A systematic review comparing the health effects of dual use of electronic and conventional cigarettes with health effects of exclusive smoking of conventional cigarettes

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Research Article

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Abstract

Background: A high prevalence of dual use (DU) of e-cigarettes and conventional cigarettes has been reported across the world. In some countries most users of e-cigarettes are dual users (DUs). We wanted to investigate the health effects of DU and compare with the health effects of exclusive smoking of conventional cigarettes (ESCC).

Methods: A systematic search was carried out in PubMed, EMBASE, CINAHL, and Cochrane library. The last search was conducted on April 26, 2021. We included original articles on any topic relevant to health, in all languages. Reviewers independently assessed the main risks of bias without the use of automated tools. We followed the PRISMA guidelines. Both reviewers independently screened and read all publications.

Results: Fifty-five publications (52 studies) were included, 12 of the studies were prospective. There was great heterogeneity across studies both in methodology and outcome. Several studies, especially experimental studies with short-term outcome, found higher levels of harmful substances in ESCC than in DUs, however, the two largest population-based studies, with low risk of selection-bias, found higher levels of harmful substances in DUs than in ESCC. Most studies investigating symptoms or risk of disease were large population-based surveys. One study found that DUs reported a significantly better health than ESCC, while fifteen found a higher risk of e.g., pulmonary, cardiovascular or metabolic risk factors/symptoms, self-reported general health or cancer in DUs than in ESCC. The study with the longest follow-up, six years, found that DUs had an adjusted odds ratio of 1.48 (95% confidence interval 0.81–2.70) of a possibly smoking-related disease (confirmed by hospital discharge abstracts) compared with ESCC. Many methodological weaknesses were identified, such as risk of reverse causality. We found a correlation between high tobacco consumption in DUs and findings of negative health outcomes.

Conclusion: Due to many methodological weaknesses, it is difficult to draw any strong conclusions, but the results indicate that DU might be as or even more harmful than ESCC. Well-designed longitudinal studies are needed. Before recommending EC for smoking cessation health authorities should consider the high risk of DU and its potential consequences.

Introduction

The number of electronic cigarette/e-cigarette (EC) users has been increasing rapidly, and it is estimated that the number of adults who vape will reach almost 55 million by 2021 (1). Available evidence on the benefits and risks of EC use are mixed and interpreted differently. Some believe that ECs have the potential to reduce the burden of disease in smokers (2, 3) while others worry about the impact on public health and do not recommend, or even ban, their use (4, 5).

The most common reason for EC use is smoking cessation (6, 7). Smokers buy e-cigarettes (ECs) in order to quit smoking, but even though many succeed to switch to ECs for a short period, most relapse to smoking of conventional cigarettes (CCs). Unfortunately many continue using ECs as a supplement to CCs, a so-called *dual use* (DU) (8-12). A review found that dual users (DUs) perceive ECs to be safer and less addictive than CCs (13).

A high prevalence of DU has been reported in several studies across the world (8-11, 14-16). Studies from South Korea found that up to 97% of current EC users also smoked (17-19), whereas a large population-based study

from the United Kingdom (UK) reported that only 37% of adult EC users also used CCs (20). In a study based on almost one million adults in the United States of America (USA), 64% of EC users also smoked (21). This corresponds to approx. 1–3% of the population being DUs (18, 20-24).

DU might be a short transition period before quitting smoking completely. However, a cohort study with six years of follow-up found that most DUs relapse to exclusive smoking of CC (ESCC) and few transition exclusively to EC use (25, 26). Several other studies have reported the same findings (27-31).

A further concern is that there may not be a significant reduction in DUs' consumption of CCs (32-34). For example, a study from Poland found that the frequency of DU was higher than exclusive use of a single product among adolescents and DUs did not smoke fewer CCs per day (CPD) than ESCC (35).

While health effects of smoking as well as vaping have been extensively studied, it is important to understand health effects of dual use. To our knowledge, only one review has investigated the health effects of DU (in pregnancy) (36)). The aim of this systematic review was to gather the existing evidence comparing the health effects of DU with the health effects of ESCC.

Methods

We have followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines whenever meaningful.

Eligibility criteria

Original articles on DU of ECs and CCs on any topic relevant to health in any language.

Exclusion criteria

Several cross-sectional studies have investigated the association between mental health problems and DU. These studies were not included, as we found it difficult to distinguish between mental health problems being a result of DU or a predictor of DU.

Information sources

A search was carried out in PubMed, EMBASE, CINAHL, and Cochrane library (Appendix 1, detailed search).

Search strategy

The first search was conducted on January 12, 2021. The last search was conducted on April 27, 2021. We used the keywords "dual use" AND "e-cigarette" OR "e-cigarettes" OR "electronic cigarette" OR "electrically heated cigarette" OR "electronic nicotine delivery system" OR "electronic nicotine delivery device". Keywords had to be included in the title, abstract, and/or full text. We used no other filter or limits.

Selection process

We identified 2,023 titles (Figure 1) of which 1,312 were duplicates, leaving 711 for screening. The screening process was blinded (Covidence was used for screening), and agreement of both authors was necessary to

include/exclude a title. After reading the title and abstract, 623 titles were clearly not about the health effects of DU of ECs and CCs, leaving 88 papers eligible for full-text review. All were in English. Full documents were obtained for a thorough reading and a further 42 papers were excluded due to the following criteria: wrong outcome (e.g. smoking cessation or level of nicotine dependence), comparison between DU and ESCC was not possible (no analyses performed), article retracted, not EC-CC dual use (Figure 1), leaving 46 papers. An overview table of all excluded titles including the reason for exclusion, can be found in Appendix 2. Additionally, references from the screened full text papers were carefully examined for missed papers, and our own reference data base was hand-searched for possible overlooked titles. Nine relevant studies were identified and included, leaving a total of 55 papers in the final analysis.

Data collection process

During the data collection process, each reviewer independently read and extracted data from each paper to a predefined table framework. Results from the independent data collection were then compared, discussed and merged into one detailed table (Appendix 3).

