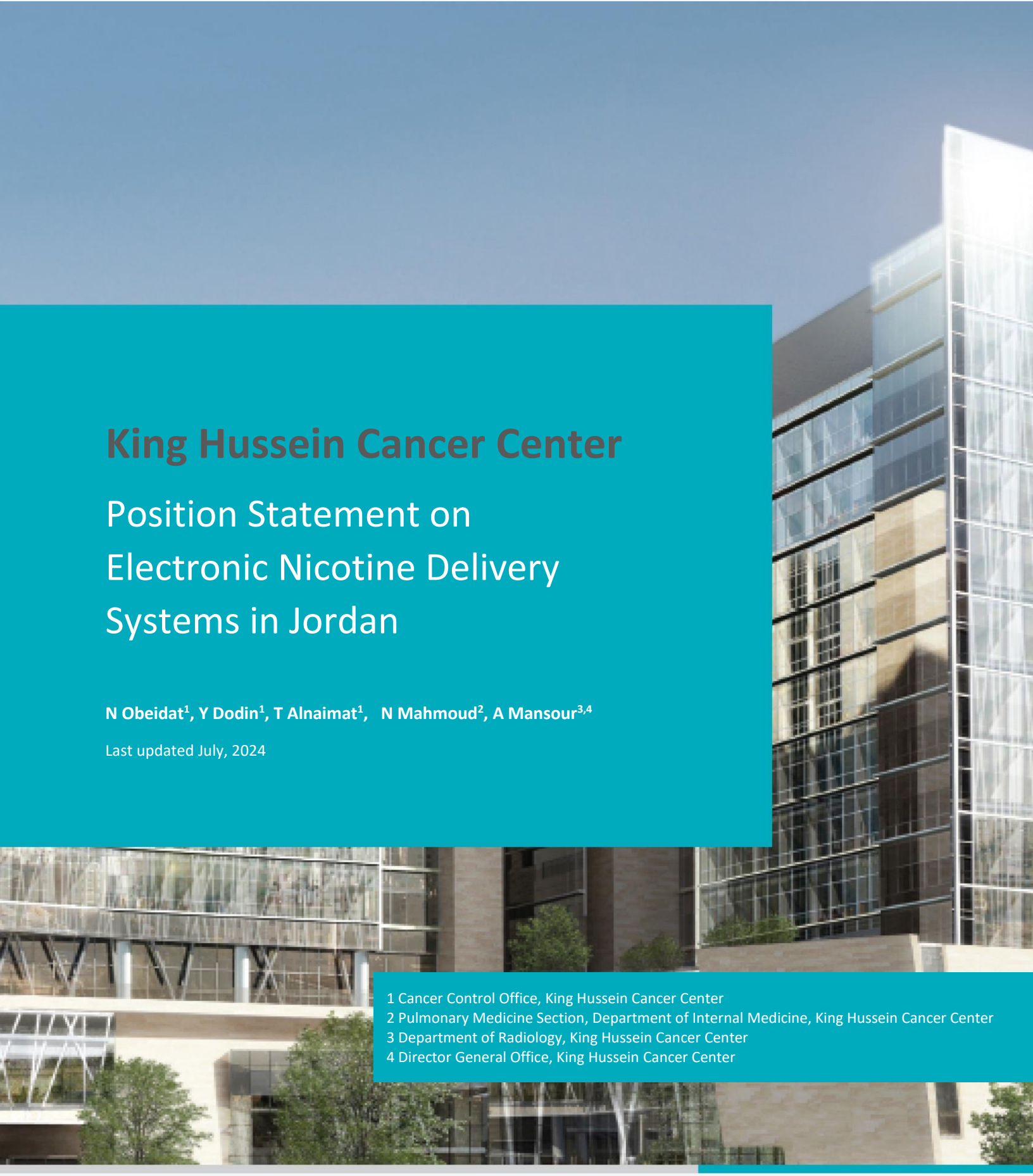

King Hussein Cancer Center

Position Statement on Electronic Nicotine Delivery Systems in Jordan

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مركز الحسين للسرطان
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About this position statement

Electronic Nicotine Delivery Systems or ENDS, known by many names (e.g. electronic cigarettes, Electronic Nicotine Delivery Devices, e-cigs, pods, pod-mods, tanks, vaping devices, vapes, vape pens),[1] are battery-operated devices that heat a liquid (a solvent typically containing nicotine, flavorants, and other chemicals) to generate an aerosol that is inhaled (rather than burn a tobacco mixture as with conventional cigarettes). While ENDS began appearing in some global market as early as 2006,[2] these products became officially licensed for sale in Jordan in 2019,[3] and have gained popularity in the community, particularly among adolescents, young adults, and females.

ENDS have been marketed globally by the tobacco industry as smoking cessation tools and as safer "smoke-free" alternatives to combustible cigarettes.[2] However, there are various on-going concerns regarding ENDS, including their safety profile; their potential to fuel nicotine dependence as well as normalize smoking; their role as gateway products to other tobacco use; and the conflicting evidence about their use as smoking cessation tools. [4]

King Hussein Cancer Center (KHCC) – from the perspective of a clinical entity that treats both cancer patients and smokers, and seeks to contribute to the well-being of the Jordanian community – has issued this statement to highlight the key findings to date regarding the clinical and public health effects of ENDs; and to provide to healthcare practitioners and decision-makers with recommendations specific to the Jordanian context with regards to these products.

Key messages

- ✓ While Jordan has attempted to regulate ENDS, the country's current regulatory framework has not been sufficient to curb the emergence of specialty vape shops and booths which have marketed hundreds of attractive youth and gender-oriented flavors and colors in a largely unrestricted manner, particularly through digital media.
- ✓ Jordan has faced longstanding challenges in tobacco control implementation. Historically, there have been inconsistent efforts from various governmental and nongovernmental entities to proactively support the Ministry of Health (MoH) in its tobacco control efforts. There is strong concern that the wide spread use of ENDS in the country will further complicate the country's national tobacco control goals.
- ✓ The evidence available thus far indicates that ENDS are not safe, and have the potential to impact health, with further research and long-term follow-up being required.
- ✓ In the absence of continually updated youth surveillance systems, we lack knowledge regarding the true impact of ENDS availability on current and potential tobacco use in the country, particularly among community groups that would have been less likely to become tobacco users in the absence of ENDS.

- ✓ The use of ENDS for smoking cessation has been based on studies with methodological limitations. Furthermore, these studies largely evaluate combustible cigarette smoking cessation, rather than complete cessation from both tobacco and recreational nicotine products.
- ✓ Due to the current tobacco and ENDS-related regulatory and implementation challenges, and due to the absence of continual monitoring of national public trends in use, healthcare professionals in Jordan should be cautious regarding these products, which may be imposing more harm than purported good to public health in the country.
- ✓ Jordan's MoH has expanded its smoking cessation clinics to now include 25 clinics across the country. These clinics utilize evidence-based medications for smoking cessation, and should consistently be the first line of interventions promoted in Jordan for those seeking smoking cessation.
- ✓ In the event of failure of all lines of evidence-based therapy for smoking cessation, clinicians should not promote ENDS as smoking cessation tools. Rather, specific messaging regarding the ramifications of use of ENDS should be provided, with a disclaimer that these products cannot be clinically recommended by Jordanian healthcare practitioners.

The Burden of Tobacco in Jordan

Globally, tobacco control efforts have resulted in the decline of combustible cigarette smoking. However, this decline has been disparate across countries and the number of smokers has been increasing in certain low and middle-income countries.[5] Current estimates indicate that approximately 80% of smokers reside in low and middle-income countries (LMICs),[6] areas which the tobacco industry is increasingly targeting.[7] The disproportionate burden of tobacco use warrants more intensive efforts to address events and emerging products that may further contribute to the tobacco epidemic.

Smoking rates in Jordan are some of the highest in the world, and have been increasing. From 2007 to 2019, overall smoking prevalence increased by 45% (29% vs 42%).[8, 9] As of 2019, the smoking prevalence in men and women was 66.1% and 17.4%, respectively.[9] In 2014, adolescent smoking in Jordan (children aged 13 to 15) was reported by approximately a quarter of students,[10] a value that is likely increasing, given the trends being observed in adult rates of smoking. More concerning, these proportions exist within a challenging environment for tobacco control, namely an environment with limited implementation of Jordan's Public Health Law articles that pertain to tobacco control, coupled with a flooding over recent years, of ENDS in the Jordanian market.[11] It is noteworthy that globally, tobacco use has been declining across several countries, placing Jordan in stark contrast to global trends.

