Physiological Effects of Electronic Cigarette:
A Systematic Review and Meta-Analysis

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A Thesis
In
The Department
of
Health, Kinesiology and Applied Physiology

Presented in Partial Fulfillment of the Requirements
for the Degree of Master of Science (Exercice Science) at
Concordia University
Montreal, Quebec, Canada

December 2020

CONCORDIA UNIVERSITY
School of Graduate Studies

This is to certify that the thesis prepared

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Entitled: Physiological Effects of Electronic Cigarette : a systematic review with meta-analysis

and submitted in partial fulfillment of the requirements for the degree of

Master of Exercice Science

complies with the regulations of the University and meets the accepted standards with respect to originality and quality.

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ABSTRACT

Thesis title : Physiological Effects of Electronic Cigarette: A Systematic Review and Meta-Analysis

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Importance: Electronic cigarettes (e-cigs/ EC) are widely used devices that were initially created to aid in smoking cessation. However, their acute physiological effects are unclear and there have been a number of e-cig and vaping acute lung injury (EVALI) events recently reported.

Objective: To conduct a systematic review and meta-analysis of articles assessing acute physiological effects, i.e., cardiovascular, respiratory or blood-based responses, of e-cig in humans.

Data Sources: PubMed, Web of Science, Cochrane and Scopus databases were searched for published articles until 20th May 2020.

Study Selection: English or French peer-reviewed articles measuring at least one physiological parameter before and after using an e-cig.

Data extraction and synthesis: This study followed PRISMA guidelines and assessed article quality using the Downs and Black checklist. Independent extraction was conducted by two reviewers. Data were pooled using random effect models. Sensitivity analysis and meta-regression was performed to explore heterogeneity.

Main outcomes: Systolic and diastolic blood pressure, heart rate, augmentation index (AIx75), fraction of exhaled nitric oxide (FeNO), and spirometry were the most frequently assessed parameters and were therefore chosen for meta-analyses.

Results: Of 17102 articles screened, 37 articles were included for the qualitative synthesis, and 23 articles (800 patients) were included in the meta-analysis. Acute use of nicotine e-cig was associated with increased heart rate (SMD=0.51; 95%CI 0.34-0.68), systolic blood pressure (SMD=0.33; 95%CI 0.13 -0.52), diastolic blood pressure (SMD=0.50; 95%CI 0.26-0.73), and augmentation index AIx75 (SMD=0.58; 95%CI 0.22- 0.94), along with a decrease in FeNO (SMD=-0.33 ; 95%CI -0.60 – -0.06). E-cig exposure wasn't associated with significant changes in any spirometry measure.

Conclusions and Relevance: Acute use of nicotine e-cigs was associated with significant acute cardiovascular and respiratory responses. Despite being considered safe, these devices have a physiological impact that need to be further explored especially in term of long-term consequences.

ACKNOWLEDGEMENTS

I would like to thank my supervisor, Dr. Simon Bacon, for his precious help all along the master's degree and even before it began; I couldn't have spent this year abroad without his support through the numerous procedures to get there. His patience and wise advices were essential to constantly improve this work.

I would also like to thank Dr. Kim Lavoie for her meaningful help and input about this work but also for her dynamism and enthusiasm that were truly motivating;

To Dr. Robert Kilgour, thank you for being in my committee, always kind, accommodating and available if needed

To Dr. Paula Ribeiro, your statistical knowledge was invaluable and none of this work would have been possible without you. I will not forget your patience and kind guidance throughout all this process

To Tasfia Tasbih; I am grateful for our efficient partnership throughout this master degree, this was not an easy task but we made it together.

Finally, I would like to thank the amazing team of MBMC lab, Guillaume and Geneviève of course but also my favorites doctor students, Vincent, Anda and Claudia: this year would have been so different without you! I'm lucky to have met you , I will cherish all this nices memories, our Thursday at the lab and co working in the city … I hope we will keep this friendship throughout the years no matter the distance !

CONTRIBUTION OF AUTHORS

Florent Larue performed the background research, the database searches, the data extraction, interpretation and writing of the current review.

Dr. Simon Bacon contributed to all phases of the systematic review, from idea development, to interpretation of the results but also guidance and feedback for the writing.

Dr. Paula Ribeiro performed all statistical calculation for the meta analysis, sensitivity analysis and meta regression but also provided feedback on the manuscript.

Dr. Kim Lavoie provided guidance regarding structure and physiological response interpretation.

Tasfia Tasbih was the second reviewer, she assessed study eligibility , study quality, performed data extractions and contributed to tables and figures conception.

Tasfia Tasbih and Florent Larue performed and interpreted the meta-analysis of the data with the aid of Simon Bacon and Paula Ribeiro.

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Introduction

A. Tobacco Consumption

1. Epidemiology

Current worldwide tobacco consumption is estimated at 1.1 billion individuals [4]. Tobacco related death kills more than AIDS, malaria and wars combined[4]. With 6 million deaths per year worldwide attributed to tobacco, smoking is considered the leading preventable cause of death in the world[5]. This includes around 600 000 deaths related to second hand smoke exposure [4]. Despite many efforts in term of policy and public health campaigns, predictions are that by 2030, the number of premature deaths due to tobacco smoking could reach 10 million per year.[5] Moreover, life-long smokers are losing about a decade of life expectancy [6] and half of them are dying from a tobacco-related disease. Therefore, tobacco remains a major public health issue and reducing smoking rates is considered one of the most efficient measures in term of improving public health.

In 2000, 24% of Canada's population was smoking, compared to only 16.2 % by 2017[7]. Even if it still represents almost 4.6 millions of people[7], positive signs appear among youth (12-17 years old) who represent the category with the lowest tobacco consumption rate (3,5% in 2017)[4]. The prevalence of youth having ever tried smoking a cigarette is at an all-time low since it was first monitored among Canadian youth[8]. Tobacco use continues to decline in Canada and the WHO thinks that the target of a 30% relative decrease from 2010 to 2025 is achievable, which means that less than 12% of the population would be smoking[7]. However, some new products such as electronic cigarettes could counteract this decline in tobacco consumption, by providing another way to pursue nicotine addiction, especially among the younger population.

2. Health Risks

Tobacco smoking is recognized as one of the most important cardiovascular risk factors [6, 9] . The risk of stroke and myocardial infarction increase by 30% for passive smokers and 80% in active smokers[6, 9]. A causal relationship between tobacco consumption and diabetes has also recently been discovered [10].Moreover, it has been shown that smoking is the main cause of Chronic Pulmonary Obstructive Disease (COPD) and also worsens asthma outcomes in adults[6]. Containing over 50 carcinogenic substances, tobacco smoke is related to more than 13 different sites of cancer in the whole body [11]and it is considered as the most frequent cause

of cancer worldwide. The strongest associations are seen for lung, oral-tracheal and upper digestive track cancers[11]. Indeed, tobacco is involved in 85% of lung cancer cases which is currently the cancer associated with the highest rates of death worldwide[6]. Adding to that, smoking worsens the prognosis of patients with any type of cancer [11]. Tobacco smoking is not only a major burden to the healthcare system, but it also impairs individual quality of life and life expectancy.

3. Components of tobacco smoke

Tobacco smoke is a toxic carcinogenic mixture of more than 5,000 chemicals[12]. A key chemical is nicotine, which comes from the tobacco leaf and is known for its psychoactive properties[5, 6]. It is recognized as the major tobacco dependence inducer and can also be poisonous, with a toxicity threshold at 1mg/kg being lethal for a child[6]. Smoking a cigarette delivers approximately 1mg of nicotine and 35mg of tar to the user, tar being mainly responsible for tobacco-associated cancers [6, 11]. The aerosol produced when using a cigarette is a complex association of liquid droplets (the particulate matter which contains the nicotine) suspended in gas such as carbon monoxide and semi volatile compounds coming from chemical reactions occurring with combustion[13]. Combustion products are therefore a major issue in understanding the harms associated with cigarette consumption. More than 50 carcinogenic substances have been discovered in tobacco smoke. Among them can be found polynuclear aromatic hydrocarbons (PAH), aromatic amines and tobacco specific nitrosamines (TSNA)[14], and heavy metals such as cadmium, mercury, lead, chromium Tobacco smoke is not only dangerous because of its carcinogenic properties, it also kills through cardiovascular and pulmonary toxicity. In total, there are 98 hazardous substances [12] that are known to be present in combustible cigarette smoke and above the toxicologic threshold.

4. Acute physiological effects of combustible cigarette smoking

Physiological effects associated with combustible cigarette consumption are numerous. After smoking, nicotine rapidly reaches the blood stream and then the brain within 1 minute after the first puff[15]. It is then eliminated through urine excretion with a half-life of 2 hours[15].

a) Cardiovascular effects

Acute effects of combustible cigarette smoking are well known and includes cardiovascular effects such as tachycardia and hypertension [16] which occur less than 30 min after the consumption and are mainly induced by nicotine[16]. The effects of combustible

cigarettes on vascular health go through vessel vasoconstriction and coagulation impairment[17]. All these physiological effects lead to adverse cardiovascular effects over time.

b) Pulmonary effects

Combustible cigarette smoking impairs respiratory function through the airway bronchospasm associated with an increase in mucus production and a decline in Forced Expiratory Volume (FEV1) after smoking [6, 18]. Smoke is an irritant for the airway and paralyzes the cilia, which are involved in clearing the respiratory track from the harmful substances. As such, smokers tend to experience more cough as it is the only way to evacuate the smoke waste [6]. This cilia function impairment associated with immune modification also makes smokers more vulnerable to respiratory track infection [6].

c) Psycho-active effects

Combustible cigarettes are mainly consumed for their psycho-active properties, such as feelings of relaxation and stress relief that many smokers think they need in order to deal with their stressful lives[19]. However, studies have shown that smoking is associated with increased levels of chronic anxiety and stress, partially due to nicotine addiction, and that consuming a cigarette only provides temporary stress relief [19].

5. Smoking Cessation: from policies to individual methods

a) Policies

Many efforts have been made in order to efficiently decrease combustible cigarette smoking and help with smoking cessation. At a societal level, taxes have been increased in order to increase the financial barrier to purchasing cigarettes[20]. Policies have been enacted which forbid tobacco use in public places and to decrease second hand smoke exposure[20]. In 2018, The Government of Canada announced $80.5 million of new funding in order to better acknowledge the problems related to tobacco cessation[20]. As part of Canada's tobacco strategy [20], the Tobacco and Vaping Products Act (TVPA) was enacted on May 23, 2018, which regulates the manufacture, sale, labelling and promotion of tobacco products and vaping products sold in Canada[20]. Taking into consideration the harmful effects these products could have, the goal of this act was to both protect young people and non-smokers from initiating tobacco consumption and increases information and help in smoking cessation efforts.[20]

b) Smoking cessation methods

Most smokers fail to quit tobacco. For example, 85% of those who try to quit on their own relapse, most within a week[21]. This makes cigarette smoking among one of the most addictive products known[22]. Indeed, tobacco addiction is both due to behavioural factors and the physical addiction to nicotine[23, 24]. Through nicotine activation of reward pathways, the physical symptoms of withdrawal appear within the first hours of cessation, such as anxiety, irritability, depression, and cravings of consuming[25]. However, the relationship between smokers and tobacco is more complex than that. Smoking a cigarette is also a behaviour of its own and underlies a lot of habits that may be as hard or harder to change than the addiction to nicotine[24].

There are many efficacious treatments that have been shown to help current smokers to quit smoking. Among them, nicotine replacement therapy (NRT) using gum or dermal patches is the first recommended cessation method by many clinical guidelines[23]. The 'use of NRT's increase the likelihood of abstinence at 6 months by 70% in comparison to placebo[23]. Using gum or patches provides a nicotine supply that helps decrease withdrawal symptoms. Other ways of nicotine supply exist such as tablets or nasal sprays which can deliver quick doses of nicotine in order to help deal with the acute cravings. Cognitive Behavioural Therapy (CBT) can help the smoker recognize the specific environmental set up leading to the consumption of cigarettes[23, 26]. Some drugs have also been developed in order to decrease the central drive for craving and the addiction pathway[26]. Varenicline fixes itself on the brain nicotine receptor, whereas Bupropion acts on the dopamine pathway[25]. Nevertheless, drugs are far from being the perfect solution to nicotine addiction[26]. Indeed, they can have serious side effects which impact their uptake as a cessation method[26]. In this context, alternative nicotine inhalers were developed, including electronic cigarettes or e-cigs. Containing nicotine but not using combustion to release it from tobacco leaves, e-cig use is growing at an impressive rate[27].