Study risk of bias assessment

Both reviewers independently assessed the main risks of bias without the use of automated tools. Due to the heterogeneity of study methods, it was not possible to use a universal assessment method. When assessing selection bias, we considered sampling, volunteer bias and attrition bias. We also looked to see whether data were weighted for non-participation and if the study had taken confounding into account.

Effect measures

Effect measures varied depending on the outcome. Most papers on symptoms or disease risk presented unadjusted and adjusted odds ratios with a 95% confidence interval (CI). We present adjusted odds ratios if available (aOR, Appendix 3). Papers on toxic effects typically presented geometric means and 95% CI and/or ranges and interquartile intervals.

Data items

Papers were included if any outcome data comparing DU with ESCC were presented, even if significance levels between ESCC and DU were not shown. We extracted the same predefined information from all papers (Appendix 3). If data on any variable were missing, we searched in supplementary material and/or in study protocols.

Synthesis methods

There was great heterogeneity both in methods and outcomes across papers, so merging of results in a meta-analysis was not possible. After completing Appendix 3, which gave us an overview of all studies, we distributed papers according to four categories: toxicity/carcinogenicity, pulmonary effects, cardiovascular and metabolic effects, and other health effects (Tables 1–4). Some studies reported on more than one type of health outcome (e.g. both pulmonary and cardiovascular disease) and are therefore to be found in more than one of the tables. Results were synthesized into five overall categories, marked by signs (##, #, ¤, *, **) (Tables 1–4).

Results

Appendix 4 shows the characteristics of studies, study design, definition of use and prevalence of use in detail.

Study design (Appendix 4 for details)

The majority of studies reported results of cross-sectional analyses, mostly using self-reported data from large population-based surveys. One study was an experimental animal study (38), three were switch-of-product experimental studies (37, 41, 48). Fifteen papers/12 studies reported results from studies with a prospective design (25, 26, 37-49).

Definitions of use (Appendix 4 for details)

There was great variation both in duration and in frequency of use of products for details. The definitions of ESCC, EC users and DUs were based on self-reports and varied a lot across studies.

Conflict of interest

Sixteen (29%) of the studies had a conflict of interest (COI): two with an EC manufacturer (50, 51), two had received financial support from anonymous contributors (26, 40), and the remaining had a COI with pharmaceutical companies. One study was tobacco-industry-sponsored and found a beneficial effect of replacing ESCC with the ECs they manufactured, also in DUs (41).

Overall findings

Many studies did not find a significant difference between DU and ESCC. After having excluded the study sponsored by the tobacco industry, seven studies found that ESCC had significantly worse outcome than DUs (25, 37, 48, 52-54), two of these were experimental switch-of-product studies with short term outcome (37, 48). Eighteen studies found that DUs had significantly worse outcome than ESCC (11, 17-19, 21, 23, 25, 55-64).

Toxicity and carcinogenicity (Table 1)

Fourteen studies investigated the levels of harmful and potentially harmful substances in urine, blood, hair and saliva of DUs of ECs and CCs and in ESCC. Some studies measured only one or two harmful substances (50, 53, 65) while others tested up to 50 (11). Six studies found that levels of harmful substances were higher in ESCC (37, 41, 48, 52-54). One study found that DUs had higher values for most substances tested, but it did not test for significance (51). Three studies found significantly higher levels of harmful biomarkers in DUs (11, 55, 56), and nine studies found no significant difference. Results of the largest population-based studies, with low risk of selection bias, indicate that real-world DUs' might be exposed to higher levels of several harmful substances than ESCC.

Three studies had an experimental design with short-term follow-up. In one study, DUs should switch to ESCC for one week. The same or higher levels of carcinogen metabolites were measured in the ESCC period compared

with the DU period (37). In the second study, smokers who wanted to stop smoking should switch from ESCC to ECs. After one month, 52% used both ECs and CCs (DUs) but had reduced their tobacco consumption significantly (approx. half of them had smoked less than five CCs in the last week). DUs had significant reductions in carbon monoxide and a major metabolite of acrolein (48), a bladder carcinogen. One study was tobacco-industry-sponsored: ESCC were randomized to DU for five days. DUs' who had halved the number of CPD had significant reductions in most of the harmful biomarkers assessed (41).

Two studies included long-term users who had used ECs and CCs for at least six months. One study included almost 500 persons (54) and found that DUs and ESCC had similar levels of toxic and carcinogenic substances, but ESCC had significantly higher levels of three tobacco-specific nitrosamines and acrylonitrile than DUs. The other long-term study included almost 200 persons and found that DUs and ESCC had similar levels of toxic and carcinogenic substances, but DUs had a significantly higher level of benzene, a carcinogenic substance (56).

Three studies measured carcinogen and toxin exposure in large samples of the general population, reflecting the levels of real-world use (11, 55, 66). The largest study measured 50 biomarkers of toxicity/carcinogenicity in urine in more than 5,000 adults and found that DUs had significantly higher concentrations of most biomarkers than ESCC (11). The second largest study included almost 3,000 adults, measured over 40 biomarkers of toxicity/carcinogenicity in urine and blood and found that DUs had significantly higher levels of some toxic and carcinogenic biomarkers compared to ESCC (55). A third large population-based study included more than 1,100 persons and found the same levels of metals in DUs and ESCC (66). All three studies had low risk of selection bias, had weighted data and adjusted for relevant confounding (11).

Studies investigating health outcomes (Table 2-4)

One study found that ESCC had significantly worse health outcome than DUs, while 15 studies found the opposite.

Pulmonary outcomes (Table 2)

Fourteen studies investigated pulmonary outcomes. Except for a register-based study (47), all were large population-based surveys including between > 8,000 (67) and almost 900,000 participants (21). Studies presented self-reported symptoms/diagnoses. Two had a longitudinal design (46, 47).

Two studies in adolescents, based on the same survey in 2018, found that odds of asthma were higher in DUs than in ESCC (68, 69), but significance tests were not presented. One of the studies found higher odds of allergic rhinitis (68) in DUs than in ESCC, whereas the other study found comparable odds (69). The same odds of asthma were found in one study, but in analyses of complete data of current users, DUs had a significantly higher risk of asthma than ESCC (67). Three other studies found higher odds of asthma in adolescent (70) and adult DUs (59, 71) than in ESCC, but significance levels were not tested.

