

# A Systematic Review and Meta-analysis on the Health and Safety Implications of Electronic Nicotine Delivery Systems

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## ABSTRACT

**Objectives:** Cigarette smoking is a proven and avoidable cause of adverse health implications to smokers and by-standers accounting for about 6 million deaths every year. Despite the knowledge and legal measures adopted to discourage cigarette smoking, the global trend is otherwise. Various less harmful avenues of nicotine delivery claiming to be devoid of toxins, including electronic nicotine delivery systems (ENDS), have therefore emerged as a measure of tobacco harm reduction (THR). **Study design:** A systematic review and meta-analysis of published scientific literature was performed based on the principle of PICOSL in order to compare the toxicities of nicotine, other chemicals and metal ions produced during cigarette smoking vis-à-vis ENDS use, and to evaluate the health and safety aspects of ENDS. **Methods:** Research articles relevant to the use of ENDS among smokers and nonsmokers were retrieved through various databases and published articles from other sources. **Results:** Toxic chemicals such as the class 1 carcinogens and carcinogenic metal ions were found to be present in significantly higher quantities in conventional cigarette smoke than in ENDS vapor. ENDS usage was found to be 4.13-fold higher among former smokers than nonsmokers ( $p < 0.05$ ), while the prevailing use of ENDS was 7.53-fold higher among current smokers than nonsmokers ( $p < 0.05$ ). **Conclusion:** Our study establishes that new generation ENDS may serve as an efficient means of meeting the nicotine demand of a person addicted to smoking, without the grave health consequences of conventional cigarettes. While the cessation of smoking would undoubtedly reduce the associated risks significantly, ENDS may serve as an effective aid to smokers in their efforts to quit smoking, thus acting as a valuable tool of THR. Rational policies are required to extend the benefits of ENDS to smokers, while preventing their misuse, especially by adolescents.

**Keywords:** Cigarette, electronic nicotine delivery system, nicotine, smoking, vaping, tobacco harm reduction

An electronic nicotine delivery system (ENDS), popularly known as 'electronic cigarette' or simply 'e-cigarette', is a patented device used for the delivery of nicotine to users, thus also serving as a substitute for cigarettes. It comprises sequentially interconnected air inlet, atomizer, an aerosol passage and a mouth piece with an atomizer and liquid supply containing only nicotine.<sup>1</sup> The nicotine in ENDS is dissolved in propylene glycol or vegetable

glycerine with or without different flavoring agents. This solution is heated by a battery operated heating element, producing a nicotine-containing aerosol which appears like vapor, and is inhaled by the user.<sup>2</sup> Hence, users call this habit 'vaping'. In a conventional cigarette, combustion of tobacco produces inhalable nicotine accompanied with smoke, carbon monoxide and tar - a complex mixture of an estimated 4000 chemicals, including carcinogens and toxins.<sup>3</sup> Since there is no combustion in ENDS,<sup>2</sup> the delivered nicotine is claimed to be either poor in or free from the toxic chemicals found in abundance in combustible, tobacco-based cigarettes.<sup>4,5</sup>

Tobacco smoking via conventional cigarettes continues to rise and is estimated to result in about 6 million deaths globally every year.<sup>6</sup> Nicotine replacement therapies (NRTs) such as nicotine patches and oral medications have proved ineffective in meeting the desired targets of smoking cessation across the globe.<sup>6</sup> In a worldwide survey of 19,414 users of ENDS,

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81% of former smokers reported complete substitution of smoking while current smokers had reduced smoking from 20 to 4 cigarettes per day. Participants also reported significant benefits in physical status and improvement in pre-existing disease conditions, including respiratory diseases such as asthma and chronic obstructive pulmonary disease (COPD). Furthermore, the study revealed that ENDS can be effective as a smoking cessation tool even in highly dependent smokers. Majority of respondents used high levels of nicotine at initiation and tried to reduce nicotine consumption subsequently, while a small minority (3.5%) used non-nicotine liquids.<sup>7</sup> Hence, a group of scientists, social activists, policy makers and governments view ENDS as a potential tobacco harm reduction (THR) avenue and project it as a safe alternative to the highly deleterious cigarette smoking habit.<sup>2,6</sup> On the other hand, another group claims that THR tools, including ENDS, are not effective since all aspects of their health implications and safety have not been scientifically explored.<sup>8</sup>

Thus, while the serious health implications of tobacco-based conventional smoking are unambiguously accepted, the effectiveness of ENDS as a less harmful smoking cessation alternative and its role in THR efforts have become a matter of intense debate, with no conclusive information available in current literature.

In this study, we have undertaken a systematic review followed by a meta-analysis of published scientific literature in order to test the hypothesis that the use of ENDS does not contribute to significant health risk to

a user vis-à-vis the use of conventional cigarettes and that ENDS can effectively aid a smoker's efforts to cease smoking.

