Bourke L, Bauld L, Bullen C, Cumberbatch M, Giovannucci E, Islami F, McRobbie H, Silverman DT & Catto JWF (2017) E-cigarettes and Urologic Health: A Collaborative Review of Toxicology, Epidemiology, and Potential Risks, *European Urology*, 71 (6), pp. 915-923.

DOI: 10.1016/j.eururo.2016.12.022

Manuscript type: Invited collaborative review

Title: E-cigarettes and Urological Health: Toxicology, Epidemiology and Potential Risks: a collaborative review

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Accepted for publication in *European Urology* published by Elsevier.

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Manuscript Word Count: 4441

Abstract Word Count: 287

Keywords: electronic cigarettes, smoking cessation, toxicology, urological health

Abstract

Context: Use of electronic cigarettes (ECs) is on the rise in most high income countries. Smoking conventional cigarettes is a known risk factor for urological malignancy incidence, progression and mortality as well as for other urological health indicators. The potential impact of EC use on urological health is therefore of clinical interest to the urology community.

Objective: To review the available data on current EC use including potential benefits in urological patients, potential issues linked to toxicology of EC constituents and how this might translate into urological health risks.

Evidence Acquisition: A Medline search was carried out in August 2016 for studies reporting urological health outcomes and EC use. Snowballing techniques were also used to identify relevant studies from recent systematic reviews. A narrative synthesis of data around EC health outcomes, toxicology, potential use in smoking cessation and health policy was carried out.

Evidence synthesis: We found no studies to date that have been specifically designed to assess prospectively urological health risks, even in an observational setting. Generating such data would be an important contribution to the debate on the role of ECs in public health and clinical practice. There is evidence from a recent Cochrane review of RCTs that ECs can support smoking cessation. There are emerging data around potentially harmful components of ECs such as tobacco-specific nitrosamines, polyaromatic hydrocarbons and heavy metals could be linked to possible urological health risks.

Conclusions: ECs might be a useful tool to encourage conventional cigarette smoking cessation. However, data collection around EC specific impact on urological health is needed to clarify the possible patient benefit, outcomes and adverse events.

Patient summary: Whilst ECs might help some people to stop smoking, their overall impact on urological health is not clear.

1. Introduction

Tobacco smoking is an established cause of bladder and kidney cancer (50% and 20% of incident cases, respectively [1]). For people who smoke, there are clear benefits of quitting. For people who don't smoke, or would never have started smoking in the absence of EC, there are potential risks. As such, it is important for urologists and urological health researchers to understand the possible implications of EC use in urology patients.[2]

1.1 What are e-cigarettes?

Electronic cigarettes (ECs) are battery-powered devices that all work by heating a liquid ('e-liquid') to create an aerosol that is then inhaled. The aerosol produced is more commonly referred to as vapour, and the use of the device as 'vaping'. Some are designed to resemble traditional cigarettes ('cigalikes' or first generation products), whereas newer generation (tank systems) are modular and can be personalised. The cigalike devices are closed systems and are, generally, not refillable. They may be made for single use (i.e. disposable) or they can have a rechargeable battery and replaceable cartridges that contain the heating coil (or atomizer) and liquid. The newer generation products are generally greater in size and consist of a high capacity lithium battery, sometimes with variable power, an atomizer, and a tank that the user fills with liquid. The atomizer is usually manually activated, which gives greater control over vapour production than the automated systems. Most people start out using a cigalike device, but regular vapers generally use tank system ECs [3].

There are three main components of the e-liquid; propylene glycol or glycerol or a mix of these, nicotine, and flavouring. The propylene glycol/glycerol mix is important for user satisfaction (e.g. a high propylene glycol content gives a greater 'throat hit'), but may also be important for nicotine delivery.[4] Nicotine concentrations vary from 0 to 36mg/ml, with 18mg/ml being the most commonly used.[5, 6] However the European Tobacco Products Directive, which came into effect on 20 May 2016, now limits the concentration to a maximum of 20mg/ml. The directive also restricts the volume of bottles of e-liquid to 10ml and volume of EC tanks to 2ml, as well as a number of other measures including restrictions on advertising and promotions and packaging and labelling requirements. EC liquid (e-liquid) is available in numerous flavours, which are important for user satisfaction. In Great Britain, the most commonly used flavour by current vapers is tobacco, followed by fruit and mint/menthol flavours.[3] The flavours used are considered safe for oral ingestion, but the effects of heating these and then inhaling them are unknown. Some flavours appear to be more cytotoxic than others (e.g. strawberry [7] and cinnamon [8]) and associated with increased risk of respiratory disease (e.g. diacetyl, [9] which gives a buttery flavour).