One study found the same odds of respiratory symptoms (72), and another study found higher odds in DUs than in ESCC (22) without, however, testing the significance level. Two studies found significantly higher odds of COPD, emphysema and chronic bronchitis (21, 57) and a third of breathing difficulties (58) in DUs rather than in ESCC. Further, one study found higher odds of COPD (71) and one of respiratory disease (46) in a cohort study, but significance levels were not tested.

In a cohort of military personnel incident cases of acute respiratory infections (in- and outpatient diagnoses) in the last 9 months were investigated, and the study found that DUs had higher incident rate of acute respiratory infections than ESCC but significance level was not tested (47). Finally, different pulmonary responses were found in mice exposed to both aerosol from EC and smoke from CC than in mice exposed to smoke from CC only. Dual exposure increased airway resistance compared with mice exposed to smoke from CC only but significance level was not stated (38).

Cardiovascular and metabolic outcomes (Table 3)

Eleven studies investigated the cardiovascular and metabolic outcomes in DUs and in ESCC. All, except two studies (48, 73), were large population-based surveys with self-reported symptoms/diagnoses, including from almost 3,500 (74) to almost 450,000 (23) adults.

The largest study from the general population found significantly higher odds of self-reported CVD (stroke, myocardial infarction or coronary heart disease) (23) and significantly higher odds of self-reported premature CVD in DUs than in ESCC. The second largest nationally representative study found significantly higher odds of self-reported stroke (61) in DUs compared with ESCC, and another large survey found a significantly greater proportion of DUs reporting past/current arrhythmia than ESCC (58). Further, a large survey found that DUs had higher odds of myocardial infarction and stroke than CCU, but significance levels were not tested (75).

Three surveys investigated cardiovascular risk factors. One found that DUs had a significantly higher prevalence odds ratio of cardiovascular risk factors and diagnosis of metabolic syndrome than ESCC (17). One found that DUs had significantly higher odds of elevated human c-reactive protein, a biomarker of inflammation and predictor of cardiovascular disease, than ESCC (60). The last found that DUs had significantly higher odds of abdominal obesity than ESCC, but otherwise found no significant differences, even though there was a tendency to higher odds in DUs than in ESCC, except for blood pressure, for which ESCC had higher odds (18). This contrasts with a survey finding that DUs had higher odds of hypertension than ESCC, but a significant difference was not reached (24).

Three population-based surveys investigated diabetes-related measures. One study found that DUs had similar fasting glucose as ESCC (17), and another found that DUs had higher glycosylated hemoglobin levels than ESCC, but the significance level was not tested (76). A third study found the same levels of insulin resistance (74). In a clinical study, non-invasive vascular function testing was performed in almost 500 young persons, and the study found that DUs had similar arterial stiffness as ESCC (73).

Other health effects (Table 4)

Twenty studies investigated other health effects. Eight of the studies were based on cohorts (42) (25, 26, 39, 40, 43-45), four of these were follow-ups to the same study (25, 26, 40, 45).

In the prospective study with the longest follow-up, almost 1,400 persons were included at baseline (26). Adherence was high for six years. After one year, DUs had the same self-reported health as ESCC (45). Two years after baseline, DUs still had the same self-reported health as ESCC and a significantly higher probability of serious adverse events (25). However, six out of ten DUs stopped using ECs and continued to smoke, those who still were DUs at the 24-month follow-up had significant improvement in self-rated health. After four years, there

was still no significant difference in self-reported health score and possible smoking-related disease between the DU group and CC users, but the study found generally worse outcomes in DUs (40). After six years, a possibly smoking-related disease was recorded in 10% of the participants, with no significant differences from the baseline group. Moreover, self-reported health showed a very small change over time in all groups. DUs had an adjusted odds ratio (OR) 1.48 (0.81–2.70 95% CI) of a possibly smoking-related disease and an adjusted coefficient 0.16 (-0.08, 0.39 95% CI) of self-rated health compared with ESCC. The results did not differ substantially when the sample was restricted to those who did not switch smoking/vaping group or to those who were visited or had their outcomes confirmed through a linkage with hospital discharge abstracts (26). Advanced analyses and adjustment for many confounders was performed.

Pregnancy outcomes

Four studies included pregnant women. Two found higher odds of giving birth to a small-for-gestational-age child among DUs than ESCC, but significance level was not tested (42, 43) whereas one found that DUs and ESCC had the same risk of small-for-gestational-age (49). This study also found that DUs had lower odds of preterm birth than ESCC, but significance level was not tested (49). The last study found that offspring of DUs had same birthweight, Apgar score and mean gestation at delivery as ESCC and that offspring of DUs had a higher rate of admission to neonatal intensive care unit and higher incidence of birthweight <10th centile than ESCC, but significance level was not tested (39). Further, a prospective study found lower fecundability ratio in DUs than in ESCC, but not significantly different (44).

Two large surveys looked at sleep in adolescents. One study found that high-school students with DU were significantly more likely to report insufficient sleep compared with ESCC (64). The other study also found that DUs had a higher risk of sleep-related complaints than ESCC, but it was not significant (77). The third study including adolescents found higher odds of dental problems than ESCC, but the significance level was not tested (78).

Two large population-based surveys investigated SARS-CoV-2(COVID-19)-related issues. Both found that DUs had higher odds of symptoms and higher odds of confirmed/suspected COVID-19 diagnosis than ESCC, but significance levels were not tested (20, 79).

Further, population-based surveys found significantly worse median general health scores (58) and significantly higher levels of uric acid and prevalence of hyperuricemia (19) in DUs than in ESCC and the same prevalence of poor physical health (72). An interview survey in more than 4,000 homeless adults found that DUs had significantly higher rates of cancer compared to ESCC (63). A large survey in male soldiers found that DUs had significantly worse fitness than ESCC (62). Finally, a clinical study found that DUs had higher levels of most biomarkers of systemic inflammation than ESCC, but the difference was not significant (80).

