

Risk and safety profile of electronic nicotine delivery systems (ENDS): an umbrella review to inform ENDS health communication strategies

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ABSTRACT

Objectives This umbrella review aims to summarise the evidence about electronic nicotine delivery systems' (ENDS) risk and safety health profile to inform ENDS health communication strategies.

Data sources and study selection Six databases were searched for systematic reviews presenting evidence on ENDS-related health effects. Ninety reviews divided into five categories were included: toxicity=20, health effects=40, role in smoking cessation=24, role in transition to combustible cigarettes (CCs)=13 and industry marketing claims=4.

Data extraction Findings were synthesised in narrative summaries. Meta-analyses were conducted by study type when appropriate. Quality assessment was conducted using the Measurement Tool to Assess Systematic Reviews. The Institute of Medicine's Levels of Evidence Framework was used to classify the evidence into high-level, moderate, limited-suggestive and limited-not-conclusive.

Data synthesis We found high-level evidence that ENDS exposes users to toxic substances; increases the risk of respiratory disease; leads to nicotine dependence; causes serious injuries due to explosion or poisoning; increases smoking cessation in clinical trials but not in observational studies; increases CC initiation; and exposure to ENDS marketing increases its use/intention to use. Evidence was moderate for ENDS association with mental health and substance use, limited-suggestive for cardiovascular, and limited-not-conclusive for cancer, ear, ocular and oral diseases, and pregnancy outcomes.

Conclusions As evidence is accumulating, ENDS communication can focus on high-level evidence on ENDS association with toxicity, nicotine addiction, respiratory disease, ENDS-specific harm (explosion, poisoning) and anti-ENDS industry sentiment. Direct comparison between the harm of CCs and ENDS should be avoided.

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INTRODUCTION

Advances in tobacco control have helped curtail combustible cigarette (CC) smoking worldwide, but this progress is potentially compromised by an alarming increase in the use of electronic nicotine delivery systems (ENDS) products.^{1 2} ENDS are

WHAT IS ALREADY KNOWN ON THIS TOPIC

- ⇒ Communication of electronic nicotine delivery systems' (ENDS) risks to young people has been identified by major health and regulatory bodies as a priority strategy to limit ENDS use.
- ⇒ The development of effective ENDS health messages requires an extensive and robust review of the evidence about these products' harmful and beneficial potential.

WHAT THIS STUDY ADDS

- ⇒ This umbrella review summarised the evidence about ENDS health profile into five domains: toxicity, health effects, role in smoking cessation, role in the transition to combustible cigarettes (CCs) and ENDS industry marketing claims.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- ⇒ ENDS messages can currently be centred on high-level evidence related to ENDS association with toxicity, nicotine addiction, asthma exacerbation, ENDS-specific harm (explosion, poisoning) and anti-ENDS industry sentiment.
- ⇒ Avoiding direct comparison between the harm of CCs and ENDS is important given the uncertainty about this information, mainly because of the variation in ENDS types/generation, nicotine content, the widespread dual and polytobacco use, and the scarcity of standardised comparative studies.

now the leading tobacco product among young people in the USA.^{3 4} Young people are particularly drawn to ENDS use due to the novelty of the devices, nicotine buzz, flavours, targeted industry marketing and the perception of their safety.⁵⁻⁷ ENDS have their own health risk profile including emitting toxic substances, prompting nicotine dependence and increasing the risk of initiating CC product use.^{8 9} Nicotine exposure has also been found to interfere with healthy brain development among youth, and its influence can remain until the mid-20s.¹⁰ In addition, while ENDS have shown some promise in helping CC smokers with quitting under controlled randomised clinical trial (RCT)



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conditions,¹¹ evidence from observational studies suggests that ENDS use can reduce the likelihood of cessation and increase dual use.^{12–14}

Communication of ENDS risks to young people has been identified by major health and regulatory bodies as a priority strategy to limit ENDS use.¹⁵ It is also aligned with the US Food and Drug Administration's (FDA) statutory obligation, according to the Family Smoking Prevention and Tobacco Control Act.¹⁶ From a consumer rights perspective, communication of product-associated risks is important to: (1) protect consumers from health and safety hazards in the marketplace, and (2) give them adequate information to enable them to make informed choices.¹⁷ In this regard, children are particularly sensitive to deception or exaggerated advertising claims and represent a vulnerable population who needs protection against misleading and false safety claims.¹⁷ Moreover, exaggerating the risk of consumer products beyond the bound of evidence carries the risk of undermining trust in public health measures, hinders their potential benefit to some groups (eg, smokers in a clinical cessation setting) and opens the door to challenges to these claims. Hence, the development of effective ENDS health messages requires an extensive and robust review of the evidence about the potential harmful and beneficial profiles of these products.

In 2018, the US National Academies of Sciences, Engineering and Medicine released a report on the health consequences of ENDS.⁸ However, the report included evidence available before August 2017. Since then, there has been a marked growth in scientific evidence about these products. This umbrella review, which is a review of systematic reviews and meta-analyses,^{18 19} aims to systematically update the evidence on ENDS health profile categorised across five domains: toxicity, health effects, smoking cessation, transition to CC and industry marketing. Results will inform and guide the development of evidence-based health communication strategies for ENDS.

METHODS

Search strategy

The study protocol was registered on PROSPERO (CRD42021241630). We followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses reporting guideline.²⁰ A comprehensive search was performed using PubMed, MEDLINE, EMBASE, PsycINFO, CINAHL and the Cochrane Database up to November 2021. We used a combination of terms and keywords related to the scope of this review (eg, e-cigarette, ENDS, cancer, initiation, cessation) (online supplemental table 1).

Inclusion criteria

Inclusion criteria were kept broad to perform a comprehensive assessment of the current state of the evidence. We included all reviews that: (1) met the definition of a systematic review (eg, thorough search strategy, minimising bias); (2) published in English; (3) with/without meta-analysis of observational studies and RCTs; and (4) presented evidence on ENDS effects in one or more of the five domains (toxicity, health effects, smoking cessation, transition to CCs, industry marketing). We excluded reviews that were funded by the tobacco/ENDS industry.

Data screening and extraction

Study selection, quality appraisal, and data collection were performed by six reviewers independently and in

duplicate using Covidence software.²¹ Titles and abstracts were screened to identify potentially relevant articles. Full texts of these articles were assessed for eligibility based on the inclusion/exclusion criteria. Extracted data included: the title, first author, country, publication year, number and design of included studies, outcomes, summary of results (effect size, ORs or relative risk (RR) when applicable), conflicts of interest and funding source. We resolved all discrepancies by discussion and consensus.

Quality assessment

We conducted quality appraisal using the Measurement Tool to Assess Systematic Reviews.²² A score between 0 and 11 was calculated based on this tool, and the quality of the review was determined low (0–4), medium (5–8) or high (9–11).²³

Summary measures and synthesis of results

Findings were synthesised separately in narrative summaries. First, two reviewers collected the data independently, then they cross-referenced these data to ensure validity. Second, the authors conducted a narrative synthesis of the reviews. Finally, the authors compiled a list of main outcomes for ENDS based on the data synthesis from all reviews. Where appropriate, ORs from the studies in the integrated systematic review were combined using a random-effects model.²⁴ Heterogeneity of study effect estimates was assessed by I^2 statistics.²⁴ All analyses were conducted using Stata V.16.1.

Evidence about potential harmful/beneficial effects was graded into four levels using the Institute of Medicine's 'Levels of Evidence Framework': high-level, moderate, limited-suggestive and limited-not-conclusive.²⁵ Given the preliminary nature of evidence, expert judgement in the evaluation of studies was involved. We performed six meta-analyses to estimate the effect of ENDS on asthma, alcohol use, marijuana use, smoking cessation (RCTs, 67 observational studies) and CC smoking initiation. Effect sizes were reported as RR, OR, adjusted OR (AOR) or mean differences. When raw data were not available, we used the effect size and CIs to estimate the overall effect for our review using the generic inverse variance method.²⁵

Patient and public involvement

No patients were involved, and no patient identifiers were collected.

RESULTS

Study selection and quality assessment

A total of 4582 reviews were identified for title/abstract screening; 3368 remained after exclusion of duplicates; 349 were identified for full-text screening; and 90 reviews were eligible and included in our review (online supplemental figure 1). Eight reviews were included in two domains, one review was included in three domains and one review was included in three categories in ENDS health effect. The quality assessment is presented in online supplemental tables 2–6. Overall, 14% of the included reviews were of high quality, 30% of medium quality and 36% of low quality. A list of excluded studies can be found in online supplemental table 7.