## METHODS

### Literature Search

Research articles relevant to the use of ENDS among smokers and nonsmokers were retrieved through "Google Scholar", "PubMed", "PubMed Central", "Elsevier Science Direct" using the search terms "e-cigarettes", "ENDS", "Nicotine delivery systems", "risk of e-cigarette", "disadvantages of e-cigarettes", "world smoking report", "tobacco report", "smoking toxicants", "ENDS and smoking cessation". In addition, we also included some literature related to the above-mentioned search terms from sources other than the internet, and articles on the techniques used for systematic reviews and meta-analyses.

### Inclusion and Exclusion Criteria

Criteria for inclusion and exclusion were formulated on the basis of the principle of PICOSL (Population, Intervention, Comparison, Outcome, Study-design, Language),<sup>9</sup> and are enlisted in Table 1.

### Statistical Analyses

For the meta-analysis, risk ratio (RR) with 95% confidence interval (CI) was calculated using unconditional logistic regression with the help of Review Manager (RevMan)

**Table 1.** Inclusion and Exclusion Criteria Based on the PICOSL Principle

PICOSL principle	Inclusion criteria	Exclusion criteria
Population	Cigarette smokers, users of traditional burnt tobacco, former cigarette smokers, cigarette nonsmokers, only ENDS users, former smokers who used ENDS for quitting, quitline callers, respondents of surveys on ENDS	Users of chewing tobacco, users of NRTs such as nicotine patches and oral medications
Intervention	Exposure to cigarette smoking and/or ENDS	Combined exposure to cigarette smoking, ENDS and NRT
Comparison	Comparison of smokers with nonsmokers, smokers with former smokers, smokers with ENDS users, populations of countries with restrictions on ENDS with populations of countries where use of ENDS is not restricted	Placebo studies, surveys comparing ENDS users and nonusers with inconclusive findings
Outcome	Exposure to toxins and carcinogens, disease risk, health implications, bioavailability of nicotine, smoking cessation, public opinion and perception on ENDS	No effects, no health implications, no opinion
Study design	Case-control, surveys with conclusive findings, epidemiological findings, studies on public opinion regarding ENDS, all types of research articles, reviews, reports, letters, etc. pertaining to ENDS and/or conventional cigarette	Articles advertising ENDS, studies on specific brands of ENDS, articles dealing with the ethics of ENDS use, articles not on ENDS or conventional cigarettes, duplicate articles
Language	Studies in English	Studies in languages other than English

statistical software (version 5.3.5). All findings were considered significant at  $p < 0.05$ . To determine the heterogeneity across studies, Cochran's Q statistics was used, which was considered significant at  $p < 0.05$ .<sup>10</sup> The random effect model (DerSimonian and Laird method) was used to calculate the pooled RR in case of significant heterogeneity.<sup>11</sup> Otherwise, the fixed effect model (Mantel-Haenszel method) was used.<sup>12</sup> Box-plots were plotted using SPSS (version 16.0) for comparison of the tobacco smoking population of different countries with respect to income level and ENDS regulations.

## RESULTS

### Included Articles

A total number of 299 articles relevant to the study were retrieved and screened from May 2016 to 21st August 2018 and 59 articles were found to meet the inclusion criteria. Among these, 35 articles were used for retrieval of qualitative information regarding ENDS, conventional cigarettes, NRT, THR, policies regarding ENDS, surveys regarding ENDS use, public perception of ENDS, smoking cessation and techniques of meta-analysis; 16 studies (4, 13-15, 20, 21, 42, 44-46, 49, 55-59) were used for quantitative analysis of relative chemical and metal ion content of ENDS vapor and conventional cigarette smoke, relative abundance of nicotine in blood plasma and urine of ENDS and conventional cigarette users, and the prevalence of cigarette smoking in different countries; and, 8 articles (34-41) were used for meta-analysis in order to evaluate the prevalence of ENDS usage among smokers and nonsmokers, and also among current smokers and nonsmokers (Fig. 1).

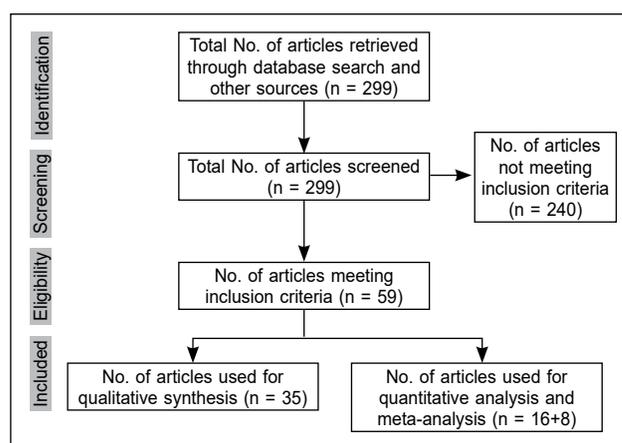
### Health Implications

#### Toxicity of nicotine

The amount of nicotine delivered to the blood plasma of users by second-/third-generation ENDS was compared to the amount of nicotine delivered by conventional cigarettes.<sup>13,14</sup> The physiological amounts of nicotine delivered to users of both ENDS and conventional cigarette were found to be nearly identical (Fig. 2A), but the amount of nicotine excreted in the urine of traditional cigarette smokers was about 0.5-fold higher in comparison to that of ENDS users (Fig. 2B).<sup>15</sup>