Discussion

This is the first systematic review comparing the (general) health effects of DU with ESCC. We identified 55 papers/52 studies. There was great heterogeneity across studies, both in the definition of use, in methodology and in outcome measurement. Only 12 studies had a prospective design, and many studies had methodological weaknesses, so it is difficult to draw strong conclusions.

Several studies, especially experimental studies with short-term outcome, found higher levels of toxic/carcinogenic substances in ESCC than in DUs, however, the largest population-based studies with low risk of selection bias indicate that real-world DUs' might be exposed to higher levels of harmful substances than ESCC. Most studies investigating symptoms or risk of disease were large population-based survey. The longest follow-up of a cohort was six years. One study found that DUs reported a significantly better health than ESCC while fifteen found a higher risk of e.g., pulmonary, cardiovascular or metabolic risk factors/self-reported symptoms, self-reported general health or cancer in DUs than in ESCC.

If smokers replaced most of the CCs with ECs, there might be a beneficial effect of DU (81). The included studies found that DUs smoked the same number of CPD as ESCC (11, 17, 26, 41, 45, 55, 62), one study actually found a significantly higher number of CPD in DUs than in ESCC (58). This is in agreement with other studies, not included in this review (32-34, 82, 83). Thus, known and unknown (84) harmful compounds and transformation products formed during the vaping process of ECs (85) (81) are added to the harmful substances in tobacco smoke.

The experimental studies confirm a correlation between the number of CPD and harm in DUs, DUs who had substantially reduced the number of CPD with ECs exhibited reduced biomarker levels (41, 48) proportional to the reduced numbers of CPD (41). Also, a large population-based study showed that the frequency of CC use was positively correlated with toxicant concentration (11). Most of the studies that reported the same or higher tobacco consumption in DUs as in ESCC found significantly worse health outcomes in DUs than in ESCC (11, 17, 26, 55, 58, 62). None of the studies where DUs reported smoking a lower number of CPD than ESCC found significantly worse outcome in DUs (50, 51, 54), in fact, one of them found that ESCC had a worse outcome (54).

Only two studies investigated the potential impact of the frequency/dose of EC use by DUs. A survey found that the risk of premature CVD was significantly higher in DUs with a daily use of ECs than in those with occasional use of ECs (23). Another survey found increased odds of COPD with increasing frequency of EC use among people who had never smoked, indicating a stepped harm of EC use (57). The impact of frequency/dose of EC use and potential biological interactions of ECs and CCs need further investigation.

It is important to note that the majority of studies were cross-sectional (conclusions on causality cannot be drawn) and most DUs have been ESCC for decades and might have persistent smoking related disease. Further, some of the studies investigating disease asked if participants *ever* had been diagnosed with, for example, heart disease (23) or stroke (61), without taking into account if this occurred before or after they started using ECs. The study by Bhatta found $p<0.001$ for reverse causality (46).

Confounding factors could also be a reason for the tendency towards worse health outcomes in DUs. Almost all studies adjusted for sociodemographic factors and many adjusted for other relevant factors, such as exposure to second-hand smoke (68). However, few studies adjusted for differences in previous tobacco consumption, years smoked or age at smoking debut. The Italian cohort study, however, had adjusted for years of tobacco smoking and still found that the risk of possible smoking-related disease tended to be slightly worse in persistent DUs after six years (26).

Few of the included studies were designed to compare DUs with ESCC. Also, the definition of DU varied a lot across studies and disease was mostly self-reported, which imposes the risk of both recall and misclassification bias. However, a large retrospective survey using hospital records also found a tendency towards a higher risk of respiratory infections in DUs (47). Misclassification might also be a problem when it comes to smoking/vaping status (86).

On the other hand, the included studies had also several strengths. Some were very large. Most surveys weighted data, and almost all studies took confounding into account. Regarding the misclassification of disease diagnoses, the Italian cohort study also performed analyses on participants who had their outcomes confirmed through a linkage with hospital discharge abstracts (26), and reached the same conclusion.

Well-designed longitudinal studies on health effects of DU are needed.

Limitations

Due to the large heterogeneity of the studies, we were unable to assess the quality of studies in a systematic way. Due to the large heterogeneity in outcome measurement we were not able to perform a meta-analysis.

Strengths

Both authors independently read all abstracts and full text of papers and extracted data. Eventual disagreements were discussed. Potential COIs that might influence the findings were described.

Conclusion

A high prevalence of DU of ECs and CCs has been reported across the world. In some countries a majority of users of ECs are DUs. Our findings indicate that DU might be as or maybe even more harmful than ESCC, but strong conclusions cannot be drawn due to many methodological weaknesses. Well-designed longitudinal studies on health effects of DU are needed. Before recommending e-cigarettes for smoking cessation or implementing a legislation that favours use of EC health professionals and decision makers should consider the high risk of DU and its consequences on public health.

Abbreviations

CC
conventional cigarette
CCs
conventional cigarettes
CPD
cigarettes per day
DU
dual use
DUs
dual users
EC

e-cigarette
ECs
e-cigarettes
ESCC
exclusive smokers/smoking of conventional cigarettes

Declarations

Ethics approval and consent to participate: not applicable

Consent for publication: not applicable

Availability of data and materials: not applicable, all studies are available in search databases.

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Authors' contribution: The corresponding author attests that both listed authors meet authorship criteria and that no others meeting the criteria have been omitted. CP planned the study and is guarantor with full responsibility of the study. CP and SKBR conducted the study together. SKBR ran the search and wrote first part of the method section. CP wrote first draft of the other sections. Both screened abstracts, read and interpreted results of included papers and decided on exclusion of papers. Both contributed to the revisions of the paper and read and approved the final draft.

