ORIGINAL ARTICLE

SWITCHING FROM CIGARETTES TO ELECTRONIC NICOTINE DELIVERY SYSTEM: RAPID SYSTEMATIC REVIEW AND META-ANALYSIS AND ECONOMIC ASPECTS

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ABSTRACT

Objectives. To assess how and in what extent the electronic nicotine delivery systems (ENDS) use substituted the consumption of traditional combustible cigarettes (c-cigarettes, c-cig). **Materials and Methods.** We performed a systematic review of the literature up to August 2019 in scientific databases. Primary outcomes were proportion of complete or partial substitution of conventional to electronic cigarettes and related economic aspects. Secondary outcomes were odds ratio of substitution and country-wise time trends. **Results.** We retrieved 3,628 references and included 49 studies, providing economic and epidemiological data. Economic studies of cross-price elasticity showed that combustible cigarettes are partially substitutable for electronic cigarettes. Most studies reported that electronic cigarettes consumption prevalence increased over time. Three studies reported a significant reduction of combustible cigarettes consumed per day among dual users (combustible- plus electronic- cigarettes users) versus combustible-cigarettes users. The pooled adjusted odds ratio of quitting combustible cigarettes among electronic cigarettes users versus never or past electronic cigarettes (e-cigarettes, e-cig) users was 1.19 (95% confidence interval 1.09 to 1.30; heterogeneity score 0%). Longitudinal studies showed globally a growing prevalence of electronic cigarettes use, mainly in adolescents. A negative relationship between consumption and price increase of electronic and combustible cigarettes was found. **Conclusion.** The chance of quitting smoking combustible cigarettes among current electronic nicotine delivery systems users was increased with respect to never- or past- electronic nicotine delivery systems users. Economic studies reported that electronic cigarette is partially substitutable for combustible cigarettes.

Keywords: Electronic Nicotine Delivery Systems; Nicotine; Tobacco Use Disorder; Cigarette Smoking; E-Cigarette Vapor; Systematic Review; Meta-Analysis (source MeSH NLM).

INTRODUCTION

Smoking is the second leading risk factor for disability, behind only hypertension [1]. Although its global prevalence has declined over the past fifty years, smoking is estimated to be responsible for approximately seven million deaths each year and about 200 million disability-adjusted life years (DALYs). Exposure to smoking may be higher in high-income countries, although nearly 80% of traditional tobacco users live in low-income countries [1-3].

The World Health Organization (WHO) launched the Framework Convention on Tobacco Control (FCTC) in 2003, setting a milestone for public health promotion [4]. The better cost-effective strategies to combat the global tobacco epidemic were identified in the Centers for Disease Control and Prevention (CDC) MPOWER document [5]. Also, in 2009, the implementation of the Global Adult Tobacco Survey (GAS) started, with the objective of describing smoking behavior with a standard questionnaire for all countries, and indirectly measuring the impact of control measures and public policies [6].

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The addictive property of nicotine is the key factor used by the tobacco industry to promote the consumption of its products [7,8]. By using filters and modifying tar levels, the tobacco industry attempted to argue that these cigarettes were "healthier"; however, studies failed to demonstrate these benefits [9]. Electronic nicotine delivery systems (ENDS) are battery-operated devices for inhaling or "vaping" a flavored solution containing a specific concentration of nicotine. The most common types of ENDS are the electronic cigarette, electronic hookah, or vaporizer pens, as nicotine delivery options promoted by their manufacturers as "healthier" replacements for conventional cigarettes and which in recent years have become a disruptive technology in nicotine consumption [10]. The growth in the use of ENDS has been significant, mainly in the young population, generating a partial replacement or switch to traditional tobacco [10,11]. The possibility of adding different flavors and transforming them into vehicles for the consumption of other substances, such as oils based on tetrahydrocannabinol (THC), cannabidiol (CBD) and butane, contributed to the rapid expansion and switch to ENDS [12]. Recent studies have shown that, in addition to nicotine, there are a large number of substances harmful to health in ENDS associated with cases of lipoid pneumonia with fatal outcomes worldwide [12].

The analysis of the economic behavior of markets defines the term substitution as the interaction of two products, where an increase in the price of one would lead to an increase in the purchase of another with a fixed price. This relationship is modeled mathematically using the concept of cross-price elasticity. A substitute is defined as a product that has positive cross-price elasticity, where switching from conventional cigarettes to alternative products would depend on consumer characteristics, as well as the type and number of alternative products [13]. In particular, ENDS have shown more switching between potentially less harmful alternative products, depending on the nicotine dose they include [13].

However, there is a knowledge gap on the current status of ENDS as substitute products for conventional cigarettes with debate focusing on the long-term effects of these products and their consequences in the younger population [10,13,14]. The aim of this rapid systematic review is to assess how and to what extent a switch from conventional cigarettes to electronic nicotine delivery systems (ENDS) occurs.

KEY MESSAGES

Motivation for the study: There is little evidence on the current status of electronic nicotine delivery systems as substitutes for traditional tobacco products. The debate is focused on the long-term effects of these products and their consequences in young people.

Main findings: Cessation of conventional cigarette smoking is more likely among e-cigarette users compared to non-users. The prevalence of e-cigarette use is increasing, mainly among teenagers. Increasing prices of conventional and e-cigarettes may be helpful in stopping smoking.

Implications: These findings should be considered in public health strategies for tobacco control.

MATERIALS AND METHODS

A rapid systematic review with meta-analysis was conducted; the report followed the guidelines established in the Cochrane Manual [15] and the PRISMA statement [16,17]. The review protocol was registered in PROSPERO under number CRD42019142089.

Selection criteria and outcomes

The following study types were included: a) controlled before-and-after trials (CBA); b) uncontrolled before-and-after trials (UBA); c) interrupted time series studies (ITS) with at least three data points before and after the intervention, with or without comparison groups; d) cohort studies; and e) cross-sectional studies. Systematic reviews were considered as a source of studies. Regarding the type of participants, studies should include smokers or ex-smokers of any age, sex, and country of residence who changed their consumption pattern.