ENDS use in Jordan

Jordan, in its efforts to curb illegal entry of ENDS into the country, developed policies in 2019 to legalize ENDS,[*] but these policies have not deterred the mushrooming of ENDS products that are clearly marketed in an aesthetic and irresponsible manner to target community groups. Data about ENDS prevalence of use at the national level are scarce. The 2018/2019 STEPs survey was the first national survey in Jordan that asked respondents about ENDS use (daily, non-daily, and ever-used). Despite ENDS not yet being licensed for sale in the country at the time of the survey, approximately 16% and 3% of male and female adult respondents, respectively, used ENDS (9.6% overall). Notably, while in men smoking cessation was the most frequently cited reason for use, among the smaller group of women using these products, enjoyable flavors were the most commonly cited reason.[9] In another national survey conducted a few months after ENDS legalization,[*] approximately 11% and 14% of male and female adult respondents, respectively, reported use of ENDS (11.7% overall). [12] In studies subsequent to these surveys, ENDS use continued to be documented: 11% of college students surveyed between October 2020 and January 2021 reported ENDS use;[13] while in other surveys of college students, there have been higher rates of use reported. Specifically, in two additional studies, 15.8% and 37.4% of students reported ever-use of ENDS.[14, 15]

A closer look at ENDS

The design features of ENDS

ENDS have evolved dramatically since they first emerged in the market. First generation ENDS resembled combustible cigarettes in exterior but have gradually changed in appearance, becoming sleeker and less emblematic of the combustible cigarette with time, while also delivering higher concentrations of nicotine in a faster [and more addictive] manner. ENDS (ranging from first generation to fourth generation devices) present in various forms including both disposable and refillable, with a wide variety of nicotine concentrations; different types of nicotine (salt versus freebase; synthetic versus tobacco-derived);

[*] ENDS were legalized in May of 2019 and published in the National Gazette in July of 2019.

variable voltage; a countless number of possible e-liquid constituents; and variable 'hacking' potential, all which alter their safety, nicotine bioavailability profiles, and regulatory mechanisms.[1, 16, 17] There is limited [publicly available] information regarding market consumption data and market shares of specific types/characteristics of ENDS in Jordan.

Toxicology of ENDS

ENDS heat liquids that typically contain nicotine (free-base or salt), flavors, water, and humectants such as propylene glycol and vegetable glycerin.[18] In addition to the chemicals originating from the e-liquid, the heating of the e-liquid involves chemical reactions which further generate additional compounds with the potential to be toxic. Contrary to what many may believe, the liquids in ENDS are not simple solutions that may or may not contain nicotine. Rather, hundreds of chemicals – many with carcinogenic or toxic, inflammatory characteristics – have been identified in ENDS liquids and aerosols, including nicotine, propylene glycol, tobacco-specific nitrosamines, aldehydes, metals, volatile organic compounds, phenolic compounds, polycyclic aromatic hydrocarbons, flavorings, and tobacco alkaloids (the concentrations of these compounds are generally lower than combustible cigarettes, but are highly variable across ENDS devices and liquids).[19-21] In addition, some ENDS liquids may be infused with drugs such as tetrahydrocannabinol.[19]

It is important to note that concerns have been raised regarding labeled nicotine content in ENDS liquids: studies have demonstrated that these liquids, including "nicotine-free" labelled liquids, can be mislabeled and may contain higher or more variable concentrations of nicotine than those specified in the label.[22, 23]

Health impacts of ENDS

Since their marketing, there has been a pervading public perception that ENDS are less harmful than combustible cigarettes.[24-27] Moreover, health authorities such as Public Health England have endorsed a widely cited claim that ENDS are "95% less harmful" than combustible cigarettes,[28] a claim that has been critiqued as one based on scientific opinion from a group of 12 experts, rather than clear, hard evidence; moreover, this claim has a limited perspective of what constitutes harm; and was based on limited knowledge about older ENDS.[29-31]

In reality, there are limited longitudinal epidemiological studies linking long-term health effect of exposure to e-cigarettes. Most of the evidence on the direct effects of ENDS relies on in vitro and animal studies; human studies are largely limited to acute pathophysiologic mechanisms and intermediate health endpoints.[32] There are methodological challenges related to measuring the health effects of these devices, including: the limited time that ENDS have been in the global market; the evolving nature of device characteristics and heterogeneous nature of vaping topography; and the availability of thousands of e-liquids that contain various flavorings, nicotine amounts, and other constituents.[19] Moreover, many ENDS users are former or current tobacco smokers, rendering the teasing apart of ENDS health effects from those of combustible tobacco use methodologically challenging. Nevertheless, some limited evidence regarding ENDS is available that can be used to better understand the potential harms of these products.

Cardiovascular health

Nicotine activates the sympathetic nervous system resulting in increased heart rate and blood pressure, and coronary vasoconstriction, and there is some evidence to suggest that ENDS use also is linked to

detrimental changes in biomarkers of oxidative stress, an increase in systolic blood pressure, increased endothelial dysfunction and arterial stiffness, and impaired autonomic cardiovascular control.[19, 33, 34] With regards to cardiovascular disease (CVD), a cross-sectional analysis of 175,549 respondents revealed that lifetime incidence of myocardial infarction (MI) was associated with ENDS use only among current tobacco smokers,[35] and a review has also suggested that ENDS use (exclusive or with combustible cigarettes) is associated with an increased MI risk.[36] However, there is still insufficient evidence to draw conclusive statements regarding the risk of clinical cardiovascular disease among ENDS users who are non-tobacco smokers.[37, 38] The lack of association should be interpreted cautiously, and should not be taken as evidence that ENDS are harmful only when combined with smoking, particularly because exclusive ENDS users (who are nonsmokers) tend to be younger,[39] and because of the shorter follow-up period in studies evaluating MI risk with ENDS use. Thus, the lack of statistically significant associations of ENDS use with CVD (such as MI) among exclusive ENDS users may be due to the insufficient time to develop clinically significant CVD in these studies.[38] Berlowitz et. al. also reported insignificant differences in CVD risks among dual users and exclusive cigarette smokers which weakens the popular notion that adding ENDS use in smokers could lower CVD events.

Taken together, and given the evidence gaps about the cardiovascular effects of ENDS,[40] ENDS should not be labelled as cardiovascular- safe products or as products which will definitely lower the risks of CVD in tobacco smokers.

Respiratory health

ENDS use in youth was significantly associated with higher reported respiratory adverse events when compared to nonsmokers.[41, 42] There is moderate certainty that ENDS are associated with less serious respiratory adverse events (wheezing, cough, chest pain, shortness of breath, and phlegm production) among ENDS users compared with combustible cigarette smokers.[37] There is insufficient evidence to support the possibility that switching to ENDS (exclusive or dual use) in asthmatic and Chronic Obstructive Pulmonary Disease (COPD) patients could reduce respiratory exacerbations or disease progression.[37] While few studies have explored this association and reported improved symptoms in asthma and COPD, these studies have been limited in size and power.[43, 44]

During the summer of 2019, e-cigarette or vaping product associated lung injury (EVALI) outbreaks were reported almost exclusively in the United States, and as of February 18, 2020, a total of 2807 hospitalized patients with nonfatal cases and 68 deaths of EVALI have been reported to the United States Centers for Disease Control and Prevention (CDC).[45] Additional cases have been reported worldwide, including Jordan. [45-49] There is conclusive evidence that the EVALI epidemic was caused by the use of ENDS,[50] and while lung injury was linked to vitamin E acetate (an additive used in tetrahydrocannabinol-containing e-liquids), the exact etiology of EVALI is yet to be determined.[40, 45]

Nicotine dependence

Nicotine is the primary psychoactive addictive constituent that drives sustained smoking, while other non-nicotine factors associated with tobacco self-administration (e.g., taste, aroma, throat irritation, airway sensations, sight, and the hand-to-mouth movements) as well as other chemicals in tobacco products (such as acetaldehyde) play a role in fueling the nicotine addiction.[51, 52] As with combustible cigarettes, ENDS are designed to deliver nicotine. Moreover, the nicotine being delivered through ENDS is increasingly being delivered in higher amounts and with faster time to peak concentration as ENDS' design features have changed and e-liquids have become more concentrated.[53, 54] ENDS use also is

accompanied by enjoyable sensory stimuli that further promote their use.[55, 56] It is therefore not surprising that signs of dependence have been reported in ENDS users who do not smoke tobacco,[57] and that evidence is conclusive that ENDS use leads to nicotine addiction.[37] Relatedly, ENDS features (flavors, designs, concentrations) may alter user experiences, and require further study in order to better understand how the rapidly evolving features of ENDS affect use as well as the potential for abuse of these products. It is important to emphasize that 'low nicotine' e-liquids are not an assurance that a user will inhale lower amounts of nicotine or toxic chemicals: vaping behavior, puffing topography (puff duration, puff volume and inter-puff interval), and device wattage are amongst the factors that can lead to higher exposure to nicotine and other toxic chemicals in users of low nicotine e-liquids.[58, 59]

Given the association of ENDS use with development (or perpetuation) of nicotine dependence, the concerns regarding tobacco smoking's effect [via nicotine] on adolescent cognitive function and brain development as a result of neurochemical changes with prolonged nicotine exposure, also apply to the use of ENDS.[60-62] Furthermore, nicotine use in adolescents has been associated with other substance abuse,[63] and given the potential for e-liquids to be modified, this concern becomes even more serious when considering adolescent ENDS use.

Mental health

In both adults and adolescents, ENDS use has been associated with various mental health conditions and symptoms, including anxiety, depression, suicidality, impulsivity, stress, and problems with concentration.[64-72] The directionality of these associations is unclear and requires further study, but it is evident that ENDS use warrants caution, given its potential to predispose to and/or worsen certain mental health conditions.