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Tables

Table 1. Studies investigating levels of harmful and potentially harmful substances in urine, blood, hair and saliva

First author, year of publication, country, conflict of interest	Method	Participants	Risk of selection bias/weighted data/adjusted analyses	Major outcomes	Overall findings Sign. higher risk/prevalence/level in ESCC ## Higher risk/prevalence/level in ESCC, sign. level not tested or not sign. # Same risk/prevalence/level in ESCC and DUs ¤ Sign. higher risk/prevalence/level in DUs * Higher risk/prevalence/level in DUs, sign. level not tested or not sign. **
Carroll D.M. (65) 2018, USA None	Cross-sectional study	94 volunteer adults of American Indian descent	High/-/(no)	Carcinogen metabolite (NNAL) in urine	DUs same level of carcinogen biomarker as ESCC ¤
Clemens M.M. (43) 2019, USA None	Population-based surveillance system before and during pregnancy	248 pregnant women	Low/yes/yes	Carcinogen metabolites (TSNAs) in hair samples	DUs same level of carcinogen biomarkers as ESCC ¤
Czoli C.D. (37) 2018, Canada Yes	Human experimental within-subjects crossover study (7 days x 3)	48 volunteer adults with DU	-/-/no (Adherence not confirmed)	Carcinogen metabolites (1-HOP, NNAL) in urine	Experimental DU-period same level of carcinogen biomarkers, or sign. lower level, compared to CC only-period ¤ ##
Goniewicz M.(11) 2018, USA Yes	Cross-sectional analyses of nationally representative cohort study	5,105 adults	Low /yes/yes	50 biomarkers of toxicity (TSNAs, metals, PAHs & VOCs) in urine	DUs: sign. higher concentration of most biomarkers of toxicity/carcinogenicity than ESCC **
Jain R. (66) 2019, USA None	Cross-sectional analyses of population-based survey	1,139 adults	Low/yes/yes	Harmful metals (cadmium, lead, and	DUs same levels of harmful metals in blood as ESCC ¤

				mercury) in blood	
Keith R. (52) 2020, USA None	Cross-sectional analysis of cohort study	371 volunteer adults	Low/no/yes	Volatile organic compound (VOC) metabolites in urine	DUs and ESCC had similar levels of most VOC metabolites, except four, which were significantly higher in ESCC than in DU ¤ ##
McRobbie H. (48) 2015, UK Yes	Smoking cessation study 4 weeks	44 healthy volunteer smokers	High/-/no	Urinary 3-HPMA, a major metabolite of acrolein and carbon-monoxide (CO)	DUs had sign. reductions of 3-HPMA and CO after switching from ESCC in experimental setting (sign. reduction in cotinine in DU) ##
O'Connell G. (41) 2016, USA Yes ▲	Human experimental forced-switch study (5 days)	105 healthy volunteer adult smokers	High/-/no (Forced reduction of number of CC)	Harmful and potentially harmful constituents (such as NNAL, NNN and nitric oxide) in urine	DUs who had reduced half of their number of CC: significant reductions in most of the biomarkers assessed (20–35% reduction) from baseline CC use only ##
Piper M (53) 2018, USA None	Cross-sectional analysis of cohort study	422 volunteer adults	Low/no/yes	Carcinogen metabolite (NNAL) in urine	DUs had sign. lower levels of NNAL than ESCC ##
Prokopowicz A. (50) 2019, Poland Yes▲	Cross-sectional study	156 young volunteer adults	High/-/yes	Harmful metals cadmium (Cd) and lead (Pb) in blood	DUs: levels of harmful metals not sign. different than ESCC ¤
Prokopowicz A. (51) 2020, Poland Yes▲	Cross-sectional study	88 young volunteer adults	High/-/yes	11 toxic metals in urine	Sign. level between ESCC and DUs not tested, but DUs had higher values for 8 out of 11 metals in urine *
Rostron B. L. (55) 2019, USA None	Cross-sectional analysis of a nationally representative cohort	2,710 adults	Low/yes/yes	Carcinogen and toxin exposure, biomarkers (VOCs, PAHs and TSNAs) in urine and blood	DUs: sign. higher levels of some toxic and carcinogenic biomarkers (NNAL, 1-HOP, HPMA and MHB3) compared to ESCC ** ¤

Shahab L. (56) 2017, UK Yes	Cross-sectional study	181 volunteer adults with long-term use	High/-/yes	Carcinogen and toxin exposure, biomarkers (VOCs and TSNAs) in urine and saliva	DUs and ESCC had similar levels of toxic and carcinogenic substances, but DU had sign. higher level of one carcinogenic substance, benzene than ESCC ¤ **
Smith D. (54) * 2020, Poland, UK and USA Yes	Cross-sectional study	456 volunteer adults with long-term use	High/-/yes	Carcinogen and toxin exposure biomarkers (VOCs, TSNAs and minor alkaloids) in urine and saliva	DUs and ESCC had similar levels of toxic and carcinogenic substances, but ESCC had sign. higher level of three TSNAs and acrylonitrile than DUs ¤ ##

* Participants from UK, Shahab 2017, also included in this study

Abbreviations and symbols used in the four tables:

★ Conflict of interest: financial support from anonymous contributors

▲ Conflict of interest with the tobacco or e-cigarette industry

➡ Prospective design

EC= e-cigarettes

ESCC= exclusive smokers of conventional cigarettes

ECU= e-cigarette users

DU= dual use of conventional cigarettes and e-cigarettes

DUs= dual users of conventional cigarettes and e-cigarettes

CC= conventional cigarettes

CCU= conventional cigarette users

TPU= users of combustible tobacco products (CC, cigarillos, cigars, pipe, water pipe)

NU= Non-user of conventional cigarettes and e-cigarettes

1-HOP= 1-hydroxypyrene (PAH)

3-HPMA =Urinary 3-hydroxypropyl mercapturic acid, a major metabolite of acrolein

CO= carbon monoxide HPHC = harmful and potentially harmful constituents

COPD = chronic obstructive pulmonary disease

CRP = human c-reactive protein

CYMA: a metabolite of acrylonitrile (VOC)

TSNA = Tobacco-specific *N*-nitrosamines

PAH = polycyclic aromatic hydrocarbons

GTT = glucose tolerance test

HbA1c = glycosylated haemoglobin

HOMA-IR = homeostatic model assessment of insulin resistance

HPMA: N-acetyl-S-3-hydroxypropylcysteine, a metabolite of acrolein (VOC)

MHB3, a metabolite of 1,3-butadiene (VOC)