The primary outcome was defined as a complete switch when the person started using ENDS and stopped smoking, or partial switch if the person started using ENDS and reduced daily consumption of conventional cigarettes, as well as the economics of this switch (price-demand and other types of elasticity and retail prices). Secondary outcomes were defined as outcome measures: a) Odds ratio (OR) of the switch, b) magnitude of change by country, c) time trends by country.

Search strategies

The literature search was conducted in PubMed, Embase, CINAHL, LILACS and Global Health (OVID) on August 30, 2019. The search strategy was created for PubMed and adapted to other electronic databases; no language restrictions were applied (see Supplementary Material Annex 1).

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Selection of studies and extraction of results

For studies with multiple published papers, we included the one with the largest data set. Article selection and data extraction were carried out independently by peer reviewers (FRC and GS). Discrepancies were resolved by consensus of the entire team. These phases were completed using Covidence, an online platform designed for the development of systematic reviews [18]. Authors were contacted when necessary to obtain missing or supplementary information. A predesigned data extraction form was used after pilot testing. The following information was extracted: year of publication, journal name, authors' names, language, study location (geographic region, country, province, city), study setting (urban vs. rural), study design, including risk of bias assessment domains, participants, selection criteria used, full or partial switch rate, and reasons for switching, among other data of interest.

Quality assessment

The evaluation of the bias risk (quality) of the epidemiological studies identified was carried out using the National Institutes of Health (NIH) quality assessment tool for observational cohort and cross-sectional studies [19]. On the other hand, it should be taken into consideration that no specific instrument has been developed to evaluate studies aimed at estimating price elasticities and/or cross-price elasticity of demand. In this regard, to assess the quality of the included economic studies, we developed and proposed an *ad hoc* instrument, based on two previous systematic reviews that analyzed the elasticities of tobacco products [20,21]. The items of the instrument include aspects of the studies related to data, methods, evidence, and reporting of results (supplementary material, appendix 2 and 3).

Data analysis

A descriptive analysis was conducted to determine the frequency of total or partial switching (defined as the reduction of conventional cigarettes consumed per day) by country, and year of publication (taking into consideration when ENDS entered the market). The results are described using frequencies and measures of dispersion (median and interquartile range). A meta-analysis of the adjusted ORs was also carried out using Statsdirect software [22]. Results were presented with 95% confidence intervals (CI). Intervention heterogeneity was described using the I^2 statistic as follows: 1) 0-30% as not important; 30-70% as moderate; and more than 70% as considerable heterogeneity. To assess the impact of statistical heterogeneity, results were compared using fixed- and random-effects models. It was assumed that clinical heterogeneity (populations, interventions) was very likely to occur given the nature of the interventions included, so results from the random-effects model were reported. Overall effects were reported by the inverse variance method. We planned to convert continuous data to mean difference (MD) when necessary.

RESULTS

We found 3,628 studies of which 49 were finally included (Figure 1). Of these, 14 were economic studies and 35 provided epidemiological data on the switch from cigarettes to ENDS or the consumption of both (concurrent).

Economic studies

Fourteen economic studies were considered, including cost studies and/or economic evaluations [23-36] (Table 1), of which eight were from the United States, and the rest from England, New Zealand, and South Korea (one study for each of these countries). Three studies included several countries. Two of them considered data from 20 middle- and low-income countries. Most of the studies were cross-sectional in design (64%) and used a variety of data sources, including retail sales databases, cigarette purchase questionnaires, and online surveys. Nine studies (64%) evaluated health policy interventions. The most frequently evaluated or simulated intervention was price increases for e-cigarettes or conventional cigarettes (89%).

We assessed the quality of the evidence of economic studies (Supplementary Material, Annex 4). Eleven of fourteen studies (79%) used household, retail or individual-level data. Almost all studies reported price/revenue and demand/sales/purchases outcomes. Half of the studies included a set of control variables in the analysis, and eight out of ten studies had an adequate sample size. Nine out of eleven studies estimated an adequate econometric model and are based on microeconomic theory. However, of the nine studies, only six (67%) tested the results for model validation or misspecification. About half of the studies (46.2%) reported results by subgroups. The average positive score across studies was 69.3%, ranging from 33.3% as the lowest value to 87.5% as the highest value. The identified studies suggest a negative relationship between consumption and price increases of e-cigarettes and conventional cigarettes. Four studies reported the price elasticity of the e-cigarette,