Neurological diseases

ENDS use has been linked to neurological symptoms including seizures. The United States Food and Drug Administration issued a special announcement alerting of seizure reports received by the FDA and the American Association of Poison Control Centers in some ENDS users.[73] Seizures have typically been reported with poisoning (e-liquid ingestion),[37] but surveillance reports indicate that ENDS use in their intended manner (inhalation) has also been linked seizures as well as other neurological symptoms (tremors, syncope).[74]

Cancer

Given the long latency period between carcinogen exposure and cancer formation, evidence on the effect of ENDS use on carcinogenesis in humans is extremely sparse.[37] Findings from laboratory studies suggest a carcinogenic potential of ENDS,[75-77] and samples taken from ENDS users exhibit DNA alterations consistent with those observed with cigarette smokers.[78, 79] There is therefore a clear scientific premise for the carcinogenicity of ENDS.[80, 81] Nevertheless, this association requires further extensive investigation.[82] It is relevant to note that Cancer Organizations have warned against the widespread use of ENDS,[83, 84] and that the American Cancer Society does not recommend their use as cessation aids.[84]

Other effects

Less serious effects that have been associated with ENDS use include cough, throat irritation, dizziness or lightheadedness, dry mouth, headache and nausea.[37, 85-87]

Unintended effects

ENDS use has been associated with poisoning due to intentional or accidental e-liquid ingestion (leading to symptoms such as vomiting, diarrhea, abdominal pain, and seizures); burns and injuries; and environmental hazards due to an increase in airborne particulate matter, particularly in in-door environments.[37, 88]

ENDS and smoking cessation

ENDS, since their availability in the global market, have been promoted as "safer" tools to quit tobacco smoking.[19] Several studies have attempted to evaluate the efficacy of ENDS for smoking cessation (rather than nicotine cessation). It is important to distinguish smoking cessation from nicotine cessation in the context of ENDS.

Reviews have varied in their conclusions regarding ENDS as smoking cessation tools, largely due to the variability (in design and quality) of studies.[89] A recent Cochrane review indicated that the use of ENDS could help smokers [followed for six months to one year] abstain from tobacco product use.[90] Specifically, nicotine-containing ENDS relative to non-nicotine containing ENDS increased the chances of tobacco cessation by 46%; while nicotine-containing ENDS relative to nicotine replacement therapies increased the chances of tobacco cessation by 59%. These relative findings were translated to the following anticipated absolute effects:

Comparison (A) [90]	**Nicotine-containing ENDS:** 10 out of 100 abstained at 6 months to a year relative to NRTs (6 out of 100 abstained at 6 months to a year)
Comparison (B) [90]	**Nicotine-containing ENDS:** 10 out of 100 abstained at 6 months to a year relative to non-nicotine-containing ENDS (7 out of 100 abstained at 6 months to a year)
Comparison (C) [90]	**Nicotine-containing ENDS:** 8 out of 100 abstained at 6 months to a year relative to behavioral support or no support (4 out of 100 abstained at 6 months to a year)
Comparison (D) [91]	**Combination forms of NRTs*:** 174 out of 1000 abstained, relative to 137 out of 1000 in single-form NRTs (studies with atleast 6 months follow-up included)
Comparison (E) [92]	**Varenicline:** 14 per 100 abstained, relative to 6 per 100 with placebo (at 6 to 12 months)
Comparison (F) [92]	**Nicotine-containing ENDS:** 14 per 100 abstained, relative to 6 per 100 with placebo (at 6 to 12 months)
Comparison (G) [92]	**Fast-acting NRT or nicotine patch:** 8 to 9 per 100 abstained, relative to 6 per 100 with placebo (at 6 to 12 months)

** NRTs: Nicotine replacement therapies*

The studies reporting abstinence with ENDS referred to tobacco use abstinence rather than nicotine abstinence.[93] In fact, nicotine abstinence is far more likely when using evidence-based pharmacotherapies such as nicotine replacement therapy than when using ENDS: specifically, for every 100 smokers that were given nicotine replacement therapy, 7 were predicted to stop both smoking and nicotine use while 2 were predicted to stop smoking but continue to use the nicotine replacement therapy (a well-established and safe medicament). For every 100 smokers that were given ENDS, 3.7 were predicted to stop both smoking and nicotine use while 10.6 were predicted to stop smoking but continue ENDS use.[93]

In addition it is also important to note that of the seven studies which compared ENDS to NRTs in the Cochrane review, [90] only two studies demonstrated a significantly higher (than NRT) rate of tobacco use

cessation;[94, 95] and in both of these studies, the use of NRTs was suboptimal (e.g. limited coverage, or coverage for a shorter period of time than is recommended for use). A more recent study published after the 2024 Cochrane review also reported significantly higher rates of abstinence from smoking at 6 months with ENDS when compared to "optional" NRTs. In this study, NRT use also was suboptimal: vouchers of a negligible monetary amount (50 USD, which could have been used for any purpose) were distributed to those in the NRT arm, while those in the ENDS arm received six months of free ENDS (including various flavors and paraphernalia). [96] Finally, all the

In light of these arguable numbers as well as various methodological limitations and concerns,[97] it is important to reiterate the value of well-established and objectively evaluated evidence-based pharmacological and behavioral approaches, which are the foundation of Jordan's Tobacco Dependence Treatment guidelines,[98] guidelines employed by the MoH's 29 tobacco dependence treatment clinics that have been established across the Kingdom.[99]

Messaging regarding ENDS as cessation tools

In the event that healthcare practitioners may need to discuss ENDS with smokers, they should do so realizing the various caveats specific to Jordan, as well as the general caveats of using these products. Several recommendations with regards to messaging about ENDS as cessation tools have been proposed.[100] Some of these recommendations have been adapted to the Jordanian context and are included below with other important points for Jordanian healthcare practitioners to note:

i. Provision of intensive tobacco dependence treatment or referral to a smoking cessation clinic (e.g. clinics within primary healthcare centers in the MoH [99]) is the first line of action for healthcare practitioners. If a smoker is seeking to quit, they should exhaust structured behavioral strategies and first-line, evidence based regimens such as nicotine-replacement therapies, varenicline, and bupropion.
ii. Practitioners should not encourage or endorse ENDS as smoking cessation tools. If smokers request information regarding ENDS, healthcare practitioners should have a clear discussion with patients to explain that although there a few studies that ENDS can help people stop smoking combustible cigarettes, the studies are limited in their timeframes as well as generalizability to the Jordanian smoker. Furthermore, resorting to ENDS as a smoking cessation tool could result in continued use of ENDS and perpetuation of nicotine addiction. Dual use is also a possible consequence, meaning that the risks of tobacco use have not been completely eliminated. It is also important to note that the Jordanian Food and Drug Administration (JFDA) has not approved ENDS specifically as cessation aids (unlike smoking cessation medications).
iii. Although ENDS may produce lower quantities of harmful products than combustible cigarettes, ENDS use is not harmless, and the long-term impact of their use still needs to be studied. Because of the uncertainty still attached to ENDS use, those who opt to use them should still plan on quitting them as soon as possible. It is also necessary to note that ENDS pose harms due to both the nature of how they operate (heating an e-liquid, regardless of whether or not the e-liquid is labelled "nicotine-free") as well as their nicotine delivery in potentially addictive and harmful concentrations (when e-liquids contain nicotine).
iv. Any evidence-based cessation method requires a behavioral support component in order to increase the likelihood of quitting success. 'Quitting' merely by switching to ENDS use ignores the complexity of nicotine addiction and tobacco use.

v. It is difficult to determine precisely what is delivered to an ENDS user in terms of nicotine or toxicants. E-liquids vary tremendously, and puff topography as well as device characteristics alter the concentrations of chemicals released and delivered to the user. The ENDS market in Jordan contains various selections of devices, nicotine concentrations, and flavors. This makes the role of a healthcare practitioner in advising or monitoring an ENDS user challenging.
vi. It is important that ENDS users be warned about hacking or altering commercial ENDS.
vii. Any problems associated with ENDS use should be reported immediately to the JFDA.
viii. ENDS use should be discouraged in people who do not use combustible tobacco products.

Dual use of ENDS and tobacco products

Dual use of ENDS and combustible cigarettes is reported in studies of ENDS users. The reasons behind dual use and the associated health effects require further investigation.[101, 102] With the availability of ENDS and an accessible tobacco product market, dual users of both ENDS and smoked tobacco products are likely to become more prevalent in Jordan.

ENDS use as a gateway to smoking

The subject of whether or not ENDS use in nonsmokers increases the likelihood of their transitioning to tobacco smoke continues to be studied. No consensus has been reached, with studies providing evidence supporting this theory, and others suggesting no effect.[103-107] It is important to note that tobacco use and vaping rates are influenced by country-level environmental and policy factors and country-specific details.[108-112]

Until Jordan fully implements its tobacco control related articles of its Public Health Law and sound surveillance systems become established within its tobacco control efforts, the potential for current vaping trends in the country to fuel a greater tobacco epidemic cannot be ruled out, particularly due to the high rates of use of both cigarettes and waterpipe. Jordan has faced longstanding challenges in tobacco control implementation pre-ENDS era,[11] particularly due to the historically limited efforts [from other governmental and nongovernmental entities] to engage with the MoH's tobacco control efforts. It is therefore highly likely that the wide spread use of ENDS in the country will further deter the country from lowering its tobacco use rates.

The ENDS regulatory framework

Jordan signed the World Health Organization's Framework Convention on Tobacco Control (FCTC) in 2004, and has since then attempted to match the majority of its regulatory tobacco policies with the FCTC treaty. With the emergence of ENDS, the WHO, during its seventh conference of the parties to the WHO FCTC, emphasized the importance of countries implementing additional measures to regulate ENDS.[113] In addition to the global demand for regulatory measures, it became clear that illegal ENDS markets were emerging in Jordan.[114] In fact, during a market study conducted by King Hussein Cancer Center during 2018/2019 (i.e. when ENDS were still illegal), 63 types of ENDS and 75 e-liquid brands (with a variety of flavors) were identified in the selection of 42 traditional point of sales and 32 online point of sales that were included in the study.[115] As a result of global tobacco control calls as well as a seemingly inevitable influx of ENDS into the country, Jordan in 2019 expanded its commitments under the FCTC treaty, established ENDS-specific regulatory measures, and legalized ENDS.[116] However, unlike previous tobacco product regulations which were developed through the MoH and the Jordan Standards and

Metrology Organization (JSMO), ENDS regulations were established under the JFDA[†].[117] In December of 2021, Jordan's FDA reported registering 184 entities to sell ENDS.[118] As of 2022, there were over 570 e-liquid (nicotine salt and free base nicotine) variations and 223 device variations registered in the Jordanian market (internal data). In other countries, analyses of the chemical and toxicant components of ENDS on the market has informed how these products should be regulated.[119] To date, no studies on the chemical constituents of these products (specifically in the Jordanian market) have been conducted or else made publicly available.