#### Toxicities of other constituents

Various studies comparing the toxic contents of cigarettes with those of ENDS have often used different units, posing difficulties in direct comparison of data. Data from these studies were therefore collected and



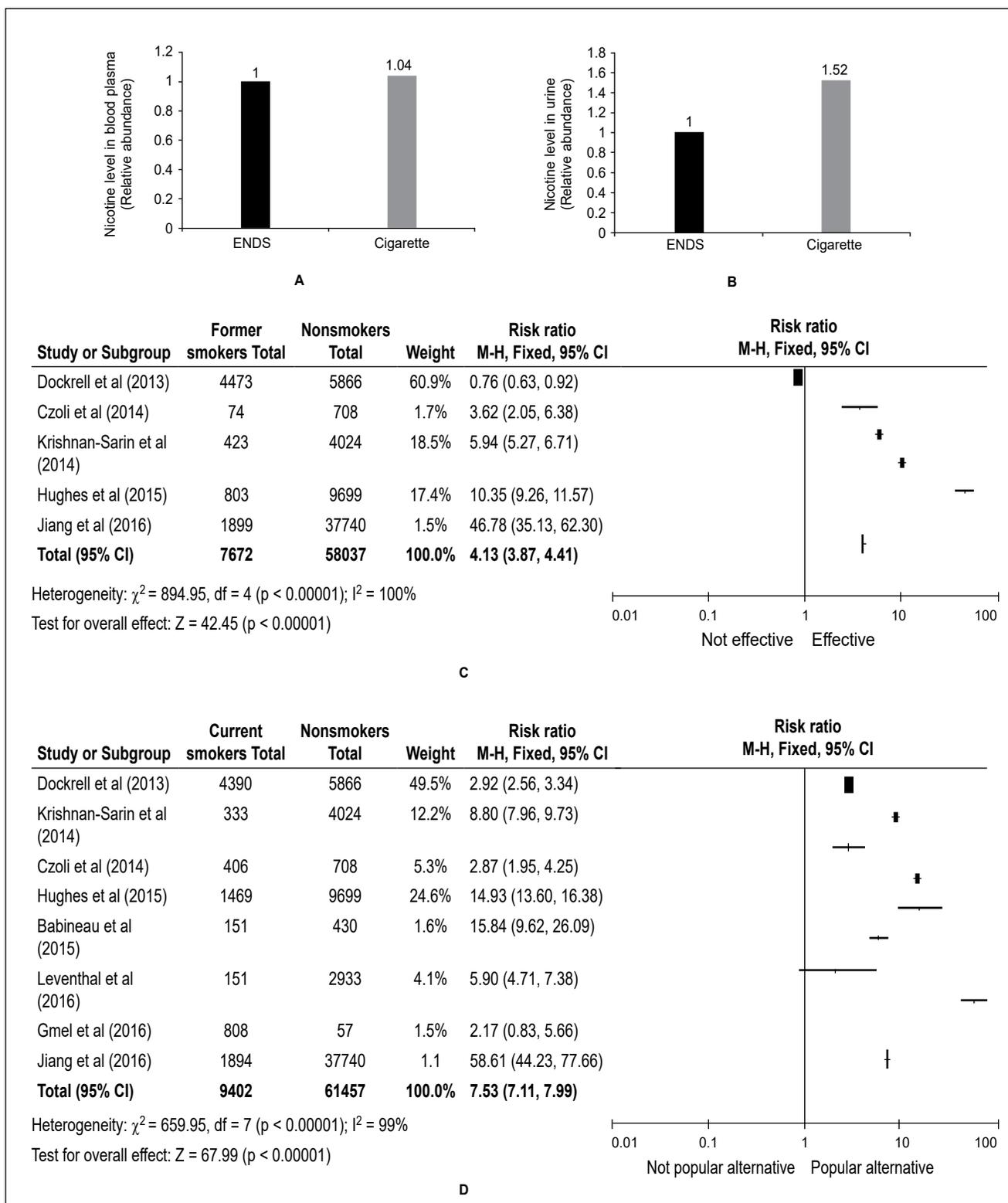
**Figure 1.** Flow chart showing the procedure of literature selection.

recalculated where possible, to represent them in terms of fold difference (Table 2). Where it was not possible, we have indicated the average values of contents in cigarette smoke in comparison to the average contents in ENDS vapor (Table 2). The classification of chemicals as 'carcinogen' is based on the International Agency for Research on Cancer (IARC), Lyon.<sup>16</sup> The classification of other 'toxicant' is based on Food and Drug Administration (FDA), USA.<sup>17</sup>