MU = *trans,trans*-Muconic acid (VOC, benzene)

NNAL = 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol, the principal metabolite of the lung carcinogen NNK (TSNA)

NNN = N0-nitrosonornicotine (TSNA)

NRT=nicotine replacement therapy

PHEMA= N-Acetyl-S-(1 and 2-phenyl-2-hydroxyethyl)-L-cysteine (VOC, styrine)

PMA= benzene

VOC= Volatile organic compounds

Table 2. Studies investigating pulmonary outcomes

Table 3. Studies investigating cardiovascular and metabolic outcomes

First author, reference, year of publication, country, conflict of interest	Method	Number included	Risk of selection bias/weighted data/adjusted analyses	Major outcomes	Overall findings Sign. higher risk/prevalence/level in ESCC ## Higher risk/prevalence/level in ESCC, sign. level not tested or not sign. # Same risk/prevalence/level in ESCC and DUs ¤ Sign. higher risk/prevalence/level in DUs * Higher risk/prevalence/level in DUs, sign. level not tested or not sign. **
Bhatta D. N. (46) 2020, USA None	Nationally representative cohort study	32,320 adults	Low/yes/yes	Self-reported respiratory disease (chronic obstructive pulmonary Disease (COPD), chronic bronchitis, emphysema, or asthma)	DUs: higher odds of reporting of respiratory disease than ESCC but sign. level not tested *
Cho J. H. (70) 2016, South Korea None	Nationally representative survey	35,904 adolescents	Low/no?/yes	Self-reported diagnosed with asthma	DUs higher odds of reporting asthma than ESCC but not sign. in adjusted analyses *
Chung S. J. (68) 2019, South Korea None	Nationally representative survey	60,040 adolescents	Low/yes/yes	Self-reported diagnosed with asthma or/and allergic rhinitis	DUs had higher odds for current allergic rhinitis but lower odds of current asthma than ESCC, but sign. level not tested * #
Hedman L. (22) 2018, Sweden Yes	2 population-based surveys	30,272 adults	Low/no/yes	Self-reported respiratory symptoms: long-standing cough, sputum production, wheeze	DUs had higher odds of self-reported respiratory symptoms than than ESCC but sign. level not tested *

Lee A. (69) 2019, South Korea None	Population-based survey	58,336 adolescents	Low/yes/yes	Self-reported asthma, allergic rhinitis and atopic dermatitis	DUs har lower odds of asthma than ESCC, but comparable odds of allergic rhinitis and atopic dermatitis. Sign. level not tested # ¤
Li D. (72) 2020, USA Yes	Nationally representative survey	28,171 adults	Low/yes/yes	Self-reported respiratory symptoms	DUs same odds of respiratory symptoms as ESCC ¤
Osei A. (57) 2020, USA Yes	Nationally representative survey	705,159 adults	Low/yes/yes	Self-reported diagnosed with COPD/ emphysema/ chronic bronchitis	DUs had sign. higher odds of COPD/ emphysema/ chronic bronchitis than ESCC **
Parekh T. (71) 2020, USA None	Nationally representative survey	161,965 young adult women	Low/yes/yes	Self-reported diagnosed with COPD/ emphysema/ chronic bronchitis and asthma	DUs had higher odds of asthma and COPD compared than ESCC, but sign. level not tested *
Sanou A. Z. (47) 2020, USA None	Register study using a cohort	802,621 adult military members	Low/no/yes	Incident cases of acute respiratory infections (in- and outpatient diagnoses)	DUs had higher incident rate of acute respiratory infections than ESCC but sign. level not tested *
Wang J. B. (58) 2018, USA Yes	Internet population - based survey	39,747 adults	Low/no/yes	Self-reported cardiopulmonary symptoms in the last months	DUs had sign. higher/worse breathing difficulty score than ESCC **
Wills T. A. (67) 2019, USA None	Population-based survey	8,087 adults	Low/yes/yes	Self-reported diagnosed with asthma, COPD	DUs and ESCC same odds of asthma DUs higher odds of COPD than ESCC but not sign. ¤ *
Wills T. A. (59) 2020, USA None	Nationally representative survey	14,765 adults	Low/yes/yes	Self-reported diagnosed with asthma	DUs higher odds of asthma than ESCC, but not sign. Complete data, current users: DUs had sign. higher risk

					of asthma than ESCC * **
Xie Z. (21) 2020, USA None	Nationally representative survey	887,182 adults	Low/yes/yes	Self-reported diagnosed with COPD	DUs had sign. higher risk of self-reported COPD than ESCC **

First author, reference, year of publication, country, conflict of interest	Method	Number included	Risk of selection bias/weighted data/adjusted analyses	Major outcomes	Overall findings Sign. higher risk/prevalence/level in ESCC ## Higher risk/prevalence/level in ESCC, sign. level not tested or not sign. # Same risk/prevalence/level in ESCC and DUs ¤ Sign. higher risk/prevalence/level in DUs * Higher risk/prevalence/level in DUs, sign. level not tested or not sign. **
Choi D-W (76) 2018, South Korea None	Nationally representative survey	8,809 adults	Low/yes/yes	Diabetes (HbA1c)	DUs had higher HbA1c levels than ESCC but sign. level not tested *
Fetterman J. (73) 2020, USA None	Human clinical study with noninvasive vascular function testing	467 younger adults	High/-/yes	Cardiovascular health (augmentation index)	DUs had similar arterial stiffness as ESCC ¤
Kim C. (17) 2020, South Korea None	Population-based survey	7,505 adult men	Low/yes/yes	Cardiovascular risk factors (waist circumference, blood pressure, triglycerides, fasting glucose, HDL-cholesterol, diagnosis of metabolic syndrome)	DUs had sign. higher prevalence odds ratio of cardiovascular risk factors (waist circumference, triglycerides, HDL-cholesterol, blood pressure) and diagnosis of metabolic syndrome than ESCC DUs had similar fasting glucose as ESCC ¤ **
Kim T. (18) 2020, South Korea	Nationally representative survey	14,738 adults	Low/yes/yes	Cardiovascular risk factors (waist circumference,	DUs had sign. higher odds of abdominal obesity than ESCC