B. Electronic cigarettes (e-cigs)

1. Epidemiology

The first e-cig was invented in 2003, by Chinese pharmacist Hon Lik whose father died from tobacco-related lung cancer[28]. It was then introduced in 2004 on the Chinese market as a safer alternative to combustible cigarettes[28]. Their growing popularity brought them to the American market in 2007, where their use continued to rise with an annual growth rate of 115% between 2009-2012[27]. In 2018, the USA e-cig market was worth as much as 5.5 billion dollars

[27]. E-cigs are becoming highly popular among cigarette smokers who are unable/unwilling to quit nicotine but are willing to switch to less-harmful tobacco substitutes [29]. Some notable organisations are touting them as an effective smoking cessation tool, for example, the Public Health England (PHE) has suggested that they could be considered 95% less harmful than combustible cigarettes [28]. The e-cig industry continues to evolve, with new products being developed and brought to the market. Whereas combustible cigarette consumption has steadily declined during the last two decades[4], e-cig consumption has increased rapidly to reach 3.2% of the Canadian population above 15 years old [30], which represents more than 1 million vapers (i.e., someone having used an e-cig in the past 30 days [30]). Among youth and young adults (15-24 years old), this prevalence was two times higher with 6.3% reporting e-cig use in the past month [30].

2. Policy

The Food and Drug Agency (FDA) warned in 2010 about the health risks of e-cigs by including them in the drug delivery device category[31], but policies have taken time to develop and manufacturers have done their best to keep e-cigs out of the “drug and drug delivery device” category [31]. There has been a call for more regulation so that variability among products can be minimized[31]. For example, it has been shown that some nicotine free e-cig cartridges actually contained nicotine, with differences in concentrations sometimes up to 50% compared to the announced amount of nicotine [32]. It is only recently that laws have emerged in order to deal with this emerging health issue. Since 2015 in Quebec, sales to minors and e-cig advertisements have been prohibited and the device is subjected to the same control rules as any other tobacco containing products including prohibition of vaping in public spaces [20, 33]. Nicotine is already approved for use in existing smoking cessation aids such as patches and gum[33]. As of May 2018 with the Tobacco and Vaping Product Act (TVPA), nicotine can also be legally present in vaping products in Canada[33]. However, e-cigs are considered as “recreational products” and none of them have been legally approved as a “therapeutic product” [33].

3. E-cig use among young healthy people

It is unclear how appealing e-cigs are to young people, and there is concern they may cause nicotine addiction or act as a gateway to tobacco use [34]. Indeed, nicotine is a very addictive substance to which youth are especially sensitive [34, 35]. Nicotine is also known to alter brain development and can affect concentration as well as memory[34]. In 2013-2014,

81% of current youth e-cigarette users cited the availability of appealing flavors as the primary reason for their use [36]. Most youth are not aware of e-cigarette nicotine content and are potentially being misled by their healthy image and appealing taste [36]. In Canada, between 2013-2017, past 30 day e-cigarette use went from 2.6% to 6.3 % among 15-19 years olds [30]. Given that 7.9% of the same age group in Canada were considered as a current smoker [30] and that traditional smoking in this group is decreasing, it is anticipated that E-cigarettes will soon be the most commonly used tobacco product among youth[30]. It is interesting to note that this is already the case in USA [35].

4. The e-cig device

E-cigs are made of three main components: a battery; a tank or cartridge (which can be filled with a liquid often containing nicotine associated with vegetal glycerin and propylene glycol); and a vaporizing chamber (see Figure 1)[37]. Using the battery power supply, which is activated when the user inhales, the liquid is heated through a metallic coil (the atomizer) and vaporized in order to create an aerosol[37]. Upon exhalation, the contact with air moisture induce condensation of the aerosol into a thick fog[37].

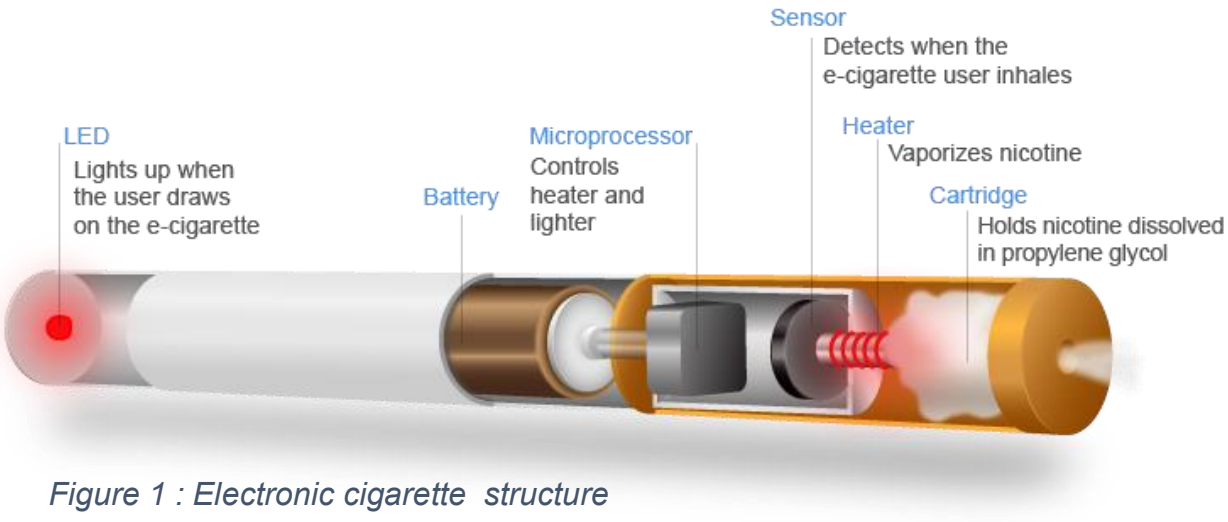

Figure 1 : Electronic cigarette structure

Since 2003, three generations of the devices have been made (see Figure 2)[33] The first generation e-cigarettes look like traditional cigarettes, they are cheap, easily accessible and often times disposable. Unlike the first-generation e-cigs that used ultrasound to vaporize the e-liquid, the second generation contain a clearomizer[38]. The clearomizer was developed in 2009, and was the first technology that contained the wicking material, a reservoir and an atomizer coil (heating resistance) all within a single unit [37]. The second generation tends to be considerably larger, rechargeable and has a separate tank and battery. The third generation is even larger than the second one, and can be customized (size, shape, amount of e-liquid) and the power output can be changed[37]. The e-cig devices evolution has led to an increase in nicotine delivery that has a closer pharmacokinetic profile to that of combustible cigarettes [3] where peak concentrations of nicotine in the blood is reached in only 7 minutes [39] (see figure 3). The most recent device in the electronic cigarette family is named after the company who designed it[40], the JUUL. It arrived on the market on June 2015 producing vapor from nicotine salt instead of freebase nicotine. With the shape of a USB stick, they rapidly attracted consumers, and especially younger people mostly unaware of their nicotine content.[40]

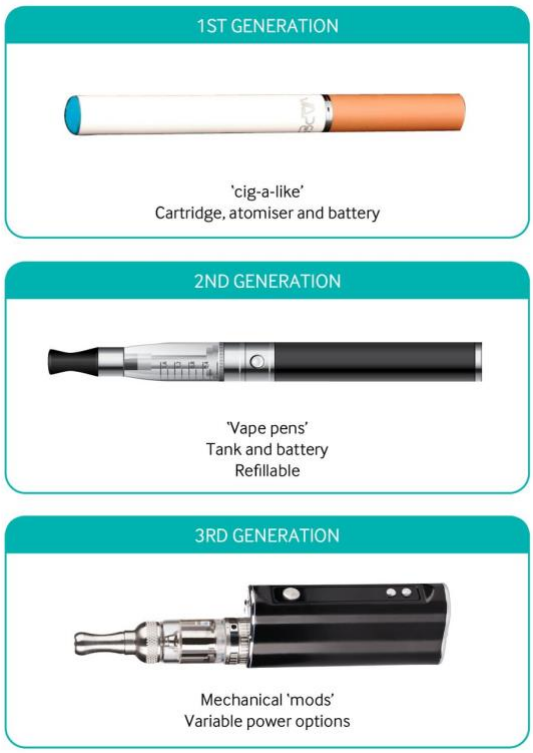

Figure 2 : Different generations of E-cigarettes[2]

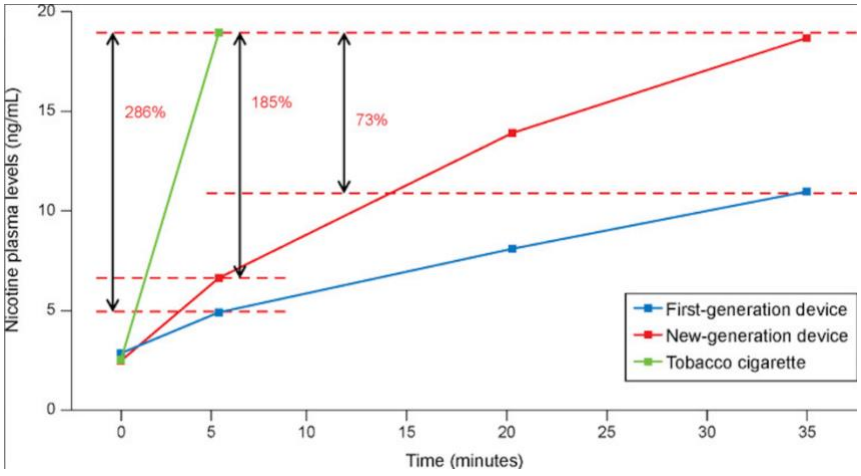

Figure 3: Evolution of Nicotine Delivery with E-cig generation [3]

5. E-cig aerosol content

a) E-liquid composition

The e-liquid contained in the cartridge is a solution made of glycerol and/or propylene glycol, both of which are considered safe when ingested.[37] They are often used as flavoring carriers in food products, food coloring and medication[41]. In addition, various flavourings, distilled water, and often nicotine are present and held in suspension thanks to the glycerol/propylene glycol base[37]. The nicotine concentration varies from absent to 24mg/ cartridge with various intermediate concentrations available[41]. Moreover, the aerosol production requires heating the e-liquid which can create other new chemical components[41].

b) Aerosol Components

The majority of tests carried out on e-cigarettes until now consisted of analyzing the chemicals directly present in the e-liquid before use[37]. However, this is not enough to truly assess the toxic properties of e-cig vapor since many carcinogens found in e-cig vapor are due to the aerosol formation process, which involves heating the e-liquid using an incandescent metal coil[1]. The heated coil can reach temperatures above 300°C [42] and under such conditions chemical reactions may result in formation of new compounds [37]. Hundreds of Chemical substances and ultrafine particles known to be toxic or carcinogenic have been identified in e-cigarette aerosols [1, 37]. Though they don't have the thousands of chemicals as with tobacco smoke, the most important groups of toxic compounds present in tobacco smoke can also be found in e-cig vapor [1]. There are carbonyl compounds (some of them volatile and therefore part of the very broad category of Volatile Organic Compounds (VOCs = every chemical compound containing a carbon chain that is volatile at room temperature)), tobacco-specific

nitrosamines (TSNAs), and metals [1] (see figure 4). Nevertheless, they are found in much lower quantity than in combustible cigarette smoke[1].