Heating nicotine-containing e-liquid produces nicotine-containing vapour; however, the association between the concentration of nicotine in the e-liquid and in vapour is inconsistent. Other factors such as heating of the liquid, voltage and amperage resistance, and how the user inhales on the EC also have a role to play. ECs also do not deliver as much nicotine on a puff by puff basis as standard cigarettes.[10] Therefore, vapers typically take longer puffs than with standard cigarettes (e.g. a mean of 2.4 seconds for conventional cigarettes versus 4.3 seconds for ECs).[11]

1.2. Epidemiology/demographics around EC use

Since being introduced, the prevalence of EC use has seen a relatively rapid increase in many high-income countries from which national longitudinal data are available, notably North American and European countries. For example, the prevalence of ever-use among individuals aged ≥15 years in 27 states of the European Union increased from 7.2% in 2012 to 11.9% in 2014 (Table 1).[12] On average, 15.3% of ever e-cigarette users became current users in 2014. The greatest increases in the European Union occurred in Malta (5.5% increase), Ireland (5.1%), Sweden (4.5%), and France (4.3%). In that survey, the lowest prevalence in 2014 was reported from Portugal (5.7%), whereas the prevalence was 10% or more in 15 countries, with the highest prevalence in France (21.3%).[12] Experimenting and ever use of ECs is generally common among youth,[13] but in Europe, prevalence of regular EC use is much higher in older adults who smoke. In 2014, prevalence of ever EC use in individuals aged ≥15 years in the United Kingdom was 15.5%, and approximately one quarter of them transitioned to current users.[12] Among adolescents aged 11–18 years in Great Britain, prevalence of ever use of ECs in 2014 was 8.2%, while it was 1.7% for monthly or more use.[14]

On the other hand, prevalence of more regular use is higher in youth than older adults in North America. In 2013, 8.5% and 1.8% of Canadians reported ever and current (past 30-day) use of ECs, respectively.[15] The highest prevalence of current use was in age 20–24 (3.9%), followed by age 15–19 (2.6%).[15] In the United States, the prevalence of current use among individuals aged ≥18 years in 2013–2014 was 3.3%.[16] However, there has been a substantial increase in ECs use among high-school students in the United States, with current use prevalence increasing from 1.5% in 2011 to 16.0% in 2015.[17] The recent US

Surgeon General's report warned that in 2014, current use of ECs by young adults 18–24 years of age surpassed that of adults 25 years of age and older. The report points to potentially harmful constituents of ECs: particularly nicotine which can lead to addiction and can harm the developing adolescent brain.[18]

Information on EC use at the national level from countries in other regions is limited. In a survey of Chinese adults (age 15–65 years) in Hong Kong in 2014, the prevalence of ever EC use was 2.3%.[19] Among individuals aged ≥15 years in New Zealand in 2014, 13.1% had ever used ECs and only 0.8% were current users. The highest prevalence of current use was in age 22–44 years (1.2%), followed by age ≥45 (0.7%).[20] Prevalence of ever and current use of ECs among students aged 13–18 years in South Korea in 2011 was 9.4% and 1.4%, respectively.[21] Since 2011, questions on ECs use have been added to the Global Adult Tobacco Survey (GATS), which is a nationally representative household survey of individuals aged ≥15 years in a number of countries.[22] The prevalence of current EC use in four countries with available data was 0.3% in Indonesia and 0.8% in Malaysia in 2011 and 0.9% in Qatar and 1.9% in Greece in 2013.[22] It should be noted that due to rapid changes in prevalence of EC use in some countries, prevalence of use across countries, especially among youth, may not be comparable using results of surveys conducted in different years.

