aerosols OR toxic* OR "Heavy metal*" OR "chemical*" OR e-liquid* OR flavor* OR nicotine OR tobacco alkaloids OR glycols OR glycerin OR "volatile organic compound*" OR aldehyde OR formaldehyde OR acetaldehyde OR acrolein OR acetone OR crotonaldehyde OR biomarkers of carcinogenic OR tobacco specific nitrosamines (TSNA) OR polycyclic aromatic hydrocarbons (PAH)	Urine OR blood OR "nicotine dependence" OR "nicotine addiction" OR cotinine OR saliva cotinine	"Respiratory diseases" OR "Lung injur*" OR "Pulmonary Syndromes" OR "Chronic obstruct* pulmonary disease" OR asthma OR COPD OR "Vaping-associated lung injury" OR EVALI OR "Cardiovascular disease*" OR CVD OR "Acute myocardial infarction" OR "heart rythm" OR Stroke OR Cerebrovascular OR "Thermal injur*" OR "Oral health" OR "throat irritation" OR cough OR nausea OR dizziness OR "Periodontal disease*" OR "Urologic Health" OR "Neurodegenerative disorders" OR "cognitive decline" OR "Psychosocial effects" OR "Spinal health" OR "bone health" OR "Systemic inflammation" OR Diabetes OR "Fetal defect*" OR "Multiple organ systems" OR morbidity OR mortality OR "health outcome*" OR "Adverse effect*" OR "chronic disease*" OR Cancer OR "Oxidative stress markers"	Dual-use OR "dual use" OR poly use OR "cigarette initiation" OR "smoking initiation" OR "smoking cessation" OR smoking reduction OR "Marijuana use" OR "Gateway" OR "smoking uptake" OR "Alcohol use" OR "harm reduction"

Table 2. The quality assessment of reviews that were included in ENDS toxicity (Domain 1)

Studies	1	2	3	4	5	6	7	8	9	10	11	Score	Low/Medium/High
Bjurlin 2020	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes	No	No	6	Medium
Salam 2020	No	Yes	No	No	No	No	no	No	No	No	No	1	Low
Lee 2020	No	Yes	Yes	No	No	Yes	Yes	Yes	No	No	Yes	6	Medium
Bozier 2020	No	No	No	Yes	No	Yes	No	No	No	No	No	2	Low
Zhao 2020	No	Yes	Yes	No	No	Yes	Yes	Yes	No	No	No	5	Medium
Ward 2020	No	Can't answer	Yes	Yes	No	Yes	Yes	Yes	No	No	No	5	Medium
Wang 2019	No	Can't answer	Yes	No	No	Yes	No	No	No	No	No	2	Low
Gaur 2019	No	No	No	Yes	No	Yes	No	No	No	No	No	2	Low
Armendáriz-Castillo 2019	No	No	No	No	No	No	No	No	No	No	No	1	Low
Zulkifli 2018	No	No	No	No	No	Yes	No	No	No	No	No	1	Low
Farsalinos 2018	No	No	No	No	No	No	No	No	No	No	No	0	Low
Kaur 2018	No	No	Yes	Yes	No	No	No	No	No	No	No	2	Low
Zainol-Abidin 2017	No	No	Yes	No	No	Yes	No	No	No	No	No	2	Low
Fernandez 2015	No	No	No	No	No	No	No	No	No	No	No	0	Low
Cheng 2014	No	No	Yes	No	No	Yes	No	No	No	No	No	3	Low
Callahan-Lyon 2014	No	No	Yes	No	No	No	No	No	No	No	No	1	Low
Farsalinos 2014	No	No	No	Yes	No	No	No	No	No	No	No	1	Low
Burstyn 2014	No	No	No	Yes	No	No	No	No	No	No	No	1	Low
Pisinger 2014	No	Yes	Yes	Yes	No	No	No	No	No	No	Yes	4	Medium
Schroeder 2014	No	Can't answer	Yes	No	No	Yes	Yes	Yes	No	No	No	4	Medium

1.Was an 'a priori' design provided?
2.Was there duplicate study selection and data extraction?
3.Was a comprehensive literature search performed?
4.Was the status of publication (i.e. grey literature) used as an inclusion criterion?
5.Was a list of studies (included and excluded) provided?
6.Were the characteristics of the included studies provided?
7.Was the scientific quality of the included studies assessed and documented?
8.Was the scientific quality of the included studies used appropriately in formulating conclusions?
9.Were the methods used to combine the findings of studies appropriate?
10.Was the likelihood of publication bias assessed?
11.Was the conflict of interest stated? Score: Low/Medium/High

Table 3. The quality assessment of reviews that were included in ENDS health effects (Domain 2)

Studies	1	2	3	4	5	6	7	8	9	10	11	Score	Low/Medium/High
1. Respiratory diseases													
Bravo-Gutiérrez 2021	No	No	No	No	No	No	No	No	No	No	Yes	1	Low
Wills 2021	No	Yes	Yes	Yes	No	Yes	No	No	Yes	No	No	5	Medium
Xian 2021	No	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	No	7	Medium
Gonsalves 2021	Yes	No	Yes	Yes	No	No	No	No	No	No	No	3	Low
Xantus 2021	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	8	High
Prasetyo 2021	No	Yes	Yes	No	No	Yes	Yes	Yes	No	No	No	5	Medium
Jonas 2020	No	No	No	No	No	Yes	No	No	No	No	No	1	Low
Goniewicz 2020	No	Yes	No	Yes	No	Yes	Yes	Yes	No	No	No	6	Medium
Cedano 2020	No	No	No	No	No	Yes	No	No	No	No	No	1	Low
Tzortzi 2020	No	Yes	Yes	Yes	No	Yes	no	No	No	No	No	4	Medium
Chaaban 2020	No	No	No	No	No	Yes	No	No	No	No	No	1	Low
Sharma 2020	No	Yes	Yes	No	No	No	No	No	No	No	No	2	Low
Kaur 2018	No	No	Yes	Yes	No	No	No	No	No	No	No	2	Low
2. Cardiovascular diseases													
Martinez 2021	No	No	No	Yes	No	Yes	No	No	No	No	No	2	Low
Garcia 2020	No	No	No	No	No	No	No	No	Yes	No	No	2	Low
Goniewicz 2020	No	Yes	No	Yes	No	Yes	Yes	Yes	No	No	No	6	Medium
Sharma 2020	No	Yes	Yes	No	No	No	No	No	No	No	No	2	Low
Kennedy 2019	No	No	Yes	No	No	No	No	Yes	No	No	No	7	Medium
Skotsimara 2019	No	No	Yes	No	No	Yes	Yes	No	Yes	No	No	6	Medium
3. Cancer													
Flach 2019	No	No	Yes	No	No	Yes	Yes	Yes	No	No	No	4	Medium
4. Passive exposure to ENDS aerosol													
Hess 2016*	No	No	Yes	No	No	Yes	No	No	No	No	Yes	3	Low
Zainol-Abidin 2017	No	No	Yes	No	No	Yes	No	No	No	No	No	2	Low
5. Ear diseases													
Patel 2020	No	No	No	No	No	No	No	No	No	No	No	0	Low
6. Ocular diseases													
Martheswaran 2021	Yes	No	Yes	No	No	No	No	No	N/A	No	No	2	Low
7. Pregnancy outcomes													
Romer 2021	Yes	No	Yes	No	No	Yes	Yes	Yes	Yes	No	No	6	Medium
Calder 2021	Yes	No	Yes	No	No	No	Yes	Yes	No	No	No	5	Medium
Cardenas 2019	No	No	Yes	No	No	No	No	No	No	No	No	1	Low
Riley 2016	No	No	No	No	No	Yes	Yes	Yes	No	No	No	3	Low
8. Oral health													
Figuered 2020	Yes	Yes	No	Yes	No	Yes	Yes	Yes	No	No	No	6	Medium
Yang 2020	No	Yes	Yes	No	No	Yes	Yes	Yes	No	No	Yes	6	Medium
Ralho 2019	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	No	No	7	Medium
9. Injuries													
Vyncke 2020	No	Can't answer	Yes	No	No	No	No	No	No	No	No	2	Low
Tzortzi 2020	No	Yes	Yes	Yes	No	Yes	No	No	No	No	No	4	Medium
Scarpino 2020	No	Yes	Yes	No	No	Yes	No	No	No	No	No	3	Low
Seitz 2018	No	No	Yes	No	No	Yes	No	No	No	No	No	2	Low
Yang 2014	No	No	Yes	No	No	Yes	No	No	No	No	No	2	Low
10. Mental health													
Becker 2021	Yes	Yes	Yes	Yes	No	No	Yes	Yes	No	No	No	6	Medium
Sharma 2020	No	Yes	Yes	No	No	No	No	No	No	No	No	2	Low
11. Addiction													
Bozier 2020	No	No	No	Yes	No	Yes	No	No	No	No	No	2	Low
Armendáriz-Castillo 2019	No	No	No	No	No	No	No	No	No	No	No	1	Low

12. Substances use													
Rothrock 2020	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	9	High
Chadi 2019	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	8	High
Breitbarth 2018	No	No	Yes	No	No	Yes	No	No	No	No	No	2	Low
Hershberger 2017	No	Yes	Yes	Yes	No	Yes	No	No	No	No	No	4	Medium

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6.Were the characteristics of the included studies provided?
7.Was the scientific quality of the included studies assessed and documented?
8.Was the scientific quality of the included studies used appropriately in formulating conclusions?
9.Were the methods used to combine the findings of studies appropriate?
10.Was the likelihood of publication bias assessed?
11.Was the conflict of interest stated? Score: Low/Medium/High

Table 4. The quality assessment of reviews that were included in ENDS effect on smoking cessation (Domain 3)

Studies	1	2	3	4	5	6	7	8	9	10	11	Score	Low/Medium/High
Chan 2021	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	9	High
Grabovac 2021	Yes	No	Yes	No	No	Yes	Yes	Yes	Yes	No	No	6	Medium
Ibrahim 2021	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	10	High
Barufaldi 2021	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes	No	No	6	Medium
Zhang 2021	No	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	No	7	Medium
Calder 2021	Yes	No	Yes	No	No	No	Yes	Yes	No	No	No	5	Medium
Wang 2021	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	No	8	High
Pound 2021	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	No	8	High
Hartmann-Boyce 2020	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	10	High
Patil 2020	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	8	High
Gentry 2019	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	8	High
Maglia 2018	No	No	Yes	Yes	No	No	No	No	No	No	No	2	Low
Liu 2018	No	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes	No	6	Medium
El Dib 2017	No	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	No	6	Medium
Glasser 2017	No	No	No	Yes	No	No	No	No	No	No	No	1	Low
Kalkhoran 2016	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	10	High
Khoudigian, 2016	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	8	High
Malas, 2016	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	9	High
Gualano 2015	No	No	Yes	No	No	No	Yes	Yes	No	No	No	3	Low
Lam 2015	No	Yes	Yes	No	No	Yes	Yes	Yes	No	No	No	5	Medium
Waghel 2015	No	No	Yes	No	No	Yes	No	No	No	No	No	2	Low
Callahan-Lyon 2014	No	No	Yes	No	No	No	No	No	No	No	No	1	Low
Franck 2014	No	Yes	Yes	Yes	No	Yes	Yes	Yes	No	No	No	6	Medium
Rahman 2014	No	No	Yes	No	No	Yes	Yes	Yes	Yes	No	No	5	Medium

Was an 'a priori' design provided?
2.Was there duplicate study selection and data extraction?
3.Was a comprehensive literature search performed?
4.Was the status of publication (i.e. grey literature) used as an inclusion criterion?
5.Was a list of studies (included and excluded) provided?
6.Were the characteristics of the included studies provided?
7.Was the scientific quality of the included studies assessed and documented?
8.Was the scientific quality of the included studies used appropriately in formulating conclusions?
9.Were the methods used to combine the findings of studies appropriate?
10.Was the likelihood of publication bias assessed?
11.Was the conflict of interest stated? Score: Low/Medium/High