Studies' characteristics

Overall, 20 reviews were included in toxicity, 40 in health effects, 24 in smoking cessation, 9 in transition to CCs and 4 in

ENDS marketing. Characteristics of included reviews are shown in online supplemental file B, sections 1–5.

Summary of findings

Toxicity

Twenty reviews that assessed 968 studies were included in this category (online supplemental table 8). Eleven reviews looked at the overall toxicity profile of ENDS (nicotine, carbonyls, harmful chemicals, metals, carcinogens) in e-liquids and aerosols.^{26–36} The majority of these reviews indicated that ENDS could not be regarded as safe because they produce several harmful chemicals with known adverse health effects (eg, glycols, aldehydes, volatile organic compounds (VOCs), polycyclic aromatic hydrocarbons (PAHs), tobacco-specific nitrosamines (TSNAs), metals, silicate particles).^{28–30 32–34} TSNAs and carbonyls are designated carcinogens according to the International Agency for Research on Cancer because they have cytotoxic effects and can alter gene expression.^{32 37}

Five reviews examined nicotine levels in ENDS.^{26–28 32 35} One review found that nicotine yield from automated smoking machines is less than from CCs.³⁸ Another review compared levels of nicotine in aerosol from JUUL with other ENDS products and found that JUUL has lower free nicotine in the pod liquid and aerosol compared with other products (5%–6% and 13%–95%, respectively), but a high total nicotine content in the form of benzoate salt.³⁹

Two reviews confirmed the presence of hazardous trace metals (eg, lead, aluminium) in ENDS aerosol, liquid and human biosamples.^{40 41} Metal levels showed substantial heterogeneity depending on sample type (liquid, aerosol), source of liquid (bottle, cartridge, tank/open wicks) and device type (cig-a-likes, tank). For example, trace metal levels in liquid from cartridges or tank/open wicks were higher than those from bottles, possibly due to coil contact. Notably, metal levels in the biosamples of ENDS users were similar to or higher than the levels found in CC or cigar users.⁴¹ Exposure to these metals is associated with serious adverse effects. For example, lead is associated with an increased risk of cardiovascular and kidney disease and is a major neurotoxicant, particularly for children and the elderly.^{42 43} Exposure to aluminium at high levels can lead to impaired lung function and fibrosis as well as decreased performance in motor and cognitive functions.⁴⁴

Four reviews explored the association between ENDS and carcinogenic biomarkers.^{33 45 46} One review identified six biomarkers that have a strong link to bladder cancer in the urine of ENDS users.⁴⁷ Among these, 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-fold and 1.3-fold higher levels than never ENDS users. Two reviews indicated that the levels of PAH 1-hydroxypyrene, a carcinogenic biomarker, were significantly higher in ENDS users than in never users,⁴⁸ and their levels did not decrease in CC smokers who switched to ENDS.⁴⁹ In a review that was focused on head and neck cancer, most in vitro studies demonstrated the cytotoxicity of exposure to ENDS aerosols, with several levels of DNA damage and oxidative stress induced by toxic components.⁴⁶

Two reviews reported that some flavours in ENDS liquids (eg, vanillin, cinnamaldehyde) could affect cellular function, including phagocytosis and cytokine production in both in vitro and in vivo studies.^{26 27} A meta-analytical review highlighted the possible correlation of the chemical reactivity of flavour compounds with the toxicant formation in ENDS aerosols.⁵⁰

Three reviews investigated ENDS' environmental emissions.^{51–53} All confirmed that ENDS use under real conditions releases toxicants including nicotine, carbonyls, metals, VOCs and particulate matter (PM) in indoor environments, and that passive exposure to exhaled aerosol from ENDS can lead to adverse health effects.^{51–53} For example, compared with background air levels, nicotine in ENDS emissions was 10–115 times higher, acetaldehyde 2–8 times higher and formaldehyde about 20% higher. Conversely, when compared with CC, smoke levels of heavy metals were generally lower in ENDS aerosol. One review indicated that the total amount of suspended PM emissions was higher in vapour from nicotine-free ENDS (11.6 µg/m³) compared with nicotine ENDS (1.2 µg/m³).⁴¹

High-level evidence exists that most ENDS products contain and/or emit toxic substances (eg, metals, carcinogens) that are capable of causing DNA damage and mutagenesis, and that ENDS emissions increase airborne toxicants (eg, metals), PM and nicotine in indoor environments compared with background levels.

Health effects

Forty reviews, divided into 12 categories, were included in this domain (online supplemental table 9).

Respiratory disease

Thirteen reviews were included in this category. Six reviews related to 'e-cigarette or vaping-associated lung injury' (EVALI) indicated that vitamin E acetate (an additive in some tetrahydrocannabinol-containing ENDS) is the primary, but not only, cause of EVALI.^{54–59} Four reviews demonstrated a consistent and strong association between ENDS use and respiratory disorders (eg, asthma exacerbation) among adolescents and adults.^{36 60–62} In Wills *et al*, the pooled AORs from 15 studies for the association between ENDS use and asthma were 1.39 (95% CI 1.28 to 1.51) and 1.49 (95% CI 1.36 to 1.65) for the association between ENDS use and multiple respiratory symptoms.⁶⁰ This review also confirmed that exposure to ENDS liquid or aerosol increases levels of pro-inflammatory biomarkers that are relevant to these respiratory diseases in laboratory studies as well.⁶⁰ Furthermore, two longitudinal studies showed that ENDS use might predate the onset of asthma.^{63 64} Similar results were reported in another review.⁶¹ We performed a meta-analysis of these two reviews that included 26 studies (online supplemental figure 2A); our pooled RR showed an increased risk of asthma (1.13 (95% CI 1.09 to 1.18); n=2 114 396).

One review indicated that ENDS use could cause nasal mucociliary clearance impairment,⁶⁵ while another review found that acute eosinophilic pneumonia had a similar presentation and clinical course to that associated with CC smoking.⁶⁶ Finally, one review found that former CC smokers who transitioned to ENDS showed ~40% lower odds of respiratory outcomes (eg, asthma, wheezing) compared with current exclusive CC users.⁶⁷ However, this estimate was based on a limited number of epidemiological studies with important limitations.

High-level evidence exists that ENDS use can exacerbate asthma yet limited-not-conclusive evidence exists that ENDS may cause chronic obstructive pulmonary disease, nasal mucociliary clearance impairment and acute eosinophilic pneumonia.

Cardiovascular diseases

Six reviews reported on the effect of ENDS use on cardiovascular disease (CVD) outcomes.^{59 67–71} Three reviews reported that benefits for CVD may be observed when switching from CCs to

ENDS.^{67 69 71} On the other hand, three indicated a possible association between ENDS and CVD.^{59 68 70} One review demonstrated that ENDS use (with/without nicotine) might result in short-term elevations of both systolic and diastolic blood pressure (BP).⁶⁸ In another review, most included studies (75%) found potentially harmful effects of ENDS on CVD through inducing sympathetic nerve activation, oxidative stress, endothelial dysfunction and platelet activation.⁷⁰ For example, human studies in this review largely showed increases in heart rate (HR) and BP as a result of ENDS use, as well as abnormalities in HR variability, suggestive of sympathetic nerve activation. Both in vitro and in vivo studies showed increased reactive oxygen species production and a reduction in antioxidants after ENDS exposure, constituting an atherosclerotic risk. Importantly, most studies suggest the potential for CVD harm from ENDS use, mainly through mechanisms that increase the risk of thrombosis and atherosclerosis.⁷⁰ For example, human studies showed increases in HR and BP as well as abnormalities in HR variability, indicating sympathetic nerve activation, one of the key neurohumoral mechanisms that are operative in heart failure.⁷² In vitro studies reported various measures of arterial stiffness, indicative of endothelial dysfunction, a prognostic of atherosclerosis.^{73–76} Platelet haemostatic processes were reported across murine, human in vitro and human in vivo studies, which can increase thrombotic risk.^{73 77 78} This review also indicated that studies with conflicts of interest (eg, related to the tobacco industry) were less likely to identify potentially harmful effects. In another review, ENDS use was linked to some CVDs such as atherosclerotic plaque formation and myocardial ischaemia.⁵⁹

Despite the absence of long-term exposure–effect studies, we found limited but suggestive evidence that ENDS use increases the risk of CVD.