ENDS are classified under tobacco products in the JFDA (i.e. they are not food, pharmaceutical or other products). Important elements of Jordan's ENDS regulations established by its FDA include:[116, 120]

- Age restrictions (not available to those younger than 19);
- Including a warning label regarding nicotine and its addictive nature;
- Limiting concentrations of nicotine (free nicotine: up to 20 mg/ml; nicotine salt: up to 25 mg/ml);
- Limiting the volume of e-liquids (refillable tanks 2 ml; refill solutions 60 ml);
- Prohibiting the promotion of ENDS;
- Prohibiting the sales of ENDS within a 500 m radius from schools and hospitals; and
- Restricting the display and promotion of ENDS.

The current ENDS regulations do not explicitly state what flavors are considered appealing to youth, nor do they explicitly state which flavors are not allowed. Given what has been observed through internal documents related to licensed brands and flavors of ENDS in the country, as well as the diversity of products observed in the Jordanian market, it is evident that the Jordanian ENDS market has an extensive selection of youth-appealing flavors and device appearances.

Implementation of the ENDS regulatory framework in Jordan

To date, the current JFDA regulations have not been evaluated with regards to extent of implementation. However, in light of the numerous points of sales for ENDS that have now become a norm in Jordan, it is reasonable to state that more efforts are needed to control these products in the Jordanian market. ENDS are available in diverse, attractive flavors. Although prices and affordability of ENDS in Jordan have not been studied, these products appear to be accessible. Surges of ENDS use at schools were reported as early as 2019.[121, 122] In a more recent field study conducted by Tobacco-free Jordan and King Hussein Cancer Center, data collectors scoped the 150m radius of 94 schools in two districts of Amman and found [across 213 shops within this radius] that 69.0% of stores were directly violating Jordan's Public Health law by selling at least one tobacco/electronic nicotine product (approximately 12% sold ENDS or e-liquids) around schools.[123]

The tobacco backdrop in Jordan and ENDS regulations

The ENDS regulatory framework in Jordan cannot be presented in isolation of Jordan's other tobacco control regulations. In theory, Jordan's current laws prohibit the sales of tobacco products to those younger than 18, while ENDS products cannot be sold to those younger than 19; smoking "in all its forms"

[†] More recently, the regulation of all tobacco products as well as ENDS and heat-not-burn tobacco are under the jurisdiction of JFDA, which nevertheless continues to work with other entities to regulate these products.

is banned in public places and public transit; promotion of any form of tobacco products is prohibited; and the regulations authorize considerable penalties on entities or persons violating these regulations.[124] In reality, the implementation of these regulations has been problematic. Minors can easily access tobacco products, exposure to tobacco smoke is rife, penalties are insufficiently enforced, and tobacco and ENDS use is prevalent and normalized.[9]

To effectively address ENDS in the Jordanian market, regulations for both ENDS as well as tobacco products must be aligned and comprehensively enforced, in order to preempt complementary or substitutive effects between products. In fact, there have been concerns that the emergence of ENDS (in addition to new tobacco products) will likely distract from reaching a tobacco endgame,[125] and in Jordan's current environment, this is highly possible.

ENDS regulations and other country experiences

Globally, the approach to tobacco control has entailed the regulation of ENDS alongside other tobacco products in order to avoid the further fueling of a long-existing tobacco epidemic.[126] Even in the UK, one of the few countries to attempt to medicalize ENDS, the availability of ENDS has also been accompanied with calls for tighter regulations (both tobacco and ENDS-specific) to enable achieving "smoke-free" objectives for the country.[127]

The regulation of ENDS has been proposed through various means including:[100, 128-132]

i. Pre-Marketing authorizations
ii. Restricting nicotine concentration of e-liquids
iii. Minimum age of purchase
iv. Restricting volumes of e-liquids
v. Prohibiting or regulating ENDS marketing
vi. Excise tax on ENDS
vii. Bans or restrictions on ENDS use in public places
viii. Health warnings on ENDS
ix. Child-resistant packaging
x. Entire bans on ENDS
xi. Banning specific forms of ENDS such as disposables
xii. Restricting access to ENDS as prescription-only products
xiii. Ban on non-tobacco flavored ENDS
xiv. Ban on non-tobacco and non-menthol flavored ENDS
xv. Ban on nicotine-containing ENDS
xvi. Plain packaging

With regards to Jordan, approaches (i) through (viii) are in theory part of Jordan's tobacco regulations. However, their implementation, particularly with regards to promotions, minimum age of purchase, affordability, and use in public places, does not appear to be rigorous. Social media promotion of ENDS is pervasive; ENDS are sold widely in appealing forms and flavors to all age groups and smoking/non-smoking groups; ENDS and their [alluring to youth and women] paraphernalia are affordable and easily accessible in the Jordanian market; and smoking as well as vaping are prevalent in public spaces.

Recommendations

The World Health Organization's call for more intensive efforts to control ENDS should be heeded in Jordan.[133] The status quo in the country with regards to tobacco and ENDS control is to its disadvantage, and presence of these devices have complicated a pre-existing epidemic. To encourage a conducive change, various clinical and public health recommendations to address the current ENDS situation in Jordan are included below:

1. With regards to smokers seeking cessation tools, evidence-based pharmacotherapeutic and behavioral solutions are available. Healthcare practitioners should not encourage smokers to use products [ENDS] for which comprehensive advice regarding safety and methods of use are either incomplete or difficult to provide. ENDS (both devices and liquids) as well as ENDS user behaviors are highly heterogeneous,[134] and render difficult the provision of information regarding the quantification of ENDS use and nicotine/toxic chemical exposure. Given that the rates of nicotine abstinence are low with ENDS use, and the rates of smoking abstinence are not considerably higher than those observed with approved pharmacotherapies, ENDS should not be promoted as viable cessation tools.

2. The short and long-term effects of ENDS use on physical as well as psychological health and their potential to lead to subsequent tobacco product use require further research. There is a global deficit of health information with regards to ENDS due to their relative recency in the market. Given the tobacco industry's well-documented history of fueling tobacco use through misleading claims regarding its products,[135] coupled with the wide promotion of these products to vulnerable groups that is being observed in Jordan, ENDS should not be readily accepted nor promoted as "safer" alternatives. This position should be assumed until ENDS are more stringently regulated, and the tobacco industry in Jordan (represented by both manufacturers, distributors and sellers) clearly demonstrates that these products are not being marketed to vulnerable groups, and access to them is controlled.

Establishing the risk/benefit ratio of ENDS and their effects on public health in Jordan requires the integration of current and emerging evidence on both the direct and indirect exposures and effects while also considering Jordanian contextual factors and baselines, as well as country-specific regulatory elements. Until reliable data become available, healthcare practitioners in Jordan are unable to make clear statements regarding the wider impact of ENDS on Public Health in the country (i.e. impact on health as well as tobacco and ENDS use in the community).

3. Surveillance systems are indispensable tools that inform how tobacco and ENDS use has changed over the years.[136, 137] In the US for example, large longitudinal cohort studies such as PATH (Population Assessment of Tobacco and Health) monitor the changing rates of tobacco and ENDS use,[138] and have alerted decision makers with regards to escalating rates of ENDS use. Such continually updated surveillance systems are currently lacking in Jordan – particularly those pertaining to youth and young adults. Thus, as of yet, we are unaware of the true impact of this loosely regulated group of products on current and potential tobacco use, particularly on vulnerable groups and groups that would have been less likely to become tobacco users in the absence of ENDS.

4. Regulation of ENDS to deter the promotion of these products to vulnerable groups, and to avoid a surge in nicotine addiction and the possibility of transitions to combustible cigarette or waterpipe smoking, requires that Jordan's authorities and the tobacco control community (led by the MoH and

inclusive of the various governmental and nongovernmental stakeholders) collectively promote and implement all tobacco and ENDS regulations towards one end goal (protecting public health and ending the tobacco epidemic). In Jordan, multiple authorities oversee the regulation of ENDS and tobacco products and their markets (e.g. MoH, Ministry of Industry and Trade, the Ministry of Finance Income and Sales Tax Department, Ministry of Local Administration, Ministry of Interior, Ministry of Education, JFDA, JSMO, Jordan Customs, affiliated institutions, and several other institutions). Objectives across these stakeholders do not always align (some arguably have competing objectives), and differences in tobacco product (versus ENDS) regulations create confusion. The current regulatory environment has impeded a comprehensive tobacco and ENDS control process, and has impeded regulation of ENDS through more rigorous means.