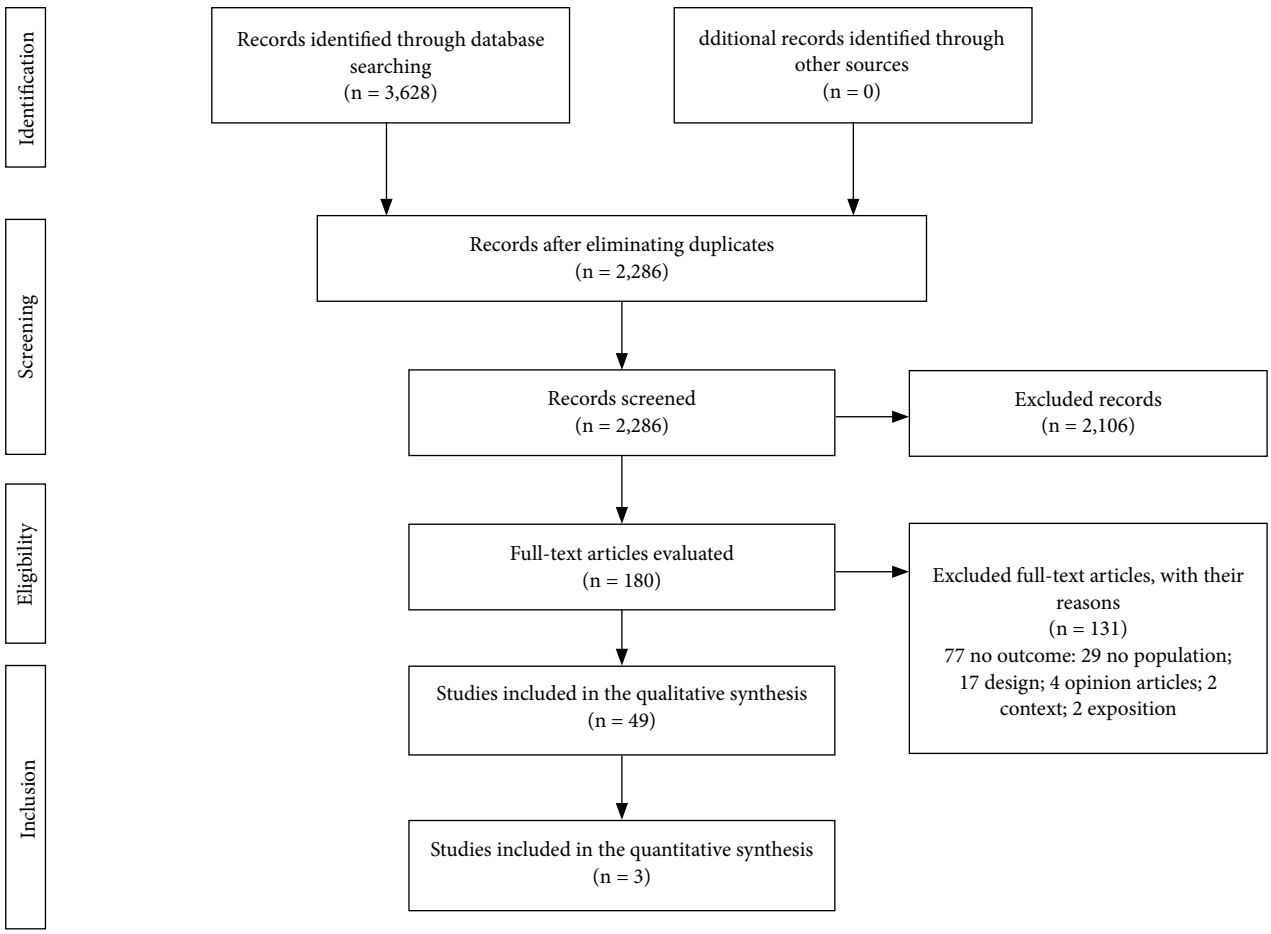

Figure 1. Flow of study selection according to the PRISMA statement.

and two showed that demand for this product is inelastic (elasticity below one, indicating that variations in demand for e-cigarettes are lower than variations in price, *ceteris paribus*). Overall, with the exception of the study by Zheng *et al*. that performs an elasticity analysis in different geographic areas in the United States [23], the rest of the studies did not report elasticity estimates for population subgroups by socioeconomic or age characteristics.

Five studies reported the cross-price elasticity of the e-cigarette [25,29,31,33,35] (Table 1). The positive values of the cross-price elasticity of e-cigarettes show that e-cigarettes are partially interchangeable with conventional cigarettes, i.e., the demand for e-cigarettes increases when the price of conventional cigarettes increases, *ceteris paribus*.

Epidemiological studies

As for epidemiological studies, 35 were useful in assessing the switch from conventional cigarette smoking to ENDS; 24 were from the United States [37,38,47-56,39,57-60,40-46], three from Italy [61-63], three from the United Kingdom [64-66], and one each from Germany [67], Czech Republic [68], France [69], and Poland [70]. Finally, one European study was multi-country [71]. More than half were cross-sectional studies (55%), while the rest were retrospective cohort studies. Nineteen studies reported outcomes and measures of effect regarding sustainability (Table 2).

After applying the NIH assessment tool for each article, studies with low risk of bias were categorized as "good" (86%), while those with moderate risk were classified as "fair" (14%). No studies with high risk of bias were found (Supplementary Material, Annex 5).

Regarding the complete switch from conventional cigarettes to ENDS, three studies reported the adjusted OR of quitting conventional cigarettes, of current ENDS users versus nonusers or former ENDS users (Figure 2) [38,51,55]. The adjusted OR (with random effects) of the conventional cigarette smoking cessation group among ENDS users (whether daily or otherwise) was 1.19-fold (95% CI 1.09-

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Table 1. Characteristics and main results of the economic studies.