EC use has the potential to help smokers to quit cigarette smoking or reduce smoking intensity.[23] However, one of the primary concerns of EC use is the maintenance of tobacco use in current smokers (without any substantial decrease in smoking intensity), re-initiation in former smokers, and in particular, nicotine dependence in adolescents,[24-28] as EC user adolescents may show a higher intention to smoke traditional cigarettes.[25, 27]

However, in many countries, the rate of EC use by never-smokers or smoking initiation following EC use has been relatively low, although there might be some variations across countries. In a survey conducted in 2014 in the European Union, initiation of tobacco use by using ECs was reported by 0.8% of participants who had used any tobacco product. Use of nicotine-containing EC among never smokers was low (1.3%), with 0.09% reporting daily use.[29] The prevalence of current EC use among never-smokers in 2013 was 0.3% in Canada [15] and 1.4% in the United States.[26] Among adolescents, EC use at least monthly was reported by only 0.2% of adolescents aged 11–18 years in Great Britain in 2014.[14] Among middle and high school students in the United States in 2011–2013, prevalence of current EC use was 0.3% among never smokers.[24] Prevalence of ever and current use of ECs only (no other tobacco products) in age 13–18 years in South Korea in 2011 was 1.4% and 1.1%, respectively.[21] Despite low rates of ECs use among never smoker adolescents, this group could include a substantial number of children, as generally prevalence of tobacco smoking in this age group is low. For example, the group of never smoker students that were current ECs users (0.3% of never smokers) in the United States in 2013 included 263,000 children.[24]

2. Evidence acquisition

In order to identify any eligible trials addressing EC use and urological health outcomes, a search of the electronic databases MEDLINE was carried out from inception to August 2016. MEDLINE search terms were (e-cigarette or electronic-cigarette) AND (bladder or prostate or kidney or urol*). In addition to database searches, recent systematic reviews of EC use were hand searched for any potentially eligible trials. To add context to the any available trials data, evidence around smoking

cessation, available toxicology data and health policy around EC regulations are presented in this review. Quality appraisal was done subjectively according to expertise and clinical judgement of the authors. Given that EC use and urological outcomes is an emerging clinical issue with a fragmentary evidence base and involves rapidly evolving technologies, a narrative synthesis of these data was undertaken.[30]

3. Evidence synthesis

3.1 Current urological health outcomes and trials of EC use

We found no published clinical studies, which are *a priori* designed to evaluate the impact of ECs on urological health outcomes. We were able to find only one published protocol for a prospective observational study that will document hospitalizations and adverse events that could report urological health outcomes (although not specifically designed to do this).[31]

3.2 Toxicity data and potential urological health impacts from ECs

ECs were introduced into the US and UK markets in 2007 [32] and so their long-term health risks are not yet clear. Reducing the use of conventional cigarettes has numerous obvious health benefits including links to incidence and progression of urological malignancies [33] and complications after primary treatment for urological cancer.[34] EC operation does not involve combustion and so no smoke or other harmful combustion products, such as tar and carbon monoxide, are formed. Reduced excretion of tobacco-specific nitrosamines and other carcinogens has been found in the urine of vapers compared with smokers. [35, 36] ECs are thought to be much safer for long-term health by the public than traditional tobacco cigarettes.[37] It is however, important to recognise that these devices are not entirely benign. Due to the nature and components of these devices, ECs have a diverse hazard

profile. Operation of EC at high temperatures can generate relatively high levels of aldehydes [38, 39], which have carcinogenic potential. However vapers naturally avoid this, as it creates an unpleasant taste (commonly known as a ‘dry puff’)[39, 40]. A recent systematic review highlighted adverse events linked between EC use and the respiratory, gastrointestinal, cardiovascular, neurological and immune system; serious leg burns due to exposure of the battery; serious oral burns, lacerations and fractures from an account of an EC 'explosion'; both accidental and intentional nicotine overdoses (suicide attempts).[41]

Data regarding the constituents of ECs is evolving in the literature. Levels of each component can be varied (e.g. Allen et al (2016) describe over 7000 flavours[42]) and there is heterogeneity amongst manufacturers.[43] For example, nicotine levels were seen to vary from 0 mg/ml to 87 mg/ml across studies, and there were reported deviations from the device label of ingredients of up to 100%.[43] Furthermore, there is inconsistency in the delivery of chemicals within each puff from the same device or brand. This may be due to subtle differences in the size of particulate matter within each refill solution and the delivery system that is used.