References

1. **U.S. Department of Health and Human Services - Center for Disease Control and Prevention. E-cigarette, or Vaping Products Visual Dictionary. Available from https://www.cdc.gov/tobacco/basic_information/e-cigarettes/pdfs/ecigarette-or-vaping-products-visual-dictionary-508.pdf**.
2. **National Center for Chronic Disease Prevention and Health Promotion (US) Office on Smoking and Health. E-Cigarette Use Among Youth and Young Adults: A Report of the Surgeon General [Internet]. Atlanta (GA): Centers for Disease Control and Prevention (US); 2016. Available from: https://www.ncbi.nlm.nih.gov/books/NBK538680/**.
3. **Principles of Tobacco and Nicotine Products, Including Electronic Products, of 2019. Issued by the Jordan Food and Drug Administration based on the Council of Ministers Decision No. 4569 of May 8, 2019, and Article 7(l) of Jordan Food and Drug Administration Law No. 41 of 2008. Available from https://assets.tobaccocontrollaws.org/uploads/legislation/Jordan/Jordan-JFDA-2019-Standard-native.pdf (Arabic) and https://assets.tobaccocontrollaws.org/uploads/legislation/Jordan/Jordan-JFDA-2019-Standard.pdf (English translation).**
4. Ravara S, Corrêa PC, Calheiros J, Pisinger C: **The public health impact of e-cigarette use: Revisiting Geoffrey Rose's prevention strategies**. *Pulmonology* 2023, **29**(6):452-454.
5. Reitsma MB, Kendrick PJ, Ababneh E, Abbafati C, Abbasi-Kangevari M, Abdoli A, Abedi A, Abhilash ES, Abila DB, Aboyans V *et al*: **Spatial, temporal, and demographic patterns in prevalence of smoking tobacco use and attributable disease burden in 204 countries and territories, 1990–2019: a systematic analysis from the Global Burden of Disease Study 2019**. *The Lancet* 2021, **397**(10292):2337-2360.
6. **World Health Organization. Tobacco. Available from https://www.who.int/news-room/fact-sheets/detail/tobacco#:~:text=Around%2080%25%20of%20the%20world's,(WHO%20FCTC)%20in%202003.**
7. Gilmore AB, Fooks G, Drope J, Bialous SA, Jackson RR: **Exposing and addressing tobacco industry conduct in low-income and middle-income countries**. *Lancet (London, England)* 2015, **385**(9972):1029-1043.
8. **World Health Organization. Jordan STEPS Survey 2007 Fact Sheet. 2007. Available from https://cdn.who.int/media/docs/default-source/ncds/ncd-surveillance/data-reporting/jordan/steps/2007-fact-sheet-jordan.pdf?sfvrsn=df1a70ea_2&download=true.** .
9. **World Health Organization. STEPwise Approach to NCD Risk Factor Surveillance (STEPS). 2019. Available from https://cdn.who.int/media/docs/default-source/ncds/ncd-surveillance/data-reporting/jordan/jordan-steps-2019-report---english.pdf?sfvrsn=ff35dbfa_1&download=true.** .
10. **Ministry of Health WHO, Centers for Disease Control and Prevention. GYTS Factsheet Jordan 2014. Geneva, Switzerland: World Health Organization; 2015.** .
11. **FCTC 2030 evaluation final report, October 2022. Available from https://fctc.who.int/who-fctc/development-assistance/fctc-2030**.
12. Abdel-Qader DH, Al Meslamani AZ: **Knowledge and Beliefs of Jordanian Community Toward E-cigarettes: A National Survey**. *Journal of community health* 2021, **46**(3):577-586.
13. Al-Sawalha NA, Almomani BA, Mokhemer E, Al-Shatnawi SF, Bdeir R: **E-cigarettes use among university students in Jordan: Perception and related knowledge**. *PloS one* 2021, **16**(12):e0262090.

14. Alaraj M, Altaif K, Almaaytah AMS, M.J., Kosinska I, Tabieh A: **E-cigarettes culture among university students in Jordan: a cross-sectional study.** . *Pharmacologyonline* 2021, **2**.
15. AlMuhaissen S, Mohammad H, Dabobash A, Nada MQ, Suleiman ZM: **Prevalence, Knowledge, and Attitudes among Health Professions Students toward the Use of Electronic Cigarettes**. *Healthcare (Basel, Switzerland)* 2022, **10**(12).
16. Benowitz NL: **The Central Role of pH in the Clinical Pharmacology of Nicotine: Implications for Abuse Liability, Cigarette Harm Reduction and FDA Regulation**. *Clinical pharmacology and therapeutics* 2022, **111**(5):1004-1006.
17. Zettler PJ, Hemmerich N, Berman ML: **Closing the Regulatory Gap for Synthetic Nicotine Products**. *Boston College law review Boston College Law School* 2018, **59**(6):1933-1982.
18. Stefaniak AB, Ranpara AC, Virji MA, LeBouf RF: **Influence of E-Liquid Humectants, Nicotine, and Flavorings on Aerosol Particle Size Distribution and Implications for Modeling Respiratory Deposition**. *Frontiers in public health* 2022, **10**.
19. **National Academies of Sciences, Engineering, and Medicine; Health and Medicine Division; Board on Population Health and Public Health Practice; Committee on the Review of the Health Effects of Electronic Nicotine Delivery Systems. Public Health Consequences of E-Cigarettes. Eaton DL, Kwan LY, Stratton K, editors. Washington (DC): National Academies Press (US); 2018 Jan 23. PMID: 29894118.** .
20. Margham J, McAdam K, Cunningham A, Porter A, Fiebelkorn S, Mariner D, Digard H, Proctor C: **The Chemical Complexity of e-Cigarette Aerosols Compared With the Smoke From a Tobacco Burning Cigarette**. *Front Chem* 2021, **9**:743060.
21. Bonner E, Chang Y, Christie E, Colvin V, Cunningham B, Elson D, Ghetu C, Huizenga J, Hutton SJ, Kolluri SK *et al*: **The chemistry and toxicology of vaping**. *Pharmacol Ther* 2021, **225**:107837.
22. Naeem MNM, Zain SMSM, Ng C, Noh MFM: **Chemical Constituents in E-Cigarette Liquids and Aerosols**. *Journal of Environmental Protection* 2020, **11**(09):664-681.
23. Miller DR, Buettner-Schmidt K, Orr M, Rykal K, Niewojna E: **A systematic review of refillable e-liquid nicotine content accuracy**. *Journal of the American Pharmacists Association : JAPhA* 2021, **61**(1):20-26.
24. Karasneh R, Al-Azzam S, Nusair M, Hawamdeh S: **Perceptions, symptoms, and practices of electronic cigarette users: Descriptive analysis and validation of Arabic short form vaping consequences questionnaire**. *PloS one* 2021, **16**(1):e0245443.
25. Barakat M, Assaf AM, Al-Qudah R, Thiab S, Alhamed M, Al-Obaidi HJ, Jirjees FJ, Basheti I: **Perception of adults toward electronic cigarettes: a cross-sectional study from Jordan**. *Primary health care research & development* 2021, **22**:e3.
26. Moola S, Tyagi J, Miller M, Gudi N, Pettigrew S, Bhaumik S: **The effects of e-cigarette advertising, promotion, and sponsorship on people's attitudes, beliefs and perceptions, intentions, and behaviours: a mixed methods systematic review. Sydney: The George Institute for Global Health. Available from https://www.georgeinstitute.org/sites/default/files/2022-06/Evaluation%20Report.pdf**. 2021.
27. Sharma A, McCausland K, Jancey J: **Adolescent's Health Perceptions of E-Cigarettes: A Systematic Review**. *American journal of preventive medicine* 2021, **60**(5):716-725.
28. McNeill A, Brose LS, Calder R, Hitchman SC, Hajek P, McRobbie H: **E-cigarettes: an evidence update A report commissioned by Public Health England. Available from https://assets.publishing.service.gov.uk/media/5b6c3f57ed915d30f140f822/Ecigarettes_an_evidence_update_A_report_commissioned_by_Public_Health_England_FINAL.pdf**; 2015.
29. **Burrowes KS, Beckert L, Jones S. Human lungs are created to breathe clean air: the questionable quantification of vaping safety "95% less harmful". N Z Med J. 2020 Jun 26;133(1517):100-106. PMID: 32595224.**