Author	Country	Study design	Information source	Observation unit	Sample size	Does it report the retail price for the e-cigarette consumer?	E-cigarette price elasticity	E- cigarette cross-price elasticity	Is a public intervention being evaluated?	Main results
Rutter 2017 [34]	England	Cross-sectional	Online survey	Individual	314	No	NR	NR	Increase in the price of electronic cigarettes	44% of individuals stated that they would switch to e-cigarettes if tobacco became unaffordable.
Liber 2017 [28]	Multiple countries [1]	Descriptive	Euromonitor International	Cigarette sales	NA	Yes	NR	NR	No	The initial cost to purchase a rechargeable e-cigarette presents a significant cost barrier to switching from smoking to vaping.
Liber 2019 [26]	Multiple countries [1]	Descriptive	Euromonitor International	Cigarette sales	NA	Yes	NR	NR	No	In 17 of 46 countries included, the use of electronic cigarettes was reported to be cheaper than the use of conventional cigarettes.
Stocklosa 2016 [35]	Multiple countries [2]	Time Series	Nielsen detail scanner data	Cigarette sales and prices	NA	Yes	SM: -0.79 to -0.84; STDM: -0.26 to -0.27; LTDM: -1.13 to -1.18	4.55 to 3.60 (SM); 6.46 to 6.54 (LTDM)	Increase in the price of electronic cigarettes	A 10% increase in e-cigarette prices is associated with a drop in e-cigarette sales of approximately 8.2%. According to dynamic models, the drop in sales can be 2.7% in the short term and 11.5% in the long term.
Grace 2015 [29]	New Zealand	Cross-sectional	Cigarette Purchase Task Questionnaire	Individual	210	Yes	NR	0.16 (95% CI: 0.09-0.24) (conventional cigarette)	Increase in the price of conventional cigarettes	Simulated demand for conventional cigarettes at current market prices decreased by 42.8% when e-cigarettes were available.
Han 2019 [24]	South Korea	Cross-sectional	South Korea community health survey (2015).	Individual	45,686	No	NR	NR	No	After tobacco prices increased, 3.8%, 22.8% and 5.4% of subjects quit smoking, reduced smoking or switched to e-cigarettes respectively.
Chen 2018 [32]	United States of America	Model-based (Markov)	National Youth Smoking Survey (2014).	Individual	20,695	No	NR	NR	No	E-cigarettes were more attractive than conventional cigarettes, but the behavior of smoking conventional cigarettes was more stable than that of smoking e-cigarettes.
Cheng 2019 [25]	United States of America	Cross-sectional	Smoking and vaping survey and Nielsen Scanner data	Individual	2.078	Yes	-0.40 (nicotine vapor product)	0.14 (conventional cigarette)	Regulation of vaping in the workplace	Higher nicotine vape product (NVP) prices were associated with a lower likelihood of NVP use, concurrent use, and complete switch to smoking NVP ($p > 0.05$).
Johnson 2017 [33]	United States of America	Cross-sectional	Single Commodity Purchasing Task Questionnaire	Individual	331	No	NR	0.15 (conventional cigarette)	Increase in the price of electronic cigarettes	When e-cigarettes or tobacco cigarettes were the only product available, as the price per puff increased, purchases decreased.
Liber 2018 [27]	United States of America	Descriptive	Nielsen detail scanner data	Tobacco markets	NA	Yes	NR	NR	No	Prices for combustible cigarettes and e-cigarette refills increased during 2011- 2015, while prices for disposable and rechargeable e-cigarettes decreased.
Minami and Theo 2019 [36]	United States of America	Cross-sectional	Online survey	Individual	918	No	NR	NR	Variations in the price of electronic and conventional cigarettes	With the reduction in e-cigarette prices, more than 50% of current cigarette smokers reported that they would reduce or quit smoking.

Notes: SM: static model; STDM: short-term dynamic model; LTDM: long-term dynamic model; NA: not applicable; NR: not reported.

[1] Countries included in the study: Australia, Austria, Azerbaijan, Belarus, Bosnia-Bulgaria, Bulgaria, Chile, China, Colombia, Croatia, Czech Republic, Denmark, Ecuador, Egypt, Estonia, Finland, France, Germany, Greece, Guatemala, Hungary, Ireland, Italy, Kazakhstan, Latvia, Lithuania, Macedonia, Nigeria, Norway, Pakistan, Peru, Philippines, Poland, Portugal, Romania, Russia, Serbia, Slovakia, Slovenia, South Africa, South Korea, Spain, Sweden, Netherlands, Ukraine, England, United States of America.

[2] Countries included in the study: Estonia, Ireland, Latvia, Lithuania, Sweden, England. *(Continued on page 544)*

Table 1. Characteristics and main results of the economic studies. *(Comes from page 543)*

Author	Country	Study design	Information source	Observation unit	Sample size	Does it report the retail price for the e-cigarette consumer?	E-cigarette price elasticity	E- cigarette cross-price elasticity	Is a public intervention being evaluated?	Main results
Pesko 2018 [31]	United States of America	Cross-sectional	Monitoring to Future Survey (2014 y 2015)	Individual	24,370	No	-0.113 (95% CI: -.635 – 0.409)	0.194 (95% CI: -0.028 – 0.415) (Conventional cigarette)	Increase in the price of electronic cigarettes	A 10% increase in e-cigarette prices is associated with a reduction in the number of vape days among e-cigarette users by 9.7% and is associated with a reduction in the number of vape days by 17.9%.
Quisenberry 2017 [30]	United States of America	Cross-sectional	Brief questionnaire on the need to smoke	Individual	21	No	No	Yes	Increase in the price of conventional cigarettes	The user profile of cigarette smokers (e.g., gender, age) is associated with behavioral economic measures of alternative product exchange.
Zheng 2017 [21]	United States of America	Cross-sectional	Nielsen detail scanner data	Cigarette sales	NA	Yes	-2.054	NR	Increase in the price of electronic and conventional cigarettes	The unconditional own-price elasticities for cigarettes, small cigars / large cigars, electronic cigarettes, smokeless tobacco and loose smoking tobacco are -1.188, -1.428, -1.501, -2.054, -0.532 and -1.678, respectively.

Notes: SM: static model; STDM: short-term dynamic model; LTDM: long-term dynamic model; NA: not applicable; NR: not reported.

[1] Countries included in the study: Australia, Austria, Azerbaijan, Belarus, Bosnia-Bulgaria, Bulgaria, Chile, China, Colombia, Croatia, Czech Republic, Denmark, Ecuador, Egypt, Estonia, Finland, France, Germany, Greece, Guatemala, Hungary, Ireland, Italy, Kazakhstan, Latvia, Lithuania, Macedonia, Nigeria, Norway, Pakistan, Peru, Philippines, Poland, Portugal, Romania, Russia, Serbia, Slovakia, Slovenia, South Africa, South Korea, Spain, Sweden, Netherlands, Ukraine, England, United States of America.

[2] Countries included in the study: Estonia, Ireland, Latvia, Lithuania, Sweden, England.

1.30) compared with never or former ENDS users, with an I^2 of 0%. Finally, four included studies were not meta-analyzed and are described narratively because of substantial heterogeneity [49,53,61,71].