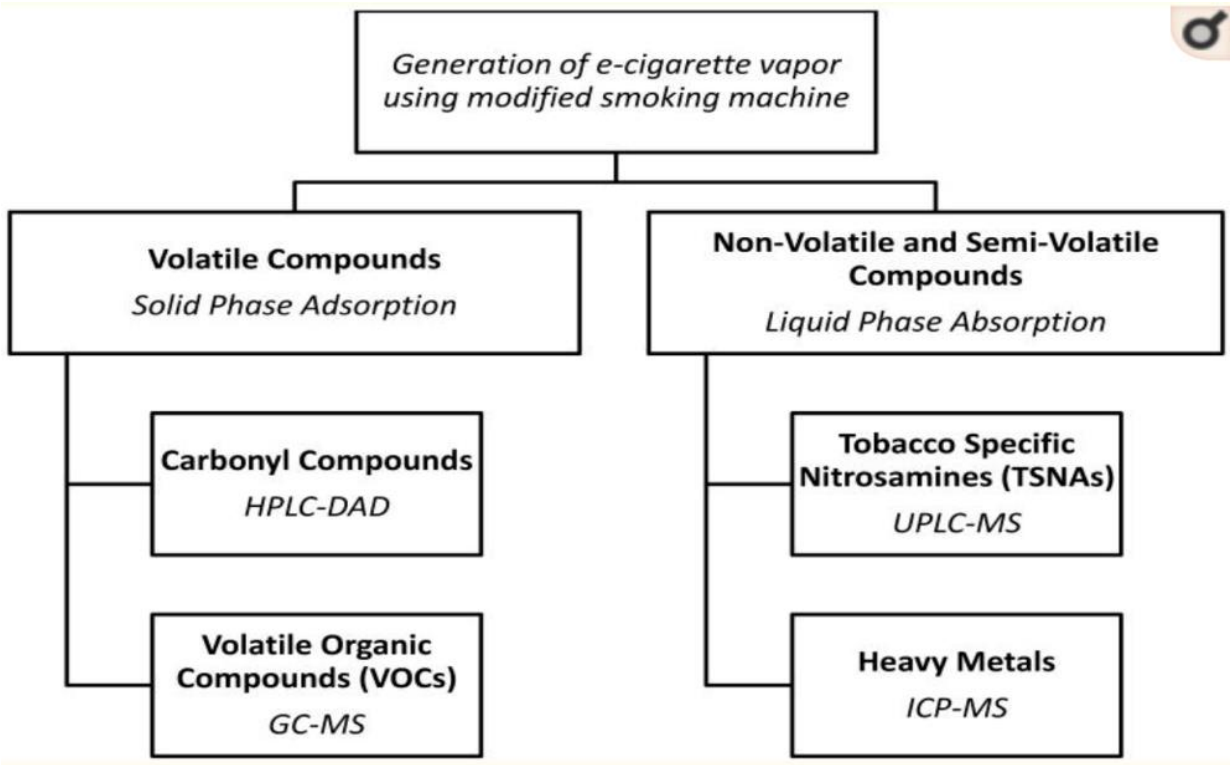

Figure 4 : E-cig aerosol chemical constituants[1]

VOCs and Carbonyls compounds: The main carbonyl compounds which can be found in e-cigs are formaldehyde, a known carcinogenic substance (group 1 by IACR [43]), acetaldehyde (possibly carcinogenic to human, group 2B IARC [43]), and acrolein, which is responsible for cardiovascular toxicity and irritant properties[1]. These carbonyls are thermal dehydration products coming from propylene glycol and glycerol present in the e-liquid [1] . Studies have shown that an increase in battery voltage from 3.3V to 4.8V leads to a tremendous increase in formaldehyde (x3) and acrolein formation (x10) [41]. Despite that, acrolein concentration remain 15 times lower in e-cig vapor than in combustible cigarette smoke [1]. Volatiles organic compounds, such as toluene and xylene, as well as polycyclic aromatic hydrocarbons can also be found in e-cig smoke[1]. They also have known carcinogenic properties [1]

TSNA's and metals: Tobacco specifics nitrosamines such as NNN (N-Nitrosonornicotine) and NNK (Nicotine-derived nitrosamine ketone) have also been found in e-cig vapor [1]. These

substances are derived from nicotine and they have known carcinogenic properties [1]. Even if there concentration ranges from 40 to 380 times lower than in combustible cigarette smoke [1], TSNA's concentrations need to be monitored since they are considered as some of the most carcinogenic compounds in tobacco smoke[1]. The metals, cadmium, chromium, lead, nickel, silver, tin, and silicates[44] have been found in e-cig vapour [1] and their presence seems to be due to the coil used to vaporize the e-liquid[1]. These metals have known cardiotoxic properties [37]

Others: E-cigarette vapor contains hundreds of different chemicals, but it is interesting to mention here the ones with known links to health issues. Among them, the presence of free radicals responsible of DNA damage and toxic gases such as carbon monoxide, ammonia and sulfur dioxide, all of which are carcinogenic and cardiovascular toxicants.[1] Of particular note are the microparticles emitted by electronic cigarette[41]. The aerosol inhaled by the user is made up of two phases, one made of gases and one made of microdroplets containing non volatile compounds[41]. Particles generated by e-cigs are reported to have a bimodal size distribution, including both nanoparticles and submicron particles with similar particle size as combustible cigarette smoke[37]. The toxicity of nanoparticles as well as microparticles is mostly unknown in e-cigs, but we know that they can spread through the blood stream to almost any part of the organism and can be inhaled by passive smokers[37].

Overall, it is obvious that E-cig vapour is far from being simple safe water vapour and more attention and research is needed regarding its potential physiological and health effects.

6. E-cigs as a smoking cessation tool

Among both current and former smokers, the most commonly cited reasons for the use of e-cig were perceived health benefits when compared to combustible cigarettes, followed by assistance with smoking cessation [45]. Considering the combustion products present in classic cigarettes, and their dramatic health impact, most smokers see e-cigs as a safer way to pursue their nicotine consumption[29]. They even have the possibility of progressively decreasing the e-liquid nicotine concentration and therefore avoid the craving associated with abstinence[26]. Although e-cig seem to have many attractive points as a cessation tool, it is in practice more complex than that. Seven systematic reviews with meta-analyses have been done over the last 4 years in order to assess the efficacy of e-cigs as a cessation method [26]. However, their results are inconsistent and insufficient to conclude to the efficacy of e-cig in comparison to the

classic nicotine replacement therapy[26]. Therefore, we can only conclude that e-cig use is associated with reduction of combustible cigarette use and that further research is needed on this matter.

When e-cig and combustible cigarette are both used at the same time, this is called dual use and it seems to be a very common phenomenon since 62% of Canadians report dual use [30]. It seems, therefore, that some smokers would only use e-cigs as a way to reduce their combustible cigarette consumption without quitting totally. This is particularly worrying since a partial decrease in conventional cigarette use doesn't reduce the cardiovascular risk and only modestly impacts cancer risk.[37]

7. Known health consequences of e-cigarettes

Acute physiological effects of e-cig are the object of many studies[46-48] but many of the chemicals present in e-cig smoke still lack evaluation of their health effects. Being relatively new on the market, it is even harder to know what long-term health effects e-cig use could have. It is already known that exposure to e-liquids, including accidental ingestion, direct eye contact, or skin exposure can lead to adverse health effects such as vomiting , diarrhea and palpitations all of them being symptoms of nicotine intoxication [33]. It has also been shown that chronic e-cigs users have increased resting cardiac sympathetic nerve activity and increased susceptibility to oxidative stress [46] both being associated with increased cardiovascular morbidity[49]. A recent study found that e-cig consumption was significantly associated with risk of myocardial infarction, even after adjustment on combustible cigarette consumption and other cardiovascular risk factor [50]. Associations have also been seen between COPD and e-cig consumption among a vast cohort of US adults[51]. However, as these studies are associational studies, it is still too early to know if a causal link exist between e-cig and COPD or cardiovascular disease. Nevertheless, understanding the acute physiological effect that e-cigs have may help scientists foresee what their chronic health effects could be.

8. Acute physiological effects of e-cigs

The effect of e-cig consumption on physiological parameters has been the subject of a number of recent studies, with the general conclusion that the acute effects seems to be less pronounced than the ones observed after combustible cigarette consumption[52]. However, a number of components in e-cig vapour still need to be evaluated. Animal studies, as well as in vitro studies, have been contradictory. For example, some of them have shown e-cig-induced systematic inflammation with multi-organ fibrosis, cardiovascular toxicity and DNA damages [53,

54], whereas others observe no specific mutagenicity [55]. Focusing on human studies, e-cig consumption would seem to have important negative cardiovascular effects, such as vascular dysfunction (increased blood pressure, endothelial dysfunction), platelet dysfunction, lipid metabolism modification and increased insulin resistance [44]. Theoretically, these effects could lead to accelerated atherosclerosis and therefore increased risk of cardiovascular events in e-cig users. Despite nicotine's potential role in these effects (as detailed in the tobacco smoke section), it isn't the only chemical in e-cig to have cardiovascular toxicity. Acrolein and aldehydes are also present in tobacco smoke, and can lead to increased risk of myocardial ischemia and cardiovascular related death.[44]

E-cig aerosol exposure also generates free radicals, and this free radical exposition is known to be involved in cancerogenesis through DNA damage[56]. Electronic cigarette consumption is also associated with negative pulmonary effects such as increased airway resistance, increased airway hyperreactivity[47], cough and inflammatory lung response. Moreover, vaping has been shown to impair the ability to react to infection and decreased the epithelial performance in clearing pathogens from the airways[47]. Finally , E-cigarette use has an acute sympathomimetic effect which may be mainly attributable to the inhaled nicotine[46] and could lead to multiple other phyisiological modification considering the wide implication of the autonomic nervous system in human homeostasis.

Rational, objectives and hypothesis

In summary, there is evidence that there are many potential physiological effects of e-cigs. However, these are from small sample size studies with variable results and there is a real need to synthesise the literature. A lot of studies have focused on the in vitro effect of e-liquid, animal studies, or participants' responses to questionnaires to subjectively assess the effects of e-cigs. Moving forward it would be important to systematically assess the acute physiological effects of e-cigs in humans and create more powerful results by gathering them in a large meta-analysis. To our knowledge, this is the first time that a systematic review with meta-analysis will be conducted on this matter. This systematic review will allow us to summarize the existing knowledge on the acute effects of e-cig among humans in terms of cardiovascular, respiratory and hematological changes.

Regarding the recent published studies and the knowledge already available in this field, we hypothesise that we will see a comparable effect of vapor and tobacco smoke in term of cardiovascular and respiratory parameters but also in blood and immune responses.

Manuscript

This manuscript was submitted to JAMA on December the 1st 2020

Acute physiological effects of Electronic Cigarettes in humans: a systematic review and Meta-Analysis

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Keypoints

Question: What are the acute physiological effects, i.e., cardiovascular, respiratory and blood-based responses, of electronic cigarettes (e-cigs) in humans?

Findings: This systematic review included 37 articles of which 23 studies (n= 800 patients, 8 outcomes) were included in the meta-analyses. Acute use of e-cigs significantly impacted the cardiovascular system (heart rate and blood pressure), arterial stiffness, and airway inflammation (FeNO).

Meaning: As confirmed by the recent EVALI epidemic, the acute effects of e-cig consumption could be harmful as it impacts the cardiovascular, respiratory and inflammatory systems

Background

Tobacco consumption is a major public health issue with an estimated 8 million deaths per year worldwide attributed to tobacco [57]. The negative impact of smoking is partly due to the numerous toxic substances coming from the combustion process of tobacco leaves [6], leading to serious health outcomes such as cancer, COPD, and cardiovascular disease, as well as impairing not only life expectancy but also quality of life [6, 11]. At present, with 1.1 billion smokers worldwide [4], smoking cessation continues to be a key public health focus.

Electronic cigarettes (e-cigs) were invented in 2003 as a potential smoking cessation aid [37]. They use a battery to heat a metallic coil, turning 'e-liquids' into a smoke-like vapor [37]. This e-liquid is usually a mixture of propylene glycol, glycerol, various flavoring, and quite often nicotine, which is turned into an aerosol without the tar found in combustible cigarettes [37]. Despite the lack of evidence of its innocuity [2, 58, 59] and the inconsistent results concerning its efficacy for smoking cessation [60], these devices have attracted a lot of consumers including both smokers and non-smokers [61]. The number of e-cig users worldwide is rising considerably, from 35 millions in 2016, to an expected 55 millions by 2021 [62]. The popularity of this device is especially concerning among youth. In the USA, the proportion of high school students vaping increased significantly in 3 years going from 11.7% in 2017 to 19.6% in 2020 [63]. In term of worldwide vaping sales, they are expected to triple between 2018 and 2023, reaching over 40 billion dollars [64].

E-cig vapors are likely to be less toxic than cigarette smoke, but there is insufficient data to quantify the precise level of risk associated with them [65]. The WHO stated in 2019 that e-cigs are "undoubtedly harmful" and should, therefore, be subject to regulation [66]. The identification and rapid rise in the rates of Electronic-cigarette or Vapor Associated Lung Injury (EVALI) provide a stark waring about the potential negative health impacts of e-cigs [67]. As of April 2020, there were 2,807 hospitalizations and 68 deaths due to EVALI, most of which were in young adults [68]. Although vitamin E acetate seemed strongly linked to the EVALI outbreak [69], it is impossible to rule out the role of other chemicals found in e-cig [67]. Among them, flavors is a broad unregulated category which elicit questions upon its innocuity [70] .As an example, diacetyl which has been found in 75% of e-cig flavor additives [71] is thought to lead to Bronchitis obliterans, also known as Popcorn Lung [72]. Some studies also warned about the presence of authentic toxicant in e-cig vapor such as heavy metals, carbonyls, acrolein,

Tobacco Specific Nitrosamines (TSNA's), and free radicals which have all been found in the e-cig vapour [1, 56]. As a consequence of these discoveries, evidence of negative physiological effects have been increasingly observed among e-cig users [33, 47, 54]. Despite this growing evidence, this is to our knowledge, the first systematic review and series of meta-analyses to assess multiple physiological effects of acute e-cig usage in humans.