30. **E-cigarettes: Public Health England's evidence-based confusion**. *Lancet (London, England)* 2015, **386**(9996):829.
31. Eissenberg T, Bhatnagar A, Chapman S, Jordt SE, Shihadeh A, Soule EK: **Invalidity of an Oft-Cited Estimate of the Relative Harms of Electronic Cigarettes**. *American journal of public health* 2020, **110**(2):161-162.
32. Travis N, Knoll M, Cadham CJ, Cook S, Warner KE, Fleischer NL, Douglas CE, Sanchez-Romero LM, Mistry R, Meza R *et al*: **Health Effects of Electronic Cigarettes: An Umbrella Review and Methodological Considerations**. *International journal of environmental research and public health* 2022, **19**(15).
33. Skotsimara G, Antonopoulos AS, Oikonomou E, Siasos G, Ioakeimidis N, Tsalamandris S, Charalambous G, Galiatsatos N, Vlachopoulos C, Tousoulis D: **Cardiovascular effects of electronic cigarettes: A systematic review and meta-analysis**. *European journal of preventive cardiology* 2019:2047487319832975.
34. Critselis E, Panagiotakos D: **Impact of Electronic Cigarette use on Cardiovascular Health: Current Evidence, Causal Pathways, and Public Health Implications**. *Angiology* 2023:33197231161905.
35. Critcher CR, Siegel M: **Re-examining the Association Between E-Cigarette Use and Myocardial Infarction: A Cautionary Tale**. *American journal of preventive medicine* 2021, **61**(4):474-482.
36. Ashraf MT, Shaikh A, Khan MKS, Uddin N, Kashif MAB, Rizvi SHA, Khalid H, Sam SJ, Sohail A: **Association between e-cigarette use and myocardial infarction: a systematic review and meta-analysis**. *Egypt Heart J* 2023, **75**(1):97.
37. **Banks E, Yazidjoglou A, Brown S, Nguyen M, Martin M, Beckwith K, Daluwatta A, Campbell S, Joshy G. Electronic cigarettes and health outcomes: systematic review of global evidence. Report for the Australian Department of Health. National Centre for Epidemiology and Population Health, Canberra: April 2022. Available from https://openresearch-repository.anu.edu.au/bitstream/1885/262914/1/Electronic%20cigarettes%20health%20outcomes%20review_2022_WCAG.pdf**.
38. Berlowitz JB, Xie W, Harlow AF, Hamburg NM, Blaha MJ, Bhatnagar A, Benjamin EJ, Stokes AC: **E-Cigarette Use and Risk of Cardiovascular Disease: A Longitudinal Analysis of the PATH Study (2013-2019)**. *Circulation* 2022, **145**(20):1557-1559.
39. Mirbolouk M, Charkhchi P, Orimoloye OA, Uddin SMI, Kianoush S, Jaber R, Bhatnagar A, Benjamin EJ, Hall ME, DeFilippis AP *et al*: **E-Cigarette Use Without a History of Combustible Cigarette Smoking Among U.S. Adults: Behavioral Risk Factor Surveillance System, 2016**. *Annals of internal medicine* 2018.
40. Rose JJ, Krishnan-Sarin S, Exil VJ, Hamburg NM, Fetterman JL, Ichinose F, Perez-Pinzon MA, Rezk-Hanna M, Williamson E: **Cardiopulmonary Impact of Electronic Cigarettes and Vaping Products: A Scientific Statement From the American Heart Association**. *Circulation* 2023, **148**(8):703-728.
41. Chaffee BW, Barrington-Trimis J, Liu F, Wu R, McConnell R, Krishnan-Sarin S, Leventhal AM, Kong G: **E-cigarette use and adverse respiratory symptoms among adolescents and Young adults in the United States**. *Preventive medicine* 2021, **153**:106766.
42. Chaiton M, Pienkowski M, Musani I, Bondy SJ, Cohen JE, Dubray J, Eissenberg T, Kaufman P, Stanbrook M, Schwartz R: **Smoking, e-cigarettes and the effect on respiratory symptoms among a population sample of youth: Retrospective cohort study**. *Tobacco induced diseases* 2023, **21**:08.
43. Polosa R, Morjaria JB, Prosperini U, Russo C, Pennisi A, Puleo R, Caruso M, Caponnetto P: **Health effects in COPD smokers who switch to electronic cigarettes: a retrospective-prospective 3-year follow-up**. *International journal of chronic obstructive pulmonary disease* 2018, **13**:2533-2542.

44. Polosa R, Morjaria JB, Caponnetto P, Caruso M, Campagna D, Amaradio MD, Ciampi G, Russo C, Fisichella A: **Persisting long term benefits of smoking abstinence and reduction in asthmatic smokers who have switched to electronic cigarettes**. *Discovery medicine* 2016, **21**(114):99-108.
45. (2020) NCfCDPaHP: **Outbreak of lung injury associated with e-cigarette use, or vaping. Office on Smoking and Health. Available from https://www.cdc.gov/tobacco/basic_information/e-cigarettes/severe-lung-disease.html.** .
46. Friedman AS: **Association of vaping-related lung injuries with rates of e-cigarette and cannabis use across US states**. *Addiction (Abingdon, England)* 2021, **116**(3):651-657.
47. Baker MM, Procter TD, Belzak L, Ogunnaike-Cooke S: **Vaping-associated lung illness (VALI) in Canada: a descriptive analysis of VALI cases reported from September 2019 to December 2020**. *Health promotion and chronic disease prevention in Canada : research, policy and practice* 2022, **42**(1):37-44.
48. Sund LJ, Dargan PI, Archer JRH, Wood DM: **E-cigarette or vaping-associated lung injury (EVALI): a review of international case reports from outside the United States of America**. *Clinical toxicology (Philadelphia, Pa)* 2023, **61**(2):91-97.
49. **Interview with Dr. Feras Hawari about the first EVALI case in Jordan. Available from https://www.youtube.com/watch?v=SyuG8gvr8BA.** ; 2019.
50. Banks E, Martin M, Harris M: **Framework for the public health assessment of electronic cigarettes**. *Tobacco control* 2022, **31**(5):608-614.
51. Benowitz NL: **Nicotine addiction**. *The New England journal of medicine* 2010, **362**(24):2295-2303.
52. Prochaska JJ, Benowitz NL: **Current advances in research in treatment and recovery: Nicotine addiction**. *Sci Adv* 2019, **5**(10):eaay9763.
53. Hajek P, Przulj D, Phillips A, Anderson R, McRobbie H: **Nicotine delivery to users from cigarettes and from different types of e-cigarettes**. *Psychopharmacology* 2017, **234**(5):773-779.
54. Diaz MC, Silver NA, Bertrand A, Schillo BA: **Bigger, stronger and cheaper: growth in e-cigarette market driven by disposable devices with more e-liquid, higher nicotine concentration and declining prices**. *Tobacco control* 2023.
55. DiPiazza J, Caponnetto P, Askin G, Christos P, Maglia MLP, Gautam R, Roche S, Polosa R: **Sensory experiences and cues among E-cigarette users**. *Harm reduction journal* 2020, **17**(1):75.
56. Leventhal AM, Madden DR, Peraza N, Schiff SJ, Lebovitz L, Whitted L, Barrington-Trimis J, Mason TB, Anderson MK, Tackett AP: **Effect of Exposure to e-Cigarettes With Salt vs Free-Base Nicotine on the Appeal and Sensory Experience of Vaping: A Randomized Clinical Trial**. *JAMA network open* 2021, **4**(1):e2032757.
57. Hammond D, Reid JL, Rynard VL, O'Connor RJ, Goniewicz ML, Piper ME, Bansal-Travers M: **Indicators of dependence and efforts to quit vaping and smoking among youth in Canada, England and the USA**. *Tobacco control* 2021.
58. Smets J, Baeyens F, Chaumont M, Adriaens K, Van Gucht D: **When Less is More: Vaping Low-Nicotine vs. High-Nicotine E-Liquid is Compensated by Increased Wattage and Higher Liquid Consumption**. *International journal of environmental research and public health* 2019, **16**(5).
59. Wadkin R, Allen C, Fearon IM: **E-cigarette puffing topography: The importance of assessing user behaviour to inform emissions testing**. *Drug testing and analysis* 2023, **15**(10):1222-1232.
60. Mahajan SD, Homish GG, Quisenberry A: **Multifactorial Etiology of Adolescent Nicotine Addiction: A Review of the Neurobiology of Nicotine Addiction and Its Implications for Smoking Cessation Pharmacotherapy**. *Frontiers in public health* 2021, **9**:664748.
61. Goriounova NA, Mansvelder HD: **Short- and long-term consequences of nicotine exposure during adolescence for prefrontal cortex neuronal network function**. *Cold Spring Harb Perspect Med* 2012, **2**(12):a012120.

62. Yuan M, Cross SJ, Loughlin SE, Leslie FM: **Nicotine and the adolescent brain**. *The Journal of physiology* 2015, **593**(16):3397-3412.
63. Ren M, Lotfipour S: **Nicotine Gateway Effects on Adolescent Substance Use**. *The western journal of emergency medicine* 2019, **20**(5):696-709.
64. Xie C, Xie Z, Li D: **Association of electronic cigarette use with self-reported difficulty concentrating, remembering, or making decisions in US youth**. *Tobacco induced diseases* 2020, **18**:106.
65. Becker TD, Arnold MK, Ro V, Martin L, Rice TR: **Systematic Review of Electronic Cigarette Use (Vaping) and Mental Health Comorbidity Among Adolescents and Young Adults**. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco* 2021, **23**(3):415-425.
66. Kim JY, Kang HS, Jung JW, Jung SY, Park HJ, Park JS, Park JH, Lee SH, Chun EM, Park DI *et al*: **Nicotine Dependence and Stress Susceptibility in E-Cigarette Smokers: The Korea National Health and Nutrition Examination Survey 2013-2017**. *Tuberc Respir Dis (Seoul)* 2021, **84**(2):159-166.
67. Javed S, Usmani S, Sarfraz Z, Sarfraz A, Hanif A, Firoz A, Baig R, Sharath M, Walia N, Cherrez-Ojeda I *et al*: **A Scoping Review of Vaping, E-Cigarettes and Mental Health Impact: Depression and Suicidality**. *Journal of community hospital internal medicine perspectives* 2022, **12**(3):33-39.
68. Adzrago D, Fujimoto K, Harrell MB, Jones A, Wilkerson JM: **Association between e-cigarette use behaviors and perceived harmfulness of e-cigarettes and anxiety/depression symptoms among Black/African American Adults**. *Preventive medicine reports* 2023, **31**:102080.
69. Bautista M, Mogul AS, Fowler CD: **Beyond the label: current evidence and future directions for the interrelationship between electronic cigarettes and mental health**. *Frontiers in psychiatry* 2023, **14**:1134079.
70. Khan AM, Ahmed S, Sarfraz Z, Farahmand P: **Vaping and Mental Health Conditions in Children: An Umbrella Review**. *Substance abuse : research and treatment* 2023, **17**:11782218231167322.
71. Tran DD, Davis JP, Ring C, Wang J, Fitzke RE, Leventhal AM, Pedersen ER: **Associations between depression, stress, and e-cigarette use among OEF/OIF veterans**. *Mil Psychol* 2023, **35**(3):245-251.
72. Wang Y, Sung HY, Lea Watkins S, Lightwood J, Yao T, Max W: **The association of current exclusive e-cigarette use and dual use of e-cigarettes and cigarettes with psychological distress among U.S. adults**. *Preventive medicine reports* 2023, **36**:102425.
73. **Felberbaum, M. August 2019. FDA In Brief: FDA encourages continued submission of reports related to seizures following e-cigarette use as part of agency's ongoing scientific investigation of potential safety issue. Available from https://www.fda.gov/news-events/fda-brief/fda-brief-fda-encourages-continued-submission-reports-related-seizures-following-e-cigarette-use.** . 2019.
74. Faulcon LM, Rudy S, Limpert J, Wang B, Murphy I: **Adverse Experience Reports of Seizures in Youth and Young Adult Electronic Nicotine Delivery Systems Users**. *The Journal of adolescent health : official publication of the Society for Adolescent Medicine* 2020, **66**(1):15-17.
75. Zahedi A, Phandthong R, Chaili A, Remark G, Talbot P: **Epithelial-to-mesenchymal transition of A549 lung cancer cells exposed to electronic cigarettes**. *Lung cancer (Amsterdam, Netherlands)* 2018, **122**:224-233.
76. Schaal CM, Bora-Singhal N, Kumar DM, Chellappan SP: **Regulation of Sox2 and stemness by nicotine and electronic-cigarettes in non-small cell lung cancer**. *Molecular cancer* 2018, **17**(1):149.