A number of toxic chemicals were found to be significantly more abundant in conventional cigarette smoke than in ENDS vapor (Table 2). These include the Class 1 carcinogens (CA-1) and some possible carcinogens (CA-2b) (Table 2). Furthermore, some probable as well as possible carcinogens are found in conventional cigarette smoke, but their presence in ENDS vapor has not been reported (Table 2). Respiratory toxicants (RT), cardiovascular toxicants (CT) and reproductive or developmental toxicants (RDT) were also several fold more abundant in cigarette smoke than in ENDS vapor (Table 2). Notable among them is carbon monoxide (CO), a product of partial combustion of tobacco in cigarettes and a recognized CT, which is not produced in combustion-free ENDS.<sup>18</sup>

While metal ions play vital roles in cellular and subcellular physiology and metabolism,<sup>19</sup> heavy metal ions could also be toxic, causing serious health and pathophysiological conditions. We have therefore compared the metal ion content of conventional cigarette smoke with that of ENDS vapor (Table 3).

We observed that most metal ions were abundant in cigarette smoke as compared to ENDS vapor (Table 3). Notable among them are (a) cadmium, a potent CA-1, RDT as well as RT, and lead, a CA-2b. The seemingly nontoxic lanthanum is also several hundred-folds



**Figure 2.** Bar diagram plots showing the relative abundance of nicotine absorbed in blood plasma (A) and excreted in urine (B) measured following ENDS vaping and cigarette smoking. Forest plot and data of risk ratio (RR) at 95% confidence interval (CI) showing (C) the existing level of ENDS usage was 4.13-fold higher among former smokers than nonsmokers making ENDS an effective means of nicotine inhalation and (D) ENDS vaping was 7.53-fold more popular alternative to cigarette smoking among current smokers as compared to nonsmokers suggesting that while ENDS vaping was a popular alternative to cigarette smoking primarily among former smokers, it was poorly inculcating the habit of vaping among nonsmokers.

more abundant in cigarette smoke than in ENDS vapor (Table 3). In contrast, some other metal ions, such as sodium, iron, aluminum, copper, nickel and silver were found to be marginally more abundant in ENDS vapor (Table 3). Among these, nickel is of concern since it is a weak CA-2b and a toxin (Table 3).

### Safety Implications

#### Risk of acute toxicity from direct ingestion of nicotine

Acute ingestion of about 60 mg (range 30-60 mg) of nicotine could be fatal to humans.<sup>20</sup> Oral ingestion of 60 mg of pure nicotine would cause a blood plasma concentration of 0.18 mg nicotine l<sup>-1</sup> of blood, which is about 5% of actual toxic level. Such high acute concentration of nicotine in blood is possible only by accidental or intentional (e.g., to commit suicide) ingestion of nicotine and not due to smoking or vaping. Indeed, a cigarette with 10-15 mg nicotine in tobacco delivers only 1 mg of nicotine in blood<sup>4</sup> and equivalent ENDS vaping is likely to deliver about the same amount.<sup>20,21</sup> However, with an increase in the popularity of ENDS, the risk of accidental ingestion of nicotine is also likely to rise. Nicotine content in the ENDS refill ranges from 160 to 1,000 mg. These quantities of nicotine could be fatal if ingested accidentally.<sup>21</sup>

#### Risk of ENDS use during pregnancy

E-cigarette conditioned media is reported to significantly reduce trophoblast invasion and tube formation in HTR-8/SVneo cells, suggesting that an evaluation of the safety of e-cigarette use during pregnancy is urgently required.<sup>22</sup>

#### Risks from the physical make-up of the nicotine delivery device

With the increased production and sale of ENDS, manufacturers have introduced various advanced designs for increasing user satisfaction, leading to a rapid evolution from the first-generation to the third-generation of ENDS devices ('mods'). The 'mods' have larger tank size for refills which make exposure to higher doses of nicotine possible. They also have longer lasting rechargeable batteries which pose risks similar to other electronic devices. Although uncommon, ENDS may be used, with or without modification, for pulmonary administration of banned substances such as, narcotics, marijuana, steroids and tetrahydrocannabinol (THC).<sup>21</sup> In fact, respondents of an internet survey perceived vaping cannabis through e-cigarettes or e-vaporizers as healthier and more discrete than smoking it.<sup>23</sup>

Poor materials and build quality, lack of quality control and improper use of ENDS can give rise to a condition called "thermal runaway" in lithium rechargeable batteries. This can potentially lead to explosion or fire hazard, though the risk may not be as high as that associated with burning cigarette butts. Technological advancements with thermal power cut-offs, overcharging protection circuits and other safety features in ENDS have by and large overcome these concerns.<sup>24</sup>