Manzoli *et al.* compared abstinence in a prospective cohort conducted in Italy. Data at 24 months were available for 229 e-cigarette users, 480 tobacco smokers, and 223 of those using both [61]. Of the e-cigarette users, 61.1% remained abstinent from tobacco (whereas 23.1% and 26.0% of tobacco smokers and users of both achieved abstinence from tobacco). The rate (18.8%) of quitting either product (tobacco and/or e-cigarettes) was not higher for e-cigarette users compared to tobacco smokers or smokers of both.

Giovenco *et al.* pooled data from the 2014 and 2015 U.S. National Health Interview Survey (NHSIS) and restricted the sample to recent smokers and the analysis to daily e-cigarette users [49]. A quarter of the sample (25.2%) were former smokers. The prevalence of quitting smoking was significantly higher among daily e-cigarette users compared with never users (52.2% vs. 28.2%; prevalence ratio: 3.15; 95% CI: 2.66-3.73). Among those with a recent history of smoking, daily use of e-cigarettes had the strongest association with quitting smoking.

Farsalinos *et al.* assessed changes in smoking status due to e-cigarette use and the correlation with e-cigarette use in European Union (EU) member states in 2014 [71]. Through a survey of 27,460 citizens ≥15 years of age from the 28 EU member states. Researchers found that 31.1% of current smokers, 10.8% of former smokers, and 2.3% of never smokers reported ever using e-cigarettes; and that 35.1% (95% CI: 30.7-39.5) of current e-cigarette users reported quitting smoking conventional cigarettes because of e-cigarettes, while 32.2% (95% CI: 29.9-36.5) reported a reduction in conventional cigarette consumption. Being a smoker (OR: 21.23; 95% CI: 18.32-24.59) or former smoker (OR: 6.49; 95% CI: 5.49-7.67) were the strongest associations with e-cigarette use.

Chet *et al.* reported that e-cigarette users with one (adjusted OR: 2.5; $p < 0.001$) or multiple tobacco-free/menthol-free flavors (adjusted OR: 3.0; $p < 0.001$) were more likely to have reduced or stopped cigarette use during the past year compared with non-users of e-cigarettes [53].

To analyze the outcome of conventional cigarette smoking cessation rates, Ekanem *et al.* included 4,465 participants from the USA [52]. Most current smokers who

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Table 2. Epidemiological studies reporting switching outcomes and measures of effect.

Outcome	Author	Country	Design	N	Follow-up (years)	Point estimate	95% CI
Switching from conventional cigarettes to electronic cigarettes [a]	Farsalinos 2016 [71]	Europe	Cross-sectional	27,460	NA	OR 5.1	3.77-6.86
	Manzoli 2017 [61]	Italy	Cohort	1,355	2	OR 5.56	3.89-7.95
	Ekanem 2017 [52]	USA	Cross-sectional	4,465	NA	OR 0.53	0.34-0.63
	Zhu 2017 [37]	USA	Cross-sectional	161,054	NA	RR 1.73	NR
	Giovenco 2018 [49]	USA	Cross-sectional	15,332	NA	OR 3.15	2.66-3.73
	Chen 2018 [53]	USA	Cohort	4,645	1	OR 2.5	1.6-3.8
	Young-Wolff 2018 [38]	USA	Cohort	7,926	1	OR 1.17	1.05-1.31
	Berry 2019 [55]	USA	Cohort	5,124	1	OR 1.46	0.95-2.23
	Farsalinos 2020 (51)	USA	Cross-sectional	24,689	NA	OR 1.21	1.03-1.43
Switching from conventional cigarettes to electronic cigarettes [b]	Kasza 2018 (46)	USA	Cohort	12,862	1	RR 1.3	0.8-2.22
Decrease in conventional cigarette consumption per day	Kralikova 2013 (68)	Czech Republic	Cohort	1,738	NR	c	NR
	Brose 2015 [d] (65)	England	Cohort	4,064	1	OR 2.49	1.14-5.45
	Flacco 2019 [e] (63)	Italy	Cohort	915	4	OR 68	4.27-9.34
Transition from conventional cigarettes to electronic cigarettes	Barrington-Trimis 2018 (57)	USA	Cohort	6,258	1	9.3%	NR
	Niaura 2019 (43)	USA	Cohort	8,060	3	0.058 prob	0.047-0.069
	Hair 2019 (48)	USA	Cohort	15,275	2,5	HR 0.725	0.44-1.17
Dual transition to electronic cigarette	Barrington-Trimis 2018 [57]	USA	Cohort	6,258	1	15%	NR
	Niaura 2019 [43]	USA	Cohort	8,060	3	0.075 prob	0.058-0.094
	Hair 2019 [48]	USA	Cohort	15,275	2.5	HR 0.94	0.89-1
Conventional vs. dual cigarette abstinence	Piper 2019 [41]	UAE	Cohort	322	1	p 0.03 [f] p 0.07 [g]	NR
Prevalence of switching from conventional cigarettes to electronic cigarettes [h,i]	Park 2017 [42]	USA	Cross-sectional	40,558	NA	2.8%	2.6-3.1
	Anic 2018 [60]	USA	Cross-sectional	20,270	NA	25.7%	22.9-28.4

Dual: conventional cigarette and e-cigarette user; USA: United States of America; UAE: United Arab Emirates; Prob: probability; OR: odds ratio; RR: relative risk; HR: hazard ratio; NA: not applicable; NR: not reported.