Cancer

Only one review related to head and neck cancer and ENDS use reported the results from two cohort studies, two case–control studies and one case series.⁴⁶ The case series described two patients with a history of chronic ENDS use (20–30 times/day for 13 years) who developed oral cancers, indicating a possible link between the long-term consumption of ENDS and this type of cancer.⁷⁹ Another study was able to identify a known carcinogen (N²-nitrosornicotine) in the saliva of ENDS users.⁸⁰ In contrast, a cohort study could not identify a higher number of micronuclei, indicators of genomic instability, in ENDS users compared with non-smokers.⁸¹ Another cohort study found no differences in terms of pre-cancerous oral mucosal lesions between ENDS users and former CC smokers. Overall, all included studies were judged as having poor quality with small sample sizes and limited exposure time to ENDS, and they suffered from limitations in their design (eg, lack of proper control groups, selection bias, not accounting for confounders).

Limited-not-conclusive evidence exists on the link between ENDS use and cancer in the clinical environment.

Passive exposure to ENDS aerosol

Two reviews reported on the effect of passive exposure to ENDS.^{52 82} The first review reported on two studies (out of four total) that measured biomarkers of exposure to nicotine and other VOCs in biological samples, with conflicting results. While one study showed a statistically significant difference in urinary cotinine between those exposed to ENDS with nicotine compared with ENDS without nicotine,⁸³ the other study observed no significant difference between the non-users living

in homes with ENDS users compared with non-users living in control homes.⁸⁴ The second review identified four studies, all with small sample sizes, that directly assessed passive exposure in human volunteers.⁸² In one study, salivary and urinary cotinine levels were significantly lower in volunteers from non-smoking control homes than in volunteers exposed to either ENDS or CC smoke, with CC smoke having the highest cotinine levels.⁸⁴ In another experiment, serum cotinine and lung function measures were taken for 15 non-smokers who were passively exposed for 1 hour to CC smoke or ENDS vapour generated by a smoking machine.⁸⁵ No difference was found in lung function for the non-smokers passively exposed to ENDS vapour compared with no exposure, but participants' serum cotinine levels were raised comparable with those of volunteers passively exposed to CC smoke. Similarly, inflammatory markers were not affected by passive exposure to ENDS vapour for 1 hour in another study involving 10 non-smokers.⁸⁶ Only one animal study in this review examined the effect of passive ENDS exposure to either room air (controls) or ENDS vapour (with or without nicotine) for 20 min once or twice a day on newborn mice.⁸⁷ Results showed that mice exposed to ENDS (with or without nicotine) weighed significantly less than mice exposed to room air only. Mice exposed to ENDS with nicotine also showed impaired lung growth and elevated plasma and urine cotinine levels. Based on these results, the authors concluded that chronic exposure to ENDS among susceptible groups (eg, infants, children, patients with asthma, the elderly, pregnant women) can be a health concern.

Limited-not-conclusive evidence exists on the health effect of passive exposure to ENDS, yet exposure studies clearly show that bystanders are exposed to ENDS-emitted toxicants such as carbonyls, metals, VOCs, PM and nicotine.

Ear diseases

Only one review reported on the effect of ENDS use in otology and indicated that these effects are still largely unknown.⁸⁸ In this review, an in vitro study indicated that ENDS liquid can induce cytotoxic effects on human middle-ear epithelial cells and reduce their viability from 100% to 32%–62%,⁸⁹ particularly when nicotine was included in the liquid. This is consistent with animal studies (not related to ENDS) showing that nicotine has a direct deleterious effect on cochlear outer hair cells, with reports of distorted shape, heterochromatic nuclei and vacuolated cytoplasm.⁹⁰ However, data on the clinical implications of nicotine from ENDS in otology in humans do not exist.

Limited-not-conclusive evidence exists on the link between ENDS use and ear diseases.

Ocular diseases

Only one review reported on the effect of ENDS use on ocular diseases.⁹¹ The review indicated that ENDS use might induce dry eye,⁹² reduce tear film stability⁹² or reduce ocular blood flow.⁹³ The review further suggested that these effects present both short-term and long-term health risks to the eyes and vision.⁹⁴

Limited-not-conclusive evidence exists on the link between ENDS use and ocular diseases.

Pregnancy outcomes

Four reviews reported conflicting results on the effects of ENDS use on pregnancy outcomes.^{95–98} Romer *et al* indicated that exposure to nicotine in ENDS could cause low birth weight, miscarriage and stillbirth.⁹⁶ Calder *et al* indicated that ENDS use has less effect on birth weight outcomes than CC smoking.⁹⁵

However, these outcomes were similar to CC smoking in pregnant women who used both ENDS and CCs. Another review of animal studies suggested that exposure to nicotine in ENDS alters DNA methylation, induces birth defects, reduces birth weight, and affects the development of the heart and lungs of the offspring.⁹⁷

Limited-not-conclusive evidence exists on the effect of ENDS use on pregnancy outcomes.

Oral health

All three included reviews indicated an increased risk of gum disease and changes to the oral microbiome in ENDS users.⁹⁹⁻¹⁰¹ Results from three reviews on ENDS and oral health suggest that ENDS use might induce mouth, throat, and periodontal symptoms and lead to different lesions including nicotinic stomatitis, hairy tongue, and angular cheilitis.⁹⁹⁻¹⁰¹ Commonly reported mouth symptoms related to ENDS use or direct liquid exposure included dryness, burning, irritation, bad taste, bad breath and pain.¹⁰⁰ Finally, extensive dental damage as a result of ENDS explosions was reported.

Limited-not-conclusive evidence exists on the effects of ENDS on oral health.

Injuries and poisoning

Four reviews reported on traumatic ENDS-related explosion injuries to the skin and soft tissue.^{62 102-104} Burn severity was typically second-degree (35%) or second- and third-degree burns (20%).¹⁰² Three reviews reported on poisoning (accidental, intentional) through the ingestion or injection of ENDS liquid.^{62 103 105} In some cases, patients mixed liquid with alcohol, methadone or benzodiazepines.¹⁰³ Most of these patients were either found to be dead or were admitted to the emergency rooms with cardiac arrest, respiratory muscle paralysis or brain death. Other reported serious injuries included infant death from choking on a flavour cartridge and nicotine overdoses associated with psychotic symptoms (suicide attempts).¹⁰³

High-level evidence exists that ENDS devices can explode and cause burns, and that intentional or accidental nicotine poisoning from ENDS liquid can cause seizures, anoxic brain and death.

Mental health

Two reviews reported consistent results warning that vaping may exacerbate mental illness.^{59 106} Becker *et al* found that ENDS use is associated with greater depression, suicidality, attention-deficit/hyperactivity disorder, eating disorders and stress among adolescents.¹⁰⁶ ENDS use was also associated with sensation seeking among young adults.¹⁰⁶ Sharma *et al* indicated that long-term use of ENDS may have a detrimental effect on brain health due to cerebral oxidative stress.⁵⁹ Although the longitudinal evidence linking ENDS use to subsequent psychopathology remains limited, this evidence is consistent with existing models of nicotine's effects on the neurodevelopment of young people.¹⁰⁷ It is well established that nicotine adversely affects adolescent neurodevelopment and increases the risk of cognitive and psychiatric disorders.¹⁰⁸ Evidence from animal models also suggests that prolonged nicotine exposure may induce epigenetic changes and increase vulnerability to stress sensitivity and the subsequent development of mood disorders, schizophrenia, and substance use disorders.¹⁰⁹

Moderate evidence exists that ENDS use is associated with mental health problems among adolescents and young adults.

Addiction

Two reviews were included in this category.^{26 27} The first found that behavioural effects related to nicotine addiction are regularly seen in ENDS users and that dual use of ENDS and CCs generates more addiction to nicotine than exclusive ENDS use.²⁶ Nicotine in ENDS liquids is a well-understood compound with known central and peripheral nervous system effects associated with a high risk of addiction.⁸ The second review indicated that most commercial ENDS products contain nicotine.²⁷ In a large-scale population-based sample, depressive symptoms were associated with ENDS use and their nicotine concentration.¹¹⁰ In addition, inhaled vaporised nicotine via ENDS was shown to increase 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 in users.¹¹¹

High-level evidence exists that the use of ENDS with nicotine results in symptoms of nicotine dependence.