METHODS

This systematic review followed the PRISMA (Preferred reporting items for systematic reviews and meta-analysis) guidelines [73], and the protocol was registered in PROSPERO (CRD42017062693).

Inclusion and exclusion

We selected English and French original peer-reviewed studies that reported physiological data on cardiovascular, respiratory, blood-based markers both before and after active e-cig vaping among human participants. Data on combustible cigarette comparison arms were also included, but studies focused only on combustible cigarette use were excluded.

Study search and Screening

Four databases (PubMed, Web of Science, Scopus and Cochrane Library) were searched. The search terms as well as the detailed search strategy used for each database can be found in eSupplementary material A. An initial search was conducted on all studies up to January 2019, this was updated to include all studies up to May 20th, 2020. Reviewers were not blinded to the journal of publication, author names, or their institutions. The screening and full-text assessment was performed by two independent reviewers (FL and TT). In cases of discrepancy, a third reviewer (SB) resolved disagreements. Endnote software (Thomson Reuters) was used for all steps.

Data extraction

Data extraction was done by two reviewers independently using a standardized extraction sheet developed for the project. The following data were extracted: general characteristics of the studies; population characteristics; smoking protocol; and the outcomes of interest. The outcomes included the following physiological parameters: cardiovascular; respiratory; and blood-based responses. In cases of missing data, study authors were contacted by e-mail, with up to two reminders sent one week apart.

Quality assessment

Study quality was evaluated independently by two reviewers using the Downs and Black Checklist [74] which was adapted for acute laboratory study design. A total of 13/27 items with the following subscales (reporting, external validity and internal validity) were assessed. Inter-reviewer agreement was 90% and discrepancies were resolved by consensus.

Data analysis

A minimum of 4 studies measuring an outcome of interest was required to conduct a meta-analysis, which ensures more reliable results and corresponds to standards found in the literature [75]. Three different smoking groups were created for analysis: e-cig with nicotine (EC+), e-cig without nicotine (EC-) and combustible cigarette (CC). Imputation or transformation methods were used for studies that reported confidence intervals or interquartile. Data analyses were performed using comprehensive meta-analysis software (CMA, Biostat Inc.), random-effects models were used for overall effects. Standardized Mean Difference (SMD), with 95% confidence intervals (CI), between pre and post smoking outcomes were calculated. According to Cohen's recommendation, effect sizes were considered as small (0.2 - 0.4), moderate (0.5 - 0.8), or large (≥ 0.8).

Statistical heterogeneity was explored using the I^2 test, Q values, sensitivity analysis, and meta-regression techniques. Possible moderators such as study design, health status, flavors, nicotine content, and time between the end of vaping and first post-vaping measure of the outcome were explored. To identify potential publication bias, a contour-enhanced funnel plot of each trial's effect size against the standard error was created [77-79]. Funnel plot asymmetry was evaluated using Begg and Egger's test, and a significant publication bias was considered if *P* value was <0.10[78].

RESULTS

Study selection

Of 17102 articles, 8964 articles were screened, of which 68 eligible articles were extracted for full-text review. From those articles, 31 articles were excluded (see Figure 1), leaving 37 included articles in the qualitative analysis. Twelve authors were contacted for missing data and among the eight that answered, five authors provided us with useful data. Finally, a total of 23 articles (800 patients), were eligible to be included in meta-analyses.

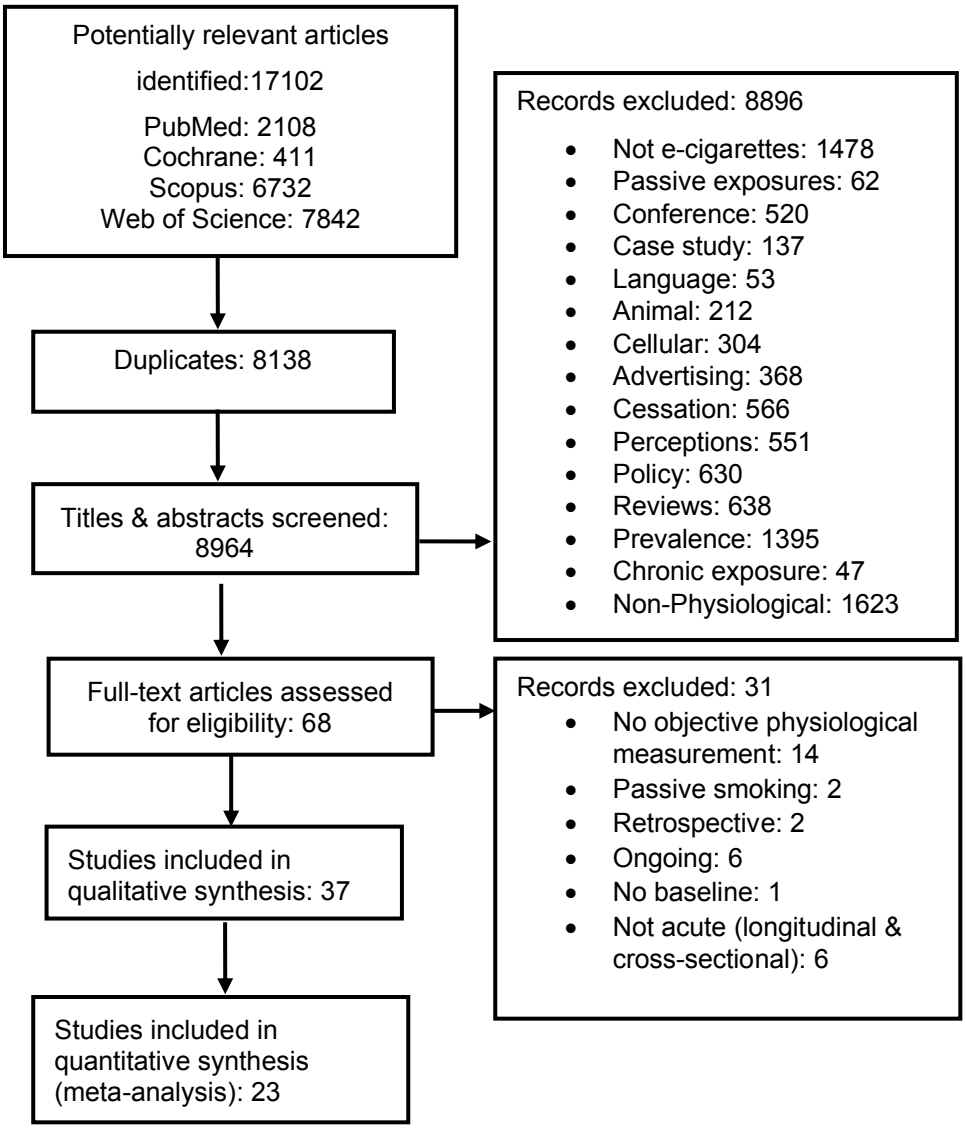


Figure 5: Flow diagram for the study selection process for the systematic review & meta-analysis

Study characteristics

Among the 23 studies included in our meta-analyses, 500 patients were exposed to EC+, 338 patients to EC- and 339 to a combustible cigarette. As indicated in eTable 1, 80% of the included studies were cross-over studies and the rest of the studies were randomized parallel-group studies. The average mean age in the studies was 29.8 (range 22.2 - 40.4), with nearly 50% of participants being women. The majority of studies included healthy participants (91%) with three studies including patients with mild asthma and one including patients with COPD. The majority of studies only included current smokers (60%). However, seven studies only

included non-smokers, seven included both smokers and non-smokers, and one only included previous smokers.

Smoking protocols

Included studies used different brands of e-cigs with different nicotine concentrations (0 mg/ml to 36 mg/ml). Variations in terms of propylene glycol/glycerol ratio (PG/GLY) as well as flavors of e-liquid were observed and the most frequently used e-liquids were 70/30 (PG/GLY) with tobacco flavor**.** This was consistent with the most frequently used e-liquids among adults and especially smokers [80]. The average number of e-cig puffs was between 9 to 180 puffs with the duration of e-cig smoking ranging from 3 to 30 mins. The first post-inhalation assessment of the physiological outcome of interest occurred between 1 and 30 minutes post-smoking. Some studies also compared the effects of e-cigs to a combustible cigarette (0.6mg nicotine on average), sham vaping (e-cig turned off or without e-liquid) or heated not burn product. However, some of the studies (12/34 studies) did not provide specific information on smoking protocol. Details of the smoking protocols can be found in eTable 2.

Results

Blood-based responses and qualitative synthesis of the results

Eleven studies looked at hematological responses to smoking e-cigarettes, though no parameter had enough data for meta-analyses. EC+ seemed to induce hematological changes such as endothelial dysfunction, oxidative stress as well as an increase in pro-thrombotic state and inflammatory levels[85]. The detail of the hematological impact of e-cig can all be found in eTable 3.

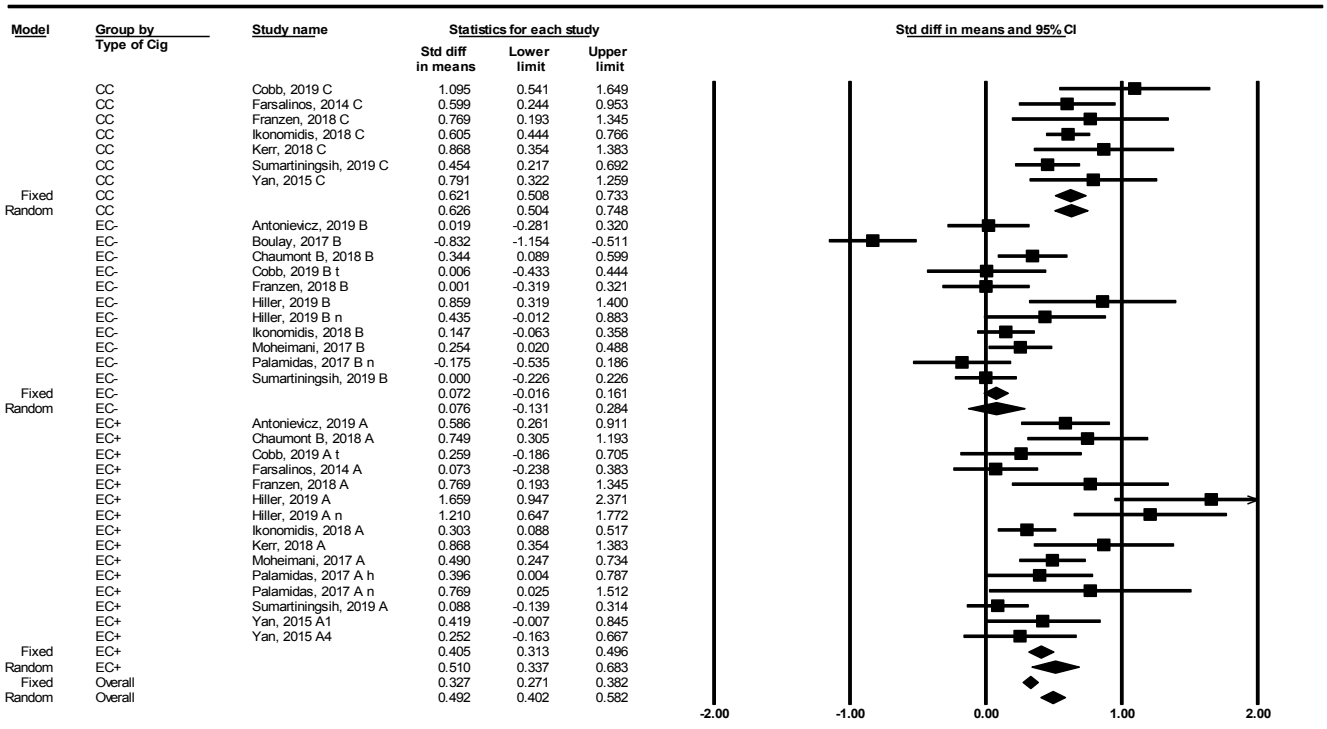
In addition to hematological changes, multiple other physiological changes were identified in qualitative synthesis (eTable 4-5-6) though none had enough data for meta-analyses. The following are some of the key highlights that were identified from these studies. Four studies found an increase in arterial stiffness through pulse wave velocity increase, after EC+ consumption two studies found an decrease in flow mediated dilation, suggesting endothelial dysfunction two studies reported an impact on autonomic nervous system in favor of a sympathetic activation through muscle sympathetic nerve activity (MSNA) [91] and heart rate variability changes. Among the respiratory changes, some studies found a significant respiratory dysfunction with an increase in respiratory resistance [90, 92, 93] after EC+ and a significant decrease in oxygen saturation after vaping EC-