Table 5. The quality assessment of reviews that were included in ENDS effect on smoking initiation (Domain 4)

Studies	1	2	3	4	5	6	7	8	9	10	11	Score	Low/Medium/High
O'Brien 2021	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	No	7	Medium
Baenziger 2021	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	Yes	8	High
Zhang 2021	No	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	No	7	Medium
Bozier 2020	No	No	No	Yes	No	Yes	No	No	No	No	No	2	Low
Chan 2020	Yes	No	Yes	Yes	No	Yes	Yes	Yes	No	Yes	No	7	Medium
Khouja 2020	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	9	High
Aladeokin 2019	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	7	Medium
Soneji 2017	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	8	High
Zhong 2016	No	Yes	Yes	No	Yes	Yes	No	Can't answer	Yes	Yes	No	6	Medium

Was an 'a priori' design provided?
2.Was there duplicate study selection and data extraction?
3.Was a comprehensive literature search performed?
4.Was the status of publication (i.e. grey literature) used as an inclusion criterion?
5.Was a list of studies (included and excluded) provided?
6.Were the characteristics of the included studies provided?
7.Was the scientific quality of the included studies assessed and documented?
8.Was the scientific quality of the included studies used appropriately in formulating conclusions?
9.Were the methods used to combine the findings of studies appropriate?
10.Was the likelihood of publication bias assessed?
11.Was the conflict of interest stated? Score: Low/Medium/High

Table 6. The quality assessment of reviews that were included in ENDS and tobacco industry marketing clams (Domain 5)

Studies	1	2	3	4	5	6	7	8	9	10	11	Score	Low/Medium/High
Lee 2020	No	Yes	Yes	No	No	Yes	Yes	Yes	No	No	Yes	6	Medium
Collins 2019	No	Yes	No	No	No	Yes	Yes	No	No	No	No	3	Low
Lee 2018	Yes	Yes	Yes	Yes	No	Yes	No	No	No	No	Yes	6	Medium
Glasser 2017	No	No	No	Yes	No	No	No	No	No	No	No	1	Low

Was an 'a priori' design provided?
2.Was there duplicate study selection and data extraction?
3.Was a comprehensive literature search performed?
4.Was the status of publication (i.e. grey literature) used as an inclusion criterion?
5.Was a list of studies (included and excluded) provided?
6.Were the characteristics of the included studies provided?
7.Was the scientific quality of the included studies assessed and documented?
8.Was the scientific quality of the included studies used appropriately in formulating conclusions?
9.Were the methods used to combine the findings of studies appropriate?
10.Was the likelihood of publication bias assessed?
11.Was the conflict of interest stated? Score: Low/Medium/High

Table 7. Excluded studies

Author/Year/Title	Reason for exclusion
Patnode 2021. Interventions for Tobacco Cessation in Adults, Including Pregnant Persons: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force.	Umbrella review
Doshi 2020. Systematic review of systematic reviews: Do e cigarettes affect smoking cessation?	Umbrella review
Peruzzi 2020. Vaping Cardiovascular Health Risks: an Updated Umbrella Review.	Umbrella review
Hershberger 2020. Electronic nicotine delivery system use is related to higher odds of alcohol and marijuana use in adolescents: Meta-analytic evidence.	Duplicate
Schroeder 2014. Electronic cigarettes and nicotine clinical pharmacology	Duplicate
Martinez-Morata 2020. Electronic Cigarette Use and Blood Pressure Endpoints: a Systematic Review.	Duplicate
Rahman 2014. E-cigarettes and smoking cessation: evidence from a systematic review and meta-analysis.	Duplicate
Cheng 2014. Chemical evaluation of electronic cigarettes.	Duplicate
Callahan-Lyon 2014. Electronic cigarettes: human health effects.	Duplicate
Yang 2014. Electronic cigarettes: incorporating human factors engineering into risk assessments	Duplicate
Bjurlin 2020. Carcinogen biomarkers in the urine of e-cigarette users and implications for potential bladder cancer: A systematic review	Duplicate
Hartmann-Boyce 2016. Electronic cigarettes for smoking cessation	Duplicate
Chan 2021. Gateway or common liability? A systematic review and meta-analysis of studies of adolescent e-cigarette use and future smoking initiation.	Duplicate
Ibrahim 2020. Efficacy of e-cigarettes for smoking cessation: A systematic review and meta-Analysis.	Duplicate
Akiyama 2021. Systematic review of biomarker findings from clinical studies of electronic cigarettes and heated tobacco products.	Funded by industry
Albano 2016. A systematic review on the health and safety of electronic cigarettes	Full-text not available
Antonopoulos 2019. A systematic review and meta-analysis of the cardiovascular effects of E-cigarette	Full-text not available
Huang 2019. MS15.04 Approaching Cessation in the Patient Using Electronic Cigarettes	Full-text not available
KrÃsemann 2018. An overview of the role of flavors in e-cigarette addiction	Full-text not available
Skotsimara 2018. Exposure to E-cigarette adversely affects blood pressure and heart rate in healthy individuals: A systematic review and meta-analysis	Full-text not available
Mukhanova 2019. Chemical evaluation of electronic cigarettes	Full-text not available
Wakhlu 2018. Electronic cigarettes: Review of safety and use	Full-text not available
Mayel 2018. Are vapes an effective device for smoking cessation or a gateway to conventional tobacco smoking? Canadian Society of Respiratory Therapists Annual Education Conference May 24-26, 2018 Vancouver, British Columbia	Full-text not available
Stuart 2019. The effects of e-cigarettes and their performance as smoking cessation tools	Full-text not available
Charles 2020. Electronic nicotine delivery systems use and asthma in adolescents: A systematic review and meta-analysis	Full-text not available
Becker 2020. 42.9 Electronic cigarette use (vaping) and mental health comorbidity: a systematic review of studies among adolescents	Full-text not available
Foley 2015. The use of electronic cigarettes is not associated with cessation of smoking: A systematic review and meta-analysis	Full-text not available
Alghanam 2021. Association between electronic cigarette use and asthma symptoms among adolescents: A systematic review	Full-text not available
FernÃ¡ndez 2018. Exposure to second-hand aerosol produced by electronic cigarettes: A systematic review	Full-text not available
Villalobos 2019. Electronic cigarettes for smoking cessation: An individual patient meta-analysis of randomized controlled trials	Full-text not available
Vanderkam 2016. Efficacy and security of electronic cigarette for tobacco harm reduction: Systematic review and meta-analysis	Not published in English
Dupont 2019. Exposure of vapers to formaldehyde and acrolein: A systematic review	Not published in English
Claire 2020. Pharmacological interventions for promoting smoking cessation during pregnancy.	Not related to EC
Glover 2020. Potential effects of using non-combustible tobacco and nicotine products during pregnancy: a systematic review.	Not related to EC
Kwon 2019. Adolescent substance use and its association to sleep disturbances: A systematic review.	Not related to EC
Charles 2020. Effect of smoking on COVID-19 severity: A systematic review and meta-analysis	Not related to EC
Holliday 2019. Effect of nicotine on human gingival, periodontal ligament and oral epithelial cells. A systematic review of the literature.	Not related to EC
Tahiri 2011. Unconventional smoking cessation aids: A metaanalysis of randomized controlled trials	Not related to EC
Srikanth 2021. Intersection of smoking, e-cigarette use, obesity, and metabolic and bariatric surgery: a systematic review of the current state of evidence	Wrong study outcome[d]
Evans 2014. Electronic cigarettes: abuse liability, topography and subjective effects	Wrong study outcome
Coleman 2015. Pharmacological interventions for promoting smoking cessation during pregnancy.	Wrong study outcome
Sewer 2020. A meta-analysis of microRNAs expressed in human aerodigestive epithelial cultures and their role as potential biomarkers of exposure response to nicotine-containing products	Wrong study outcome
Erku 2021. Does the content and source credibility of health and risk messages related to nicotine vaping products have an impact on harm perception and behavioural intentions? A systematic review.	Wrong study outcome
Sharma 2021. Adolescent's Health Perceptions of E-Cigarettes: A Systematic Review.	Wrong study outcome

Tomashefski 2016. The perceived effects of e-cigarettes on health by adult users: A state of the science systematic literature review.	Wrong study outcome
Erku 2020. Beliefs and Self-reported Practices of Health Care Professionals Regarding Electronic Nicotine Delivery Systems: A Mixed-Methods Systematic Review and Synthesis.	Wrong study outcome
Pepper 2014. Electronic nicotine delivery system (electronic cigarette) awareness, use, reactions and beliefs: a systematic review.	Wrong study outcome
Chapman 2014. E-cigarette prevalence and correlates of use among adolescents versus adults: a review and comparison.	Wrong study outcome
Kinouani 2020. Motivations for using electronic cigarettes in young adults: A systematic review.	Wrong study outcome
Farsalinos 2017. Carbonyl Emissions in E-cigarette Aerosol: A Systematic Review and Methodological Considerations.	Wrong study outcome
Villanti 2018. How do we determine the impact of e-cigarettes on cigarette smoking cessation or reduction? Review and recommendations for answering the research question with scientific rigor.	Wrong study outcome
Briganti 2020. Content analysis of electronic nicotine delivery system publications in core clinical journals from 2012 to 2018	Wrong study outcome
Pisinger 2019. A conflict of interest is strongly associated with tobacco industry-favourable results, indicating no harm of e-cigarettes.	Wrong study outcome
Hendlin 2019. Financial Conflicts of Interest and Stance on Tobacco Harm Reduction: A Systematic Review.	Wrong study outcome
Wang 2018. Smoking by family members and friends and electronic-cigarette use in adolescence: A systematic review and meta-analysis.	Wrong study outcome
Khanagar 2019. Impact of electronic cigarette smoking on the Saudi population through the analysis of literature: A systematic review.	Wrong study outcome
Campbell 2020. Factors influencing the uptake and use of nicotine replacement therapy and e-cigarettes in pregnant women who smoke: a qualitative evidence synthesis.	Wrong study outcome
Habibagahi 2020. A review of the analysis of biomarkers of exposure to tobacco and vaping products.	Wrong study outcome
Xu 2016. E-Cigarette Awareness, Use, and Harm Perception among Adults: A Meta-Analysis of Observational Studies.	Wrong study outcome
Amin 2020. Social Influence in the Uptake and Use of Electronic Cigarettes: A Systematic Review.	Wrong study outcome
Greenhill 2016. Adolescent Awareness and Use of Electronic Cigarettes: A Review of Emerging Trends and Findings.	Wrong study outcome
Miller 2021. A systematic review of refillable ENDS liquid nicotine content accuracy.	Wrong study outcome
Claire 2020. Pharmacological interventions for promoting smoking cessation during pregnancy	Wrong study outcome
Allehebi 2015. Efficacy and safety of electronic cigarettes for smoking cessation: A systematic review	Wrong study outcome
Meernik 2019. Impact of non-menthol flavours in e-cigarettes on perceptions and use: an updated systematic review.	Wrong study outcome
Srikanth 2021. Intersection of smoking, e-cigarette use, obesity, and metabolic and bariatric surgery: a systematic review of the current state of evidence.	Wrong study outcome[a]
Brown 2014. Electronic cigarettes: product characterization and design considerations	Wrong study outcome
Evans 2014. Electronic cigarettes: abuse liability, topography and subjective effects.	Wrong study outcome
Heydari 2014. A comparative study on tobacco cessation methods: a quantitative systematic review.	Wrong study outcome[b]
Zare 2018. A systematic review of consumer preference for e-cigarette attributes: Flavor, nicotine strength, and type.	Wrong study outcome
Feldman 2020. A scoping review of inhaled vitamin e acetate, vitamin e (tocopherol), and pyrolyzed acetate	Wrong study design
Durmowicz 2014. The impact of electronic cigarettes on the paediatric population.	Wrong study design
Chang 2014. Research gaps related to the environmental impacts of electronic cigarettes	Wrong study design
Stobbs 2016. E-cigarettes in ENT: what do we need to know?	Wrong study design
Grana 2014. E-cigarettes: a scientific review.	Wrong study design
Nagpal 2021. Vaping During Pregnancy: What Are the Potential Health Outcomes and Perceptions Pregnant Women Have?	Wrong study design
Serror 2018. Burns caused by electronic vaping devices (e-cigarettes): A new classification proposal based on mechanisms.	Wrong study design
Orr 2014. Electronic cigarettes in the USA: a summary of available toxicology data and suggestions for the future.	Wrong study design
Gugala 2021. Pulmonary Health Effects of Electronic Cigarettes: A Scoping Review.	Wrong study design
Feldman 2021. Compiling Evidence for EVALI: A Scoping Review of In Vivo Pulmonary Effects After Inhaling Vitamin E or Vitamin E Acetate.	Wrong study design
Altabatabaie 2021. E-cigarette vaping and periodontium: A systematic review	Wrong study design[c]
Cao 2020. Review of Health Consequences of ECs and the Outbreak of Electronic Cigarette, or Vaping, Product Use-Associated Lung Injury.	Wrong study design
Born 2015. Electronic Cigarettes: A Primer for Clinicians.	Wrong study design
Meo 2014. Effects of electronic cigarette smoking on human health.	Wrong study design
Meernik 2015. A critical review of smoking, cessation, relapse and emerging research in pregnancy and post-partum.	Wrong study design
Zborovskaya 2017. E-Cigarettes and Smoking Cessation: A Primer for Oncology Clinicians.	Wrong study design
White 2021. Risk assessment of inhaled diacetyl from electronic cigarette use among teens and adults	Wrong study design
Chatterjee 2018. Is vaping a gateway to smoking: A review of the longitudinal studies	Wrong study design