A recent review describes chemical profiles of EC solutions, cartridges, aerosols and environmental emissions.[43] Whilst ECs are designed to be devoid of tar, some ECs have been found to contain carcinogens such as tobacco-specific nitrosamines and formaldehyde. Other constituents such as polyaromatic hydrocarbons and heavy metals are known to cause cancer, and nicotine itself is thought by some to pose a urological cancer risk. [44, 45] For instance, polycyclic aromatic hydrocarbons (International Agency for Research on Cancer (IARC), Group 1 (human carcinogen)[46]), which has been associated with bladder

cancer.[47] EC have also been found to contain certain heavy metals, such as lead.[48] Lead exposure has been linked to increased kidney cancer risk. [49, 50] The concentration of lead in EC aerosol is variable but has been suggested in at least one analysis to be comparable to that found in conventional cigarettes.[51] Other heavy metals in EC such as cadmium, nickel and chromium are possible carcinogens (IARC 2b). Nickel, in particular, has been recorded at levels present in ECs that are much higher than conventional cigarettes. [51] Although these heavy metals are linked to an increase cancer risk, they have not yet been linked to urological malignancies.[49] Cresol, which has been found in aerosols from EC cartridges is also found in creosote, a suspect bladder carcinogen.[47]

In addition, in vitro data has demonstrated that EC vapour exposure, independent of nicotine content induces increased cell death. In both normal epithelial cells and cancer cell lines (head and neck squamous cell carcinoma) treated with nicotine free and nicotine-containing vapour, up to a threefold increase in DNA double strand breaks has been reported.[52] Nicotine is also negatively correlated with total sperm motility due to metabolic breakdown products cotinine and trans-3'-hydroxycotinine levels in seminal fluid.[53] Furthermore, cadmium (found in ECs) is associated with low sperm density.[54] Preliminary evidence from a murine model has reported exposure to EC refill liquid can alter anti-oxidant defence and induce histopathological changes reflecting renal collecting duct cell apoptosis.[55]

Whilst there is a theoretic potential for adverse urological health outcomes from the use of ECs it should be stressed that robust data are currently absent to offer a convincing argument for either side of the debate. A recent systematic review of the health

consequences of vaping/ECs highlighted frequent methodological problems with available studies, problematic authorship conflicts of interest, small cohort size, selection bias, conflicting results and a paucity of long-term follow-up data.[48]

3.3 Can ECs help stop tobacco smoking?

The literature on the role ECs play in smoking cessation is growing very slowly, and the messages are somewhat mixed. This section summarizes the current evidence from a range of different study designs and levels of evidence.

3.3.1 Prospective cohort studies

Five studies, with long-term outcomes, have looked at the use of ECs in people who were not ready to quit smoking. One followed 40 smokers over two years and reported that 13% achieved at least six months of CO validated abstinence from conventional cigarettes and 28% had achieved a sustained ≥50% reduction from baseline cigarette consumption.[56, 57] The second tested the same approach with 14 smokers with schizophrenia and reported 14% 30-day CO validated abstinence rates at one-year.[58] The third followed a group of 34 smokers for 8 months after discharge from hospital.[59] Over half (53%) reported no longer smoking. In the fourth, 50 smokers were provided with a second-generation device with 9mg/ml concentration of e-liquid. At 6 month follow-up 36% were biochemically validated 7-day point prevalence abstainers.[60] The fifth cohort study followed 71 smokers who purchased an EC from a vape shop. One year after their purchase 41% reported that they had not smoked at all for at least the last 30 days.[61]

Data are now being reported by the UK stop smoking services. A London-based stop smoking service offered 100 clients, all of whom wanted to quit smoking, a choice of a first or second generation EC.[62] In total, 67 accepted the offer and of these 45 (65%) were recorded as biochemically validated abstainers at the end of treatment (4-weeks post-quit date). The results from this study closely reflect the UK Stop Smoking Service monitoring data from over 450,000 people that made a quit attempt, where 4-week self-reported quit rates were 66% among people who used ECs (n=2221), compared to 48% among people who used combination NRT (n=135,719).