Meta-analysis results

A synthesis of all meta-analysis results including heterogeneity results can be found in Table 1

Cardiovascular responses

A total of 18 studies measured different cardiovascular responses to e-cigs (see eTable 4,5,7). From these there was enough data to conduct meta-analyses for: heart rate (HR); systolic (SBP) and diastolic blood pressure (DBP); and augmentation index adjusted for heart rate (AIx75). There was a significant increase in heart rate following acute smoking of EC+, with an average moderate effect size (SMD= 0.51; 95% CI 0.34-0.68) which was similar to acute combustible cigarette smoking (SMD= 0.63; 95% CI 0.50- 0.75) [18, 46, 84, 86, 89, 92, 94-99], see Figure2. Significant increases in systolic (SBP: SMD= 0.33; 95% CI 0.13 -0.52) and diastolic (DBP: SMD= 0.50; 95% CI 0.26-0.73) blood pressure were also found in response to EC+, which were comparable in magnitude to CC (SBP: SMD= 0.34; 95% CI -0.12-0.56 and DBP: SMD= 0.50; 95%CI 0.16-0.83), see Figures 3 and 4. Heart rate and blood pressure did not change in response to EC-. Augmentation index (AIx 75), a measurement of systemic arterial stiffness, was also found to increase with a moderate effect size (SMD= 0.58; 95% CI 0.22- 0.94) after acute smoking of EC+, whereas no significant effect was found after CC (SMD= 0.13; 95% CI -0.17- 0.43) nor EC- smoking (SMD= 0.18; 95% CI -0.05- 0.38) (Figure 5). Heterogeneity concerning e-cig's results was high with I^2>50 for every parameter except AIx75 (I^2=31.77 with EC-). See Table 1 for overall results on heterogeneity.



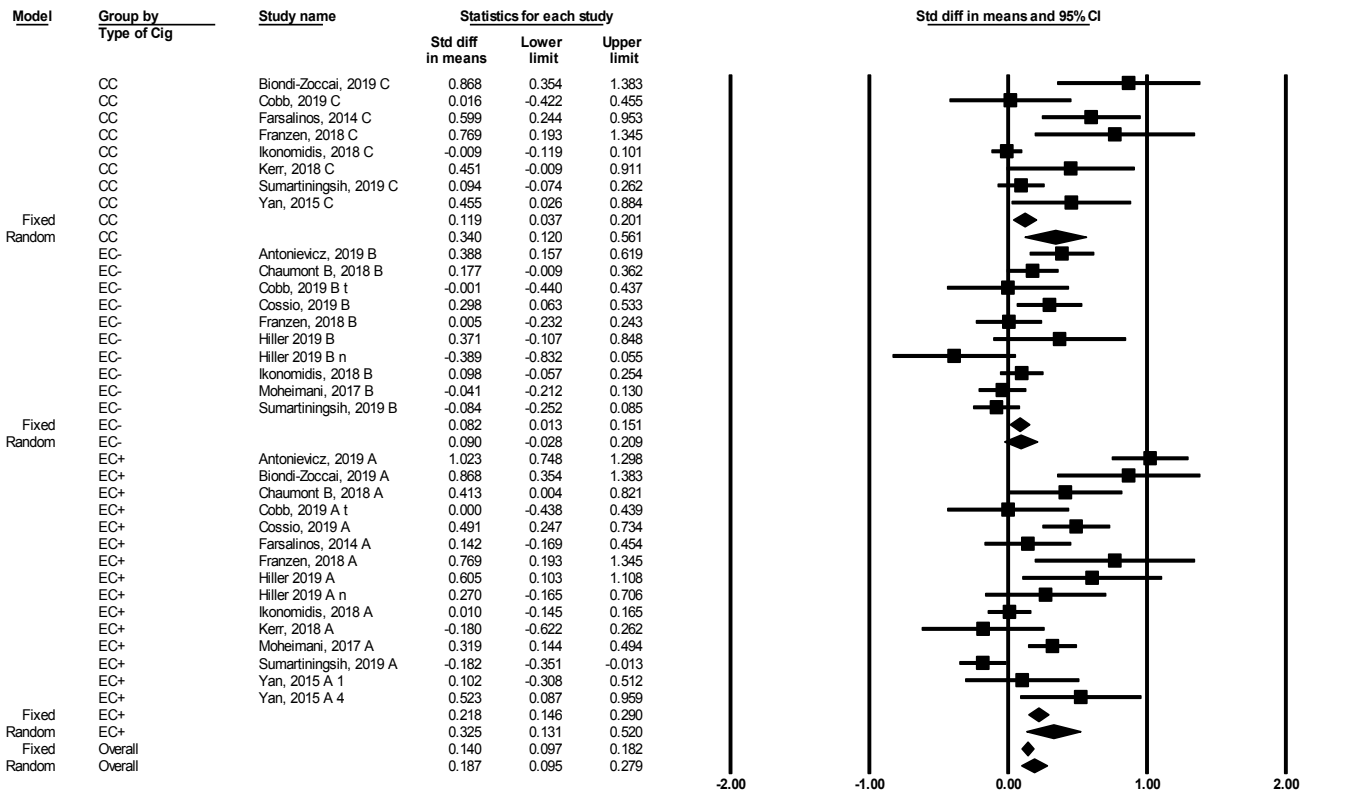
Meta Analysis

Figure 1: Forest plot reporting SMD and 95%CI for each study measuring heart rate.

Overall test for heterogeneity: I^2 = 80%; p<0.001; df (Q)= 20.14

((Note: The black diamond at the bottom of the plot indicates the average effect size of the studies.

A= EC+ (electronic cigarette with nicotine); B= EC- (electronic cigarette without nicotine); C=CC (combustible cigarette); h= healthy smoker group; n= non-smoker group; t= tobacco flavored EC; Yan, 2015 A1, A4= different nicotine & PG/GLY conc. of e-liquid)).



Meta Analysis

Figure 2:Forest plot reporting SMD and 95%CI for each study measuring systolic blood pressure

Overall test for heterogeneity: I^2 = 78%; p<0.001; df (Q)= 6.33

((Note: The black diamond at the bottom of the plot indicates the average effect size of the studies.

A= EC+ (electronic cigarette with nicotine); B= EC- (electronic cigarette without nicotine); C=CC (combustible cigarette); t= tobacco flavored EC; Yan, 2015 A1, A4= different nicotine & PG/GLY conc. of EC)).

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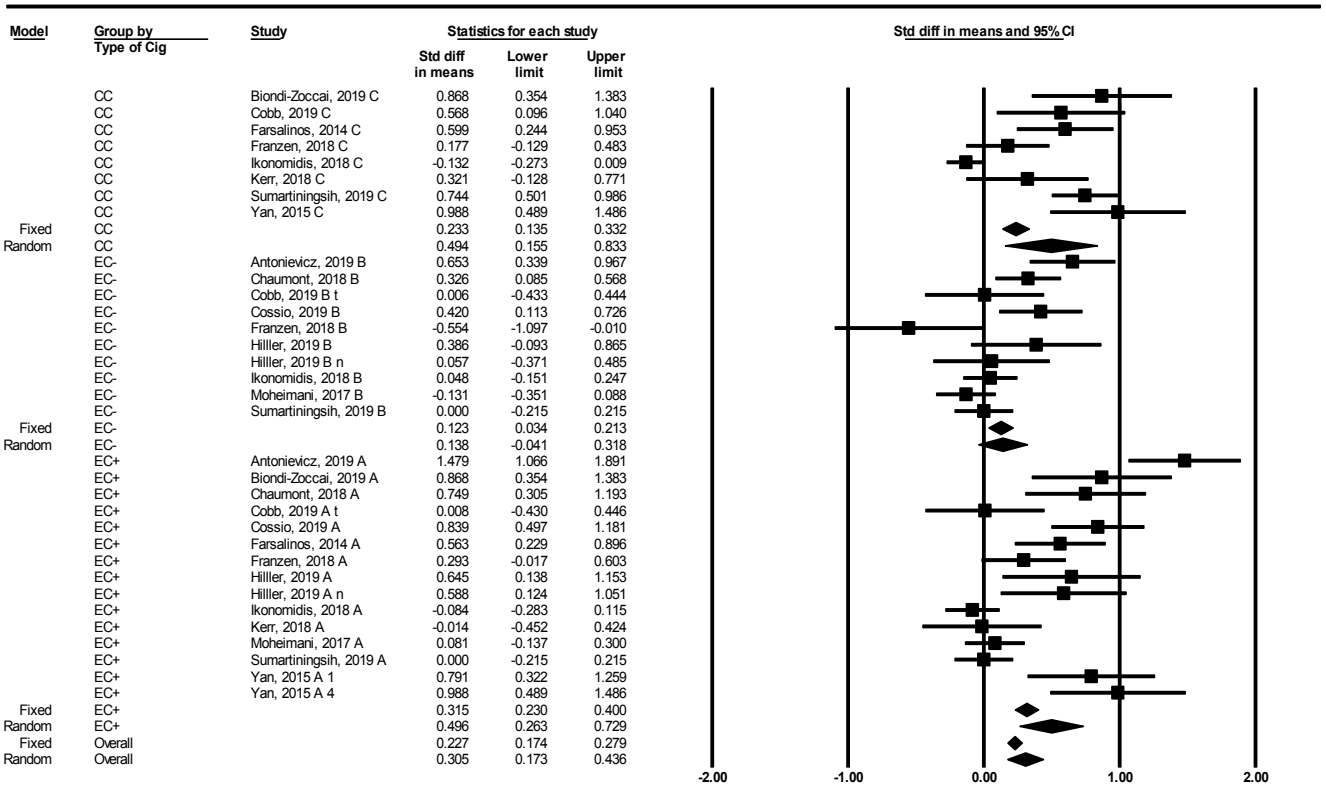

Meta Analysis

Figure 3: Forest plot reporting SMD and 95%CI for each study measuring diastolic blood pressure

Overall test for heterogeneity: I^2 = 84%; p<0.001; df (Q)= 7.08

((Note: The black diamond at the bottom of the plot indicates the average effect size of the studies.

A= EC+ (electronic cigarette with nicotine); B= EC- (electronic cigarette without nicotine); C=CC (combustible cigarette; t= tobacco flavored EC; Yan, 2015 A1, A4= different nicotine & PG/GLY conc. of EC)).

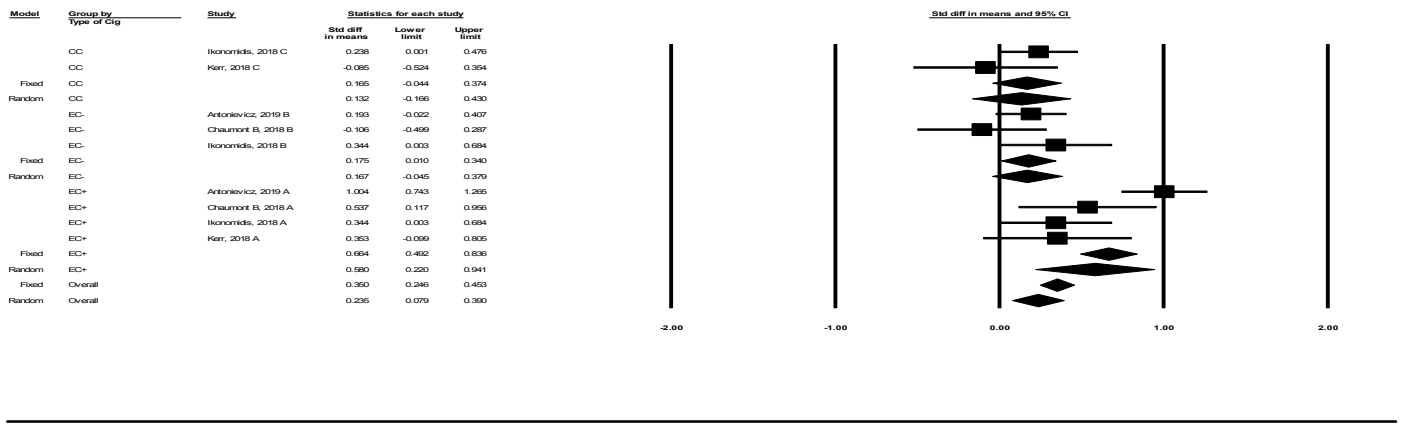

Figure 4: Forest plot reporting SMD and 95%CI for each study measuring augmentation index adjusted for heart rate (AIx 75)

((Overall test for heterogeneity: I^2 = 78%; p<0.001; df (Q)= 4.37

Note: The black diamond at the bottom of the plot indicates the average effect size of the studies.