David 2016. E-cigarettes for smoking cessation and reduction. Summary of the evidence and implications for public health programmes	Wrong study design
Hajek 2014. Electronic cigarettes: review of use, content, safety, effects on smokers and potential for harm and benefit.	Wrong study design
Struik 2020. Tactics for Drawing Youth to Vaping: Content Analysis of Electronic Cigarette Advertisements.	Wrong study design
Taylor 2021. A review of nicotine-containing e-cigarettes: Trends in use, effects, contents, labelling accuracy and detection methods.	Wrong study design
Rouabhia 2020. Impact of Electronic Cigarettes on Oral Health: a Review.	Wrong study design
O'Leary 2021.Critical appraisal of the European Union Scientific Committee on Health, Environmental and Emerging Risks Preliminary Opinion on ECs.	Wrong study design
Tobore 2019. On the potential harmful effects of EC on the developing brain: The relationship between vaping-induced oxidative stress and adolescent/young adults social maladjustment.	Wrong study design
Lemay 2020. E-cigarettes effects on the respiratory tract: a review of the literature.	Wrong study design
Szparaga 2021. Review of data on chemical content in an aerosol resulting from heating a tobacco or a solution used in e-cigarettes and in the smoke generated from the reference cigarettes.	Wrong study design
Zhang 2018. Safety Assessment of Electronic Cigarettes and Their Relationship with Cardiovascular Disease.	Wrong study design
Szukalska 2020. Electronic Cigarettes and Head and Neck Cancer Risk-Current State of Art.	Wrong study design
Rahman 2014. Electronic cigarettes: patterns of use, health effects, use in smoking cessation and regulatory issues.	Wrong study design
Ebersole 2020. Harmful chemicals emitted from electronic cigarettes and potential deleterious effects in the oral cavity.	Wrong study design
Campbell 2020. Factors influencing the uptake and use of nicotine replacement therapy and EC in pregnant women: a qualitative evidence synthesis	Wrong study design
Maessen 2020. Nicotine intoxication by e-cigarette liquids: a study of case reports and pathophysiology	Wrong study design
Nowak 2014. E-Cigarettes - Prevention, pulmonary health, and addiction	Wrong study design
Harrell 2014. Electronic nicotine delivery systems ("e-cigarettes"): review of safety and smoking cessation efficacy.	Wrong study design
Bals 2019. Electronic cigarettes: A task force report from the European Respiratory Society	Wrong study design
Li 2019. Effects of electronic cigarettes on indoor air quality and health	Wrong study design
Tsai 2020. Effects of e-cigarettes and vaping devices on cardiac and pulmonary physiology.	Wrong study design
Jankowski 2017. E-smoking: Emerging public health problem?	Wrong study design
KaunelienÄ 2018. A review of the impacts of tobacco heating system on indoor air quality versus conventional pollution sources.	Wrong study design
Casey 2020. Vaping and e-cigarette use. Mysterious lung manifestations and an epidemic.	Wrong study design
Aşkın Gülşen 2020. Health Hazards and Complications Associated with Electronic Cigarettes: A Review.	Wrong study design
Greene 2019. Developmental toxicity of e-cigarette aerosols	Wrong study design
Collaco 2018. Electronic Cigarettes: Exposure and Use Among Pediatric Populations.	Wrong study design
Alawsi 2015. Are e-cigarettes a gateway to smoking or a pathway to quitting?	Wrong study design
Cai 2017. Graphical review: The redox dark side of e-cigarettes; exposure to oxidants and public health concerns.	Wrong study design
Cahn 2011. Electronic cigarettes as a harm reduction strategy for tobacco control: a step forward or a repeat of past mistakes?	Wrong study design
Loewen 2019. Electronic Nicotine Delivery Systems: Current trends and patient education opportunities for dental hygienists.	Wrong study design
Orr 2014. Efficacy of electronic cigarettes for smoking cessation.	Wrong study design
Polosa 2016. Counseling patients with asthma and allergy about electronic cigarettes: an evidence-based approach.	Wrong study design
Clapp 2017. Electronic Cigarettes: Their Constituents and Potential Links to Asthma.	Wrong study design
Yan 2021. Epimutational effects of electronic cigarettes.	Wrong study design
Dinakar 2021. The health effects of electronic cigarettes	Wrong study design
Shields 2017. A Review of Pulmonary Toxicity of Electronic Cigarettes in the Context of Smoking: A Focus on Inflammation.	Wrong study design
Overbeek 2020. A review of toxic effects of electronic cigarettes/vaping in adolescents and young adults.	Wrong study design
Isakov 2020. A Case-Based Review of Vaping-Induced Injury-Pulmonary Toxicity and Beyond.	Wrong study design
Bold 2019. E-cigarettes: Tobacco policy and regulation.	Wrong study design
Heydari 2017. Electronic cigarette, effective or harmful for quitting smoking and respiratory health: A quantitative review papers.	Wrong study design
Khadka 2021. The Cardiovascular Effects of Electronic Cigarettes.	Wrong study design
Navas-Acien 2020. Early Cardiovascular Risk in E-cigarette Users: The Potential Role of Metals.	Wrong study design
DiCicco 2020. Potential effects of E-cigarettes and vaping on pediatric asthma	Wrong study design
Chadi 2020. Teen vaping: There is no vapour without fire	Wrong study design
Polosa 2019. The effect of e-cigarette aerosol emissions on respiratory health: a narrative review.	Wrong study design
Pataka 2012. What is the truth about electronic cigarettes?	Wrong study design
Drope 2017. Key issues surrounding the health impacts of electronic nicotine delivery systems (ENDS) and other sources of nicotine.	Wrong study design
Eltorai 2019. Impact of Electronic Cigarettes on Various Organ Systems.	Wrong study design
Lynn 2020. Cannabis, e-cigarettes and anesthesia.	Wrong study design

Asher 2019. Does using e-cigarettes increase cigarette smoking in adolescents?	Wrong study design
Ghosh 2017. Electronic cigarettes as smoking cessation tool: are we there?	Wrong study design
Leduc 2016. Is there a role for e-cigarettes in smoking cessation?	Wrong study design
McDonough 2021. Recent updates on biomarkers of exposure and systemic toxicity in e-cigarette users and EVALI.	Wrong study design
Fiani 2020. The Impact of "Vaping" Electronic Cigarettes on Spine Health.	Wrong study design
Gulland 2016. E-cigarettes help smokers quit, Cochrane review confirms.	Wrong study design
Striley 2020. World vaping update.	Wrong study design
Breland 2014. Science and electronic cigarettes: current data, future needs.	Wrong study design
Kim 2016. Review of electronic cigarettes as tobacco cigarette substitutes: Their potential human health impact.	Wrong study design
Harris 2020. Anesthesia Implications of Patient Use of Electronic Cigarettes.	Wrong study design
Chen 2019. Immunological and pathological effects of electronic cigarettes.	Wrong study design
Voos 2019. What is the nicotine delivery profile of electronic cigarettes?	Wrong study design
Sobczak 2020. E-cigarettes and their impact on health: from pharmacology to clinical implications.	Wrong study design
Hamidullah 2020. Adolescent Substance Use and the Brain: Behavioral, Cognitive and Neuroimaging Correlates.	Wrong study design
Almeida-da-Silva 2020. Effects of electronic cigarette aerosol exposure on oral and systemic health.	Wrong study design
Boakye 2020. The Promise and Peril of Vaping.	Wrong study design
Aziz-Ur-Rahman 2015. Safety and effectiveness of electronic cigarettes: A narrative review	Wrong study design
Drummond 2014. Electronic cigarettes. Potential harms and benefits.	Wrong study design
Caponnetto 2020. Well-being and harm reduction, the consolidated reality of ECs ten years later from this emerging phenomenon: A narrative review.	Wrong study design
Zakarya 2019. Epigenetic impacts of maternal tobacco and e-vapour exposure on the offspring lung.	Wrong study design
Shahandeh 2021. Vaping and cardiac disease.	Wrong study design
Ruszkiewicz 2020. Neurotoxicity of e-cigarettes.	Wrong study design
Orzabal 2019. Impact of Electronic Cigarette Aerosols on Pregnancy and Early Development.	Wrong study design
Mravec 2020. E-cigarettes and Cancer Risk.	Wrong study design
Buchanan 2020. Cardiovascular risk of electronic cigarettes: a review of preclinical and clinical studies.	Wrong study design
Odum 2012. Electronic cigarettes: Do they have a role in smoking cessation?	Wrong study design
Bekki 2014. Carbonyl compounds generated from electronic cigarettes	Wrong study design
Raja 2021. Smoke and heart should stay apart: A look at EC and other alternatives to conventional cigarettes, and their impact on cardiovascular health.	Wrong study design
Kaur 2020. Current Perspectives on Characteristics, Compositions, and Toxicological Effects of E-Cigarettes Containing Tobacco and Menthol/Mint Flavors.	Wrong study design
Li 2018. Heat or Burn? Impacts of Intrauterine Tobacco Smoke and E-Cigarette Vapor Exposure on the Offspring's Health Outcome.	Wrong study design
Huang 2018. Electronic cigarette: A recent update of its toxic effects on humans.	Wrong study design
Giroud 2015. E-Cigarettes: A Review of New Trends in Cannabis Use.	Wrong study design
Kuntic 2020. Could E-cigarette vaping contribute to heart disease?	Wrong study design
DeVito 2018. E-cigarettes: Impact of ENDS liquid Components and Device Characteristics on Nicotine Exposure.	Wrong study design
Cecchini 2020. E-Cigarette or Vaping Product Use-Associated Lung Injury: A Review for Pathologists.	Wrong study design
Chun 2017. Pulmonary toxicity of e-cigarettes.	Wrong study design
Lynch 2020. Tobacco Smoke and Endothelial Dysfunction: Role of Aldehydes?	Wrong study design
Palazzolo 2013. Electronic cigarettes and vaping: a new challenge in clinical medicine and public health. A literature review.	Wrong study design
Konstantinou 2018. Tobacco-specific nitrosamines: A literature review.	Wrong study design
Weaver 2014. Electronic cigarettes: a review of safety and clinical issues.	Wrong study design
Wolf 2019. Does utilization of electronic cigarettes facilitate smoking cessation compared to other interventions?	Wrong study design
Javed 2017. Recent updates on electronic cigarette aerosol and inhaled nicotine effects on periodontal and pulmonary tissues.	Wrong study design
Kiernan 2021. A brief overview of the National outbreak of EC, or vaping, product use-associated lung injury and the primary causes	Wrong study design
Sapru 2020. E-cigarettes use in the United States: reasons for use, perceptions, and effects on health.	Wrong study design
Suter 2020. The impact of tobacco chemicals and nicotine on placental development.	Wrong study design
Cao 2021. Toxicity of electronic cigarettes: A general review of the origins, health hazards, and toxicity mechanisms	Wrong study design
Stobbs 2016. E-cigarettes in ENT: what do we need to know?	Wrong study design
Morjaria 2017. E-cigarettes in patients with COPD: current perspectives.	Wrong study design
Fearon 2018. Nicotine pharmacokinetics of electronic cigarettes: A review of the literature.	Wrong study design
Kanniah 2021. E-cigarettes and vaping - a panacea or a bane to smoking in current times?	Wrong study design
Darville 2019. E-cigarettes and Atherosclerotic Cardiovascular Disease: What Clinicians and Researchers Need to Know.	Wrong study design
Cherian 2020. E-Cigarette or Vaping Product-Associated Lung Injury: A Review.	Wrong study design