Although there are data to support ECs as a potential aid to smoking cessation in the general population, it is important to note that in those already diagnosed with cancer, there is less certainty. Prospective cohort data from a major US cancer treatment centre reported that significantly higher percentage of EC users were highly nicotine dependent when compared with nonusers and were twice as likely to be smoking at the time of follow-up as nonusers.[63]

3.3.2 Randomised controlled trials

To date only three randomised controlled trials that have examined the effects of EC in helping people stop smoking have been published. One examined their use in people who wanted to quit,[64] and two in those who did not.[65, 66] In a study of people who wanted to quit from New Zealand [64], the investigators compared nicotine-containing ECs (n=289), with 21mg nicotine patches (n=295), and with non-nicotine ECs (placebo ECs, n=73).

Participants were provided with a referral to telephone quitline but with no face-to-face contact. In this minimal support context, there were no significant differences in validated continuous abstinence at six months (7.3% nicotine EC, 5.8% nicotine patch, and 4.1% non-nicotine EC). These findings were similar to an Italian study comparing EC use (two different doses for 12 weeks) to non-nicotine ECs in 300 smokers who were not intending to quit. [65] Biochemically validated six-month abstinence rates (at one-year follow-up) were not significantly different; 13%, 9% and 4% in the three groups, respectively. Both of these pioneering trials were underpowered and used first generation EC products with poor nicotine delivery. These ECs often malfunctioned and neither is now available on the market.

The third trial [66], from Belgium, randomised 48 smokers who did not want to quit to use an EC (a tank system) or no intervention. At 8-week follow-up, 34% of those given an EC to use had quit smoking compared to none in control group. From week 8, all participants were provided with an EC and followed up at 8 months. Among this cohort 19% of early EC users and 25% of the late starters (the control group) had stopped smoking. The results from this study are difficult to interpret because of the small sample size and design.

3.3.3 Systematic reviews

There are now 16 published systematic reviews on ECs for smoking cessation. A recently updated Cochrane review found that ECs with nicotine helped smokers quit for at least 6 months compared with no nicotine ECs (RR= 2.29, 95% CI: 1.05-4.96; 9% vs. 4%). [67] The authors of the review gave these findings a 'low' confidence rating using GRADE standards, not because of poor quality studies, but because there are only two studies. Crucially, the

'low' judgement also means that further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. The addition of more trials to this review will further strengthen the conclusions made. Other systematic reviews draw similar conclusions to the Cochrane review (e.g.[68, 69]), unsurprisingly because they include the same studies. The review and meta-analysis by Kalkohern and Glantz [70] came to the opposite conclusion (that EC use is associated with significantly lower odds of achieving abstinence; OR 0.72; 95% CI: 0.57-0.91). The data in this review included reports of many small surveys and cohort studies (all with serious limitations) rendering the findings of this meta-analysis difficult to interpret.

Given that ECs now deliver nicotine to the user in similar quantities as NRT and even cigarettes, there is little reason to doubt they could help people stop smoking. Some estimates of the numbers who have stopped using ECs have been made. For example, Farsalinos estimated 6.1 million European ever EC users have stopped smoking.[71] In England this figure is thought to be around 0.56 million. Further research and monitoring will strengthen confidence in these findings.[72]

3.4 European health policy and ECs

The use of ECs for smoking reduction or cessation is influenced by a range of factors that extend beyond the safety and efficacy of these devices. Regulation also affects their use, in particular policies that may result in changes to the price, availability or promotion of the products.[73] The global context for EC regulation is highly variable.[74] In many countries such as Argentina, Brazil, Indonesia, and Singapore, the import, distribution and sale of ECs

is banned. Other countries such as New Zealand, South Africa and Switzerland have implemented a two tier system where ECs themselves and nicotine-free cartridges or e-liquid can be sold sale of but nicotine-containing refills or e-liquid are prohibited. Other countries permit their import and sale but certain restrictions on age of sale or marketing are in place. Policies have evolved as use has become more prevalent and governments have responded to a range of concerns often about youth uptake, addictiveness or safety. Ironically, many jurisdictions now have more restrictive regulation on ECs than tobacco products.

In the European Union (EU), EC use is prevalent and countries have taken a range of approaches to regulation.[29] From May 2016 the revised EU Tobacco Products Directive (TPD) was implemented and article 20 of the Directive applies to ECs and refill containers that do not have a medicinal license.[75] Only one device, E-Voke (manufactured by British American Tobacco) has been granted a medicinal license but is not yet available on prescription or as an over the counter medication.[76] The EU TPD requires manufacturers and importers of ECs to comply with a notification process that involves providing data on: ingredients and emissions; nicotine delivery and uptake; health and addictive effects; the product components and production process; and a declaration on safety and quality when used as intended. It is anticipated that this process will remove some products from the market that can't meet these requirements.