Substance use

Four investigated the association between ENDS use and other substance use including alcohol, marijuana, and illicit drugs (eg, cannabinoid, cocaine, heroin).¹¹²⁻¹¹⁵ Results indicated a strong association between ENDS and alcohol use (OR 6.62 (5.67 to 7.72)), binge drinking (OR 6.73 (4.50 to 10.07)) and marijuana use (AOR 4.29 (3.14 to 5.87)) among adolescent ENDS users compared with non-users.¹¹²⁻¹¹⁴ Similar, but lower results were reported among young adults (OR 2.30 (1.40 to 3.79) for marijuana) and adults (OR 1.57 for alcohol and 2.04 for marijuana; $p < 0.05$). Chadi *et al*¹¹³ included three longitudinal studies suggesting that ENDS use typically predates the use of marijuana.¹¹⁶⁻¹¹⁸ While the number of these studies was small, these findings yield high clinical relevance to substance use disorders among young people.¹¹⁹ One review investigated the risk of ENDS as a drug delivery system for illicit drugs and found that almost 40% of ENDS users had used them to vape recreational drugs, with cannabis being the most common (18.0%).

For alcohol use, our pooled OR from two reviews of observational studies assessing the association of ENDS use with alcohol use was 3.72 (95% CI 2.03 to 6.83) with substantial heterogeneity among studies ($X^2 = 189.61$, $I^2 = 97\%$; $p < 0.0001$). For marijuana use, our pooled OR from two reviews of observational studies assessing the association of ENDS use and marijuana use was 2.89 (95% CI 1.61 to 5.19) with substantial heterogeneity among studies ($X^2 = 41.15$, $I^2 = 93\%$; $p < 0.0001$) (online supplemental figure 2B,C).

Moderate evidence exists on the association between ENDS use and alcohol and marijuana, particularly among youth.

ENDS' effect on smoking cessation

Twenty-four reviews were included in this category (online supplemental table 10). Thirteen RCT meta-analysis reviews indicated that ENDS use is effective in smoking cessation (compared with nicotine replacement therapy (NRT) or placebo),¹²⁰ while five reviews suggested the opposite.

We conducted a subgroup meta-analysis based on several control groups (NRT, ENDS without nicotine, placebo). The pooled RR was 1.20 (95% CI 1.12 to 1.29) for five meta-analyses comparing ENDS with NRT, 1.35 (95% CI 1.18 to 1.56) for five meta-analyses comparing ENDS with nicotine versus ENDS without nicotine or placebo, and 1.15 (95% CI 1.05 to 1.26) for two meta-analysis reviews comparing ENDS with NRT and/or placebo as control (online supplemental figure 3A). There was

moderate but not significant evidence of heterogeneity among subgroups ($X^2=6.06$, $p=0.11$, $I^2=50.5\%$). However, based on three systematic reviews of observational studies reporting on ENDS association with smoking cessation, our pooled RR for abstinence was not significant (0.96, 95% CI 0.86 to 1.08) (online supplemental figure 3B).

Three other reviews reported that ENDS use among CC smokers was associated with a 22.5%–80% reduction in CCs smoked per day.^{29 121 122} However, one review reported that the risk of relapse was twofold higher among former CC smokers who were ENDS users than non-ENDS users.¹²³ One review was focused on pregnant women and found that abstinence rates in pregnant women who were ENDS users versus non-users were not different.⁹⁵

High-level evidence shows that ENDS use is associated with increased smoking cessation in RCTs, in contrast to evidence from observational studies showing that ENDS use increases risk of relapse and impedes smoking cessation.

Transition to CC smoking

Eight reviews were included in this category (online supplemental table 11). Our meta-analysis indicated that ENDS use is associated with CC initiation, with ORs varying from 2.1 to 6.6. Our pooled RR from six meta-analyses of RCTs and observational studies for the ENDS transition to CC among adolescents was 1.61 (95% CI 1.55 to 1.67) (online supplemental figure 4).

High-level evidence exists that ENDS use increases the risk of CC initiation among youth and young adults.

Industry marketing

Four reviews indicated that exposure to ENDS industry marketing increased favourable ENDS perceptions and experimentation among youth and young adults^{39 124–126} (online supplemental table 12). ENDS shops were more likely to be concentrated near college and university campuses and were targeting white non-Hispanics with high or median incomes.¹²⁵ ENDS marketing recall was strongly associated with lower harm perceptions, and greater intention to use or use of ENDS. In contrast, exposure to ENDS warnings was associated with a lower intention to purchase ENDS.¹²⁶

High-level evidence exists that ENDS marketing targets youth and young adults, and exposure to marketing among these age groups decreases ENDS harm perceptions and increases intention to use and use of ENDS.

DISCUSSION

The main purpose of this umbrella review was to summarise and comprehensively review the current evidence on the health profile of ENDS to guide the development of evidence-based health communication messages. Below, we summarise this evidence according to domain and level of evidence.²⁵ We also try to synthesise this evidence into practical recommendations on how to frame impactful and balanced ENDS-related health risk messages. A set of potential messages based on available evidence are presented in online supplemental figure 5 to help other researchers and health-related bodies further develop and test evidence-based messages about the ENDS health profile.

For ENDS toxicity, we found high-level evidence that most ENDS products contain toxic substances (eg, metals, carcinogens) that are capable of causing DNA damage and mutagenesis, and that ENDS emissions increase airborne toxicants (eg, metals), PM and nicotine in indoor environments compared with background levels.^{30 32 34 36 51 52} For ENDS health effects, we

found high-level evidence that ENDS devices can explode and cause burns, and that intentional or accidental liquid poisoning can cause seizures, anoxic brain injury, or death.^{62 103 105} We also found high-level evidence that ENDS use exacerbates asthma, and that nicotine in ENDS can cause addiction. In addition, despite the limited clinical evidence about the effect of ENDS use on cancer risk, studies from human genomic and animal studies have consistently shown that ENDS use may be carcinogenic. For example, exposure to ENDS aerosol induces DNA damage and impairs DNA repair in human and animal lung and bladder cells.^{127 128}

Regarding ENDS' effect on smoking cessation, our meta-analysis demonstrated high-level evidence that ENDS use as a therapeutic intervention is associated with increased smoking cessation in RCTs when delivered in a clinical and tightly controlled setting.¹²⁹ In contrast, ENDS as consumer products in real-world observational studies were not significantly associated with smoking cessation,^{129 130} and several such studies show the opposite; ENDS use impedes smoking cessation.¹²³ Observational studies of these outcomes are more important to their regulation as a consumer product, consistent with the Tobacco Control Act, which requires the FDA to consider the risks and benefits of new tobacco products to the population as a whole.^{130–132}

We also found high-level evidence that ENDS use increases the risk of CC initiation among youth and young adults.^{133–136} Our meta-analysis is consistent with prior umbrella review summarising the evidence on CC uptake following ENDS use in non-smokers.¹³⁷ Finally, there was high-level evidence that exposure to ENDS industry marketing among youth decreases ENDS harm perceptions and increases intention to use and use of ENDS.^{39 124–126} Evidence was moderate for ENDS association with mental health and substance use, and limited-not-conclusive for cardiovascular, cancer, ear, ocular and oral diseases, and pregnancy outcomes.

Implications for research

Although data are expanding progressively, additional research is needed to assess the full spectrum of ENDS health effects. In particular, the direct health effects of exposure to ENDS have not been studied adequately, and data on the long-term risk of ENDS use are absent. Hence, further research is needed to establish the risk and safety profiles of ENDS with consideration of the wide variety of ENDS products (eg, power output, construction materials, design features, liquid constituents), their pattern of use (eg, daily, less frequent use) and different segments of the population (eg, children, pregnant women, patients with cancer, people with acute or chronic medical conditions). Additionally, more thoroughly designed prospective cohort studies that take place over longer periods and with larger sample sizes are necessary to gauge accurately the short-term and long-term health-related risks of ENDS. More animal and cell studies are needed to explore the mechanism of action between ENDS and the risk of various diseases.

Implications for ENDS health communication

Overall, we have presented strong evidence that ENDS users inhale an array of toxic chemicals similar to those found in CC smoke and known to cause serious diseases (lung disease, nicotine dependence). Yet, there is a lack of comparative quantitative assessments and appraisals of the clinical importance of exposure levels related to ENDS compared with CC smoking, both short and long term. Here we suggest several strategies to overcome

this gap in our knowledge and advance ENDS-related health communication based on the current level of evidence. First, ENDS communication now can focus on high-level evidence related to ENDS association with toxicity, nicotine addiction, asthma, ENDS-specific harm (explosion, poisoning) and anti-ENDS industry sentiment. Second, messages that highlight ENDS-specific harm (eg, explosion, poisoning, addiction) have the potential to capture attention and motivate behaviour change because they are serious and specific to ENDS.^{138 139} Third, an important group for communicating ENDS-related risks is dual and polytobacco users, many of whom adopted ENDS to either quit smoking or reduce their harm. Mounting evidence suggests that compared with exclusive CC smoking, dual use carries additional rather than less risk, particularly among high-risk populations for smoking (eg, children, pregnant women).⁹⁵ By increasing the opportunity to be exposed to toxicants and nicotine from both products, CCs and ENDS, dual users can be at higher risk of tobacco health effects and dependence.¹⁴⁰ Evidence suggests that compared with cigarette smokers, dual users are at higher risk of heart problems,^{141 142} lung disease,^{60 64} cancer¹⁴³ and nicotine dependence.^{144 145} Fourth, to preserve scientific credibility, public health groups need to convey evidence-transparent messages without inferring causality based on associations or cross-sectional data. Care will need to be taken in crafting statements that accurately communicate the complex and evolving science on ENDS health risks. Finally, avoiding direct comparison between the harm of CCs and ENDS is highly recommended given the uncertainty about this information, mainly because of the variation in ENDS types/generation, nicotine content, the high prevalence of dual/polytobacco use and the scarcity of standardised comparative studies.