A= EC+ (electronic cigarette with nicotine); B= EC- (electronic cigarette without nicotine); C=CC (combustible cigarette)).

Respiratory responses

A total of 16 studies measured different respiratory responses (eTable 6 and 8). From these, there was enough data to conduct meta-analyses for: forced expiratory volume in one second (FEV1); forced vital capacity (FVC); Tiffeneau's Ratio (FEV1/FVC); and fractional exhaled nitric oxide (FeNO). There were no statistically significant changes to FEV1 (SMD= -0.15; 95%CI -0.32-0.01), FVC (SMD = -0.08, CI95% -0.28 - 0.11) nor FEV1/FVC ((SMD=0.001 95%CI -0.31 - 0.31) in response to EC+. Likewise, there were no changes in these measures to EC-. In contrast, CC usage was associated with significant decreases in FEV1 (SMD= -0.44; 95%CI -0.66 - -0.22) and FEV1/FVC (SMD= -0.31; 95% CI -0.51- -0.11). Detail of these results can be found in eFigure 1,2 and 3. As seen in Figure 6, FeNO decreased in response to EC+ (SMD= -0.33; 95%CI -0.60 - -0.06) and CC (SMD= -0.76; 95%CI -1.06- -0.46), with no changes seen in response to EC- (SMD= -0.17; 95%CI= -0.51-0.18). Heterogeneity concerning e-cig's results was low for FEV1(I^2=20.83(EC+) and FVC (I^2=0.0) and high for FeNO and FEV1/FVC with I^2>50 (see Table 1 for overall results on heterogeneity).

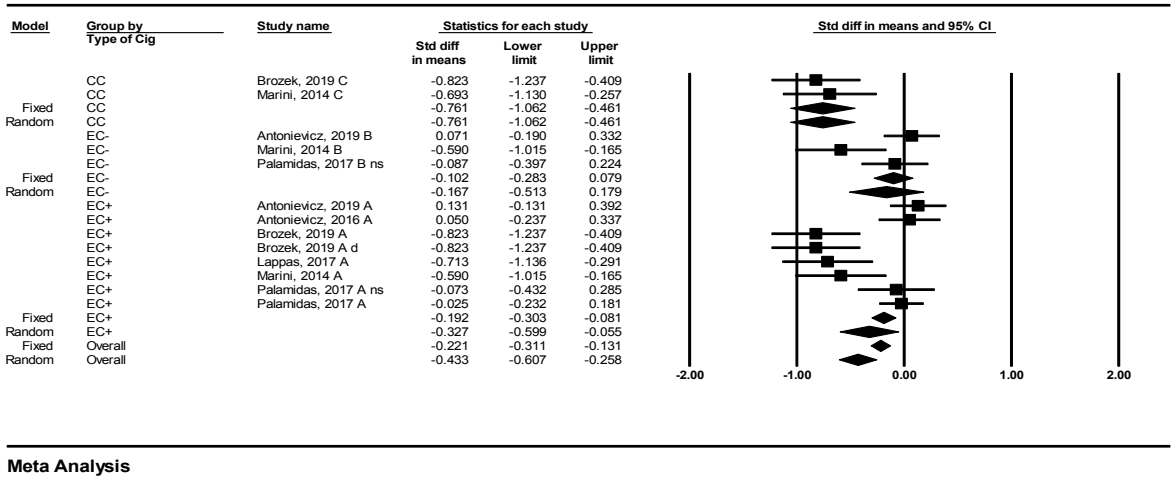

Figure 5: Forest plot reporting SMD and 95%CI for each study measuring fractional exhaled nitric oxide (FeNO)

Overall test for heterogeneity: I^2 = 80%; p<0.001; df (Q)= 7.44

((Note: The black diamond at the bottom of the plot indicates the average effect size of the studies.

A= EC+ (electronic cigarette with nicotine); B= EC- (electronic cigarette without nicotine); C=CC (combustible cigarette; d= dual smokers (both CC & EC); ns= non-smoker)).

Sensitivity analyses and meta-regression

We performed meta-regression to explore heterogeneity for HR, SBP and DBP to investigate the impact of time before first outcome measurement and e-liquid's nicotine concentration (eFigure 4). We could not include other parameters due to lack of adequate information. Significant and positive correlation was found between e-liquid nicotine concentration and HR response (R^2 analogue = 0.17, p<.001), Sensitivity analysis removing diseases and flavors didn't impact either the direction nor the intensity of the physiological changes observed.

Quality (Risk of Bias) and Publication bias assessment

Scores on the modified Downs and Black Checklist ranged from 7 to 13 (out of 13), with 29 studies scoring 10 or above which is considered as good/ excellent quality of the studies (see eTable 1). The three areas of greatest concern were where articles did not report: if the individual measuring the outcomes was blinded or not (68%); if there were probable adverse events during the studies (60%) and the source of the participants (32%).

To illustrate the potential for publication bias, we explored the most reported cardiovascular and respiratory measures (HR and FeNO). The funnel plot for HR was symmetrical (eFigure 5 ; Egger's regression two tailed p = .13), but this wasn't the case for FeNO (eFigure 5: Egger's regression two tailed p < .001). Nevertheless, less studies were included for FeNO than for HR

and the visual analysis was symmetrical (see eFigure 5). The risk of publication bias in this meta-analysis is therefore low for cardiovascular measures and probably also for the respiratory ones although the few numbers of studies included makes it difficult to assess precisely.

Table 1: Meta-analysis results with pooled effects (SMD) and 95% CI of cardiovascular and respiratory outcomes

Outcomes & smoking conditions	Sample size (*n*)	No.of studies	SMD	95 % CI	p	Heterogeneity		
						I^2(%)	Q	p
HR								
Overall	786	33	0.50	0.40 - 0.58	<0.01	80.10	20.14	<0.01
EC+	347	15	0.51	0.34 - 0.68	<0.01	67.48	43.05	<0.01
EC-	230	11	0.08	-0.13 - 0.28	0.47	80.32	50.81	<0.01
CC	209	7	0.63	0.50 - 0.75	<0.01	6.20	6.40	0.38
SBP								
Overall	822	33	0.19	0.10 – 0.28	<0.01	78.24	6.33	0.04
EC+	347	15	0.34	0.13 -0.52	<0.01	83.84	86.65	<0.01
EC-	243	10	0.09	-0.03- 0.21	0.14	60.88	23.00	0.06
CC	232	8	0.34	0.12- 0.56	<0.01	76.62	29.94	<0.01
DBP								
Overall	822	33	0.31	0.17- 0.44	<0.01	84.04	7.08	0.03
EC+	347	15	0.50	0.26- 0.73	<0.01	85.40	95.88	<0.01
EC-	243	10	0.14	-0.04 – 0.32	0.13	71.62	31.72	<0.01
CC	232	8	0.50	0.16- 0.83	<0.01	89.00	63.67	<0.01
AIx75								
Overall	260	9	0.24	0.08-0.40	<0.01	78.26	4.37	0.11
EC+	95	4	0.58	0.22-0.94	<0.01	75.23	12.11	0.01
EC-	75	3	0.17	-0.05- 0.38	0.12	31.77	2.93	0.23
CC	90	2	0.13	-0.17- 0.43	0.39	37.88	1.61	0.21
FEV1								
Overall	313	15	-0.27	-0.38- -0.14	<0.01	51.40	4.32	0.12
EC+	132	6	-0.15	-0.32- 0.01	0.07	20.83	6.32	0.28
EC-	81	5	-0.29	-0.60- 0.01	0.06	69.04	12.92	0.01
CC	100	4	-0.44	-0.66- -0.22	<0.01	10.50	3.35	0.34
FVC								
Overall	220	10	-0.10	-0.21- 0.02	0.11	<0.01	0.33	0.85

Outcomes & smoking conditions	Sample size (*n*)	No.of studies	SMD	95 % CI	p	Heterogeneity		
						I^2(%)	Q	p
EC+	97	4	-0.08	-0.28- 0.11	0.40	<0.01	1.04	0.79
EC-	43	3	-0.07	-0.27- 0.13	0.50	<0.01	1.86	0.40
CC	80	3	-0.16	-0.40-0.08	0.20	<0.01	0.16	0.92
FEV1/FVC								
Overall	283	13	-0.24	-0.40- -0.07	0.01	70.58	3.32	0.20
EC+	117	5	0.001	-0.31- 0.31	0.99	68.38	12.65	0.01
EC-	66	4	-0.48	-1.09- 0.12	0.12	86.41	22.08	<0.01
CC	100	4	-0.31	-0.51- -0.11	<0.01	<0.01	1.16	0.76
FeNO								
Overall	350	13	-0.43	-0.61- -0.26	<0.01	79.96	7.44	0.02
EC+	207	8	-0.33	-0.60- -0.06	0.02	81.50	38.57	<0.01
EC-	88	3	-0.17	-0.51- 0.18	0.34	70.45	6.77	0.03
CC	55	2	-0.76	-1.06- -0.46	<0.01	<0.01	0.18	0.67

DISCUSSION

This review found that acute exposure to e-cigs does affect several cardiovascular and respiratory measures. Compared to combustible cigarettes, the use of e-cigs with nicotine was associated with a similar significant increase in heart rate, blood pressure and arterial stiffness. There was also a significant decrease in FeNO although less pronounced than the one following combustible cigarette. In addition, there was a trend for a decrease in FEV1 in response to both e-cigs with and without nicotine. Though there wasn't enough data to conduct meta-analyses, blood-based measures also seemed to be impacted by e-cigs, with an indication of increases in endothelial dysfunction, oxidative stress and inflammation.

Magnitudes and potential mechanism of effects

In our meta-analysis, the average increase in HR following EC+ was 6 bpm. A recent meta-analysis including 46 prospective studies (including 848,320 individuals) found a linear relation between resting HR and cardiovascular mortality with an average 14,5 years follow up, with a 13% increase in death for each 10 bpm increase among patient not taking any heart rate lowering medication. The average blood pressure changes observed in our study correspond to a 3mmHg and 4mmHg increase for DBP and SBP respectively. Although this could seem low, a

recent meta-analysis published on 24 prospective cohort studies (146,986 participants) found that 10 mmHg increase in SBP was associated with 10% increase in CV events with similar risk estimation between central and peripheral SBP This same study also found that a 10% increase in AIx was associated with an 18% increase in CV events with a follow-up of average 5,9 years going from 6 months to 15 years. Of note, our meta-analysis found a 5.8% increase in AIx75 and a 6bpm increase in HR following EC+. All these studies concerning accessible cardiovascular parameters and demonstrating their long-term clinical impacts question the potential cardiovascular impact of long-lasting use of EC+. The physiological changes observed in our meta-analysis were not as important as in the above mentioned studies, but with the hypothesis that acute changes seen here would become chronic after long term e-cig use, they could relate to an increase in CV risk between 3 and 10%. Although longitudinal studies are lacking, two National Health Interview Surveys (2014 and 2016) already found a significant cross-sectional association in risk of myocardial infarction after chronic use of e-cigarette (OR:1.79 for EC vs OR= 2.72 for daily conventional cigarette smoking compared with a never smoker)

Our meta regression analysis suggested that e-cig's impact on HR might be driven by nicotine. Nicotine is a sympathomimetic drug, known to bind to nicotinic cholinergic receptors which increase sympathetic tone and activate catecholamine release leading to increased heart rate and blood pressure. Nicotine could therefore be responsible of the cardiovascular modification observed following EC+ through the sympathetic activation induced. Our qualitative synthesis also support this idea of a sympathetic activation following EC+. Heart rate variability (HRV), one of the most widely used indicator of autonomic activation has been shown to decrease after acute use of EC+ [46]. In addition, to being one of the potential mechanisms driving our cardiovascular effects, it should also be noted that disrupted HRV has also been shown to lead to increased non-fatal CV events [104].