The TPD also places a limit on nicotine concentration with devices that do not have a medicinal license limited to 20mg/ml and refill containers up to a maximum volume of 10ml. The basis for this requirement is contested and some concerns have been expressed about this limit in terms of delivering nicotine to smokers who are highly dependent.[77] ECs must

406 also be secure in terms of leakage and breakage, be child and tamper proof and contain a
407 leaflet with warnings, instructions and further information. Packaging must contain a
408 warning label about nicotine being a highly addictive substance and promotional elements
409 on packaging are also subject to regulation. Some forms of marketing are also restricted
410 under the TPD including the prohibition of all cross border advertising and sponsorship
411 although other forms of marketing such as billboards and point of sale are at the discretion
412 of member states. Finally, annual submissions on products are required to be submitted to
413 governments and a system for collecting information on adverse effects on health must be
414 in place. Other policy issues such as age of sale, use in public places and the regulation of
415 flavours are the responsibility of national governments.
416
417 **4. Discussion**
418 We were not able to find any clinical studies with prospective outcomes assessing EC use
419 and urological outcomes. We have presented data around toxicology of compounds found
420 in EC constituents and how this might impact urological health, but these must be viewed as
421 hypothesis generating and treated with caution. As such the use and potential outcomes
422 associated with EC use in urological patient populations is still to be determined. Some
423 international studies, such as the International Tobacco Control Survey,[78] are already
424 providing useful data allowing comparisons of the prevalence of EC use in adults and young
425 people, impact on smoking cessation, and harm perceptions to be examined across
426 countries. In the UK, Cancer Research UK and Public Health England have established the UK
427 Electronic Cigarette Research forum (UKECRF) which brings together researchers from a
428 range of disciplines three times a year to build new collaborations and pursue studies that
429 aim to address research gaps. The forum also produces a monthly evidence bulletin

summarising new studies. Networks of this type are needed in other countries to develop high quality proposals for EC research and generate evidence to inform policy and practice in this rapidly developing field. More research on patterns of tobacco use after e-cigarettes use, in particular among youth, is needed.[79] Also, little information is available on prevalence of use of nicotine-containing and non-nicotine e-cigarettes. Appropriate regulations are needed to protect non-smokers especially adolescents, whilst granting access to smokers to support cessation. In terms of urological health outcomes specifically, data around vapour emission quantities and compositions would be helpful and to work towards validated and standardised contents of ECs. This is an important public health question because EC have been popularised as an aid to smoking cessation, particularly among teenagers. Given the long latency of most cancers, it may take at least 15 years of follow up to identify urological cancer risk among EC users. Analysis of the urine of EC users for compounds such as nitrosamines, aldehydes, lead, arsenic, nickel, chromium and how these are associated with the development of urological malignancies over time would also be a valuable addition to the knowledge base. There is also the challenge of differentiating between conventional cigarette and EC induced health problems, given that most EC users also smoke conventional cigarettes. In this regard, methodologically robust prospective studies looking at urological malignancies in EC users would be valuable data to add to this debate.

Figure Legends:

Table 1: Selected representative prevalences of e-cigarette use

Funding: This review received no funding.

Author contributions: The views expressed here may not represent those of the authors' organizations.

Liam Bourke had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the analysis.

Study concept and design: Bourke, Catto

Acquisition of data: Bourke, Bauld, Bullen, Cumberbatch, Giovannucci, Islami, McRobbie, Silverman and Catto.

Analysis and interpretation of data: Bourke, Bauld, Bullen, Cumberbatch, Giovannucci, Islami, McRobbie, Silverman and Catto.

Drafting of the manuscript: Bourke, Bauld, Bullen, Cumberbatch, Giovannucci, Islami, McRobbie, Silverman and Catto.

Critical revision of the manuscript for important intellectual content:

Bourke, Bauld, Bullen, Cumberbatch, Giovannucci, Islami, McRobbie, Silverman and Catto.

Statistical analysis: None.

Obtaining funding: None.

Administrative, technical, or material support: None.

Supervision: Catto.

Other (specify): None.