Legitimate concerns have been voiced that health risk messages for ENDS can lead to unintended consequences such as reducing their appeal among smokers who can benefit from ENDS for smoking cessation.¹⁴⁶ These concerns need to be weighed against the massive uptake of ENDS use among young people, and the emerging evidence that while ENDS health risk messages can motivate users to quit, they do not encourage CC smoking and may instead discourage smoking.¹³⁸ In addition, such potential effects can be mitigated by promoting ENDS within clinical and smoking cessation treatment settings for those unable to quit or reduce their harm otherwise.¹⁴⁷ Most health authorities (eg, CDC, FDA) agree that 'ENDS are possibly a less harmful alternative for current smokers to quit; however, they are not for people who have never smoked.' From a consumer rights perspective, while non-smokers should be protected from the marketing of addictive and potentially harmful ENDS, CC smokers who use ENDS to quit also have the right to be informed about the risks associated with ENDS use, that no ENDS devices are FDA approved as smoking cessation aids, and that the heterogeneity among ENDS devices and liquids is so great that, even if an ENDS was approved for smoking cessation, that approval for that device/liquid combination cannot generalise to other device/liquid combinations within the ENDS product class.

Limitations

This umbrella review has several strengths and limitations that should be acknowledged. The main strength of this review includes the use of a comprehensive and rigorous methodology including a broad search strategy, as well as extraction of data and assessment of the risk of bias and quality by several independent reviewers. Furthermore, prioritising a wide scope of systematic reviews in five domains allowed the inclusion of a

large amount of research evidence covering a variety of ENDS-related health effects, while at the same time narrowing that research into easy-to-distinguish risk/benefit domains for health communication purposes. As for the limitations, first, given the wide scope of the review and inclusion of various study designs, meta-analyses of RCTs were not possible for some domains. In addition, the included reviews used numerous diverse approaches for conceptualising, operationalising and measuring the outcomes of interest. This heterogeneity significantly limited the ability to synthesise and compare study results. Also, the heterogeneity of ENDS as a product class, with varying device characteristics, liquid constituents and user-controlled features (eg, power output), as well as the swift evolution of ENDS products, is a challenge that has yet to be addressed fully in the studies reviewed here. Therefore, instead of grading the evidence from meta-analyses only, we focused on a portion of the available evidence when needed.¹⁴⁸ Second, given the wide scope of our review, it was impossible to identify articles that were included in multiple reviews. However, by their nature, umbrella reviews lead to loss of detail and redundancy as some individual studies are included in multiple reviews. Third, some health effects may have been found in multiple studies, but there has not been a review of these studies. Fourth, all included reviews did not include industry-funded studies except one review (Pisinger and Døssing) that reported that 26 out of their 76 included studies were influenced by manufacturers of ENDS.³² Finally, we completed our search in November 2021; therefore, the primary studies and reviews published after this date were not included.

CONCLUSIONS

This umbrella review provided the most up-to-date evidence on ENDS use health risk and safety profile. This evidence will inform the development of impactful messages for ENDS health communication and indicate important tracks for studies needed to assess the full spectrum of ENDS health effects. ENDS messages can currently be centred on high-level evidence related to ENDS association with toxicity, nicotine addiction, asthma exacerbation, ENDS-specific harm (explosion, poisoning) and anti-ENDS industry sentiment. Given the variation in ENDS products and the high prevalence of dual/polytobacco use, ENDS communication needs to convey evidence-transparent messages and avoid direct comparisons between the harm of CCs and ENDS.

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REFERENCES

- Health UDo, Services H. *E-Cigarette use among youth and young adults: a report of the surgeon General*, 2016.
- US Food FDA, Administration D. *Statement from FDA commissioner Scott Gottlieb, M.D., on new steps to address epidemic of youth e-cigarette use*, 2018. <https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-new-steps-address-epidemic-youth-e-cigarette-use>
- Wang TW, Neff LJ, Park-Lee E, et al. E-cigarette Use Among Middle and High School Students - United States, 2020. *MMWR Morb Mortal Wkly Rep* 2020;69:1310–2.
- Vallone DM, Cuccia AF, Briggs J, et al. Electronic cigarette and JUUL use among adolescents and young adults. *JAMA Pediatr* 2020;174:277–86.
- Keamy-Minor E, McQuoid J, Ling PM. Young adult perceptions of JUUL and other pod electronic cigarette devices in California: a qualitative study. *BMJ Open* 2019;9:e026306.
- Soule EK, Lopez AA, Guy MC, et al. Reasons for using flavored liquids among electronic cigarette users: a concept mapping study. *Drug Alcohol Depend* 2016;166:168–76.
- Wood GG, Waselewski ME, Bryant AC, et al. Youth perceptions of Juul in the United States. *JAMA Pediatr* 2020;174:800–2.
- National academies of sciences. *E. and Medicine, Public health consequences of e-cigarettes* 2018.
- Osibogun O, Bursac Z, Maziak W. E-Cigarette use and regular cigarette smoking among youth: population assessment of tobacco and health study (2013-2016). *Am J Prev Med* 2020;58:657–65.
- CDC. Facts on the risks of e-cigarettes for kids, teens. *and Young Adults* 2021 https://www.cdc.gov/tobacco/basic_information/e-cigarettes/Quick-Facts-on-the-Risks-of-E-cigarettes-for-Kids-Teens-and-Young-Adults_1.html
- Hajek P, Phillips-Waller A, Przulj D, et al. A randomized trial of e-cigarettes versus nicotine-replacement therapy. *N Engl J Med* 2019;380:629–37.
- Watkins SL, Glantz SA, Chaffee BW. Association of noncigarette tobacco product use with future cigarette smoking among youth in the population assessment of tobacco and health (path) study, 2013-2015. *JAMA Pediatr* 2018;172:181–7.
- Wang X, Zhang X, Xu X, et al. Electronic cigarette use and smoking cessation behavior among adolescents in China. *Addict Behav* 2018;82:129–34.
- Hedman L, Galanti MR, Ryk L, et al. Electronic cigarette use and smoking cessation in cohort studies and randomized trials: a systematic review and meta-analysis. *Tob Prev Cessat* 2021;7:1–16.
- Brandon TH, Goniewicz ML, Hanna NH, et al. Electronic nicotine delivery systems: a policy statement from the American association for cancer research and the American Society of clinical oncology. *Clin Cancer Res* 2015;21:514–25.
- US Food FDA, Administration D. The public health rationale for recommended restrictions on new tobacco product labeling, advertising, marketing. *and Promotion* 2019 <https://www.fda.gov/media/124174/download>
- Benöhr I, The United Nations guidelines for consumer protection. Legal implications and new frontiers. *Journal of Consumer Policy* 2020;43:105–24.
- Fusar-Poli P, Radua J. Ten simple rules for conducting umbrella reviews. *Evid Based Ment Health* 2018;21:95–100.
- Aromataris E, Fernandez R, Godfrey CM, et al. Summarizing systematic reviews: methodological development, conduct and reporting of an umbrella review approach. *Int J Evid Based Healthc* 2015;13:132–40.
- Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Int J Surg* 2010;8:336–41.
- Babineau J. Product review: Covidence (systematic review software). *J Can Health Libr Assoc* 2014;35:68–71.
- Shea BJ, Grimshaw JM, Wells GA, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. *BMC Med Res Methodol* 2007;7:1–7.
- Shea BJ, Hamel C, Wells GA, et al. AMSTAR is a reliable and valid measurement tool to assess the methodological quality of systematic reviews. *J Clin Epidemiol* 2009;62:1013–20.
- Higgins J et al. *Cochrane Handbook for systematic reviews of interventions version 6.2 (updated February 2021)*. In: *Cochrane*, 2021.
- Morton S et al. *Finding what works in health care: standards for systematic reviews*, 2011.
- Armendáriz-Castillo I, Guerrero S, Vera-Guapi A, et al. Genotoxic and carcinogenic potential of compounds associated with electronic cigarettes: a systematic review. *Biomed Res Int* 2019;2019:1–8.
- Bozier J, Chivers EK, Chapman DG, et al. The evolving landscape of e-cigarettes: a systematic review of recent evidence. *Chest* 2020;157:1362–90.
- Burstyn I. Peering through the mist: systematic review of what the chemistry of contaminants in electronic cigarettes tells us about health risks. *BMC Public Health* 2014;14:18.
- Callahan-Lyon P. Electronic cigarettes: human health effects. *Tob Control* 2014;23 Suppl 2:ii36–40.
- Cheng T. Chemical evaluation of electronic cigarettes. *Tob Control* 2014;23 Suppl 2:ii11–17.
- Farsalinos KE, Gillman GJFIP. *Carbonyl Emissions in E-cigarette Aerosol: A Systematic Review and Methodological Considerations* 2018;8.
- Pisinger C, Dossing M. A systematic review of health effects of electronic cigarettes. *Prev Med* 2014;69:248–60.
- Wang G, Liu W, Song W. Toxicity assessment of electronic cigarettes. *Inhal Toxicol* 2019;31:259–73.
- Ward AM, Yaman R, Ebbert JO. Electronic nicotine delivery system design and aerosol toxicants: a systematic review. *PLoS One* 2020;15:e0234189.
- Zulkifli A, Abidin EZ, Abidin NZ, et al. Electronic cigarettes: a systematic review of available studies on health risk assessment. *Rev Environ Health* 2018;33:43–52.
- Kaur G, Pinkston R, Mclemore B, et al. Immunological and toxicological risk assessment of e-cigarettes. *Eur Respir Rev* 2018;27. doi:10.1183/16000617.0119-2017. [Epub ahead of print: 31 Mar 2018].
- Hecht SS, Hoffmann D. Tobacco-Specific nitrosamines, an important group of carcinogens in tobacco and tobacco smoke. *Carcinogenesis* 1988;9:875–84.
- Schroeder MJ, Hoffman AC. Electronic cigarettes and nicotine clinical pharmacology. *Tob Control* 2014;23 Suppl 2:ii30–5.
- Lee SJ, Rees VW, Yossefy N, et al. Youth and young adult use of Pod-Based electronic cigarettes from 2015 to 2019: a systematic review. *JAMA Pediatr* 2020;174:714–20.
- Gaur S, Agnihotri R. Health effects of trace metals in electronic cigarette Aerosols-a systematic review. *Biol Trace Elem Res* 2019;188:295–315.
- Zhao D, Aravindakshan A, Hilpert M, et al. Metal/Metalloid levels in electronic cigarette liquids, aerosols, and human Biosamples: a systematic review. *Environ Health Perspect* 2020;128:36001.