Immediately after EC+ consumption, there was a significant average FeNO reduction of 7%. Nitric oxide (NO) is a potent vasodilator, it plays an important role in regulating airway and vascular function [105], it is correlated with eosinophilic lung inflammation and oxidative stress in the airways [106], and has been widely studied as a marker of respiratory diseases. For example, lower FeNO levels have been associated with decreased respiratory function and more severe COPD stages. The FeNO decrease observed in our study suggests that e-cig aerosols disturbs the pulmonary homeostasis. It has been suggested that vaping creates oxidative stress and brings toxic or irritant substances from thermal degradation of the e-liquid

into the lungs [1], leading to bronchoconstriction, spirometric changes and potentially FeNO decrease. In addition, there was a trend for a reduction in FEV1 to both EC+ and EC-, which suggests a non-nicotine effect of vaping. Consistent with this, past studies have shown that inhalation of propylene glycol vapors (e.g. theatrical smoke) is associated with acute cough and decreased lung function. However, it is unclear if these effects are driven by the chemical content of the e-cig or it's mechanical action on the respiratory tract [93, 112, 113]

Clinical implications

The recent epidemic of EVALI cases in the USA has highlighted that e-cigs can have an acute negative physiological impact with serious clinical consequences. Though there has been much discussion about the role of THC and vitamin E acetate as the mechanisms for EVALI, it should be noted that of all cases to date 14% reported using non THC e-cigs and vitamin E acetate was only confirmed in about half of the cases [114]. Our study provides details of other possible acute pathophysiology pathways that may account for some of the non-THC and/or non vitamin E acetate cases. Our results raise sufficient concerns to warrant further studies to explore these potential connections to EVALI.

There are few that would argue that regular combustion cigarettes are worse for people than e-cigs, as evidenced by the results of this review, and this has been the basis for proposing e-cigs as a means of smoking cessation. However, there is controversial evidence concerning the efficacy of e-cigs for smoking cessation, especially when compared to nicotine replacement therapy (NRT). Although one 2019 RCT found that e-cig were more efficacious than NRT for smoking cessation at 12 months, it must be noted that 80% of the “abstinent” participants were still using e-cig whereas only 4% in the NRT group where still using patches. Furthermore, longitudinal data indicates that e-cigs increase the risk of myocardial infarction, relative to nonsmoker [50], but that NRT doesn’t increase the risk of major cardiovascular events, compared to placebo. This data coupled with the acute negative changes seen in this review, raise notable questions about the appropriateness of e-cig as a smoking cessation strategy.

Limitation and Strengths

Methodological factors such as variability of e-cig devices, e-liquid content, smoking protocols, as well as each participant's nicotine intake and smoke exposure might have influenced the

results and contributed to the heterogeneity of effects sizes. We were not able to explore all of these aspects due to insufficient data. Several outcomes (especially blood-based measures) could not be meta-analyzed because of the small number of studies and variability in measurement, suggesting that more research is needed in these areas. Despite these limitations, this systematic review was able to analyzed data from e-cig with and without nicotine. Furthermore, the quality of the systematic process followed, and the use of multiple regression and sensitivity analysis for this review offers results that add to our capacity to understand how e-cigs might impact human health, as well as providing a strong base for further study.

Conclusions

Our results suggest that e-cigs are not benign, they seem to elicit potentially negative acute physiological responses. Our meta-analyses revealed that the cardiovascular impact, in terms of heart rate, blood pressure and arterial stiffness, was comparable to that of combustible cigarettes and likely related to the nicotine content. Respiratory changes were observed with a significant decrease in FeNO. The qualitative synthesis found increases in oxidative stress, endothelial dysfunction and sympathetic activation. The acute effects of e-cig are concerning, especially in the light of the recent EVALI epidemic, and longitudinal studies to assess their long-term impacts are needed.

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Appendices

C. eTable 1 : Study characteristics

First Author (year)	Location	Study design	No. of participants	Age Mean (SD) or range	No. (%) of women	Smoking and health status	Comparator	Downs and Black score (/13)
Antoniewicz, 2016	Sweden	Cross-over	16	27 (5)	5 (31.25)	Healthy smokers	No exposure	10
Antoniewicz, 2019	Sweden	Cross-over	15	26 (3)	9 (60)	Healthy smokers	EC-[a]	11
Biondi-Zoccai, 2019	Italy	Cross-over	20	35 (13)	14 (70)	Healthy smokers	CC[a] and Heat-not-burn cigarette	11
Boulay, 2017	Canada	Cross-over	30	*1.*(21-41); *2.* (20-37)	NR[a]	Healthy and asthmatic non-smokers	Sham vaping (EC[a] w/o[a] e-liquid)	7
Brozek, 2019	Poland	Pre-post	120	22.65 (2.12)	48 (40.85)	Healthy smokers and non-smokers	CC and sham vaping (EC w/o e-liquid)	11
Caporale, 2019	USA	Pre-post	31	24.3 (1.3)	14 (45)	Healthy non-Smokers	No exposure	11
Carnevale, 2016	Italy	Cross-over	40	28 (5.3)	21 (52.5)	Healthy smokers and non-smokers	CC	11
Chaumont, 2018	Belgium	Cross-over	23	23 (0.4)	7 (30.4)	Healthy Smokers	Sham vaping (EC turned off)	7
Chaumont B,2018	Belgium	Cross-over	25	23 (0.5)	7 (28)	Healthy Smokers	Sham vaping (EC turned off)	10
Chatterjee, 2019	USA	Pre-post	16	28.7 (5.5)	NR	Healthy smokers and non-smokers	No control	9
Cobb, 2019	USA	Cross-over	20	19.9 (1.1)	NR	Healthy smokers	EC-	11
Cooke, 2015	USA	Cross-over	20	23 (1)	10 (50)	Healthy non-smokers	EC-	12
Coppeta, 2018	Italy	Cross-over	30	32.6 (2.75)	13 (43)	Healthy non-smokers	CC	9

First Author (year)	Location	Study design	No. of participants	Age Mean (SD) or range	No. (%) of women	Smoking and health status	Comparator	Downs and Black score (/13)
Cossio, 2019	USA	Cross over	16	24 (3)	7 (44)	Healthy non-smokers	Sham smoking	10
Dicpinigaitis, 2016	USA	Cross-over	30	29.8 (4.5)	15 (50)	Healthy non-smokers	EC-	10
Farsalinos,2014	Greece	Pre-post	76	NR	8 (7.8)	Healthy smokers	CC	12
Ferrari, 2015	Italy	Cross-over	20	39.3 (12.6)	9 (45)	Healthy smokers and non-smokers	CC	11
Flouris, 2012	Greece	Cross-over	30	32.84 (5.7)	14 (46)	Healthy smokers and non-smokers	CC	10
Flouris, 2013	Greece	Cross-over	30	32.84 (5.7)	14 (46)	Healthy smokers and non-smokers	CC	10
Franzen, 2018	Germany	Cross-over	15	22.9 (3.5)	10 (66.6)	Healthy smokers	CC and sham vaping	11
Fogt, 2016	USA	Cross-over	20	23.1 (2.5)	10 (50)	Healthy non-smokers	EC-	10
Hiller, 2017	USA	Cross-over	64	30.6 (9.1)	19 (30)	Healthy smokers	EC-	10
Ikonomidis, 2018	Greece	Cross-over	70	48 (5)	39.2 (56)	Smokers attending smoking cessation unit	EC- and CC	11
Kerr, 2018	United Kingdom	Cross-over	20	31.6 (10.5)	0(0)	Healthy Smokers	CC	8
Lappas, 2017	Greece	Cross-over	54	23 (3.2)	21 (38.9)	Healthy and mild asthmatic smokers	Sham vaping (EC w/o e-liquid)	9
Marini, 2014	Italy	Cross-over	25	28 (9)	11 (44)	Healthy smokers	CC	12
Mobarrez, 2020	Sweden	Cross-over	17	26 (3)	9 (60)	Healthy smokers	EC-	11
Moheimani, 2017	USA	Cross-over	29	26.3 (0.9)	20 (60)	Healthy former smokers	EC- and sham vaping	8

First Author (year)	Location	Study design	No. of participants	Age Mean (SD) or range	No. (%) of women	Smoking and health status	Comparator	Downs and Black score (/13)
Palamidas, 2017	Greece	Pre-post	75	41.6 (10.4)	32 (42)	COPD, asthma, healthy smokers and non-smokers	EC-	10
Ruther, 2017	Germany	Pre-post	20	28.5 (8.9)	0 (0)	Healthy smokers	CC	11
Schober, 2014	Germany	Cross-over	9	24.7 (4.2)	0 (0)	Healthy smokers	EC-	12
Staudt, 2018	USA	Pre-post	10	42.2 (9.7)	5 (50)	Healthy non-smokers	EC-	8
Sumartiningsih, 2019	Indonesia	Cross-over	24	23.2 (1.7)	0 (0)	Healthy smokers	EC- and CC	10
Vansickel, 2010	USA	Cross-over	32	33.6 (12)	13 (40.6)	Healthy smokers	CC and sham smoking	11
Vardavas, 2012	USA	Cross-over	30	34.8 (11)	16 (53.3)	Healthy smokers	Sham vaping (EC w/o cartridge)	12
Walele, 2016	Netherlands	Cross-over	24	21-65	0 (0).	Healthy smokers	CC and EC w/o flavor or various nicotine concentration	11
Yan, 2015	USA	Cross-over	23	38.7 (10.77)	12 (52)	Healthy smokers	CC	13

[a](EC = electronic cigarette; EC+ = electronic cigarette with nicotine; EC- = electronic cigarette without nicotine; CC = combustible cigarette; NR = not reported; w/o= without);

[b](NA= not applicable)

D. eTable 2: Smoking protocols

First Author (year)	Product use EC	Product use CC	Nicotine content of EC (mg/ml)	Nicotine content of CC (mg)	PG/GLY ratio of EC and flavor used	Duration of EC smoking protocol (min)	Smoking protocol (no. of puffs)	Duration before first measurement (min)
Antoniewicz, 2016	eGo XL	NA	12	NA	49.4/44.4; unflavored	10	10	60
Antoniewicz, 2019	eVic-VT	NA	19	NA	49.4/44.4; unflavored	30	30	0
Biondi-Zoccai, 2019	Blue Pro	Marlboro gold	16	0.6	NR; tobacco flavored	NR	9	Immediately
Boulay, 2017	NR	NA	0	NA	70/30; unflavored	60	180	0
Brozek, 2019	NR	NR	12	0.6	NR; multifruit flavored	5	NR	1
Caporale, 2019	eco series; e-puffer	NA	0	NA	70/30; flavored but not detailed	5	16	1
Carnevale, 2016	NR	NR	NR	0.6	NR; Tobacco flavored	NR	9	~30
Chaumont, 2018	V8 Baby-Q2 Core	NA	0	NA	50/50; NR	NR	25	5
Chaumont B, 2018	Smoke©, Shenzen, China	NA	3	NA	50/50; NR	12.5	25	0~30
Chatterjee, 2019	e-puffer	NA	0	NA	70/30; NR	3	16-17	30
Cobb, 2019	eGO	Own brand cigarette	36	NR	70/30; cream, tropical fruit, tobacco/menthol	Two 5 mins with 60 mins interval	20	0-5

First Author (year)	Product use EC	Product use CC	Nicotine content of EC (mg/ml)	Nicotine content of CC (mg)	PG/GLY ratio of EC and flavor used	Duration of EC smoking protocol (min)	Smoking protocol (no. of puffs)	Duration before first measurement (min)
Cooke, 2015	Clean E-CIG arettes; Green Smart Living	NA	18	NA	NR	5	10	10
Coppeta, 2018	NR	NR	18	0.6	NR; tobacco flavored	5	15	1
Cossio 2019	Cirrus 3, White Cloud Cigarette	NA	0 & 5.4	NA	NR; menthol flavored	6 min	18	Immediately
Dicpinigaitis, 2016	Blue,classic tobacco favor	NA	NR	NA	0/100; tobacco flavored	15	30	15
Farsalinos,2014	eGO T- battery & e-O C atomiser	NR	11	1	60/ NR; tobacco Flavored	7	Ad-lib	Non-specific
Ferrari, 2015	ELIPS C Series	Marlboro Red Label Box	0	0.8	NR/ 50; hazelnut flavored	5	Ad lib	immediately
Flouris, 2012	Giant, Nobacco G.P., Greece	Own brand	11	NR	60/40; tobacco Flavored	30	NR but adapted to nicotine content of combustible cigarette	Immediately
Flouris, 2013	Giant, Nobacco G.P., Greece	Own brand	11	NR	60/40; tobacco Flavored	30	10.4	Immediately
Franzen, 2018	DIPSE, eGo-T CE4 vaporizer	Philip & Morris	24	NR	55/35; tobacco flavored	5	10	~20