477

478 **Table 1.**

Reference; country, year	Age, no. of participants	Prevalence E-cigarette use	Overall, %	Never tobacco smokers, %
Filippidis et al. [12];* European Union (27 countries), 2012–2014	≥15 years 2012: 26,751 2014: 26,792	Ever use, 2012 Ever use, 2014 Transition of ever to current users	7.2 11.9 15.3 (F 14.2; M 17.7)	
Eastwood et al. [14]; Great Britain, 2013–2014	11–18 years 2013: 2,062 2014: 1,952	< monthly, 2013 Monthly or more, 2013 < monthly, 2014 Monthly or more, 2014	3.7 0.9 ∫ 6.5 1.7 ∫	0.6 0.1 1.5 0.2
Hu et al. [16]; USA, 2013–2014	≥18 years 75,233	Every or some days All 18–24 years 25–44 45–64 ≥ 65 Every/some days or rarely	 3.3 (F 2.8, M 4.0) 5.5 4.4 2.8 0.9 6.6 (F 7.9, M 5.5)	
Czoli et al. [15]; Canada, 2013	≥15 years ~2.5 million	Use in the past 30 days All 15–19 years 25–44 45–64 ≥ 45 Ever use	 1.8 (F 1.8, M 1.8) 2.6 (F 2.1, M 3.0) 3.9 (F 3.5, M 4.3) 2.4 (F NR, M 3.0) 1.0 (F 1.2, M 0.8) 8.5 (F 8.1, M 8.9)	 0.5 (F 0.5, M 0.5) 3.6 (F 3.4, M 3.9)
Singh et al. [17]; USA, 2011–2015	Middle or high school students 2011: 18,866 2015: 17,711	Use in the past 30 days High school, 2015 Middle school, 2015 High school, 2011 Middle school, 2011	 16.0 (F 12.8, M 19.0) 5.3 (F 4.8, M 5.9) 1.5 0.6	
Jiang et al. [19]; Hong Kong, 2014	15–65 years 809	Ever use All 15–29 years 30–49 50–65	 2.3 (F 1.3, M 3.6) 5.2 1.8 1.0	 1.0
Li et al. [20]; New Zealand, 2014	≥15 years 2,594	Monthly or more All 15–17 years 18–24 25–44 ≥ 45 Ever use	 0.8 (F 1.0, M 0.5) 0.0 0.2 1.2 0.7 13.1 (F 12.8, M 13.7)	 0.1
Lee et al. [21]; South Korea, 2011	13–18 years (students) 75,643	Use in the past 30 days All students Grade 7 8 9 10 11 12 Ever use	 4.7 (F 1.8, M 7.8) 2.0 3.3 4.7 7.1 6.0 6.2 9.4	 0.6
Palipudi et al. [22]; Greece, Indonesia,	≥15 years Greece (9,357),	Current use ** Greece		

Reference; country, year	Age, no. of participants	Prevalence E-cigarette use	Overall, %	Never tobacco smokers, %
Malaysia, and Qatar, 2011–2013	Indonesia (8,303), Malaysia (4,244), Qatar (8,389)	All	1.9 (F 1.8, M 7.8)	1.1 ¶
		15–24 years	0.0	
		25–44	2.8	
		45–64	2.7	
		≥ 65	0.8	
		Indonesia		
		All	0.3 (F 1.8, M 7.8)	0.0 ¶
		15–24 years	0.2	
		25–44	0.3	
		45–64	0.3	
		≥ 65	0.0	
		Malaysia		
		All	0.8 (F 1.8, M 7.8)	0.1 ¶
		15–24 years	4.4	
		25–44	5.0	
		45–64	0.0	
		≥ 65	0.0	
		Qatar		
		All	0.9 (F 1.8, M 7.8)	0.2 ¶
		15–24 years	0.5	
		25–44	1.0	
		45–64	1.3	
		≥ 65	0.0	
Bunnell et al. [24]; USA, 2011–2013	Middle or high school students 61,932	Use in the past 30 days		0.3
		Ever use	6.1	0.9

F, female; M, male; NR, not-reported.

* Prevalences for individual countries are also presented in the article.

** Those who responded "daily or less than daily" to the question "Do you currently use e-cigarettes on a daily basis, less than daily, or not at all?"

∫ Males were 2.5-times more likely to be monthly or more users than females.

¶ Among those with no current tobacco smoking.

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