- 42 Fadrowski JJ, Navas-Acien A, Tellez-Plaza M, *et al.* Blood lead level and kidney function in US adolescents: the third National health and nutrition examination survey. *Arch Intern Med* 2010;170:75–82.
- 43 Navas-Acien A, Guallar E, Silbergeld EK, *et al.* Lead exposure and cardiovascular disease—a systematic review. *Environ Health Perspect* 2007;115:472–82.
- 44 ATSDR. *Toxicological profile for aluminum*. Atlanta: US Department of Health and Human Services, Public Health Service, 2008.
- 45 Bjurlin MA, Matulewicz RS, Roberts TR, *et al.* Carcinogen biomarkers in the urine of electronic cigarette users and implications for the development of bladder cancer: a systematic review. *Eur Urol Oncol* 2021;4:766–783.
- 46 Flach S, Maniam P, Manickavasagam J. E-Cigarettes and head and neck cancers: a systematic review of the current literature. *Clin Otolaryngol* 2019;44:749–56.
- 47 Bjurlin MA, Matulewicz RS, Roberts TR, *et al.* Carcinogen biomarkers in the urine of electronic cigarette users and implications for the development of bladder cancer: a systematic review. *Eur Urol Oncol* 2021;4:766–83.
- 48 Wang Y, Sun Y, Zong Y, *et al.* Microwave absorption enhancement of nickel cobalt phosphides by decorating on reduced graphene oxide. *J Solid State Chem* 2019;277:201–8.
- 49 Shahab L, Goniewicz ML, Blount BC, *et al.* Nicotine, carcinogen, and toxin exposure in long-term e-cigarette and nicotine replacement therapy users: a cross-sectional study. *Ann Intern Med* 2017;166:390–400.
- 50 Salam S, Saliba NA, Shihadeh A, *et al.* Flavor-Toxicant correlation in e-cigarettes: a meta-analysis. *Chem Res Toxicol* 2020;33:2932–8.
- 51 Fernández E, Ballbè M, Sureda X, *et al.* Particulate matter from electronic cigarettes and conventional cigarettes: a systematic review and observational study. *Curr Environ Health Rep* 2015;2:423–9.
- 52 Zainol Abidin N, Zainal Abidin E, Zulkifli A, *et al.* Electronic cigarettes and indoor air quality: a review of studies using human volunteers. *Rev Environ Health* 2017;32:235–44.
- 53 Farsalinos KE, Gillman G. Carbonyl emissions in e-cigarette aerosol: a systematic review and methodological considerations. *Front Physiol* 2017;8:1119.
- 54 Bravo-Gutiérrez OA, Falfán-Valencia R, Ramírez-Venegas A, *et al.* Lung damage caused by heated tobacco products and electronic nicotine delivery systems: a systematic review. *Int J Environ Res Public Health* 2021;18:4079.
- 55 Gonsalves CL, Zhu JW, Kam AJ. Diagnosis and acute management of e-cigarette or Vaping product Use-Associated lung injury in the pediatric population: a systematic review. *J Pediatr* 2021;228:260–70.
- 56 Xantus G, Anna Gyarmathy V, Johnson CA, *et al.* The role of vitamin E acetate (VEA) and its derivatives in the vaping associated lung injury: systematic review of evidence. *Crit Rev Toxicol* 2021;51:15–23.
- 57 Jonas AM, Raj R. Vaping-related acute parenchymal lung injury: a systematic review. *Chest* 2020;158:1555–65.
- 58 Cedeno J, Sah A, Cedeno-Mendoza R, *et al.* Confirmed e-cigarette or vaping product use associated lung injury (EVALI) with lung biopsy; a case report and literature review. *Respir Med Case Rep* 2020;30:101122.
- 59 Sharma E, Bansal-Travers M, Edwards KC, *et al.* Longitudinal pathways of exclusive and polytobacco hookah use among youth, young adults and adults in the USA: findings from the path study waves 1-3 (2013-2016). *Tob Control* 2020;29:s155–62.
- 60 Wills TA, Soneji SS, Choi K, *et al.* E-Cigarette use and respiratory disorders: an integrative review of converging evidence from epidemiological and laboratory studies. *Eur Respir J* 2021;57. doi:10.1183/13993003.01815-2019. [Epub ahead of print: 21 01 2021].
- 61 Xian S, Chen Y. E-Cigarette users are associated with asthma disease: a meta-analysis. *Clin Respir J* 2021;15:457–66.
- 62 Tzortzi A, Kapetanstraki M, Evangelopoulou V, *et al.* A systematic literature review of e-cigarette-related illness and injury: not just for the respirologist. *Int J Environ Res Public Health* 2020;17:2248.
- 63 Bowler RP, Hansel NN, Jacobson S, *et al.* Electronic cigarette use in US adults at risk for or with COPD: analysis from two observational cohorts. *J Gen Intern Med* 2017;32:1315–22.
- 64 Bhatta DN, Glantz SA. Association of e-cigarette use with respiratory disease among adults: a longitudinal analysis. *Am J Prev Med* 2020;58:182–90.
- 65 Prasetyo A, Sadhana U, Budiman J. Nasal mucociliary clearance in smokers: a systematic review. *Int Arch Otorhinolaryngol* 2021;25:e160–9.
- 66 Chaaban T. Acute eosinophilic pneumonia associated with non-cigarette smoking products: a systematic review. *Adv Respir Med* 2020;88:142–6.
- 67 Goniewicz ML, Miller CR, Sutanto E, *et al.* How effective are electronic cigarettes for reducing respiratory and cardiovascular risk in smokers? A systematic review. *Harm Reduct J* 2020;17:1–9.
- 68 Martinez-Morata I, Sanchez TR, Shimbo D, *et al.* Electronic cigarette use and blood pressure endpoints: a systematic review. *Curr Hypertens Rep* 2021;23:1–10.
- 69 Garcia PD, Gornbein JA, Middlekauff HR. Cardiovascular autonomic effects of electronic cigarette use: a systematic review. *Clin Auton Res* 2020;30:507–19.
- 70 Kennedy CD, van Schalkwyk MCI, McKee M, *et al.* The cardiovascular effects of electronic cigarettes: a systematic review of experimental studies. *Prev Med* 2019;127:105770.