#### General perception regarding safety of ENDS

Kamat and Van Dyke, 2017, reported that there is insufficient evidence of ENDS as a smoking cessation aid, and that it is too soon to assess the long-term health consequences of ENDS use.<sup>25</sup> They also emphasized that while the premise of ENDS as a harm reductionism avenue may be valid among adults, it should not be applied to children's experimentation with and use of ENDS. Adolescents between the ages of 14 and 17 years from deprived, mixed and affluent urban areas in Scotland and England supported strict regulation of the age-of-sale, marketing and public use of e-cigarettes.<sup>26</sup> Shantakumari et al, 2015, recommended that the existing restrictions on conventional cigarettes should also be imposed on e-cigarettes, with emphasis on monitoring advertising, product placement, celebrity endorsement and other marketing approaches in order to prevent promotion of e-cigarettes, particularly among children and non-smokers.<sup>27</sup> Kaur and Rinkoo, 2017, expressed the apprehension that weak regulation of ENDS might contribute to the expansion of the ENDS market - in which tobacco companies have a substantial stake - potentially negating years of tobacco control efforts. They recommend banning ENDS in the South East Asian region until sound scientific evidence regarding ENDS as a tobacco cessation tool is available.<sup>28</sup> There is also emphasis on the need for well-designed randomized controlled trials (RCTs) to draw concrete conclusions regarding the impact of ENDS and/or electronic non-nicotine delivery system (ENNDS).<sup>29</sup> Another worker contends that while there are no data showing increased prevalence of serious diseases or health consequences in people using ENDS, the problems related to nicotine dependence such as compulsion to smoke and limited freedom, still remain.<sup>30</sup>

On the contrary, Hall et al, 2015, argue that prohibiting ENDS infringes on smokers' autonomy to use a less harmful nicotine product while inconsistently

allowing individuals to begin and continue smoking cigarettes.<sup>31</sup> They also insist that lack of access to ENDS disadvantages smokers who want to reduce their health risks, and propose that ENDS be sold in ways that allow smokers to reduce the harms of smoking while minimizing the risks of deterring quitting and increasing smoking among youth.<sup>31</sup> Vickerman et al, 2017, reported that quitline callers who used ENDS experience confusion and misinformation about ENDS, and suggest that quitlines should impart improved education about ENDS, in order to facilitate the process of smoking cessation.<sup>32</sup> Vasconcelos and Gilbert, 2018, reported that despite uncertainty about the components, e-cigarettes were mostly viewed as healthier by smoker respondents in North London. However, the lack of reliable information and strong evidence for both the effectiveness and the safety of e-cigarettes acted as a barrier to their use as an aid to quitting smoking.<sup>33</sup>

### ENDS as a Substitute for Tobacco-combustion Based Conventional Cigarettes

A meta-analysis was performed in order to determine the efficacy of ENDS as an effective avenue of quitting cigarette smoking. The analysis used data pertaining to the use of ENDS and cigarette in different population groups, including nonsmokers, former smokers and current smokers.<sup>34-41</sup> Forest plot with combined pooled RR was plotted to determine the effectiveness of ENDS as a substitute for conventional cigarettes.

ENDS usage was found to be significantly ( $p < 0.05$ ) higher among former smokers (RR = 4.13; 95% CI = 3.87-4.41) than among nonsmokers, by 4.13-fold, indicating that ENDS may be a useful tool in the smoking cessation efforts of smokers (Fig. 2C). We also addressed the question of whether ENDS may become a means of inculcating the habit of vaping among nonsmokers. Our results indicate that the prevailing use of ENDS is significantly ( $p < 0.05$ ) higher among current smokers (RR = 7.53; 95% CI = 7.11-7.99) than among nonsmokers by 7.53-fold (Fig. 2D).

We further analyzed available data from the World Health Organization (WHO) on the patterns of cigarette smoking and ENDS vaping in about 90 countries.<sup>42</sup> Box plot analysis shows that irrespective of the income level of the country (high, medium or low), the prevalence of smoking was virtually the same in majority of the population (median, 2nd and 3rd quartiles) in the countries analyzed, making cigarette smoking habit a deep rooted social behavior across all financial strata and cultures of society (Fig. 3A). However, the cigarette

smoking population exhibited a trend to decline in those countries where ENDS was freely available and its usage was not regulated as compared to countries where it was regulated (Fig. 3B).

### DISCUSSION

Davis et al (2009)<sup>43</sup> reported that nicotine administered to immunocompetent mice at doses of 1 mg/kg<sup>-1</sup> body weight thrice weekly by intraperitoneal injection, or 25 mg/kg<sup>-1</sup> body weight daily by transdermal patches, had limited capacity to initiate tumor formation, but could promote metastasis and tumor growth. They also reported that nicotine could promote cellular invasion and epithelial-mesenchymal transition in lung, breast and pancreatic cancer cells *in vitro*. Significantly, the doses of nicotine used in the study were much higher than the average intake of smokers which is reported to range between 27.3 and 42.6 mg,<sup>44</sup> amounting to a calculated intake of 0.546 mg/kg/day to 0.852 mg/kg/day by an adult with an average body weight of 50 kg. It is, therefore, likely that nicotine itself may not be carcinogenic at the low doses obtained by smokers or ENDS users.