US Preventive Services Task Force 2020. Primary Care Interventions for Prevention and Cessation of Tobacco Use in Children and Adolescents: US Preventive Services Task Force Recommendation Statement.	Wrong study design
Verhaegen 2017. Do E-cigarettes induce weight changes and increase cardiometabolic risk? A signal for the future.	Wrong study design
Phillips 2013. Tobacco harm reduction: opportunity and opposition.	Wrong study design
Vajdi 2020. Electronic cigarettes - myocardial infarction, hemodynamic compromise during pregnancy, and systolic and diastolic dysfunction: Minireview.	Wrong study design
Prochaska 2019. The public health consequences of ECs: a review by the National Academies of Sciences. A call for more research.	Wrong study design
Peterson 2017. Tobacco, e-cigarettes, and child health.	Wrong study design
Hefner 2017. Electronic cigarettes and mental illness: Reviewing the evidence for help and harm among those with psychiatric and substance use disorders.	Wrong study design
Kaliamurthy 2019. 50.1 E-cigarette: an overview	Wrong study design
Bracken-Clarke 2021. Vaping and lung cancer - A review of current data and recommendations.	Wrong study design
Ordean 2017. No. 349-Substance Use in Pregnancy.	Wrong study design
Famiglietti 2021. Are e-cigarettes and vaping effective tools for smoking cessation? Limited evidence on surgical outcomes: a narrative review.	Wrong study design
Lai 2020. Biological toxicity of the compositions in e-cigarette on cardiovascular system.	Wrong study design
Bourke 2017. E-cigarettes and urologic health: A collaborative review of toxicology, epidemiology, and potential risks.	Wrong study design
Lee 2019. Considerations related to vaping as a possible gateway into cigarette smoking: An analytical review	Wrong study design
Cohen 2013. Animal models of nicotine exposure: relevance to second-hand smoking, electronic cigarette use, and compulsive smoking.	Wrong study design
Oh 2014. Do e-cigarettes impart a lower potential disease burden than conventional tobacco cigarettes? Review on e-cigarette vapor versus tobacco smoke.	Wrong study design
Gupta 2015. Weighing the Harms and Benefits of E-cigarettes.	Wrong study design
Hage 2020. Electronic cigarettes and vaping associated pulmonary illness (VAPI): A narrative review.	Wrong study design
Jones 2019. E-cigarettes burn injuries: Comprehensive review and management guidelines proposal.	Wrong study design
Abouassali 2021. In vitro and in vivo cardiac toxicity of flavored electronic nicotine delivery systems	Wrong study design
Visconti 2019. Dermatologic manifestations associated with electronic cigarette use.	Wrong study design
Gotts 2019. What are the respiratory effects of e-cigarettes?	Wrong study design
Gugala 2020. Respiratory health effect of e-cigarettes: a literature review	Wrong study design
Knight-West 2016. E-cigarettes for the management of nicotine addiction.	Wrong study design
Franks 2018. Do Electronic Cigarettes Have a Role in Tobacco Cessation?	Wrong study design
Marsot 2016. Nicotine and Cotinine Levels with Electronic Cigarette	Wrong study design
Ismail 2018. Electronic cigarettes and oral health: A narrative review	Wrong study design
Marsot 2016. Nicotine and Cotinine Levels With Electronic Cigarette: A Review.	Wrong study design
Livingston 2019. Electronic Nicotine Delivery Systems or E-cigarettes: American College of Preventive Medicine's Practice Statement.	Wrong study design
Kostelli 2020. Effects of combustible tobacco smoking and novel tobacco products on oxidative stress: Different sides of the same coin?	Wrong study design
Chen 2017. A Comparative Health Risk Assessment of Electronic Cigarettes and Conventional Cigarettes.	Wrong study design
Johnson 2015. Adolescent Use of Electronic Cigarettes: An Emergent Health Concern for Pediatric Nurses	Wrong study design
Ilona Górna 2020. Electronic Cigarette Use and Metabolic Syndrome Development: A Critical Review.	Wrong study design
Newton 2020. Up in Smoke: An Update on Vaping, E-cigarettes, and Substance Abuse in Teenagers.	Wrong study design
Kitzen 2019. Is Some e-cigarette Use, Like Some Cigarette Use, Chronic-Pain Coping?	Wrong study design
Polosa 2017. Tobacco harm reduction and e-cigarettes	Wrong study design
Choi 2021. Electronic Cigarettes and Alternative Methods of Vaping.	Wrong study design
BinSaeedan 2020. Radiologic Review with Pathology Correlation of E-Cigarette or Vaping Product Use-associated Lung Injury.	Wrong study design
Whittington 2018. The Use of Electronic Cigarettes in Pregnancy: A Review of the Literature.	Wrong study design
Quan 2016. Electronic Cigarette and Nicotine Toxicity.	Wrong study design
Lindberg 2015. Nicotine poisoning related to the use of e-cigarettes	Wrong study design
Kar 2019. Effect of Electronic Cigarettes on the Inner Mucosa of the Craniofacial Region	Wrong study design
Nelluri 2016. The current literature regarding the cardiovascular effects of electronic cigarettes.	Wrong study design
Hamee 2018. Human health effects of electronic cigarettes: A review	Wrong study design
Rehan 2018. Vaping versus Smoking: A Quest for Efficacy and Safety of E-cigarette.	Wrong study design
Mayel 2018. Are vapes an effective device for smoking cessation or a gateway to conventional tobacco smoking?	Wrong study design
Desai 2020. Smoking and pregnancy: The era of electronic nicotine delivery systems.	Wrong study design
Dinardo 2019. Vaping: The new wave of nicotine addiction.	Wrong study design
Sailer 2019. Impact of Nicotine Replacement and Electronic Nicotine Delivery Systems on Fetal Brain Development.	Wrong study design
Szumilas 2020. The effects of ECs vapor components on the morphology and function of the male and female reproductive systems: A systematic review.	Wrong study design[c]
Domenico 2021. Combatting the epidemic of e-cigarette use and vaping among students and transitional-age youth	Wrong study design

Verea-Linares 2017. To vape or not to vape, that is the question	Wrong study design
Chang 2014. Research gaps related to the environmental impacts of electronic cigarettes.	Wrong study design
Fadus 2019. The rise of e-cigarettes, pod mod devices, and JUUL among youth: Factors influencing use, health implications, and downstream effects.	Wrong study design
Zborovskaya 2017. E-cigarettes and Smoking Cessation.	Wrong study design
Smith 2017. Electronic Cigarettes: A Burn Case Series.	Wrong study design
Bozier 2020. How harmless are E-cigarettes? Effects in the pulmonary system.	Wrong study design
Singh 2020. Addictions causing head-and-neck cancers	Wrong study design
DosSantos 2020. Vaping and dabbing: the cost of being cool	Wrong study design
Amaro 2019. Vaping and Orthopedic Surgery: A Review of Current Knowledge	Wrong study design
Pisinger 2020. A new Cochrane review on electronic cigarettes for smoking cessation: should we change our practice?	Wrong study design
Chatterjee 2016. Is vaping a gateway to smoking: a review of the longitudinal studies.	Wrong study design
Glascoe 2015. A Review of E-Cigarettes and Related Health Issues.	Wrong study design
Chopra 2013. Electronic cigarette - Reproducing pleasure of smoking without harm	Wrong study design
Qasim 2017. Impact of electronic cigarettes on the cardiovascular system	Wrong study design
Hickman 2020. Current E-Cigarette Research in the Context of Asthma.	Wrong study design
Jackson 2020. Recent findings in the pharmacology of inhaled nicotine: Preclinical and clinical in vivo studies.	Wrong study design
Durmowicz 2014. The impact of electronic cigarettes on the pediatric population	Wrong study design
Eshraghian 2021. A review of constituents identified in e-cigarette liquids and aerosols.	Wrong study design

[a]*Authors did not find any published study examining the effect of EC on the health outcome of MBS patients*

[b]*Reports on cessation practice in Iran)*

[c]*Not review although the title says "systematic review"*

[d]It was excluded from the review because authors did not find any published study examining the effect of EC on the health outcome of MBS patients

Table 8. Summary of reviews about ENDS toxicity (Domain 1)