- 71 Skotsimara G, Antonopoulos AS, Oikonomou E, *et al.* Cardiovascular effects of electronic cigarettes: a systematic review and meta-analysis. *Eur J Prev Cardiol* 2019;26:1219–28.
- 72 Moheimani RS, Bhattacharata M, Peters KM, *et al.* Sympathomimetic effects of acute e-cigarette use: role of nicotine and non-nicotine constituents. *J Am Heart Assoc* 2017;6:e006579.
- 73 Kerr DMI, Brooksbank KJM, Taylor RG, *et al.* Acute effects of electronic and tobacco cigarettes on vascular and respiratory function in healthy volunteers: a cross-over study. *J Hypertens* 2019;37:154–66.
- 74 Carnevale R, Sciarretta S, Violi F, *et al.* Acute impact of tobacco vs electronic cigarette smoking on oxidative stress and vascular function. *Chest* 2016;150:606–12.
- 75 Chaumont M, de Becker B, Zaher W, *et al.* Differential effects of e-cigarette on microvascular endothelial function, arterial stiffness and oxidative stress: a randomized crossover trial. *Sci Rep* 2018;8:1–9.
- 76 Chatterjee S, Tao J-Q, Johncola A, *et al.* Acute exposure to e-cigarettes causes inflammation and pulmonary endothelial oxidative stress in nonsmoking, healthy young subjects. *Am J Physiol Lung Cell Mol Physiol* 2019;317:L155–66.
- 77 Nocella C, Biondi-Zoccai G, Sciarretta S, *et al.* Impact of tobacco versus electronic cigarette smoking on platelet function. *Am J Cardiol* 2018;122:1477–81.
- 78 Biondi-Zoccai G, Sciarretta S, Bullen C. Acute effects of heat-not-burn, electronic vaping, and traditional tobacco cigarettes: the Sapienza University of Rome-Vascular assessment of proatherosclerotic effects of smoking (SUR-VAPES) 2 randomized trial. *J Am Heart Assoc* 2018.
- 79 Nguyen H, Kitzmiller JP, Nguyen KT, *et al.* Oral carcinoma associated with chronic use of electronic cigarettes. *Otolaryngology* 2017;07:2.
- 80 Bustamante G, Ma B, Yakovlev G, *et al.* Presence of the carcinogen N'-nitrosonornicotine in saliva of e-cigarette users. *Chem Res Toxicol* 2018;31:731–8.
- 81 Bardellini E, Amadori F, Conti G, *et al.* Oral mucosal lesions in electronic cigarettes consumers versus former smokers. *Acta Odontol Scand* 2018;76:226–8.
- 82 Hess IM, Lachireddy K, Capon A. A systematic review of the health risks from passive exposure to electronic cigarette vapour. *Public Health Res Pract* 2016;26:e2621617.
- 83 Schober W, Szendrei K, Matzen W, *et al.* Use of electronic cigarettes (e-cigarettes) impairs indoor air quality and increases FeNO levels of e-cigarette consumers. *Int J Hyg Environ Health* 2014;217:628–37.
- 84 Ballbè M, Martínez-Sánchez JM, Sureda X, *et al.* Cigarettes vs. e-cigarettes: passive exposure at home measured by means of airborne marker and biomarkers. *Environ Res* 2014;135:76–80.
- 85 Flouris AD, Poulianioti KP, Chorti MS, *et al.* Acute effects of electronic and tobacco cigarette smoking on complete blood count. *Food Chem Toxicol* 2012;50:3600–3.
- 86 Tzatzarakis MN, Tsitoglou KI, Chorti MS, *et al.* Acute and short term impact of active and passive tobacco and electronic cigarette smoking on inflammatory markers. *Toxicol Lett* 2013;221:586.
- 87 McGrath-Morrow SA, Hayashi M, Aherrera A, *et al.* The effects of electronic cigarette emissions on systemic cotinine levels, weight and postnatal lung growth in neonatal mice. *PLoS One* 2015;10:e0118344.
- 88 Patel S, Wooles N, Martin T. A systematic review of the impact of cigarettes and electronic cigarettes in otology. *J Laryngol Otol* 2020;951–6.
- 89 Song J-J, Go YY, Mun JY, *et al.* Effect of electronic cigarettes on human middle ear. *Int J Pediatr Otorhinolaryngol* 2018;109:67–71.
- 90 Huang CC, Shi GS, Yi ZX. Experimental induction of middle ear cholesteatoma in rats. *Am J Otolaryngol* 1988;9:165–72.
- 91 Martheswaran T, Shmunes MH, Ronquillo YC, *et al.* The impact of vaping on ocular health: a literature review. *Int Ophthalmol* 2021;41:2925–32.
- 92 Md Isa NA, Koh PY, Doraj P. The tear function in electronic cigarette smokers. *Optom Vis Sci* 2019;96:678–85.
- 93 Zengin MO, Cinar E, Kucukerdonmez C. The effect of nicotine on choroidal thickness. *Br J Ophthalmol* 2014;98:233–7.
- 94 Paley GL, Echaliier E, Eck TW, *et al.* Corneal laceration and ocular burns caused by electronic cigarette explosions. *Cornea* 2016;35:1015–8.
- 95 Calder R, Gant E, Bauld L, *et al.* Vaping in pregnancy: a systematic review. *Nicotine Tob Res* 2021;23:1451–8.
- 96 Römer P, Putzer AG, Kemmerich R, *et al.* Effects of prenatal electronic cigarette exposure on foetal development: a review of the literature. *Geburtshilfe Frauenheilkd* 2021;81:1224–37.
- 97 Cardenas VM, Fischbach LA, Chowdhury P. The use of electronic nicotine delivery systems during pregnancy and the reproductive outcomes: a systematic review of the literature. *Tob Induc Dis* 2019;17:52.
- 98 Riley HEM, Berry-Bibee E, England LJ, *et al.* Hormonal contraception among electronic cigarette users and cardiovascular risk: a systematic review. *Contraception* 2016;93:190–208.
- 99 Figueredo CA, Abdelhay N, Figueredo CM, *et al.* The impact of vaping on periodontitis: a systematic review. *Clin Exp Dent Res* 2021;7:376–84.
- 100 Yang I, Sandeep S, Rodriguez J. The oral health impact of electronic cigarette use: a systematic review. *Crit Rev Toxicol* 2020;50:97–127.
- 101 Ralho A, Coelho A, Ribeiro M, *et al.* Effects of electronic cigarettes on oral cavity: a systematic review. *J Evid Based Dent Pract* 2019;19:101318.
- 102 Seitz CM, Kabir Z. Burn injuries caused by e-cigarette explosions: a systematic review of published cases. *Tob Prev Cessat* 2018;4:32.