The European Union has set the maximum permissible limit of nicotine in ENDS liquids to 20 mg/mL<sup>-1</sup>.<sup>45</sup> The nicotine content in a typical cigarette made of tobacco varies between 10 and 15 mg.<sup>4</sup> This amount of nicotine from a tobacco-based cigarette is estimated to deliver in the blood of a smoker (average 10 puffs/cigarette), a systemic dose of approximately 1-2 mg of nicotine per cigarette smoked depending on the puffing regimen.<sup>4</sup> The systemic dose of nicotine in blood after an ENDS vaping (ENDS with 10 mL cartridge of 24 mg/mL<sup>-1</sup> nicotine delivering on average 300 puffs per cartridge<sup>46</sup> is estimated to be about 0.8 mg, which is close to the value in cigarette smoking.<sup>13,45</sup> The nicotine delivery to a user by vaping using older generation ENDS device was relatively poor compared to smoking. However, over time, the new generation ENDS devices have become very efficient with nicotine delivery levels matching those of conventional cigarettes (Fig. 2A). The detection of more nicotine in the urine of conventional cigarette users in comparison to that of ENDS users could indicate faster metabolism of nicotine in cigarette smokers than ENDS vapers (Fig. 2B). Notwithstanding the minor difference in these two studies,<sup>13,14</sup> it may be concluded that new generation ENDS devices are capable of delivering comparable amounts of nicotine almost free of the tobacco-related damaging chemicals present in higher quantities in conventional cigarette smoke (Tables 2 and 3). Shahab et al, 2017,<sup>47</sup>

**Table 2.** Comparison of Toxicities of Main Chemical Components of ENDS Vape with Conventional Cigarette Smoke in Terms of Ratio or Amount Present (Where Data Pertaining to ENDS Emission were not Available/Possible/Detected). The Classification of Some of the Chemicals as Toxins, Shown in the Table, is Based on FDA (2012)<sup>17</sup> and IARC (2016).<sup>16</sup> Figure in Bold Indicates Dominance of the Chemical Entity.

Chemical/Toxicants	Classification of chemical/toxicant*	Average relative (Ratio) or absolute quantity		Reference
		ENDS vape	Cigarette smoke	
Acetaldehyde	CA-2a, RT, AD	1	<b>91.17</b>	Goniewicz et al (2014), <sup>54</sup> Schripp et al (2013) <sup>55</sup>
Acrolein	CA-2b, RT, CT	1	<b>15.11</b>	
Formaldehyde	CA-1	1	<b>8.31</b>	
Toluene	CA-2b, RT, RDT	1	<b>53.07</b>	
Carbon monoxide	CT	1	<b>2.71</b>	Czogala et al (2014) <sup>56</sup>
1-Hydroxy-2-propanone	-	1	<b>62</b>	Schripp et al (2013) <sup>55</sup>
1,2-Propanediol	CA-2a	1	<b>112</b>	
2-Butanone (MEK)	-	1	<b>19</b>	
2-Furaldehyde	-	1	<b>21</b>	
2-Methylfuran	-	1	<b>19</b>	
2,3-Butanedione	-	1	<b>21</b>	
2,5-Dimethylfuran	-	1	<b>5</b>	
3-Ethenyl-pyridine	-	1	<b>24</b>	
Acetic acid	-	1	<b>5.37</b>	
Acetone	RT	1	<b>3.2</b>	
Benzene	CA-1, CT, RDT	1	<b>22</b>	
Isoprene	CA-2a	1	<b>17.76</b>	
Limonene	-	1	<b>21</b>	
m,p-Xylene	CA-2b	1	<b>18</b>	
Phenol	CA-2b, RT, CT	1	<b>15</b>	
Propanal	-	1	<b>60</b>	
Pyrrrole	-	1	<b>61</b>	
Benzo(a)pyrene	CA-2a	ND	281.7 ng h-1	Saffari et al (2014) <sup>57</sup>
Benzo(b)fluoranthene	CA-2a, CT	ND	307.2 ng h-1	
Benzo(e)pyrene	CA-2b	ND	105.6 ng h-1	
Benzo(g,h,i)perylene	CA-2b	ND	187.0 ng h-1	
Benzo(k)fluoranthene	CA-2a, CT	ND	130.4 ng h-1	
Chrysene	CA-2b, CT	ND	213.3 ng h-1	
Indeno(1,2,3-cd)pyrene	CA-2a	ND	270.2 ng h-1	
4-(methylnitroso-amino)-1-(3-pyridyl)-1-butanone	CA-1	1	<b>92.12</b>	Goniewicz et al (2014) <sup>54</sup> ; Cho and Shin (2015) <sup>58</sup> ;
N'-nitrosornicotine (NNN)	CA-1	1	<b>978.1</b>	Farsalinos et al (2015) <sup>49</sup>

\*CA-1 = Class 1 potent carcinogen; CA-2a = Class 2a probable carcinogen; CA-2b = Class 2b possible carcinogen (IARC, 2016)<sup>16</sup>; AD = Addictive substance; RT = Respiratory toxicant; CT = Cardiovascular toxicant, RDT = Reproductive or developmental toxicant (FDA, 2012)<sup>17</sup>; ND = Not determined.