Author/ Year	Country	Design	N of studies N of subjects	Primary outcome	Main results
Bjurlin 2020	USA	Systematic review of cross-sectional and longitudinal studies	• 22 • 1259	• Carcinogen biomarkers in the urine • Bladder cancer biomarkers in the urine • Carcinogen and toxicant urinary biomarkers	• 40 different parent compounds and four metals found in the urine of ENDS users • 63 unique toxicant or carcinogenic metabolite biomarkers were identified • 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). • Both o-toluidine and 2-naphthylamine, which are known to produce bladder cancer in human and animal studies, were found in ENDS users' urine at 2.3- and 1.3-fold higher levels, respectively, than never ENDS user controls. • The levels of PAH 1- hydroxypyrene (1-OHP) were found to be significantly higher in ENDS users than in never users and were not significantly different after cigarette smokers switched to ENDS.
Salam 2020	USA	Meta-Analysis - RCTs	• 11 • N/A	• Examine chemical compounds in flavored ENDS and their possible reactivities	• 189 flavored liquids and 173 distinct chemical compounds were identified and categorized into 22 chemical classes according to their functional groups. • Possible correlation of flavor compounds to aerosol toxicants was found.
Lee 2020	USA	Systematic review included cross-sectional studies	• 35 • N/A	• Nicotine delivery and exposure in JULL compared with other ENDS • Toxicants in JULL compared with other ENDS	• Nicotine: JUUL have lower free nicotine in the pod liquid and aerosol compared with other ENDS (5%-6%, 13%-95%; respectively) but a high total nicotine content in the form of benzoate salt. • Aerosol emissions: JUUL had lower levels of certain harmful constituents (benzene, volatile organic compounds, free radicals, carbonyls, formaldehyde, and total aldehydes) than other ENDS and cigarettes. • JUUL e-liquids had a cytotoxic association with human lung epithelial cells examined in vitro (1 study).
Bozier 2020	Australia	• Systematic review of in vitro/ex vivo of human samples, animal model, case study, human study.	• 225 • 72941	• Potential health effects of ENDS	• Flavor Additives: > Flavor toxicity was studies in a range of cells, with cinnamon in particular being singled out for its toxic effects. > Additional chemical compounds are generated during the vaporization process, and studies suggest adducts may form over time. > In vitro and in vivo studies have shown that flavors could affect cellular function, including phagocytosis and cytokine production. • Nicotine: Inhaled vaporized nicotine via ENDS was shown to increase heart rate (HR), arterial stiffness, and flow resistance, and in another study to decrease microcirculatory endothelial-dependent function, increase arterial stiffness, and increase BP, HR, and plasma myeloperoxidase.
Zhao 2020	USA	• Was not reported	• 24 • N/A	• Metal/metalloid levels in ENDS liquids, aerosols, and/or human bio samples	• ENDS s are a potential source of exposure to metals/metalloids. • Metal/metalloid levels in bio samples of ENDS users were similar or higher than levels found in cigarette and cigar users.
Ward 2020	USA	• Systematic review	• 92 • N/A	• ENDS aerosol constituents	• Findings were grouped into 6 major categories of potentially harmful chemicals: carbonyls, volatile organic chemicals, trace elements, reactive oxygen species and free radicals, polycyclic aromatic hydrocarbons, and tobacco-specific nitrosamines. • In general, high formaldehyde concentrations of aerosol toxicants are associated with increased power or voltage. • Aerosol toxicants are also associated with ENDS liquid flavoring agents existing as primary ingredients or as products of thermal degradation
Wang 2019	China	• Systematic review	• 47 • N/A	• Toxicity profiles of ENDS	• It is inconclusive as to which components in the e-liquids or ENDS aerosols induce adverse effects in model organisms. • The majority of ENDS toxicity profiles support that EC induce some adverse effects based on in vitro and in vivo research, although most of them agreed that ENDSs are less toxic than tobacco cigarettes. However, evidence of long-term effects is lacking. • 14 of the 15 in vivo studies of ENDS showed a certain degree of harmful effects. • Toxicology data collecting from animals were used to speculate human health effects.
Gaur 2019	India	Systematic	• 12 • N/A	• Metals in ENDS aerosols • Sources of metal in ENDS	• ENDSs are a source of hazardous trace metals.

		Review of experimental studies			• 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) • Exposure to high levels of chromium (respiratory and gastrointestinal system) • Exposure to high levels of Lead (Neurological impact in children and adult) • Exposure to high levels Aluminum (slow bone growth, mental impairments)
Armendáriz-Castillo 2019	Ecuador	Systematic Review	• 10 • N/A	• Cytotoxic and genotoxic effects of different compounds of ENDSs	• A total of 50 chemical compounds were reported to be present in ENDS • Health risks identified were eye, skin, and respiratory tract irritation (50%), cytotoxic effects (10%), and 11% of compounds with unknown effects • The presence of vanillin and cinnamaldehyde in e-liquids is highly related to toxicity • Dual users are a group of high risk because of higher nicotine absorption and the health-related effects found in common compounds between ENDS and conventional cigarettes will be increased.
Zulkifli 2018	Malaysia	Systematic review	• 4 • N/A	• Health risk assessment studies on ENDS and liquid contents.	• Most studies 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 ENDSs. • 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.
Farsalinos 2018	contributors from Greece and USA	Systematic review	• 32 • N/A	• Carbonyl emissions from ENDS compared to conventional cigarette	• Carbonyl emissions from ENDS 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.
Kaur** 2018	USA	Systematic Review	• 104 • N/A	• Aerosols • Acetaldehyde and formaldehyde • Flavors • Metals	• Although the amounts of harmful chemicals found in ENDS aerosols are far lower than conventional cigarettes, individual exposure depends on many factors such as device voltage, temperature, liquid flavour, nicotine content and smoking behaviour of the vaper. • The results demonstrate that compared to tobacco smoke, the use of ENDS 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.
Zainol Abidin 2017	Malaysia	Systematic Review	• 4 • 90	• Indoor assessment of exposure to ENDSs emissions	• The average airborne nicotine exposure among non-smokers who lived with conventional cigarette smokers was 0.74 µg/m3 while for those who lived with ENDS smokers, the nicotine level was lower (0.13 µg/m3). The airborne nicotine level in homes without smokers was 0.02 µg/m3 (50). • The geometric mean for salivary cotinine level were 0.38 ng/mL, 0.19 ng/ mL and 0.07 ng/mL among those living with conventional cigarette smokers, ENDS smokers and those living in non-smoking homes, respectively. • The concentration of urinary cotinine among those living with conventional cigarettes smokers, ENDS users and control homes were 2.46 ng/mL, 1.75 ng/mL and 0.70 ng/mL, respectively. • The concentration of aluminum in the room increased twofold from 203.0 ng/m3 to 482.5 ng/m3 before and after the vaping sessions. • The average concentration of nicotine in the homes of ENDS users was 200-fold lower [7.7 (17.2) µg/m3] compared to the homes of conventional smokers [1303 (2676) µg/m3]
Fernandez 2015	Spain	Systematic review of Environmental human study	• 8 • 45	• Composition of aerosols from ENDS originated by human vaping and the emission of particulate matter (PM2.5)	• ENDSs used under real conditions emit toxicants, including such as nicotine, carbonyls, metals, and organic volatile compounds, besides particulate matter • Total suspended particles emissions were systematically higher in vapor from ENDSs without nicotine (11.6µg/m3) than from ENDSs with nicotine (1.2µg/m3) • The PM2.5 medians in the ENDS user home and non-smokers smoke-free homes were similar, but PM2.5 peaks concurrent with the ENDS puffs
Cheng 2014	USA	Systematic review of lab studies	• 29 • N/A	• Chemicals in refill solutions, cartridges, aerosols, and environmental emissions of ENDS	• Various chemical substances and ultrafine particles known to be toxic, carcinogenic and/or to cause respiratory and heart distress have been identified in ENDS aerosols, cartridges, refill liquids and environmental emissions.

Callahan-Lyon 2014	USA	Systematic review	• 44 • NA	• Human health effects of exposure to ENDSs and their components	• ENDS aerosols may contain propylene glycol, glycerol, flavorings, nicotine, tobacco-specific nitrosamines (TSNA) and diethylene glycol. • Particulate matter (PM) evaluations of other ENDS components have not found serious health effects, but findings must be interpreted with caution due to limited data and lack of standardized testing methods.
Farsalinos 2014	Greece	Systematic review of lab studies	• 114 • N/A	• The potential risks from ENDS use compared with cigarettes	• 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 electronic cigarette vapors • Compared with cigarette, in ENDS formaldehyde, acetaldehyde and acrolein were 9–450 times lower; toluene levels 120 times lower; and NNN and NNK levels 380 and 40 times lower, respectfully
Burstyn 2014	USA	Systematic review	• 59 • N/A	• Chemistry of liquids and aerosols of ENDS	• Levels of propylene glycol in inhaled air can reach 1–6 mg/m3. • 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 is present in most ENDS 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 ENDSs in 8 hours would place the vaper at the occupational exposure limit.
Pisinger 2014*	Denmark	Systematic review	• 76 • 704	• The health consequences of vaping of ENDS	• Studies found fine/ultrafine particles, harmful metals, carcinogenic tobacco-specific nitrosamines, volatile organic compounds, carcinogenic carbonyls (some in high but most in low/trace concentrations), cytotoxicity and changed gene expression. • Of special concern are compounds not found in conventional cigarettes, such as propylene glycol. • In one study, the potential human carcinogens formaldehyde, acetaldehyde and acrolein were detected in the vapors of almost all ENDS s. • Based on 76 studies, ENDSs cannot be regarded as safe, even though they probably are less harmful than CCs.
Schroeder 2014	USA	Systematic review of clinical studies	• 16 • 143 (91 inexperienced ENDS users; 52 experienced ENDS users)	• ENDS clinical pharmacology	• Nicotine yields from automated smoking machines suggest that ENDS deliver less nicotine per puff than traditional cigarettes • Clinical studies indicate that ENDS deliver only modest nicotine concentrations to the inexperienced ENDS user.

**In 26 studies (34%) the authors had a conflict of interest. Most studies were funded or otherwise supported/influenced by manufacturers of ENDSs, but several authors had also been consultants for manufacturers of medicinal smoking cessation therapy.*

Table 9. Summary of reviews about ENDS Health Effects (Domain 2)

Author/ Year	Country	Design	N of studies N of subjects	Primary outcome	Main results
1. Respiratory diseases					
Bravo-Gutiérrez 2021	Mexico	Systematic Review	• 79 • NA	• Safety of ENDS devices and their relationship to human lung damage.	• Exposure to ENDS causes increased levels of pro-inflammatory biomarkers. • Inhalation of contaminants increases airway bacterial infection risk. • Patients with ENDS or vaping-associated lung injury (EVALI) presented leukocytosis, elevated erythrocyte sedimentation rate, and high C-reactive protein levels in peripheral blood.
Wills 2021	USA	Systematic Review and Meta-analysis of epidemiological and lab studies	• 24 • 1,094,772	• Association of ENDS use with asthma and COPD in human populations	• Asthma (15 studies): The pooled aOR was 1.39 (95% CI 1.28 - 1.51) • COPD (9 studies): The pooled aOR was 1.49 (95% CI 1.36 - 1.65). • Epidemiological studies: significant association of ENDS use with respiratory disorder (asthma, bronchitis, and COPD) was found across 23 of the 24 studies reviewed, and ENDS use typically added independently to risk derived from cigarette smoking. • Laboratory studies: ENDS 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.
Xian 2021	China	Meta-analysis	• 11 • 1,143,118	• Relationship between ENDS and asthma	• ENDS current and former use with asthma: OR 1.27, 95% CI 1.17–1.37. • ENDS current use with asthma: OR 1.30, 95% CI 1.17–1.45. • ENDS former use association with asthma: OR 1.22, 95% CI 1.08–1.39. • ENDS + traditional cigarettes: OR 1.47, 95% CI 1.13–1.91. • Teenager: OR 1.24, 95% CI 1.08–1.42 • Adult: OR 1.46, 95% CI 1.21–1.76 • Male: OR 1.09, 95% CI 0.97–1.22 • Female: OR 1.38, 95% CI 1.15–1.65 • Both (male and female): OR = 1.39, 95% CI 1.24–1.55
Gonsalves 2021	Canada	Systematic Review	• 23 • 61 13-18 years; Both male and female.	• Quantitative data on the presentation, investigative findings, patterns of lung injury, and interventions of pediatric cases of ENDS or vaping associated lung injury (EVALI) in the acute care setting.	• 10 patterns of lung injury were identified: acute lung injury/diffuse alveolar damage pattern (n=16), pneumonitis (n=7), hypersensitivity and acute (n=7), cryptogenic organizing pneumonia, eosinophilic pneumonia (acute and chronic; n=4), spontaneous pneumothorax (n=3), spontaneous pneumomediastinum, status asthmaticus (n=2), acute exogenous lipoid pneumonia (n=2), acute fibrinous organizing pneumonia, and bronchiolitis obliterans.
Xantus 2021	UK	Systematic Review	• 7 • 193	• The role of vitamin E acetate (VEA) and its derivatives in the vaping associated lung injury	• No evidence of harm associated with the administration of any VE isomers (including VEA), or significant clinical improvement in human asthma/COPD and/or ARDS/ALI. • 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.
Prasetyo 2021	Indonesia	Systematic Review	• 16 • 1400	• Nasal mucociliary clearance (NMC) in smokers	• Findings suggest that there is an impairment of NMC in ENDS 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.
Jonas 2020	USA	Systematic Review	• 169 • 216	• 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.	• 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.