77. Yu V, Rahimy M, Korrapati A, Xuan Y, Zou AE, Krishnan AR, Tsui T, Aguilera JA, Advani S, Crotty Alexander LE *et al*: **Electronic cigarettes induce DNA strand breaks and cell death independently of nicotine in cell lines**. *Oral oncology* 2016, **52**:58-65.
78. Tommasi S, Blumenfeld H, Besaratinia A: **Vaping Dose, Device Type, and E-Liquid Flavor are Determinants of DNA Damage in Electronic Cigarette Users**. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco* 2023, **25**(6):1145-1154.
79. Herzog C, Jones A, Evans I, Raut JR, Zikan M, Cibula D, Wong A, Brenner H, Richmond RC, Widschwendter M: **Cigarette smoking and e-cigarette use induce shared DNA methylation changes linked to carcinogenesis**. *Cancer Res* 2024.
80. Raj AT, Sujatha G, Muruganandhan J, Kumar SS, Bharkavi SI, Varadarajan S, Patil S, Awan KH: **Reviewing the oral carcinogenic potential of E-cigarettes using the Bradford Hill criteria of causation**. *Transl Cancer Res* 2020, **9**(4):3142-3152.
81. Vivarelli F, Granata S, Rullo L, Mussoni M, Candeletti S, Romualdi P, Fimognari C, Cruz-Chamorro I, Carrillo-Vico A, Paolini M *et al*: **On the toxicity of e-cigarettes consumption: Focus on pathological cellular mechanisms**. *Pharmacol Res* 2022, **182**:106315.
82. Braillon A, Lang AE: **The International Agency for Research on Cancer and e-cigarette carcinogenicity: time for an evaluation**. *European journal of epidemiology* 2023, **38**(4):391.
83. Herbst RS, Hatsukami D, Acton D, Giuliani M, Moushey A, Phillips J, Sherwood S, Toll BA, Viswanath K, Warren NJH *et al*: **Electronic Nicotine Delivery Systems: An Updated Policy Statement from the American Association for Cancer Research and the American Society of Clinical Oncology**. *Clinical cancer research : an official journal of the American Association for Cancer Research* 2022, **28**(22):4861-4870.
84. **American Cancer Society Position Statement on Electronic Cigarettes. Available from https://www.cancer.org/cancer/risk-prevention/tobacco/e-cigarettes-vaping/e-cigarette-position-statement.html**.
85. King JL, Reboussin BA, Wiseman KD, Ribisl KM, Seidenberg AB, Wagoner KG, Wolfson M, Sutfin EL: **Adverse symptoms users attribute to e-cigarettes: Results from a national survey of US adults**. *Drug and alcohol dependence* 2019, **196**:9-13.
86. King JL, Reboussin BA, Merten JW, Wiseman KD, Wagoner KG, Sutfin EL: **Negative health symptoms reported by youth e-cigarette users: Results from a national survey of US youth**. *Addictive behaviors* 2020, **104**:106315.
87. Amanian A, Phulka J, Hu AC: **Unintended Side Effects of Electronic Cigarettes in Otolaryngology: A Scoping Review**. *Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery* 2023, **168**(1):7-13.
88. Obertova N, Navratil T, Zak I, Zakharov S: **Acute exposures to e-cigarettes and heat-not-burn products reported to the Czech Toxicological Information Centre over a 7-year period (2012-2018)**. *Basic & clinical pharmacology & toxicology* 2020, **127**(1):39-46.
89. Wang RJ, Bhadriraju S, Glantz SA: **E-Cigarette Use and Adult Cigarette Smoking Cessation: A Meta-Analysis**. *American journal of public health* 2021, **111**(2):230-246.
90. Lindson N, Butler AR, McRobbie H, Bullen C, Hajek P, Begh R, Theodoulou A, Notley C, Rigotti NA, Turner T *et al*: **Electronic cigarettes for smoking cessation**. *The Cochrane database of systematic reviews* 2024, **1**(1).
91. Theodoulou A, Chepkin SC, Ye W, Fanshawe TR, Bullen C, Hartmann-Boyce J, Livingstone-Banks J, Hajizadeh A, Lindson N: **Different doses, durations and modes of delivery of nicotine replacement therapy for smoking cessation**. *The Cochrane database of systematic reviews* 2023, **6**(6):Cd013308.
92. Lindson N, Theodoulou A, Ordóñez-Mena JM, Fanshawe TR, Sutton AJ, Livingstone-Banks J, Hajizadeh A, Zhu S, Aveyard P, Freeman SC *et al*: **Pharmacological and electronic cigarette**

interventions for smoking cessation in adults: component network meta-analyses. *The Cochrane database of systematic reviews* 2023, **9**(9):Cd015226.
93. Hanewinkel R, Niederberger K, Pedersen A, Unger JB, Galimov A: **E-cigarettes and nicotine abstinence: a meta-analysis of randomised controlled trials**. *European respiratory review : an official journal of the European Respiratory Society* 2022, **31**(163).
94. Hajek P, Phillips-Waller A, Przulj D, Pesola F, Myers Smith K, Bisal N, Li J, Parrott S, Sasieni P, Dawkins L *et al*: **A Randomized Trial of E-Cigarettes versus Nicotine-Replacement Therapy**. *The New England journal of medicine* 2019.
95. Myers Smith K, Phillips-Waller A, Pesola F, McRobbie H, Przulj D, Orzol M, Hajek P: **E-cigarettes versus nicotine replacement treatment as harm reduction interventions for smokers who find quitting difficult: randomized controlled trial**. *Addiction (Abingdon, England)* 2022, **117**(1):224-233.
96. Auer R, Schoeni A, Humair JP, Jacot-Sadowski I, Berlin I, Stuber MJ, Haller ML, Tango RC, Frei A, Strassmann A *et al*: **Electronic Nicotine-Delivery Systems for Smoking Cessation**. *The New England journal of medicine* 2024, **390**(7):601-610.
97. **Physicians for a Smoke-free Canada. The continuing divide on E-cigarettes for smoking cessation: Part 1 – research findings, April 18, 2023. Available from https://smoke-free.ca/the-continuing-divide-on-e-cigarettes-for-smoking-cessation-part-1-research-findings/**.
98. **Jordan Tobacco Dependence Treatment Guidelines, 2020. Available from https://www.khcc.jo/uploads/2020/10/jordan-tdt-guidelines-english.pdf and https://www.khcc.jo/uploads/2019/10/khccbookletsmokingaddiction.pdf**.
99. **Jordanian Ministry of Health. https://www.moh.gov.jo/AR/Pages/smoking**
100. Warner KE, Benowitz NL, McNeill A, Rigotti NA: **Nicotine e-cigarettes as a tool for smoking cessation**. *Nature medicine* 2023.
101. Coleman SRM, Piper ME, Byron MJ, Bold KW: **Dual Use of Combustible Cigarettes and E-cigarettes: a Narrative Review of Current Evidence**. *Current addiction reports* 2022, **9**(4):353-362.
102. Pisinger C, Rasmussen SKB: **The Health Effects of Real-World Dual Use of Electronic and Conventional Cigarettes versus the Health Effects of Exclusive Smoking of Conventional Cigarettes: A Systematic Review**. *International journal of environmental research and public health* 2022, **19**(20).
103. Chen G, Rahman S, Lutfy K: **E-cigarettes may serve as a gateway to conventional cigarettes and other addictive drugs**. *Advances in Drug and Alcohol Research* 2023, **3**.
104. Lee PN, Coombs KJ, Afolalu EF: **Considerations related to vaping as a possible gateway into cigarette smoking: an analytical review**. *F1000Res* 2018, **7**:1915.
105. Martinelli T, Candel M, de Vries H, Talhout R, Knapen V, van Schayck CP, Nagelhout GE: **Exploring the gateway hypothesis of e-cigarettes and tobacco: a prospective replication study among adolescents in the Netherlands and Flanders**. *Tobacco control* 2023, **32**(2):170-178.
106. Delnevo CD: **e-Cigarette and Cigarette Use Among Youth: Gateway or Common Liability?** *JAMA network open* 2023, **6**(3):e234890.
107. Khouja JN, Suddell SF, Peters SE, Taylor AE, Munafo MR: **Is e-cigarette use in non-smoking young adults associated with later smoking? A systematic review and meta-analysis**. *Tobacco control* 2020, **30**(1):8-15.
108. Ranabhat CL, Kim CB, Park MB, Jakovljevic MM: **Situation, Impacts, and Future Challenges of Tobacco Control Policies for Youth: An Explorative Systematic Policy Review**. *Frontiers in pharmacology* 2019, **10**:981.