[a] Odds of quitting smoking among current e-cigarette users compared with previous e-cigarette users.
[b] Switch to noncigarette tobacco use among current daily use of e-cigarettes and nonusers of e-cigarettes.
[c] Among regular e-cigarette users (n = 158), 60% reported that e-cigarettes allowed them to reduce their daily consumption of conventional cigarettes. These individuals smoked a mean of 9.7 cigarettes per day (standard deviation of 6.5), whereas those who did not report reduction smoked 13.1 cigarettes per day (standard deviation of 7).
[d] Daily use of e-cigarettes during follow-up was associated with higher odds of substantial reduction compared with non-users of e-cigarettes.
[e] Among dual users at baseline vs. tobacco smokers alone at 48 months.
[f] Confirmed 7-day point prevalence abstinence from conventional cigarettes at year 1 differed significantly between the dual-use group.
[g] Self-reported 30-day point prevalence abstinence from combustible cigarettes did not differ significantly between the two-use group.
[h] Increase from 2.2% in 2012 to 4.6% in 2014 (among all smokers in the previous year).
[i] Increase from 1.9% in 20120 to 3.8% in 2014 (among former smokers).

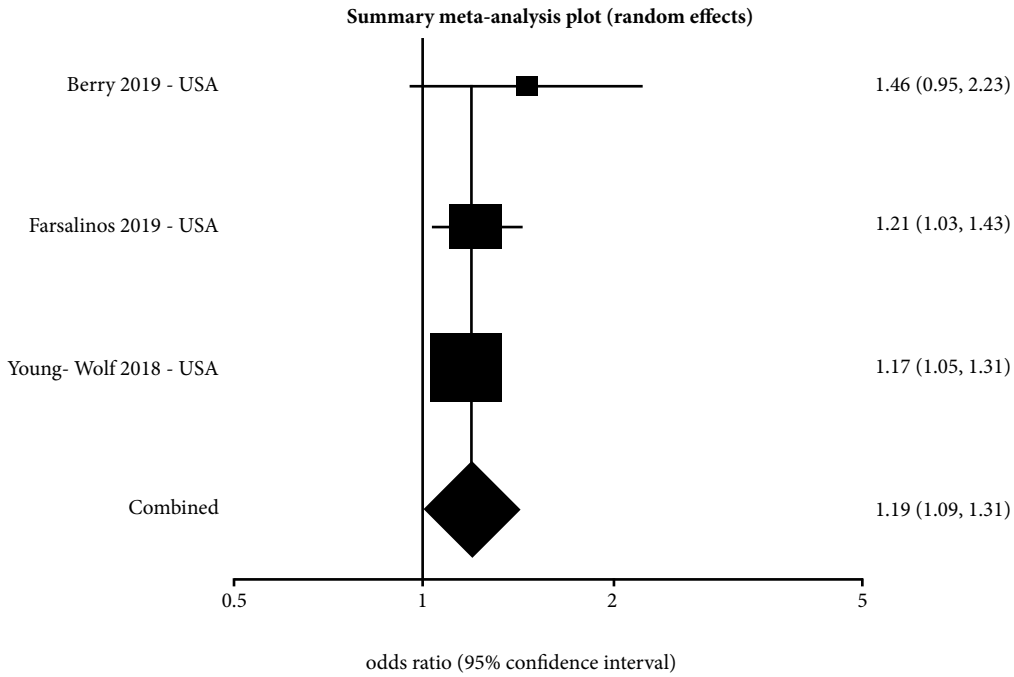

Figure 2. Forest plot of total switch of conventional cigarettes for electronic cigarettes.

reported smoking in the previous 5 years and used ENDS did not quit smoking conventional cigarettes. This study was not included in the meta-analysis because the follow-up period is much longer than in the other included studies. ENDS use was inversely associated with smoking cessation. The odds of quitting smoking among ENDS users were about half those observed for non-users of ENDS (OR: 0.53; 95% CI: 0.34-0.63; n=1,083).

Zhu *et al.* found that ENDS users had a higher rate of quitting conventional cigarettes than those who did not report using e-cigarettes, with a Relative Risk (RR) of 1.73 [37]. However, this study was not included in the meta-analysis because it lacked statistical information and used RR instead of OR. Piper *et al.* reported a confirmed abstinence from conventional cigarettes with a point prevalence of 7 days in the first year among exclusive users of conventional cigarettes versus users of the two products with a p-value of 0.03, but without reporting any measure of association (for that reason it was not considered in the meta-analysis) [41].

Regarding changes in prevalence over time, eighteen articles reported a general population estimate [39,40,59,60,62,62,64,66,67,69,70,42,44,45,47,50,54,56,58]. The prevalence of e-cigarette and conventional cigarette use by country are presented in the supplementary material, annex 6 and supplementary material, annex 7; likewise, the prevalence gap of e-cigarettes/conventional cigarettes by country was estimated (Table 3). In most cases the prevalence of e-cigarettes increased over time. Figure 3A shows the percentage prevalence of e-cigarettes and conventional cigarettes among adolescents in country-representative samples through 2018 (United States, Germany, and United Kingdom), where the prevalence of e-cigarettes among high school students in the US exceeded the prevalence of conventional cigarettes in 2018.

Figure 3B shows the prevalence of e-cigarette and conventional cigarette use among adults in Europe over time, showing, albeit slightly, an increase in the use of e-cigarettes and a decreasing trend in conventional cigarette use. Finally, Figure 3C shows how Park and Anic reported an increase in the prevalence of smokers who may switch from conventional cigarette use exclusively to ENDS over time in the U.S., both results were based on the National Adult Smoking Survey 2012-2013; 2013-2014 [42,60].

Regarding partial exchange, three studies reported a reduction in conventional cigarettes consumed per day among e-cigarette and conventional cigarette users [63,65,68]. While Kralikova reported a reduction in cigarettes over time in users of both [68], Brose *et al.* and Flacco *et al.* reported percentage reductions in conventional cigarettes consumed among users of both and nonusers of ENDS [63,65]. These three studies found a significant reduction in cigarette consumption between users of both and conventional cigarette users.

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Finally, four studies reported transition probabilities in baseline data. Niaura *et al.* [43] reported transition probability at 6 months and 3 years according to multistate probabilistic models. Hair *et al.* reported transition probability as a risk index [48]. Kasza *et al.* reported the transition to noncigarette smoking between current daily e-cigarette use and nonusers of e-cigarettes as a relative index [46]. Barrington-Trimis *et al.* reported the prevalence of percent transition from the total sample of exclusive users of conventional cigarettes and users of both at baseline to exclusive users of e-cigarettes at follow-up [57].