Goniewicz 2020	USA and Sweden	systematic review, cross-sectional, longitudinal studies	• 6 • 19, 475 to 161,529 sample	• Respiratory (COPD, chronic bronchitis, emphysema, asthma, wheezing) • Cardiovascular (stroke, myocardial infarction, coronary heart disease)	• Former smokers who transitioned to ENDS 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 ENDS 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).
Cedano 2020	USA	Systematic Review	• 7 • 27 cases • Age 21-52	• Physiopathology of confirmed EVALI (ENDS or Vaping Product Use Associated Lung Injury) with lung biopsy.	• Chest CT findings: 89% of cases had diffuse bilateral ground glass opacities. The rest of the patients reported bilateral reticulonodular opacities 3.7%, bilateral nodules in 3.7%, and one had a CXR showing bilateral infiltrates without chest CT scan results. • Pathology results: 48% had organizing pneumonia, 26% diffuse alveolar damage, 15% a combination of Acute Fibrinous Pneumonitis, 3.7% AFP, and 3.7% lipoid pneumonia.
Tzortzi 2020	Greece	Systematic Literature	• 159 • 238 individual cases	• Medical (respiratory)	• 24% respiratory cases
Chaaban 2020	USA	Systematic Review	• 12 • 12 (age 15-60 years old)	• Cases of Acute eosinophilic pneumonia (AEP) (1), marijuana, and waterpipe smoking.	• 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.
Sharma 2020	India	Systematic review	• 36	• Respiratory diseases • Cardiovascular illnesses • Brain health	• Vaping may be linked with respiratory diseases such as asthma, popcorn lung, and EVALI potentially hazardous Vitamin E acetate were found from bronchoscopy and bronchoalveolar lavage of all patients suffering from EVALI.
Kaur** 2018	USA	Systematic Review	• 104 • N/A	• Pulmonary	• There are considerable pulmonary health risks associated with ENDS use. • Prolonged exposure to ENDS constituents in aerosols might result in respiratory complications (asthma, COPD, inflammation).
2. Cardiovascular diseases					
Martinez 2021	USA	Systematic review of cross-over and observation al study	• 13 • N/A	• Association of ENDS use with blood pressure endpoints; Systolic blood pressure (SBP), and diastolic blood pressure (DBP)	• The use of ENDS with and without nicotine may result in short-term elevations of both SBP and DBP
Garcia 2020	USA	Systematic review (All study designs)	• 19 • N/A	• Cardiovascular autonomic effects estimated by: Acute and chronic changes in heart rate variability (HRV), heart rate (HR) and blood pressure (BP)	• Acute autonomic cardiovascular effect of ENDS increased HR and BP less than acute TC smoking. • Nicotine in the ENDS aerosol was responsible for the acute effects • ENDS users have chronically elevated cardiac sympathetic activation compared to non-users, as measured by HRV, but this activation does not translate into clinically detectable higher HR or BP
Goniewicz 2020	USA and Sweden	systematic review, cross-sectional, longitudinal studies	• 6 • 19, 475 to 161,529 sample	• Cardiovascular (stroke, myocardial infarction, coronary heart disease)	• Switching from smoking to ENDS 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 after switching to ENDS.
Sharma 2020	India	Systematic review	• 36	• Respiratory diseases • Cardiovascular illnesses • Brain health	• ENDS is linked to cardiovascular illnesses such as atherosclerotic plaque and myocardial ischemia • Inhalation of nicotine results in local and systemic release of catecholamine, which leads to increased heart rate, blood pressure, and heart contraction.
Kennedy 2019	UK	Systematic review of experiment al studies of in vitro, animal, and human.	• 38 • N/A	• Cardiovascular effects associated with ENDS use.	• 74.3% of studies found potentially harmful effects through inducing sympathetic nerve activation, oxidative stress, endothelial dysfunction and platelet activation. • One study found ENDS aerosol accelerated atherosclerotic plaque formation • Studies with conflicts of interest (21.1%) or median-high risk of bias were less likely to identify potentially harmful effects.
Skotsimara 2019	Greece	systematic review and meta-analysis.	• 40 • 441	• Cardiovascular effects (heart rate, diastolic, systolic/diastolic blood pressure) compared with conventional cigarette	• ENDS negatively affects endothelial function, arterial stiffness and the long-term risk for coronary events • Conflicting evidence exists in the effects of ENDS on CVD. • Despite the negative acute effects of the ENDS on heart rate, benefits may be observed in terms of blood pressure regulation when switching from CC to ENDS use.
3. Cancer					
Flach 2019	UK and Germany	systematic review, (laboratory-	• 18 • N/A	• The association between ENDS and Head and neck cancers	• There is potential dangers associated with the use of ENDS and their role in HN cancers

		based studies, Cohort and case studies)			• A few studies suggested DNA damage following exposure to ENDS potentially due to increased oxidative stress. • Flavored e-liquids appear to be more harmful. • ENDS may play active roles in the pathogenesis of other malignancies such as lung and bladder cancers • A study of lungs of mice have demonstrated that aerosol from e-cigarettes induces oxidative stress, depletes glutathione and upregulates the production of inflammatory cytokines • Measurement of bladder carcinogens in the urine of ENDS users demonstrated greater concentrations of carcinogenic aromatic amines
4. Passive exposure to ENDS aerosol					
Zainol-Abidin 2017	Malaysia	Systematic Review	• 4 • 90	• Indoor assessment of exposure to ENDS emissions	• The average airborne nicotine exposure among non-smokers who lived with conventional cigarette smokers was 0.74 μg/m3 while for those who lived with ENDS smokers, the nicotine level was lower (0.13 μg/m3). The airborne nicotine level in homes without smokers was 0.02 μg/m3 (50). • The geometric mean for salivary cotinine level were 0.38 ng/mL, 0.19 ng/ mL and 0.07 ng/mL among those living with conventional cigarette smokers, ENDS smokers and those living in non-smoking homes, respectively. • The concentration of urinary cotinine among those living with conventional cigarettes smokers, ENDS users and control homes were 2.46 ng/mL, 1.75 ng/mL and 0.70 ng/mL, respectively. • The concentration of aluminum in the room increased twofold from 203.0 ng/m3 to 482.5 ng/m3 before and after the vaping sessions. • The average concentration of nicotine in the homes of ENDS users was 200-fold lower [7.7 (17.2) μg/m3] compared to the homes of conventional smokers [1303 (2676) μg/m3]
Hess 2016*	Australia	Observational and experimental studies	• 16 • N/A	• Compared volunteers passively exposed to ENDS vapour with non-exposed volunteers	• ENDS vapour has been shown to contain PM2.5 as well as nicotine. Those passively exposed to the vapors of ENDS users are exposed to numerous pollutants at levels above background and at concentrations that are associated with potential adverse health effects. • Salivary and urinary cotinine levels were significantly lower in volunteers from nonsmoking control homes than in volunteers exposed to either ENDS vapour or CC smoke, with both the latter having elevated levels of cotinine.
5. Ear diseases					
Patel 2020	UK	Systematic Review	• 43 • N/A	• ENDS effects in the field of otology and contribution to hearing loss	• Only one in vitro study has demonstrated middle-ear epithelial cell toxicity is exacerbated by nicotine and propylene glycol in ENDS. • Increased cytotoxicity was seen with menthol and fruit flavored electronic liquid. • Nicotine increases human middle-ear epithelial cell cytotoxicity, with cell viability reduced from 100% to 25–43% suggesting nicotine may have a role in middle-ear mucosal disease.
6. Ocular diseases					
Martheswaran 2021	USA	Systematic Review	• 38	• The short-term and long-term consequences of ENDS on the eye	• Only two studies were found • ENDS may induce dry eye, reduce tear film stability, or reduce ocular blood flow, among other effects. • These effects, along with tissue damage sustained from ENDS 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.
7. Reproductive health					
Romer 2021	Germany	Systematic Review (all animal studies)	• 17 • 8 neurobiological, 8 respiratory, 4 pulmonary, 2 cardiovascular, 1 facial morphology, 1 renal sequela 5 cognition and behavior	• The effects of prenatal ENDS exposure on foetal development	• Nicotine exposure is a major cause of a wide range of adverse and pathological birth outcomes such as low birth weight, miscarriage and stillbirth. • There is a significantly increased risk of sudden infant death syndrome, obesity, type 2 diabetes, and reduction in male reproductive capacity. • Nicotine also affects neuronal development via the neurotransmitter system which may lead to errors in the processing of basic cognitive processes such as learning, memory and attentiveness, and lower global intelligence and attention deficit hyperactivity disorder. • Some of the flavored "juices" can also be even more irritating to the lungs. Cherry flavoring seems to be the most harmful, as it contains benzaldehydes that have a fetotoxic effect.

Calder 2021	UK	All design	• 23 • N/A	• Birth outcomes	• Vaping has less effect on birthweight outcomes than traditional smoking • 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 traditional cigarette smokers.
Cardenas 2019	USA	All design	• 96 (only 11 related to ENDS) • N/A	• ENDS use among pregnant women and pregnancy complications, birth complications, stillbirth low birth weight.	• No studies of the effect of ENDS use/exposure on fetus or neonates. • Experimental studies in animals suggest that nicotine in ENDS alters DNA methylation, induces birth defects, reduces the birth weight, and affects the development of the heart and lungs of their offspring.
Riley 2016	USA	Systematic Review	• 14 • NA	• Risk of using ENDS among women who use hormonal contraceptives (HC)	• Cardiovascular events are rare among ENDS users in the general population • ENDS may affect heart rate and blood pressure less than conventional cigarettes
8. Oral health					
Figuered 2020	Canada	Systematic Review	• 8 • 582	• Impact of vaping on periodontitis.	• Available evidence pointed to increased destruction of the periodontium leading to the development of the disease • ENDS users consistently showed more loss of clinical attachment compared to non-users.
Yang 2020	USA	Systematic Review	• 99 • NA	• Oral health impact of ENDS uses.	• ENDS 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 ENDS explosions were described in case reports • Commonly reported mouth symptoms related to ENDS use or direct liquid exposure included dryness, burning, irritation, bad taste, bad breath and pain and discomfort
Ralho 2019	Portugal	Systematic Review	• 8 • 730	• Adverse effects of ENDS on the oral health (cavity).	• The results suggest that ENDS are less harmful than conventional cigarettes. • Nine different lesions of the oral mucosa were detected, with nicotinic stomatitis, hairy tongue, and angular cheilitis being more prevalent in ENDS users • There is also a greater susceptibility of ENDS users to developing alterations in oral biological tissues than ex-users or nonusers.
9. Injuries and poisoning					
Vyncke 2020	Belgium	• Systematic Review	• 41 • 180	• ENDS 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).	• Hand injuries while E are held or kept in the patient's pocket resulted in severe hand burns and inability to work or care for himself/herself if the functionalities of their hands are lost. • Face injury may cause concern for upper airway injury and may warrant an admission for airway observation. • Waist/groin injuries were seen when the ENDS explodes/ignites while being stored in the individual's pocket. • House or car fire. • 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 ENDS.
Tzortzi 2020	Greece	Systematic review	• 159 • 238 individual cases	• Medical (respiratory, allergy, oral, ulcerative colitis, skin, cardio, hematology, neonatal) • Poisoning (suicidal, accidental) • Traumatic injuries (traumatic, accidental)	• Twenty-five papers presenting 28 cases of nicotine poisonings were identified. 12% poisonings • 42 publications presenting 126 cases of injury were identified. 53% traumatic injuries due to ENDS explosion or self-combustion
Seitz 2018	US, UK	Systematic review (Case reports)	• 31 • 164 cases	• Burn injuries caused by ENDS explosions	• Most patients (90%) were male and between 20 to 29 years old • In most cases (65%), ENDS exploded in pockets, compared to exploding in the face or hand. • Common burned areas included the thigh, hand, genitals, and face. Burn severity was typically second-degree burns (35%) or a combination of second degree and third-degree burns (20%). • In all, 48 patients required skin grafting, with 19 reporting a median hospital stay of 5 days.
Yang 2014	US	Systematic review	• 20 • N/A	• Adverse events (AEs) associated with ENDS use	• Of the 20 reports containing AEs, • 8 were serious including an infant death from choking on a flavor 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 ENDS liquid ingestion.
Scarpino 2020	Italy	Systematic review	• 33 • 38	• Accidental or intentional poisoning through the	• Several cases of ENDS liquid intoxication have been reported in the literature in the last 10 year.