None				blood pressure, triglycerides, fasting glucose, HDL-cholesterol, diagnosis of metabolic syndrome)	Other outcomes: no sign. difference but tendency to higher odds in DUs (except blood pressure) # * **
Mainous A. (60) 2020, USA None	Nationally representative survey	4,659 adults	Low/yes/yes	Biomarker of inflammation and predictor of cardiovascular disease (CRP)	DUs had sign. higher odds of elevated CRP than ESCC **
Miller C. R. (24) 2021, USA Yes	Population-based survey	19,147 adults	Low/yes/yes	Self-reported diagnosis of hypertension in the last 12 months	DUs had higher odds for hypertension than ESCC, but sign. difference not reached (0.99 for lower 95%CI) *
Orimoloye O. (74) 2019, USA None	Population-based survey	3,415 adults	Low/yes/yes	Insulin resistance (measured by HOMA-IR and GTT levels)	DUs had same risk of insulin resistance as ESCC ¤
Osei A. (23) 2019, USA None #	Nationally representative survey	449,092 adults	Low/yes/yes	Self-reported diagnosed with cardiovascular disease (stroke, myocardial infarction or coronary heart disease)	DUs had sign. higher odds of CVD than ESCC ** DUs had sign. higher odds of premature CVD than ESCC **
Parekh T. (61) 2020, USA None	Nationally representative survey	161,529 young adults	Low/yes/yes	Self-reported stroke	DUs had sign. higher risk of stroke than ESCC **
Vindhyal M. (75) 2020, USA None	Nationally representative survey	16,855 adults	Low/yes/yes	Self-reported diagnosed with cardiovascular disease	DUs had higher odds of myocardial infarction and stroke than ESCC, but sign. level not tested *

Table 4. Studies investigating other health outcomes

First author, reference, year of publication, country, conflict of interest	Method	Number included	Risk of selection bias/weighted data/adjusted analyses	Major outcomes	Overall findings Sign. higher risk/prevalence/level in ESCC ## Higher risk/prevalence/level in ESCC, sign. level not tested or not sign. # Same risk/prevalence/level in ESCC and DUs ¤ Sign. higher risk/prevalence/level in DUs * Higher risk/prevalence/level in DUs, sign. level not tested or not sign. **
Akinkugbe A. A. (78) 2019, USA None	Population-based survey	13,650 adolescents	Low/yes/yes	Self-reported past-year diagnosis with dental problems	DUs: higher odds of dental problems than ESCC, but sign. level not tested *
Cardenas V.M. (42) 2020, USA None	Pregnancy Risk Assessment Monitoring ⇨	1,594 pregnant women	Low/yes/yes	Risk of small-for-gestational-age	DUs: higher odds of giving birth to a small-for-gestational-age child than ESCC, but sign. level not tested *
Chen D. TH. (20) 2021, United Kingdom None	4 population-based surveys	13,077 adults	Low/yes/yes	Self-reported experience of COVID-19 symptoms and diagnosis	DUs had higher odds of covid-19 symptoms and higher odds of confirmed/suspected covid-19 diagnosis than ESCC but sign. level not tested *
Clemens M.M. (43) 2019, USA None	Pregnancy Risk Assessment Monitoring ⇨	248 pregnant women	Low/yes/yes	Risk of small-for-gestational-age (SGA)	DUs had higher risk of small-for-gestational-age than ESCC, but sign. not tested *
Dinkeloo E. (62) 2019, USA None	Online survey	2,854 men, soldiers	Low/no/yes	Physical activity (Exposure-Specific APFT performance)	DUs: sign. worse fitness than ESCC **
Flacco M. E. (40) *	Cohort study 48 months	915 adults	High/no/yes	Changes in self-reported	DUs: no sign. difference in self-

2019, Italy Yes				health score and possibly smoking-related disease	reported health score and possible smoking related disease after 4 years than ESCC, but generally worse outcomes in DUs ¤
Flacco M. E. (26) * 2020, Italy Yes	Cohort study 72 months	912 adults	High/no/yes	Changes in self-reported health score and possibly smoking-related disease	DUs had higher odds of possibly smoking related disease after 6 years than ESCC but not sign. *
Gaiha S. M. (79) 2020, USA None	National online survey	4,351 young adults	Low/yes/yes	Self-reported COVID-19 symptoms, testing and diagnosis	DUs higher risk of COVID-19 symptoms and diagnosis than ESCC but sign. level not tested *
Harlow A. (44) 2020, USA None	Cohort study, online survey	4,586 young women trying to conceive	Low/no/yes	Fecundability (menstrual cycle and achieved pregnancy)	DUs: lower fecundability ratio than ESCC but not sign. Different *
Kim T. (19) 2021, South Korea None	Nationally representative population-based survey	10,692 adults	Low/yes/yes	Levels of serum uric acid and hyperuricemia	DUs sign. higher levels of uric acid and prevalence of hyperuricemia than ESCC **
Leavens E. (63) 2020, USA None	Interview-survey	4,148 homeless adults	High/no/no	Self-reported chronic health conditions	DUs sign. higher rates of cancer compared to ESCC **
Lechasseur A. (38) 2020, Canada None	Experimental animal study	40 female mice	Applicable to humans?)/-/-	Immunological and physiological pulmonary response	Different pulmonary responses in mice exposed to aerosol from EC+ smoke from CC and from smoke from CC only. Dual exposure (EC + CC) increased airway resistance compared with mice exposed to smoke from CC only. Sign. level not stated *
Li D. (72) 2020, USA Yes	Nationally representative population-based survey	28,171 adults	Low/yes/yes	Self-perceived physical	DUs: same prevalence of poor physical health as ESCC ¤