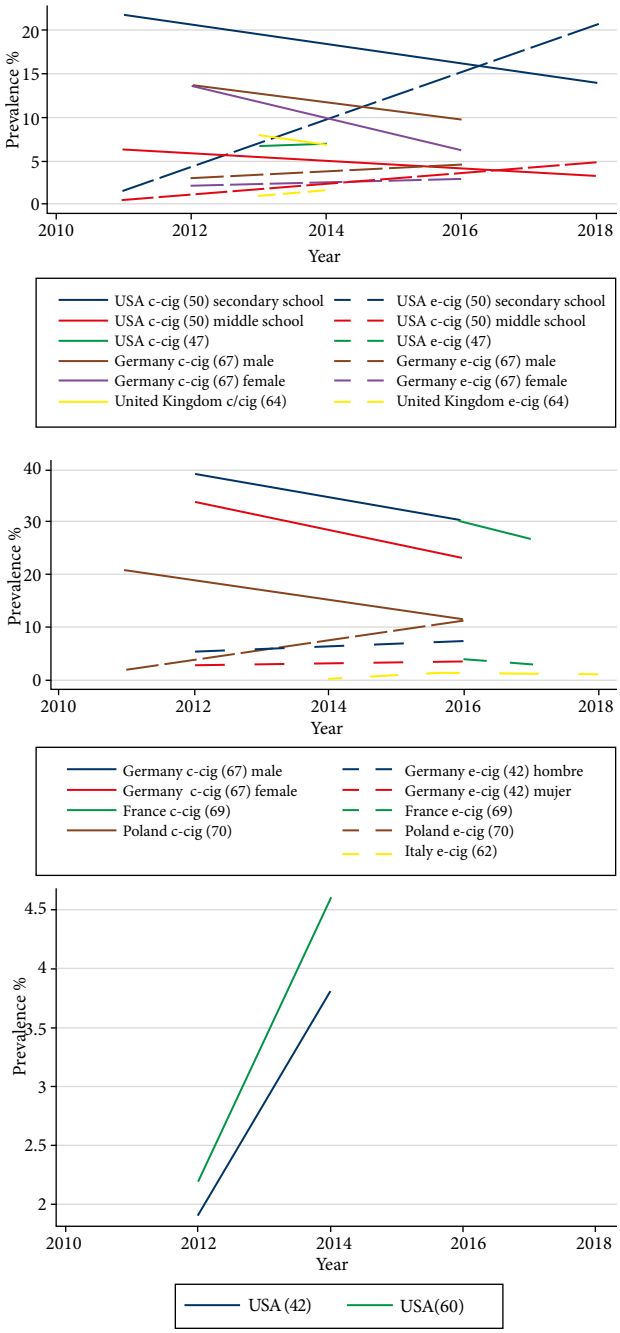
DISCUSSION

The commercial increase and the potential consequences derived from the use of ENDS in the population have transformed these devices into one of the current problems that opened a great debate in public health. Our study evaluated a little-known aspect about the different forms of switching from traditional tobacco by performing a systematic review and meta-analysis. This can be a complete switch to ENDS and also a partial switch as consumers of both products. In the first case, our meta-analysis showed an association between non-current ENDS users (daily or not) and smoking cessation compared to current ENDS users. In the second case, three studies reported a significant reduction in conventional cigarettes consumed per day among dual users (defined as users of conventional and e-cigarettes) and non-users of ENDS. Studies based on state transition models were heterogeneous. In addition, longitudinal studies showed that the prevalence of ENDS use is increasing, mainly in the teenage population, while traditional tobacco use shows a gradual decline.

Table 3. Absolute difference in the consumption prevalence of electronic cigarettes and conventional cigarettes (oldest prevalence minus most recent prevalence).

Country	Exposition	Study	n	2011	2012	2013	2014	2015	2016	2017	2018	Actual/ past	Absolute difference
France	e-cig	El-Khoury 2019 [69]	8,470	--	--	--	--	--	3.9	3	--	-0.9	2.3
	C-cig	El-Khoury 2019 [69]	8,470	--	--	--	--	--	30	26.8	--	-3.2	
	e-cig	Orth (m 12-17 y) 2018 [67]	17,540	--	3	--	--	--	4.6	--	--	1.6	5.5
	C-cig	Orth (m 12-17 y) 2018 [67]	17,540	--	13.7	--	--	--	9.8	--	--	3.9	
	e-cig	Orth (m 18-25 y) 2018 [67]	--	--	5	--	--	--	7.6	--	--	2.6	12.2
Germany	C-cig	Orth (m 18-25 y) 2018 [67]	--	--	39.3	--	--	--	29.7	--	--	9.6	
	e-cig	Orth (f 12-17 y) 2018 [67]	--	--	2.1	--	--	--	2.9	--	--	0.8	8.3
	C-cig	Orth (f 12-17 y) 2018 [67]	--	--	13.7	--	--	--	6.2	--	--	7.5	
	e-cig	Orth (f 18-25 y) 2018 [67]	--	--	2.8	--	--	--	3.4	--	--	0.6	10.9
	C-cig	Orth (f 18-25 y) 2018 [67]	--	--	33.8	--	--	--	23.5	--	--	10.3	
	e-cig	Smith 2018 [70]	5,708	2	--	--	8	--	11	--	--	9	18
Poland	C-cig	Smith 2018 [70]	5,708	21	--	--	15	--	12	--	--	9	
	e-cig	Barrington-Trimis 2016 [58]	2,055	--	--	--	6	--	--	--	--	NA	NA
	C-cig	Barrington-Trimis 2016 [58]	2,055	--	--	--	--	--	--	--	--	11.3	
	e-cig	Gentzke (Secondary school) 2019 [50]	14.6mill	1.5	--	--	--	--	--	--	20.8	19.3	27.2
	C-cig	Gentzke (Secondary school) 2019 [50]	14.6mill	21.8	--	--	--	--	--	--	13.9	-7.9	
	e-cig	Gentzke (Middle school) 2019 [50]	10.0mill	0.6	--	--	--	--	--	--	4.9	4.3	7.4
	C-cig	Gentzke (Middle school) 2019 [50]	10.0mill	6.4	--	--	--	--	--	--	3.3	-3.1	
United states of America	e-cig	Kasza (+25 y) 2018 [46]	20,183	--	--	0.9	1.3	--	--	--	--	0.4	-1.4
	C-cig	Kasza (+25 y) 2018 [46]	20,183	--	--	10.4	12.2	--	--	--	--	1.8	
	e-cig	Kasza (18-24 y) 2018 [46]	8,174	--	--	1.1	2.7	--	--	--	--	1.6	1.3
	C-cig	Kasza (18-24 y) 2018 [46]	8,174	--	--	6.7	7	--	--	--	--	0.3	
	e-cig	Loukas 2019 [44]	2,711	--	--	--	32.5	23.9	18.2	17.8	--	14.7	-6.3
	C-cig	Loukas 2019 [44]	2,711	--	--	--	38.9	32.5	30.1	30.5	--	8.4	
	e-cig	Stanton 2019 [44]	11,996	--	--	--	3.1	3.6	--	--	--	0.5	1
	C-cig	Stanton 2019 [44]	11,996	--	--	--	4.6	4.1	--	--	--	0.5	