				ingestion and/or injection of e-liquid	• 38 reported cases of ENDS liquid intoxication was included in the review. • 9 were found to be dead by the emergency team, 12 were admitted to the Emergency Department with severe onset symptoms such as cardiac arrest (N = 11) or respiratory muscle paralysis (N = 1). Of the 12 patients, 5 resulted in brain death, 2 led to death through the withdrawal of life support treatment, 3 underwent to a non-neurological death, one patient remained in a persistent vegetative state, whereas one patient recovered consciousness. • The mechanisms by which nicotine might cause severe brain damage are still unclear.
10. Mental health					
Becker 2021	United States United States; Korea, the United Kingdom, and Taiwan	Systematic review Studies included: Cross-sectional and longitudinal observational studies and case series	• 40 • N/A. Adolescents and young adults (ages 12–26)	• Mental health comorbidities of ENDS use among adolescents and young adults	• Three main categories were studied: 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). • Among adolescent studies, ENDS 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, ENDS 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.
Sharma 2020	India	Systematic review	• 36	• Respiratory diseases; Cardiovascular illnesses; Brain	• Long-term use of ENDS may have a detrimental effect on brain health due to cerebral oxidative stress.
11. Addiction					
Bozier 2020	Australia	Systematic review of in vitro/ex vivo of human samples, animal model, case study, human study.	• 225 • 72941	• Potential health effects of ENDS	• <u>Flavor Additives</u>: > Flavor toxicity was studies in a range of cells, with cinnamon in particular being singled out for its toxic effects. > Additional chemical compounds are generated during the vaporization process, and studies suggest adducts may form over time. > In vitro and in vivo studies have shown that flavors could affect cellular function, including phagocytosis and cytokine production. • <u>Nicotine:</u> Inhaled vaporized nicotine via ENDS was shown to increase heart rate (HR), arterial stiffness, and flow resistance, and in another study to decrease microcirculatory endothelial-dependent function, increase arterial stiffness, and increase BP, HR, and plasma myeloperoxidase.
Armendáriz-Castillo 2019	Ecuador	Systematic Review	• 10 • N/A	• Cytotoxic and genotoxic effects of different compounds of ENDSs	• A total of 50 chemical compounds were reported to be present in ENDS • Health risks identified were eye, skin, and respiratory tract irritation (50%), cytotoxic effects (10%), and 11% of compounds with unknown effects • The presence of vanillin and cinnamaldehyde in e-liquids is highly related to toxicity • <u>Dual users</u> are a group of high risk because of higher nicotine absorption and the health-related effects found in common compounds between ENDS and conventional cigarettes will be increased.
12. Substance use					
Rothrock 2020	USA	Systematic Review	• 28 (25 cross-sectional, 3 cohort studies) • 458,357	• Association of ENDS with alcohol use and binge drinking in adolescents.	• Compared to ENDS nonusers, ENDS users had a higher risk for any alcohol use compared to non-users (OR, 6.62, 95% CI 5.67-7.72) and a higher rate of binge drinking/drunkenness (OR, 6.73, 95% CI 4.5-10.07). • The subset of high school ENDS 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 ENDS nonusers.
Chadi 2019	USA	Meta-analysis	• 21 (3 longitudinal and 18 cross-sectional) • 128,227	• Marijuana use	• Odds of marijuana use were higher in youth ENDS users than nonusers: AOR, 3.47 95% CI 2.63-4.59. • Longitudinal studies: ENDS users are significantly more likely to use Marijuana than nonusers: AOR, 2.43 95% CI 1.51-3.90. • Cross-sectional studies: ENDS users are significantly more likely to use Marijuana than nonusers AOR, 3.70 95% CI 2.76-4.96. • Adolescents aged 12 to 17 years: AOR, 4.29 95% CI 3.14-5.87. • Young adults aged 18 to 24 years: AOR, 2.30 95% CI 1.40-3.79.
Breitbarth 2018	Australia	Systematic review	• 38 • N/A	• Illicit drug use including cannabis, synthetic cannabinoids, synthetic	• 39% of medical marijuana patients are vapers. • ENDS is becoming a popular method of use for administration of synthetic cannabinoids.

				cathinones, cocaine, gamma-hydroxybutyric acid (GHB), heroin, fentanyl, 3,4-ethylenedioxyamphetamine (MDA), 3,4-ethylenedioxymethamphetamine (MDMA), and methamphetamine	• An increasing number of individuals are using ENDS as a new method of administration for methamphetamin. • ENDS and table-top vaporizers are being used to vape MDMA. • Increase in ENDS use of a variety of synthetic cathinones. • Cocaine in its free base form (crack cocaine) is being used in ENDS. • The freebase form of heroin is being used in ENDS. • 7.3% of ENDS device users had vaped fentanyl. • A concentrated resin from the blue lotus flower (N. caerulea) was found in ENDS dripper-style' device.
Hershberger 2017	USA	Meta-analysis of cross-sectional and longitudinal studies	• 32 • 150,299 for alcohol • 89,962 for marijuana	• Marijuana and alcohol use	• Adolescents who use ENDS 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 ENDS. • Adults who use ENDS were more likely to use alcohol (OR = 1.57, p< .001) and marijuana (OR = 2.04, p< .001) than those who did not use ENDS. • ENDS use was associated with significantly greater odds of alcohol use (log OR, 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.

*Hess 2016: Three of the included articles involved in employee of tobacco company, one is funded by employee of tobacco company and one is funded by National Vapers Club.
Sharma was included in 3 categories (cardiovascular disease, respiratory disease, mental health)
Tzortzi 2020 was included in 2 categories (respiratory disease, injurie)
Goniewicz 2020 was included in 2 categories (cardiovascular disease, respiratory disease)

Table 10. Summary of reviews about the effect of ENDS on smoking cessation outcomes (Domain 3)

Author/ Year	Country	Design	N of studies N of subjects	Primary outcome	Main results
Chan 2021	Australia	Meta-analysis of RCTs	• 16 (7 meta-analysis) • 11,754	• Smoking abstinence at the end of the study	• ENDS (vs no treatment): 2.08 (1.39, 3.15) • ENDS (vs. NRT): 1.49 (1.04, 2.14)
Grabovac 2021	author affiliated country: Vienna	Systematic review and meta-analysis, RCT	• 12 (9 meta-analysis) • 8512	• Smoking abstinence compare versus NRT, or ENDS C placebo	• RR= 1.71 [1.02.2.84]: RR for abstinence in nicotine ENDS vs. placebo ENDS - each study's last follow-up • RR= 1.41 [0.87,2,28]: RR for abstinence in nicotine ENDS vs. placebo ENDS similar follow-up • RR= 1.73[1.31,2.28]: RR for abstinence in nicotine ENDS vs. NRT and/or counseling- each study's last follow-up • RR= 1.49[1.24,1.78]: RR for abstinence in nicotine ENDS vs. NRT and/or counseling- similar follow-up
Ibrahim 2021	Egypt	Systematic review and meta-analysis	• 12 • 9,863	• Efficacy and safety of ENDS versus different forms of NRT and placebo to quit smoking.	• 1-month continuous abstinence rate (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 (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). • ENDS did not significantly improve 12-month abstinence more than the control group (2 studies; N = 1184; RR 2.52, 95 % CI 0.00; 1444.26).
Barufaldi 2021	Brazil	Systematic review and meta-analysis	• 6 • 374 - 4094	• Risk of smoking relapse with the use of ENDS by former smokers.	• Risk of relapse was 2.03 (95% CI: 1.39–2.96) among former smoker ENDS users than ENDS nonusers. • Risk of relapse was 1.38 (95% CI: 1.11–1.65) when pooling the adjusted association measures.
Zhang 2021*	China	Systematic Review	• 14 out of 35 (5 meta-analysis, 9 cohort) • RCT: 4025 9 • Cohort: 22220 • Initiation: 68943 (excluded)	• Effects of ENDS on smoking cessation among smokers	5 meta-analysis: • 8.2% smokers achieved cessation in the ENDS 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: • ENDS use was not associated with smoking cessation (AOR=1.16; 95% CI: 0.88–1.54; I2=69.0%; 9 trials; n=22220). • Intensive ENDS use was more effective in achieving cessation than non- ENDS use (AOR= 2.03; 95% CI: 1.35–3.05; I2=37.8%; 4 trials, n=1144)
Calder 2021*	US, UK, Ireland	Systematic review (Cross-sectional survey, qualitative, cohort, RCT)	• 23 (only 6 studies on smoking cessation) • N/A	• Vaping and smoking cessation in pregnancy	• No difference was found between vapers and nonvapers in smoking cessation, although one study indicated that cessation effects from vaping might have been obscured by heightened motivation to quit smoking among all pregnant women. • One good-quality longitudinal study of 428 pregnant women followed for 1-month, found that those who vaped (n=36) had similar odds as those who did not vape (n=392), of having quit smoking for 7 days and of having attempted to quit smoking
Wang 2021	USA, Canada, UK, Europe, Australia and New Zealand, Asia. (author's affiliation: USA)	Meta-analysis of observational studies and RCTs	• 64 (55 observational studies and 9 RCT) • Observational studies: 57 • RCT: 9	• Smoking cessation	• 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).
Pound 2021	Canada	Systematic review and meta-analysis of RCTs	• 6 RCTs • 4151	• Smoking cessation compared to non-electronic NRT • Smoking reduction, harms, withdrawal and acceptance of therapy	• 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)
Hartmann-Boyce 2020	US, UK, Belgium, New Zealand, Italy, Switzerl	Systematic review (meta-analysis (cohort, RCT)	• 24 (3 meta-analysis) • ENDS vs. placebo: 662 • ENDS vs. NRT 584	• Smoking cessation	Meta-analysis: • ENDS vs. placebo ENDS (RR 2.29 (1.05, 4.96) (2 studies) • ENDS vs. nicotine patch (RR 1.26 (0.68, 2.34) (1 study) Cohort studies**:**