109. Choi K, Omole T, Wills T, Merianos AL: **E-cigarette-inclusive smoke-free policies, excise taxes, tobacco 21 and changes in youth e-cigarette use: 2017-2019**. *Tobacco control* 2022, **31**(6):758-761.
110. Watson LK, Weldon I, Lin GO, Nanyangwe-Moyo T, Hoffman SJ, Poirier MJP: **Beyond MPOWER: a systematic review of population-level factors that affect European tobacco smoking rates**. *European journal of public health* 2023, **33**(5):851-856.
111. de Looze ME, Henking C, Torsheim T, Currie DB, Weber MW, Alemán-Díaz AY: **The association between MPOWER tobacco control policies and adolescent smoking across 36 countries: An ecological study over time (2006-2014)**. *The International journal on drug policy* 2022, **109**:103871.
112. Özmen MU: **Causal Effect of Education on Tobacco Use in Low-and-Middle-Income Countries**. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco* 2023, **25**(8):1474-1480.
113. **WHO. 2016 (Nov). Electronic Nicotine Delivery Systems and Electronic Non-Nicotine Delivery Systems (ENDS/ENNDS). Pages 6-7. Available from https://fctc.who.int/publications/m/item/fctc-cop-7-11-electronic-nicotine-delivery-systems-and-electronic-non-nicotine-delivery-systems-(ends-ennds)**.
114. **The Jordan Times, May 2019. JFDA catches dozens of tobacco shops for illicit e-cigarette dealings. Available from https://www.jordantimes.com/news/local/jfda-catches-dozens-tobacco-shops-illicit-e-cigarette-dealings**.
115. **Internal Document of a Market Analysis, 2018/2019. Cancer Control Office, King Hussein Cancer Center. Details available upon request.**
116. **Jordanian Food and Drug Administration (JFDA) 2019.** بما فيها الأسس الخاصة بمنتجات التبغ والنيكوتين الالكترونية لسنة 2019**. Available from http://www.jfda.jo/Pages/viewpage.aspx?pageID=153 (http://www.jfda.jo/EchoBusV3.0/SystemAssets/PDF/AR/LawsAndRegulation/%20Unit%20of%20Tobacco%20and%20Nicotine/Tobacco,%20nicotine%20and%20electronic%20cigarette/%D8%A7%D9%84%D8%A7%D8%B3%D8%B3%20%D8%A7%D9%84%D8%AE%D8%A7%D8%B5%D8%A9%20%D8%A8%D8%A7%D9%84%D8%AA%D8%A8%D8%BA%20%D9%88%D8%A7%D9%84%D9%86%D9%8A%D9%83%D9%88%D8%AA%D9%8A%D9%86.pdf)**
117. **Jordanian Food and Drug Administration (JFDA). Tobacco Unit. http://www.jfda.jo/Pages/viewpage.aspx?pageID=371**.
118. **Jordan News Agency, December 2021. Available from https://petra.gov.jo/Include/InnerPage.jsp?ID=166735&lang=ar&name=news**.
119. **Scientific Committee on Health, Environmental and Emerging Risks. SCHEER Opinion on electronic cigarettes, 2021. Available from https://health.ec.europa.eu/system/files/2022-08/scheer_o_017.pdf**.
120. **Jordanian Food and Drug Administration (JFDA) 2019.** شروط عرض وبيع وتخزين منتجات البخار الالكترونية والسائل الالكتروني ومنتجات التبغ المسخنة الكترونيا**. Available from http://www.jfda.jo/EchoBusV3.0/SystemAssets/PDF/AR/LawsAndRegulation/%20Unit%20of%20Tobacco%20and%20Nicotine/%D8%B4%D8%B1%D9%88%D8%B7%20%D8%B9%D8%B1%D8%B6%20%D9%88%D8%A8%D9%8A%D8%B9%20%D9%85%D9%86%D8%AA%D8%AC%D8%A7%D8%AA%20%D8%A7%D9%84%D8%AA%D8%A8%D8%BA.pdf**
121. **Addustour, Nov 2021.** السيجارة الالكترونية تغزو الأسواق وتهدد صحة الأردنيين **Available from https://www.addustour.com/articles/1249163**.
122. **Alhayat news. 2019 (April, 7).** تجارة السجائر الالكترونية في بعض المدارس**. Available from https://alhayatnews.net/2019/04/%D8%AA%D8%AC%D8%A7%D8%B1%D8%A9-%D8%A7%D9%84%D8%B3%D8%AC%D8%A7%D8%A6%D8%B1-**

%D8%A7%D9%84%D8%A5%D9%84%D9%83%D8%AA%D8%B1%D9%88%D9%86%D9%8A%D8%A9-%D9%81%D9%8A-%D8%A8%D8%B9%D8%B6-%D8%A7%D9%84%D9%85%D8%AF/.
123. **Tobacco Free Jordan, Cancer Control Office (King Hussein Cancer Center). Protecting Jordanian School Children from Tobacco Advertising Tactics Report, 2023. Report available upon request.** .
124. **Campaign for Tobacco-Free Kids. Tobacco Control Laws: Jordan. Available from https://www.tobaccocontrollaws.org/legislation/jordan/laws**
125. Bhatnagar A, Whitsel LP, Blaha MJ, Huffman MD, Krishan-Sarin S, Maa J, Rigotti N, Robertson RM, Warner JJ: **New and Emerging Tobacco Products and the Nicotine Endgame: The Role of Robust Regulation and Comprehensive Tobacco Control and Prevention: A Presidential Advisory From the American Heart Association**. *Circulation* 2019:Cir0000000000000669.
126. O'Connor R, Schneller LM, Felicione NJ, Talhout R, Goniewicz ML, Ashley DL: **Evolution of tobacco products: recent history and future directions**. *Tobacco control* 2022, **31**(2):175-182.
127. **U.K. Department of Health and Social Care. Policy paper. Stopping the start: our new plan to create a smokefree generation. Updated 8 November 2023. Available from https://www.gov.uk/government/publications/stopping-the-start-our-new-plan-to-create-a-smokefree-generation/stopping-the-start-our-new-plan-to-create-a-smokefree-generation**.
128. **Australian Government Department of Health and Aged Care, Therapeutic Goods Administration. TGA confirms nicotine e-cigarette access is by prescription only (Dec, 2020). Available from https://www.tga.gov.au/news/media-releases/tga-confirms-nicotine-e-cigarette-access-prescription-only**
129. **Smith M, Hilton S. Global Regulatory Approaches towards E-Cigarettes, Key Arguments, and Approaches Pursued [Internet]. Sustainable Development. IntechOpen; 2022. Available from: http://dx.doi.org/10.5772/intechopen.107343**. 2022.
130. Stone E, Marshall H: **Tobacco and electronic nicotine delivery systems regulation**. *Translational lung cancer research* 2019, **8**(Suppl 1):S67-S76.
131. **UK Department of Health and Social Care, Press Release (Jan 28, 2024): Disposable vapes banned to protect children's health. https://www.gov.uk/government/news/disposable-vapes-banned-to-protect-childrens-health**.
132. **Draft Environmental Protection (Single-use Vapes) (Scotland) Regulations 2024.**

Published 23 February 2024. Available from https://www.gov.scot/publications/environmental-protection-single-use-vapes-scotland-regulations-2024/.
133. **World Health Organization. Electronic cigarettes: call to action. 14 December 2023. Technical note on call to action. Available from https://cdn.who.int/media/docs/default-source/tobacco-hq/regulating-tobacco-products/ends-call-to-action-background.pdf?sfvrsn=7dd2856e_11&download=true**
134. Soule E, Bansal-Travers M, Grana R, McIntosh S, Price S, Unger JB, Walton K: **Electronic cigarette use intensity measurement challenges and regulatory implications**. *Tobacco control* 2023, **32**(1):124-129.
135. **Harm Reduction, Tobacco Tactics, updated 22 November 2022, accessed 23 November 2023. Available from https://tobaccotactics.org/article/harm-reduction/**.
136. Seaman EL, Chandora R: **The Importance of Global Youth E-Cigarette Use Surveillance: Opportunities and Next Steps**. *American journal of public health* 2022, **112**(4):541-543.
137. Barnes C, Yoong SL, Stockings E, Bialek C, Wolfenden L: **The need for an evidence surveillance system to inform the public health response to e-cigarette use in youth**. *Australian and New Zealand journal of public health* 2023, **47**(3):100060.

138. **The Population Assessment of Tobacco and Health (PATH) Study. Available from https://nida.nih.gov/sites/default/files/PATH-StudyInfographic.pdf**.