- 103 Yang L, Rudy SF, Cheng JM, *et al.* Electronic cigarettes: incorporating human factors engineering into risk assessments. *Tob Control* 2014;23 Suppl 2:ii47–53.
- 104 Vyncke T, De Wolf E, Hoeksema H, *et al.* Injuries associated with electronic nicotine delivery systems: a systematic review. *J Trauma Acute Care Surg* 2020;89:783–91.
- 105 Scarpino M, Rosso T, Lanzo G, *et al.* Severe neurological nicotine intoxication by e-cigarette liquids: systematic literature review. *Acta Neurol Scand* 2021;143:121–30.
- 106 Becker TD, Arnold MK, Ro V, *et al.* Systematic review of electronic cigarette use (vaping) and mental health comorbidity among adolescents and young adults. *Nicotine Tob Res* 2021;23:415–25.
- 107 Yuan M, Cross SJ, Loughlin SE, *et al.* Nicotine and the adolescent brain. *J Physiol* 2015;593:3397–412.
- 108 Goriounova NA, Mansvelter HD. Short- and long-term consequences of nicotine exposure during adolescence for prefrontal cortex neuronal network function. *Cold Spring Harb Perspect Med* 2012;2:a012120.
- 109 Sinha R. The role of stress in addiction relapse. *Curr Psychiatry Rep* 2007;9:388–95.
- 110 Wiernik E, Airagnes G, Lequy E, *et al.* Electronic cigarette use is associated with depressive symptoms among smokers and former smokers: cross-sectional and longitudinal findings from the Constances cohort. *Addict Behav* 2019;90:85–91.
- 111 Antoniewicz L, Brynedal A, Hedman L, *et al.* Acute effects of electronic cigarette inhalation on the vasculature and the conducting airways. *Cardiovasc Toxicol* 2019;19:441–50.
- 112 Rothrock AN, Andris H, Swetland SB, *et al.* Association of e-cigarettes with adolescent alcohol use and binge drinking-drunkenness: a systematic review and meta-analysis. *Am J Drug Alcohol Abuse* 2020;46:684–98.
- 113 Chadi N, *et al.* Association between electronic cigarette use and marijuana use among adolescents and young adults. A systematic review and meta-analysis. *JAMA Pediatr* 2019;173:e192574–e192574.
- 114 Hershberger AR, Karyadi KA, VanderVeen JD, *et al.* Beliefs about the direct comparison of e-cigarettes and cigarettes. *Subst Use Misuse* 2017;52:982–91.
- 115 Breitbarth AK, Morgan J, Jones AL. E-cigarettes-An unintended illicit drug delivery system. *Drug Alcohol Depend* 2018;192:98–111.
- 116 Dai H, Catley D, Richter KP, *et al.* Electronic cigarettes and future marijuana use: a longitudinal study. *Pediatrics* 2018;141.
- 117 Audrain-McGovern J, Stone MD, Barrington-Trimis J, *et al.* Adolescent e-cigarette, hookah, and conventional cigarette use and subsequent marijuana use. *Pediatrics* 2018;142. doi:10.1542/peds.2017-3616. [Epub ahead of print: 06 08 2018].
- 118 Unger JB, Soto DW, Leventhal A. E-Cigarette use and subsequent cigarette and marijuana use among Hispanic young adults. *Drug Alcohol Depend* 2016;163:261–4.
- 119 Levy SJL, Williams JF, Ryan SA, *et al.* Substance use screening, brief intervention, and referral to treatment. *Pediatrics* 2016;138.
- 120 Gentry S, Forouhi NG, Notley C. Are electronic cigarettes an effective aid to smoking cessation or reduction among vulnerable groups? A systematic review of quantitative and qualitative evidence. *Nicotine Tob Res* 2019;21:602–16.
- 121 Franck C, Budlovsky T, Windle SB, *et al.* Electronic cigarettes in North America: history, use, and implications for smoking cessation. *Circulation* 2014;129:1945–52.
- 122 Gualano MR, Passi S, Bert F, *et al.* Electronic cigarettes: assessing the efficacy and the adverse effects through a systematic review of published studies. *J Public Health* 2015;37:488–97.
- 123 Barufaldi LA, Guerra RL, de Albuquerque RdeCR, *et al.* Risk of smoking relapse with the use of electronic cigarettes: a systematic review with meta-analysis of longitudinal studies. *Tob Prev Cessat* 2021;29:1–10.
- 124 Collins L, Glasser AM, Abudayyeh H, *et al.* E-Cigarette marketing and communication: how e-cigarette companies market e-cigarettes and the public engages with e-cigarette information. *Nicotine Tob Res* 2019;21:14–24.
- 125 Lee JGL, Orlan EN, Sewell KB, *et al.* A new form of nicotine retailers: a systematic review of the sales and marketing practices of vape shops. *Tob Control* 2018;27:70–5.
- 126 Glasser AM, Collins L, Pearson JL, *et al.* Overview of electronic nicotine delivery systems: a systematic review. *Am J Prev Med* 2017;52:e33–66.
- 127 Lee H-W, Park S-H, Weng M-W, *et al.* E-Cigarette smoke damages DNA and reduces repair activity in mouse lung, heart, and bladder as well as in human lung and bladder cells. *Proc Natl Acad Sci U S A* 2018;115:E1560–9.
- 128 Tang M-shong, Wu X-R, Lee H-W, *et al.* Electronic-cigarette smoke induces lung adenocarcinoma and bladder urothelial hyperplasia in mice. *Proc Natl Acad Sci U S A* 2019;116.
- 129 Wang RJ, Bhadriraju S, Glantz SA. E-Cigarette use and adult cigarette smoking cessation: a meta-analysis. *Am J Public Health* 2021;111:230–46.
- 130 Glantz SA. E-Cigarettes as consumer products. *Am J Public Health* 2022;112:e4–5.
- 131 Carvajal R, Clissold D, Shapiro J. The family smoking prevention and tobacco control act: an overview. *Food & Drug LJ* 2009;64:717.
- 132 Samet JM, Barrington-Trimis J. E-Cigarettes and harm reduction: an artificial controversy instead of evidence and a well-framed decision context. *Am J Public Health* 2021;111:1572–4.
- 133 O'Brien D, *et al.* Association between electronic cigarette use and tobacco cigarette smoking initiation in adolescents. A systematic review and meta-analysis. *BMC Public Health* 2021;21:1–10.
- 134 Zhang Y-Y, Bu F-L, Dong F, *et al.* The effect of e-cigarettes on smoking cessation and cigarette smoking initiation: an evidence-based rapid review and meta-analysis. *Tob Induc Dis* 2021;19:1–15.
- 135 Chan GCK, Stjepanović D, Lim C, *et al.* Gateway or common liability? A systematic review and meta-analysis of studies of adolescent e-cigarette use and future smoking initiation. *Addiction* 2021;116:743–56.
- 136 Khouja JN, Suddell SF, Peters SE, *et al.* Is e-cigarette use in non-smoking young adults associated with later smoking? A systematic review and meta-analysis. *Tob Control* 2021;30:8–15.
- 137 Baenziger ON, Ford L, Yazidjoglou A, *et al.* E-Cigarette use and combustible tobacco cigarette smoking uptake among non-smokers, including relapse in former smokers: umbrella review, systematic review and meta-analysis. *BMJ Open* 2021;11:e045603.
- 138 Brewer NT, Jeong M, Hall MG, *et al.* Impact of e-cigarette health warnings on motivation to vape and smoke. *Tob Control* 2019;28:e64–70.
- 139 Rohde JA, Noar SM, Mendel JR, *et al.* E-Cigarette health harm awareness and discouragement: implications for health communication. *Nicotine Tob Res* 2020;22:1131–8.
- 140 Wang JB, Olgin JE, Nah G, *et al.* Cigarette and e-cigarette dual use and risk of cardiopulmonary symptoms in the health eHeart study. *PLoS One* 2018;13:e0198681.
- 141 Alzahrani T, Pena I, Temesgen N, *et al.* Association between electronic cigarette use and myocardial infarction. *Am J Prev Med* 2018;55:455–61.
- 142 Osei AD, Mirbolouk M, Orimoloye OA, *et al.* Association between e-cigarette use and cardiovascular disease among never and current combustible-cigarette smokers. *Am J Med* 2019;132:e2:949–54.
- 143 Tommasi S, Caliri AW, Caceres A, *et al.* Deregulation of biologically significant genes and associated molecular pathways in the oral epithelium of electronic cigarette users. *Int J Mol Sci* 2019;20. doi:10.3390/ijms20030738. [Epub ahead of print: 10 Feb 2019].
- 144 Vansickel AR, Cobb CO, Weaver MF, *et al.* A Clinical Laboratory Model for Evaluating the Acute Effects of Electronic “Cigarettes”: Nicotine Delivery Profile and Cardiovascular and Subjective Effects. *Cancer Epidemiology, Biomarkers Prevention* 2010;19:1945–53.
- 145 Bullen C, McRobbie H, Thornley S, *et al.* Effect of an electronic nicotine delivery device (E cigarette) on desire to smoke and withdrawal, user preferences and nicotine delivery: randomised cross-over trial. *Tob Control* 2010;19:98–103.
- 146 Pacek LR, Rass O, Sweitzer MM, *et al.* Young adult dual combusted cigarette and e-cigarette users’ anticipated responses to hypothetical e-cigarette market restrictions. *Subst Use Misuse* 2019;54:2033–42.
- 147 Hopkinson NS, Vestbo J, Bush A, *et al.* Should e-cigarettes be licensed as medicines? *BMJ* 2022;376:n2912.
- 148 Sleddens EFC, Kroeze W, Kohl LFM, *et al.* Correlates of dietary behavior in adults: an umbrella review. *Nutr Rev* 2015;73:477–99.