	and, South Africa, Korea, Prague				• The cohort studies showed quit rates among ENDS users ranging from 14% in smokers with mental illness to 53% in a population of smokers unwilling to quit at the outset. • Of the 7 longitudinal surveys which analyzed cessation at follow-up based on ENDS use at baseline, 5 detected no significant difference, and 2 found that ENDS use at baseline was significantly associated with decreased rates of abstinence at follow-up.
Patil 2020	India	Longitudinal cohort studies	• 13 • 18,586	• Tobacco cessation	• 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-ENDS users. • Pattern of e-cigarette may have significant effect on smoking cessation capability of ENDS. • Well-designed randomized controlled clinical trials are needed to assess the clinical efficacy of ENDS in comparison with approved smoking cessation therapies.
Gentry 2019	USA, Australia, Italy, New Zealand	Systematic review (RCT. Cohort, qualitative)	• 9 • N/A	• Smoking cessation • Smoking reduction	• ENDS were as effective as NRT (moderate quality) • 4 studies suggested significant smoking reduction; however, three were uncontrolled and had sample sizes below 30. • A prospective cohort study found no differences between ENDS users and nonusers for smoking cessation/reduction.
Maglia 2018	Italy	Systematic review	• 7 • 8444	• The influence of the use of ENDS on smoking behavior among dual users	• 13-48% quit at 1 month • 14-46% quit at 1 year • 28-50% reduced smoking by 50% at 1 month • 50% reduced smoking by 50% at 1 year
Liu 2018	China	Meta-analysis	• 14 • 35665	• Smoking cessation • Smoking reduction • Adverse events	• The pooled efficacy rate of e-cigarettes ranged from 13.2% to 22.9% for smoking cessation. • The pooled efficacy rate of e-cigarettes ranged from 48.3% to 58.7% for smoking reduction • The pooled rate of adverse events associated with e-cigarettes ranged from 49.1% to 51.6% • Short-term (≤12 months) use of ENDS would benefit smoking reduction more than long-term (>12 months) use (pooled rate 7.6% vs 37.1%) (P<.05).
El Dib 2017	Brazil	Systematic review, meta-analysis, (RCT, Cohort)	• 12 (3 meta-analysis; 9 cohort studies) • Total: 14122	• Smoking cessation	• Results provided by only two RCTs suggest a possible increase in tobacco smoking cessation with ENDS in comparison with not ENDS (RR 2.03, 95% CI 0.94 to 4.38; p=0.07; risk difference (RD) 64/1000 over 6 to12 months, low-certainty evidence). • Results from cohort studies suggested a possible reduction in quit rates with use of ENDS compared with no use of ENDS (OR 0.74, 95% CI 0.55 to 1.00; p=0.051; very low certainty).
Glasser 2017*	USA	Systematic review	• 687 (only 74 on smoking cessation) • N/A	• Effect of ENDS in smoking cessation compared to NRT	• Four RCTs show that ENDS are effective in helping some adult smokers to quit or to reduce their cigarette. Regular and intensive vaping can facilitate quit attempts and cessation
Kalkhoran 2016	USA	Cohort studies, cross-sectional studies, and RCT	• 38 (18 systematic review; 20 (meta-analysis) • 40,878	• Smoking cessation	• Odds of quitting cigarettes were 28% lower in those who used ENDS compared with those who did not use ENDS. • Association of ENDS use with quitting did not significantly differ among studies of all smokers using ENDS (irrespective of interest in quitting cigarettes) compared with studies of only smokers interested in cigarette cessation. • OR 0·72, 95% CI 0·57–0·91. • OR 0·63, 95% CI 0·45–0·86 vs 0·86, 0·60–1·23; p=0·94.
Gualano 2015	Italy	Observational studies, Experimental studies	• 12 • N/A	• Smoking cessation • Smoking reduction • Withdrawal symptoms • Adverse events	• Four experimental studies and six cohort studies reported a reduction in the desire to smoke, reduction in number of cigarettes and/or withdrawal symptoms. • In all studies that analyzed the withdrawal symptoms, the ENDS decreased craving significantly after 5 min and ‘concentrate’, ‘awake’ and ‘reduce hunger’ raised significantly at all times after electronic smoking. • 2 cohort studies reported a reduction in the number of cigarette/day (from 50 to 80%) after the introduction of the ENDS. • Mouth and throat irritation, nausea, headache, and dry cough were the most frequently AEs reported.
Khoudigian 2016	UK, Italy and New Zealand (Author’s affiliation: Canada).	Systematic review and meta-analysis of RCT and comparative observational studies	• 5 • 1103	• Smoking cessation:	• The pooled effect estimates for the desire to smoke (RR -0.22; 95 % CI -0.80, 0.36) • Comparison of smoking abstinence between nicotine ENDS and placebo ENDS (RR 2.02 [0.97, 4.22] • Comparison of desire to smoke between nicotine ENDS and placebo ENDS Mean difference: -0.22 [-1.65, 0.45]: • Limited low-quality evidence of a non-statistically significant trend toward smoking cessation in adults using nicotine ENDS exists compared with other therapies or placebo.

Malas, 2016	Canada	Systematic Review	• 62 • NA	• Smoking abstinence • Smoking reduction	• 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%
Lam 2015	Canada	RCTs	• 4 • 1,045	• Smoking cessation and reduction	• ENDS may constitute an effective smoking cessation tool. • All included studies included participants that initially had no desire to quit smoking. • All studies reported a significant reduction in smoking or complete smoking cessation. • At 8 months, reduction or complete abstinence from tobacco smoking was achieved with the ENDS in 44% of participants. • At 6 months, verified abstinence was 7.3% with nicotine ENDS, 5.8% with patches and 4.1% with placebo ENDS. Reduction was 1.51 (95% CI –2.49 to 5.510) in nicotine ENDS versus patches, and 3.16 (95% CI –2.29 to 8.61) in nicotine ENDS versus placebo ENDS.
Waghel 2015	USA	Clinical trails	• 7 • 1,177	• Smoking cessation or reduction	• 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.
Callahan-Lyon 2014*	USA	Systematic Review	• 44 (12 for cessation) • 7067	• Smoking cessation and reduction	• Mixed results, with generally low sustained cessation rates (self-reported or verified (7.3-31% were abstinent at 6 months; 14% were abstinent at 1 year; 22.5-66.8% reduced smoking by 50% at 6 months).
Franck 2014	Canada	Systematic Review of RCTs	• 7 • 14 to 657	• Smoking cessation and reduction	• Abstinence rates were 7.3-22.5% at 6 months, 14.3% at 1 year, and 12.5% at 2 years • Reduction rates were 12.5% reduced smoking by 50% at 6 months, 50% reduced by 50% at 1 year; 27.5% reduced by more than 50% at 2 years.
Rahman 2014	Australia	• Systematic review and meta-analysis RCT, cross-sectional, prospective studies	• 6 • 7,551 (1242 in meta-analysis)	• Smoking abstinence • Smoking reduction	• Use of e-cigarettes is associated with smoking cessation and reduction. • 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 minimum 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).

** Reported on several domain. Only studies that were related to cessation were considered in this domain.*

Table 11. Summary of reviews about the effect of ENDS on smoking initiation (Domain 4)

Author/ Year	Country	Design	N of studies N of subjects	Primary outcome	Main results
O'Brien 2021	UK	Systematic Review + Meta-analysis	• 14 studies (9 in Meta-analysis) • Age 13-19	• The risks of ENDS use on smoking initiation among nonsmoking adolescents	• 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.
Baenziger 2021 Umbrella review	Australia	Meta-analysis	• 12 • NA	• ENDS use and combustible tobacco cigarette smoking uptake among non-smokers	• On average, non-smokers who used ENDS have around threefold the odds of either initiating smoking or currently smoking combustible cigarettes compared with non-smokers who have not used ENDS. • 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 e-cigarettes
Zhang 2021*	China	Systematic Review	• 69 (35 qualitative, 29 quantitative, 5 RCT) – 15 included here • RCT: 40259 • Cohort: 22220 • Initiation: 68943	• The risks for smoking initiation among nonsmoking adolescents	• Based on cohort studies involving 17389 adolescents and young adults aged 14-30 years indicated that ever ENDS 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 ENDS users were more likely to initiate smoking than ENDS nonusers (AOR, 2.91; 95% CI 2.61-3.23; I^2 =61.0%; 15 trials, n=68943).
Bozier 2020*	Australia	Systematic Review	• 225 (only 9 related to initiation) • 72941	• Update on the potential health effects of ENDS since the National Academies of Sciences, Engineering and Medicine report.	• A meta-analysis of 9 studies containing data from 17,389 adolescents and young adults showed that ENDS use was associated with an increased risk of subsequent initiation of tobacco smoking (OR, 3.5). • At a population level, increasing prevalence of ENDS use in the US was associated with a faster decline in tobacco smoking. • In contrast, 2 studies reported that among never smokers, adolescents who used ENDS were more likely to transition to tobacco cigarette smoking. This finding suggests that the effect of ENDS may be different at the population level and the individual level.
Chan 2020	Australia	Meta-analysis	• 11 • 246 - 17318	• The effect of ENDS on smoking initiation among adolescents	• 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. • Studies with sample sizes<1000 had a significantly higher odds ratio (OR, 6.68, 95% CI 3.63-12.31) than studies with sample sizes>1000 (OR, 2.49, 95% CI 1.97-3.15). • Existing evidence is limited by publication bias, high sample attrition and inadequate adjustment for potential confounding variables.
Khouja 2020	UK	Systematic Review and meta-analysis	• 24 (17 in meta-analyses) • 347 to 39718	• Whether ENDS use compared with non-use in young non-smokers is associated with subsequent cigarette smoking	• There is a strong consistent association in observational studies between ENDS 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 ENDS use and smoking. • When pooled in a random-effects meta-analysis, ENDS 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 3.60-5.85). • Pooling the adjusted estimates, the association was still strong but somewhat weaker (AOR, 2.92, 95% CI 2.30-3.71).
Aladeokin 2019	UK	Systematic Review and Meta-analysis (Longitudinal, cross-sectional)	• 11 (8 quantitative synthesis, 3 in meta-analysis) • ENDS users: 547 • ENDS Nonusers: 4227	• ENDS use and smoking in adolescents	• Longitudinal studies reported an increase in use of one of either ENDS or traditional cigarettes when the alternate product was initiated. • The cross-sectional surveys were only able to show an association between ENDS use and traditional cigarette smoking in British adolescents. • In the meta-analysis, ENDS users vs. nonusers: AOR, 5.55 95% CI 3.94-7.82; unadjusted OR, 26.01 95% CI 5.35-126.44.
Soneji 2017	USA	Systematic review and meta-analysis of longitudinal studies	• 9 • 17389 adolescents and young adults	• Cigarette smoking initiation among adolescents and young adults	• Adjusting pooled OR for subsequent cigarette smoking initiation was 3.62 (95% CI, 2.42-5.41) for ever vs never e-cigarette users. • The pooled OR 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.

Zhong 2016	China	Meta-Analysis, Cross-sectional, Longitudinal cohort	• 6 • 91051including 1452 ever ENDS C use	• Smoking intentions • Willingness to smoke • Openness to smoke	• Compared to those who never used ENDS, never cigarette smoking adolescents and young adults who used ENDS have more than 2 times increased odds of intention to smoke cigarette (OR, 2.21, 95% CI 1.86-2.61). • Pooled effect size for intention to smoke cigarette was OR, 2.21, 95% CI 1.86-2.61.

** Only studies reporting on initiations were counted.*

Table 12. Summary of reviews about ENDS marketing effects on consumers (Domain 5)

Author/ Year	Country	Design	N of studies N of subjects	Primary outcome	Main results
Lee 2020	Korea	Cross-sectional surveys	• 35 • N/A	• Marketing and social media communication •	• Social media marketing campaigns have 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. • 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 • 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 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.
Collins 2019	USA	Experimental, quasi-experimental, observational, qualitative, mixed methods	• 124 • (80 marketing, 44 communication) • N/A	• ENDS marketing and communication	• Cross-sectional data suggests that e-cigarette users recall more ENDS 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 ENDS marketing and lower ENDS harm perceptions, greater intention to use, and use of ENDS, although most of these studies are cross-sectional, so causality cannot be inferred. • The inclusion of warnings in ENDS advertisements may increase ENDS harm perceptions and reduce the odds of purchasing ENDS. The majority of ENDS products and retailer sites feature warnings, but the content and location of the warnings is inconsistent.
Lee 2018	USA	Not reported	• 22 • N/A	• Sales and marketing practices of vape shops	• Vape shops have potential to promote ENDS or smoking cessation but also sometimes provide inaccurate information and mislabeled products. • 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. • Vape shops are more likely to be concentrated near college and university campuses and are patterned in opposite ways of conventional tobacco retailers (i.e., targeting White residents, higher median incomes).
Glasser 2017	USA	Experimental, quasi-experimental, qualitative studies, mixed methods	• 687 • N/A	• Marketing and communication of ENDS products	• 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. • Vapers are 2-3 times more sensitive to price than smokers. • 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. • Commonly marketed as alternatives to cigarettes, ENDS advertisements often make claims, such as being an effective smoking-cessation aid. • Studies assessing online retailers found inadequate age verification methods, with one study reporting a 93.7% rate of successful youth purchases without age verification.