**Table 3.** Comparison of Toxicities of Main Metal Ionic Components of ENDS Vape with Conventional Cigarette Smoke in Terms of Fold Differences. The Classification of Some of the Metal Ions as Toxins, Shown in the Table, is Based on FDA (2012)<sup>15</sup> and IARC (2016)<sup>14</sup>. Figure in Bold Indicates Dominance of the Metal Ions

Metal ion	Average relative (Fold) content		References
	ENDS vape	Cigarette smoke	
Aluminum	<b>1</b>	0.55	Williamsetal (2013) <sup>59</sup> , Saffari et al (2014) <sup>57</sup>
Boron	<b>1</b>	<b>24.5</b>	
Cadmium <sup>†</sup>	<b>1</b>	<b>1369.37</b>	
Chromium <sup>‡</sup>	<b>1</b>	<b>13.71</b>	
Copper	<b>1</b>	0.93	
Iron	<b>1</b>	0.08	
Lanthanum	<b>1</b>	<b>575.07</b>	
Lead <sup>‡</sup>	<b>1</b>	<b>12.02</b>	
Magnesium	<b>1</b>	<b>1.06</b>	
Manganese	<b>1</b>	<b>1.5</b>	
Nickel <sup>#</sup>	<b>1</b>	0.25	
Potassium	<b>1</b>	<b>139</b>	
Silver	<b>1</b>	0.7	
Sodium	<b>1</b>	0.31	
Zinc	<b>1</b>	<b>57.74</b>	

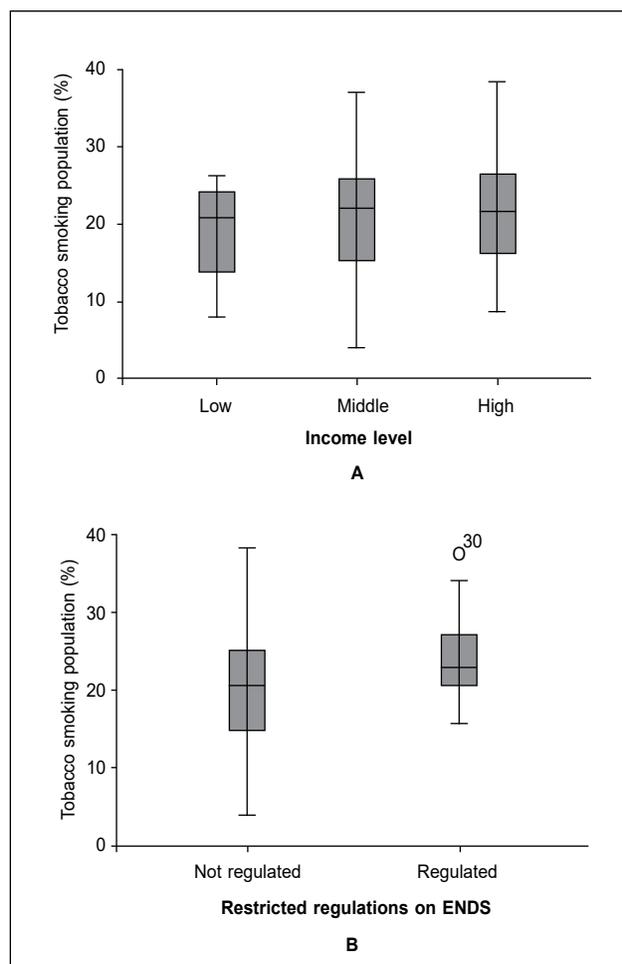
<sup>†</sup>Class 1 carcinogen (CA-1), respiratory toxicant (RT) and reproductive and developmental toxicant.

<sup>‡</sup>Class-2a probable carcinogen (CA-2a).

<sup>#</sup>Class 2b possible carcinogen (CA-2b) (IARC, 2016<sup>16</sup>; FDA, 2012<sup>17</sup>).

also reported that former smokers with long-term e-cigarette-only or NRT-only use may obtain roughly similar levels of nicotine, and are exposed to lower levels of carcinogens and toxins when compared with smokers of combustible cigarettes only.