C-cig: conventional cigarette; e-cig: electronic cigarette; m: male; f: female; y: year; NA: not applicable.



c-cig: conventional cigarette; e-cig: electronic cigarette.

Figure 3. A. Prevalence of electronic and conventional cigarettes among adolescents. B. Prevalence of electronic and conventional cigarettes among adults. C. Prevalence of smokers switching from conventional to electronic cigarettes in the United States.

We also found a negative relationship between consumption and price increases of e-cigarettes and conventional cigarettes. The positive values of the cross-price elasticity of e-cigarettes showed that e-cigarettes are partially interchangeable with conventional cigarettes, which is consistent with our epidemiological findings. To our knowledge, no specific instrument has been developed to evaluate studies aimed at estimating own-price elasticity and/or cross-price elasticity of demand. Therefore, to assess the quality of the included economic studies, we propose an ad hoc instrument, based on two previous systematic reviews that analyzed cigarette elasticities [21,72].

Given that tobacco is the leading preventable cause of cancer worldwide and that ENDS users are mostly teenagers and young people, some postulate that an alternative involving a "less harmful" option may be useful to avoid the harm caused by tobacco [3,14]. However, a large number of recent publications highlighted adverse effects related to ENDS, mainly cases of lung injury [13,73-76]. The similarities in risk factors and lung injury caused by SARS-CoV-2 alerts the scientific community that is trying to establish a link between the risk and susceptibility of ENDS users and the COVID-19 pandemic [77].

In addition, it is important to mention that most studies did not use biochemical parameters such as carbon monoxide (CO) measurement in exhaled air to confirm smoking reduction or cessation, although this method of analysis is currently under discussion [78]. On the other hand, the included studies did not consider adverse effects caused by ENDS use or the transition from ENDS users to conventional cigarettes or from use of both. For example, Wills *et al.* in a longitudinal study conducted in schools in Hawaii reported that in the teenager population, ENDS use is associated with a nearly threefold increased risk of smoking initiation [39]. Khouja *et al.* [79] conducted a systematic review on the use of electronic cigarettes in young adult nonsmokers and found a possible association with subsequent consumption of conventional cigarettes.

In 2014, McRobbie *et al.* published a Cochrane systematic review analyzing the effectiveness of ENDS for smoking cessation and reduction [80]. With only two randomized controlled trials for each outcome, the authors concluded that despite the low quality of evidence available at the time, ENDS use increased the odds of smoking cessation, which was consistent with the meta-analysis results. Unlike the study by McRobbie *et al.*, this systematic review took into account a wide variety of studies and designs, which allowed conclusions to be drawn including measures of association and longitudinal data, a situation that may be important for its external validity.

According to recent research, ENDS are known to have been designed initially for an audience of teenage non-nicotine users [81], although nicotine users remain of paramount importance for the natural history of cigarette

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smoking. Given the amount of nicotine contained in ENDS, the effectiveness of switching products may vary [78,82-84]. However, the growing wave of reports of adverse effects, mainly at the pulmonary level [13,73-76], accentuates the concern caused by these products, which is why many countries and states prohibit their commercialization, supported by greater control of these products by organizations such as the WHO or FDA, until the causes are clarified [85].

The main limitation is inherent to the nature of a rapid systematic review. Therefore, we did not search the gray literature, which could have contributed additional relevant information. Another limitation of our analysis was the heterogeneity among the included studies, which is a common finding when preparing systematic reviews of epidemiological studies [86]. Finally, additional studies might exist in bibliographic databases or regional repositories or after the search date (see supplementary material) that were not included in our review. Regarding the strengths of our review, we highlight the enrollment of the protocol in PROSPERO, the exhaustive search strategy used, the assessment of the risk of bias (quality of the studies) and the diversity of designs that we considered (the PRISMA checklist for our review is presented in supplementary material annex 8).

In conclusion, the likelihood of quitting conventional cigarette smoking among current ENDS users increased when compared to never users or ENDS users. However, this found short-term association might be different in the long term, and not directly associated with a positive effect due to the reported adverse events of ENDS, future research is needed to confirm this hypothesis. Economic studies found that the cross-price elasticity of e-cigarettes is partially interchangeable with conventional cigarettes. All these findings should be considered by decision makers to design public health strategies for tobacco control and by researchers to address highlighted evidence gaps.

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