Manzoli L. (45) * 2015, Italy None, first 2 years	Cohort study 12 months	959 adults with 1-year data	High/no/yes	Self-reported health	DUs: same self-reported health as ESCC ¤
Manzoli L. (25) * 2017, Italy None, first 2 years	Cohort study 24 months	932 adults with 2-year data	High/no/yes	Self-reported health	DUs at baseline: same self-rated health as ESCC and sign. higher probability of serious adverse events than ESCC ¤ ** DUs at 24 months follow-up: sign. improvement in self-rated health compared with ESCC ##
McDonnell BP. (39) 2020, Ireland None	Pregnancy Risk Assessment Monitoring	620 pregnant women	Low/no/yes	Delivery and neonatal outcomes	DUs: same birthweight, Apgar score and mean gestation at delivery as ESCC ¤ DUs: higher rate of admission to neonatal intensive care unit and higher incidence of birthweight <10th centile than ESCC but sign. level not tested *
Merianos A (64) 2021, USA None	School based nationally representative survey	11,296 high school students	Low/yes/yes	Self-reported duration of sleep	DUs were sign. more likely to report insufficient sleep compared with ESCC **
Riehm K. E. (77) 2019, USA Yes	Nationally representative cohort	9,588 adolescents	Low/yes/yes	Sleep-related complaints	DUs: higher risk of sleep-related complaints than ESCC, but not sign. *
Wang J. B. (58) 2018, USA Yes	Internet-based survey	39,747 adults	Low/no/yes	General health in the last month (SF-12)	DUs: sign. worse median general health scores than ESCC**
Wang X. (49) 2020, USA None	Pregnancy Risk Assessment Monitoring	31,973 pregnant women	Low/yes/yes	Preterm birth and small-for-gestational-age (SGA)	DUs had lower odds of preterm birth than ESCC, but sign. not tested DUs and ESCC had same risk of small-for-

					gestational-age # ¤
Ye D. (80) 2020, USA No	Human clinical study	48 adults	High/-/no	Systemic inflammation, oxidative stress, angiogenesis and tissue injury/repair in saliva and gingival crevicular fluid (GCF)	DUs: higher levels of most biomarkers of systemic inflammation than ESCC, but no sign. difference *

* Same cohort: (40) and (26) and (45) and (25)

Figures

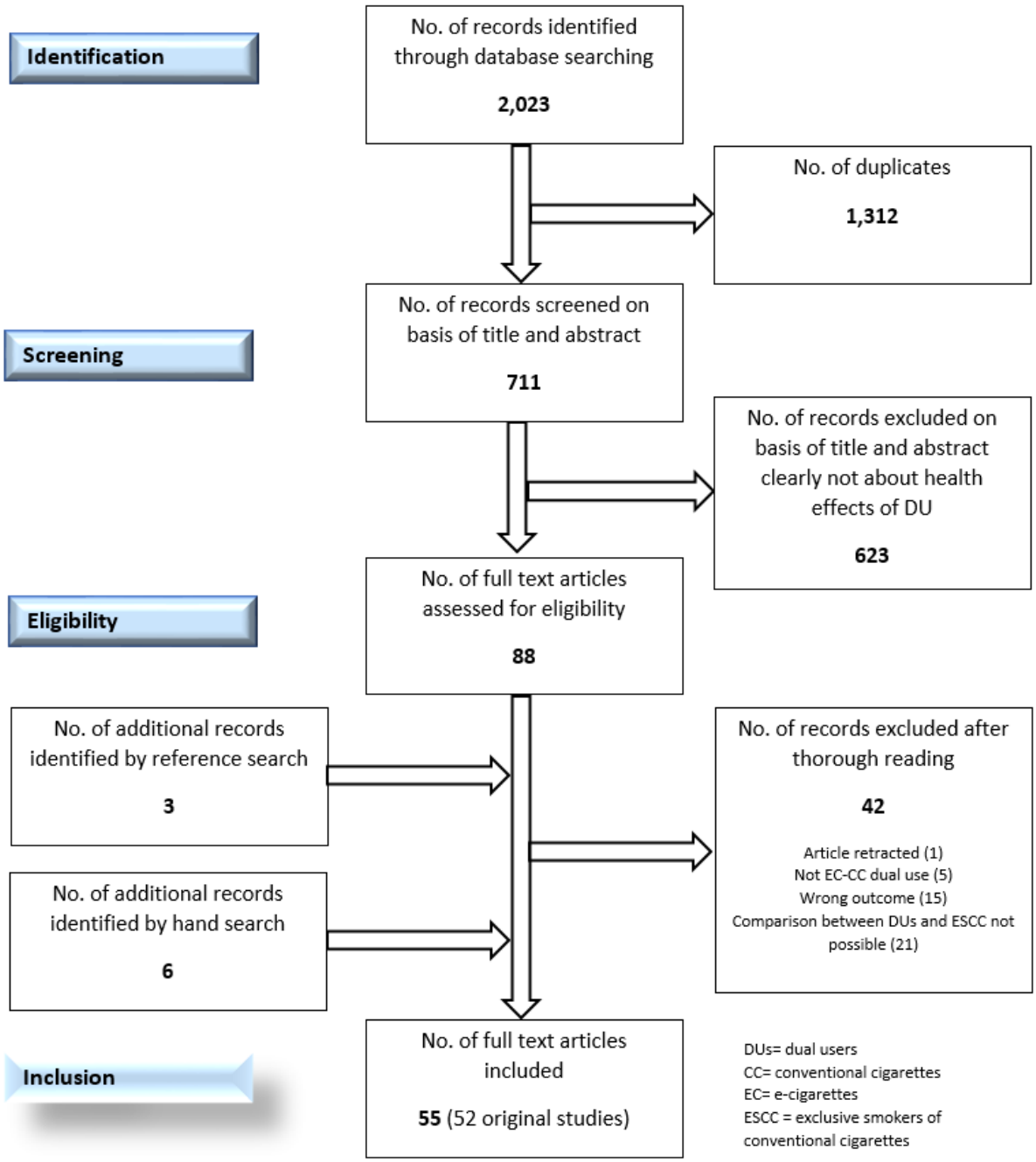

Figure 1

The PRISMA flow-chart of the search and inclusion of papers in the systematic review

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Appendix1Searchstrategy.pdf

- Appendix2Excludedstudies.pdf
- Appendix3Detailedinformationincludedstudies.pdf
- Appendix4DetailsonstudycharacteristicsanddefinitionsofuseBMCOpen.pdf