While ENDS produce fewer harmful chemicals than conventional cigarettes, it was reported that increasing the voltage of e-cigarettes from 3.2 to 4.8 V resulted in an increase in formaldehyde, acetaldehyde and acetone to the range of levels found in tobacco smoke.<sup>48</sup> Nickel may originate in ENDS vapor (Table 3) from the batteries and the nickel-coated parts (nichrome heating wire) used in the construction of atomizers in first-generation ENDS.<sup>49</sup> The origin of other metal ions in ENDS vape could also lie in the materials used. Thus, the design of the ENDS device is vital in reducing associated risks. In a risk assessment analysis, Farsalinos et al reported that smokers switching to ENDS were unlikely to have any significant health



**Figure 3.** Box diagram plot showing (A) the prevalence of cigarette smoking habit in the populations of low, medium and high income countries (data from 90 countries; see WHO, 2015).<sup>29</sup> The median as well as 2nd and 3rd quartiles show nearly similar prevalence of cigarette smoking habit among people in all financial strata across cultures. The data is suggestive of cigarette smoking habit being not significantly influenced by factors such as price or level of awareness, etc. (B) The declining trend of cigarette smoking populations in those countries where ENDS was freely available and not regulated or banned as compared to countries where ENDS was banned and tightly regulated (data from 90 countries; see WHO).<sup>29</sup> The decline was apparent on the median as well as on the 2nd and 3rd quartiles. The data is suggestive of ENDS being able to help quit cigarette smoking habit in population provided it is available as a choice.

hazards from the amount of metals emitted from ENDS.<sup>45</sup> Moreover, newer generation ENDS use pyrex glass and stainless steel parts instead of nickel. While it was observed that conventional cigarette smoke contains significantly higher levels of lead than ENDS vapor (Table 3), one study reported that quantifiable levels of lead (25.2-838.4 ppb) are present

in certain commercially available disposable e-cigarette devices, and recommends that lead testing should be incorporated in chemical analyses of ENDS devices.<sup>50</sup> Thus, more research is desirable to further ascertain and control these emissions even at minute levels in ENDS vapor.

Our meta-analysis indicates that while ENDS is able to help smokers shift to vaping easily, it does not inculcate significant vaping habit among nonsmokers, allaying fears that it may act as an avenue for introducing nicotine dependence among nonsmokers (Fig. 2C and 2D). Our results also indicate that the cigarette smoking habit is not significantly influenced by factors such as price, awareness of harmful effects of smoking or nutritional level of the population, but ENDS may act as a useful mode of NRT to decrease the harmful effects of cigarette smoking (Fig. 3). Indeed, it has been proposed that given their harm-reduction potential, warnings for e-cigarettes should increase awareness about potential e-cigarette risks and discourage e-cigarette use among never smokers while not discouraging use among current and former smokers interested in e-cigarettes for smoking cessation or maintaining abstinence.<sup>51</sup>

The American Association for Cancer Research (AACR) and the American Society of Clinical Oncology (ASCO) recommended key policies including supporting federal, state and local regulation of ENDS; requiring manufacturers to register with the FDA and report all product ingredients, requiring childproof caps on ENDS liquids and including warning labels on products and their advertisements; prohibiting youth-oriented marketing and sales; prohibiting child-friendly ENDS flavors; and prohibiting ENDS use in places where cigarette smoking is prohibited.<sup>52</sup>

## CONCLUSIONS

Within the limits of available information, our study indicates that ENDS pose minimal health and safety concerns when compared to conventional cigarettes. These findings are supported by two recent reports.<sup>53,54</sup> Our study also establishes that newer generation ENDS are an efficient means of meeting nicotine demand, and can thus aid the cigarette smoking population in quitting smoking. The need of the hour is for THR activists and scientists to join hands and further investigate the implications of ENDS on human health. There is also a need for rational policy-making with the objective of maximizing benefits and minimizing potential risks by extending the benefits of ENDS to smokers who choose to use them as smoking cessation

tools, while preventing the misuse of ENDS by never smokers, adolescents and children.

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**Competing interests:** None declared.

**Ethical Approval:** This study is a systematic review and meta-analysis based on information/data collected from published literature. Hence, no ethics approval is required.

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### Baby Cough Syrup is Recalled after Bacterial Contamination

The CNN reported that makers of DG/health Naturals baby Cough Syrup + Mucus have issued a recall of the product in the US due to a bacterial contamination.

Some of the symptoms include vomiting and diarrhea. Infants, young children and others with weakened immune systems are the most at risk if exposed. The bacteria was found after audit testing showed that one in 10 bottles showed low levels of *Bacillus cereus*, the FDA said. Production has been suspended while the FDA and the company continue their investigations as to the source of the problem.

The children's cough syrup comes in a 2-ounce bottle in a carton labeled DG™/health baby Cough Syrup + Mucus. The product is distributed nationwide in Dollar General retail stores and has the potential to put children at risk for two forms of gastrointestinal illness... (CNN)