First Author (year)	Product use EC	Product use CC	Nicotine content of EC (mg/ml)	Nicotine content of CC (mg)	PG/GLY ratio of EC and flavor used	Duration of EC smoking protocol (min)	Smoking protocol (no. of puffs)	Duration before first measurement (min)
Fogt, 2016	Green smart living	NA	18	NA	NR	10	20	10
Hiller, 2017	eGo, smoktech	NA	0, 8, 18, 36	NA	70/30; Menthol or tobacco flavored	5 min (x2)	10 (x2)	5
Ikonomidis, 2018	NOBACCO eGo Epsilon BDC 1100	NR	12	NR	70/24; flavored but not detailed	7	NR	~40
Kerr, 2018	SmokeMax	Own brand regular cigarette	18	NR	70/30; tobacco flavored	NR	15	1
Lappas,2017	New generation with adjustable voltage	NA	12	NA	46/34; tobacco Flavored	5	10	NR
Marini, 2014	NR	NR	0 & 18	0.8	NR; tobacco flavored	5	Ad lib	NR
Mobarrez, 2020	eVic-VT, Shenzhen Joyetech Co	NA	0 & 19	NA	49.4/44.4; unflavored	30	30	0
Moheimani, 2017	Greensmoke cigalike E-CIG & eGo-One	NA	0 & 12	NA	NR; strawberry Flavored	30	60	10

First Author (year)	Product use EC	Product use CC	Nicotine content of EC (mg/ml)	Nicotine content of CC (mg)	PG/GLY ratio of EC and flavor used	Duration of EC smoking protocol (min)	Smoking protocol (no. of puffs)	Duration before first measurement (min)
Palamidas, 2017	First generation of E-CIG	NA	11	NA	NR	10	Ad lib; 32;43;38;33;52	0
Ruther,2017	Cigalikes (American Heritage,Vype, Blu) Tank model Aspire/Joyetech Upgrade Set	Marlboro Red	18	0.8	NR	5	11	5
Schober,2014	NR	NA	0 & 18	NA	NR	120 min (x 5)	Ad lib	NR
Staudt, 2018	Blue brand E-CIG	NA	NR	NA	NR	NR	20	~160
Sumartiningsih, 2019	NR	NA	0 & 3	NA	NR	NR	NR	5-10
Vansickel, 2010	NPRO EC; Hydro EC	Participants preferred brand	16 & 18	NR	NR; menthol or regular	5	10	15
Vardavaas,2012	NOBACCO black line	NA	11	NA	60/ NR; tobacco flavored	5	Ad lib	NR
Walele, 2016	EVP Fontem Ventures B.V,	JPS Silver King Size CC	0, 0.54, 1.22, 2.7	0.6	70/20; unflavored or menthol	5 min (x 4)	40	25

First Author (year)	Product use EC	Product use CC	Nicotine content of EC (mg/ml)	Nicotine content of CC (mg)	PG/GLY ratio of EC and flavor used	Duration of EC smoking protocol (min)	Smoking protocol (no. of puffs)	Duration before first measurement (min)
Yan,2015	Blu Classic Tobacco; Blu Magnificent Menthol	Marlboro Gold King Size	16 & 24	0.8	0/75 or 20/50; tobacco -menthol flavored or unflavored	60; 30	Ad lib;60	15

[a](EC = electronic cigarette; EC+ = electronic cigarette with nicotine; EC- = electronic cigarette without nicotine; CC= combustible cigarette; NR = not reported; w/o= without);

[b](NA= not applicable)

E. eTable 3. **Acute cardiovascular responses to EC+ & EC-**

Study	Heart rate		Systolic blood pressure		Diastolic blood pressure		Augmentation Index (AIx 75)	
	EC+	EC-	EC+	EC-	EC+	EC-	EC+	EC-
Antoniewicz, 2019	increase	NS[c]	increase	increase	increase	increase	increase	NS
Biondi-Zoccai, 2019	increase	increase	increase	-	increase	-	-	
Boulay, 2017	-	NS	-		-		-	
Chaumont B, 2018	increase	increase	increase	increase	increase	increase	increase	NS
Cobb, 2019	increase	NS	NS	NS	NS	NS	-	
Cooke, 2015	increase	decrease	increase	decrease	increase	decrease	-	
Cossio, 2019	-		NS	NS	NS	NS	-	
Farsalinos, 2014	NS	-	NS	-	increase	-	-	
Franzen, 2018	increase	NS	increase	NS	NS	decrease	increase	NS
Fogt, 2016	NS	NS	decrease	NS	increase	NS	-	
Hiller, 2019	increase	NS	-		-		-	
Ikonomidis, 2018	NS	NS	NS	NS	NS	NS	increase	increase
Kerr, 2018	increase	-	NS	-	NS	-	NS	-
Moheimani, 2017	NS	NS	NS	NS	NS	NS	-	
Palamidas, 2017	increase	NS	-		-		-	
Ruther, 2017	increase	-	-		-		-	
Sumartiningish, 2019	increase	NS	decrease	decrease	NS	NS	-	
Vansickle, 2010	NS	-	-		-		-	
Walele, 2016	NS	NS	NS	NS	NS	NS	-	
Yan, 2015	-		increase	-	increase	-	-	

[a]

(NS= not significant); (empty cells = studies did not measure)

F. eTable 4: Other acute cardiovascular responses **to EC+ & EC-**

Parameter	Study	Outcome	
		EC+	EC-
Ach médiated vasodialtion	Chaumont B, 2018	decrease	NS
Aortic Pulse Wave velocity (aPWV)	Caporale, 2019	-	increase
Cardio-ankle vascular index (CAVI)	Cossio, 2019	NS	NS
HF (High frequency component)	Moheimani,2017	decrease	NS
LF (Low Frequency Component)	Moheimani,2017	increase	NS
LF/HF ratio	Moheimani,2017	increase	NS
Pulse Pressure (PP)	Chaumont B, 2018	increase	NS
	Franzen 2018	increase	NS
Pulse Wave Amplitude (PWA)	Kerr, 2018	decrease	-
Pulse wave velocity (PWV)	Antoniewicz, 2019	increase	NS
	Caporale 2019	-	decrease
	Chaumont B, 2018	increase	increase
	Ikonomidis, 2018	increase	NS
	Franzen 2018	increase	NS
Reactive hyperemia index (RHI)	Caporale 2019	-	decrease
	Kerr, 2018	increase	-
Subendocardial viability ratio (SEVR)	Chaumont B, 2018	increase	increase
Sodium nitroprusside mediated vasodilation (SNP)	Chaumont B, 2018	NS	NS
Vagal cardiac control (VCC)	Cooke, 2015	decrease	-

[c](NS= not significant); (empty cells = studies did not measure those outcomes)

G. eTable 5. Acute Myocardial functions **to EC+**

Study	Nicotine concentration of EC(mg/ml)	Outcome	Response
Farsalinos, 2014	11	PRP, pressure rate product	increase
		Peak early velocity	increase
		Peak late velocity	increase
		E wave deceleration time	increase
		Isovolumetric relaxation time	decrease
		Corrected to heart IVRT	decrease
		Systolic peak velocity	increase
		Early diastolic peak velocity	increase
		Late diastolic peak velocity	increase
		Myocardial performance index (Doppler flow	decrease
		Global peak longitudinal systolic strain rate	increase
		Early diastolic strain rate	increase
		Late diastolic strain rate	increase

H. eTable6: **Acute respiratory responses to EC+ & EC-**

Study	FVC		FEV1		FEV_1/FVC		FeNO	
	EC+	EC-	EC+	EC-	EC+	EC-	EC+	EC-
Antoniewicz, 2019	decrease	decrease	NS	NS	-		decrease	decrease
Antoniewicz, 2016	-		-		-		NS	-
Boulay, 2017		NS	-	NS		NS		NS
Brozek, 2019	NS	-	NS		NS	-	decrease	
Chaumont, 2018	-		-	NS		decrease	-	
Coppeta, 2018	-		decrease	-	decrease	-	-	
Ferrari, 2015	-	NS	-	decrease	-	NS		NS
Flouris, 2013	NS	-	NS	-	NS	-	NS	-
Kerr, 2018	NS	-	NS	-	NS	-	-	
Lappas, 2017	-		-		-		decrease	-
Marini,2014	-		-		-		decrease	decrease
Palamidas, 2017	-		-		-		NS	NS
Schober,2014	-		-		-		decrease	NS
Staudt, 2018	NS	NS	NS	NS	NS	NS	-	
Vardavas, 2012	-		-		-		decrease	-
Walele, 2016	NS	NS	NS	NS	NS	NS	-	

[c](NS= not significant); (empty cells = studies did not measure those outcomes)

I. eTable **7.** Other acute respiratory responses to EC+ & EC-

Parameter	Study	Outcome		Parameter	Study	Outcome	
		EC+	EC-			EC+	EC-
Airway reactance	Antoniewicz, 2019	NS	NS	MEF25 (Maximal Expiratory Flow at 25% FVC)	Brozek, 2019	NS	-
	Boulay ,2017	-	NS	MEF75 (Maximal Expiratory Flow at 75% FVC)	Brozek, 2019	decrease	-
	Lappas ,2017	increase	-	Oxygen Saturation (SvO2/ SpO2)	Brozek, 2019	NS	-
CC16 (serum) (Club Cell Protein Cell 16)	Chaumont, 2018	-	increase		Caporale,2019	-	decrease
Airway reactance	Antoniewicz, 2019	NS	NS		Chaumont, 2018	-	decrease
DLCO = Diffusion capacity of carbon monoxide	Chaumont, 2018	-	NS		Palamidas,2017	decrease	decrease
	Staudt ,2018	NS	NS		Staudt ,2018	NS	NS
eCO (exhaled Carbon Monoxide	Brozek, 2019	decrease	decrease	Resp. Impedance	Lappas ,2017	increase	-
	Ferrari, 2015	decrease	-		Vardavas,2012	increase	-
	Flouris 2013	-	NS	Resonance frequency	Antoniewicz, 2019	NS	decrease
	Ikonomidis,2018	NS	-		Lappas ,2017	increase	-
				Respiratory Resistance	Antoniewicz, 2019	increase	NS
	Kerr, 2018	NS	-		Boulay ,2017	-	NS
					Chaumont, 2018	-	NS
	Vansickel, 2010	NS	-		Lappas ,2017	increase	NS

	Walele, 2016	NS	-		Palamidas,2017	increase	increase
	Yan, 2015	-	NS		Vardavas,2012	increase	-
Exhaled breath temperature	Brozek, 2019	increase	-	Specific airway conductance	Palamidas,2017	decrease	decrease
	Palamidas,2017	NS	NS	TLC (Total Lung Capacity)	Chaumont, 2018	-	NS
FEF25 (Forced Expiratory Flow 25% FVC)	Brozek, 2019	NS	-				
	Chaumont, 2018	-	decrease				
	Coppeta, 2018	-					
	Ferrari, 2015	-	decrease				
FEF50 (Forced Expiratory Flow 50% FVC)	Brozek, 2019	NS	-				
	Chaumont, 2018	-	NS				
	Coppeta, 2018	-					
	Ferrari, 2015	-	NS				
FEF75 (Forced Expiratory Flow 75% FVC)	Brozek, 2019	NS	-				
	Chaumont, 2018	-	NS				
	Coppeta, 2018	-					
	Ferrari, 2015	-	NS				
FEF 25-75 (Forced Expiratory Flow 25-75	Brozek, 2019	NS	-				
	Chaumont, 2018	-	NS				
	Coppeta, 2018	decrease	-				
	Ferrari, 2015	-	NS				
	Flouris 2013	NS	-				
	Walele, 2016	NS	increase				

[c](NS= not significant); (empty cells = studies did not measure those outcomes)

J. eTable 8: Endothelial, Platelet, Oxidative markers responses to **EC+ & EC-**

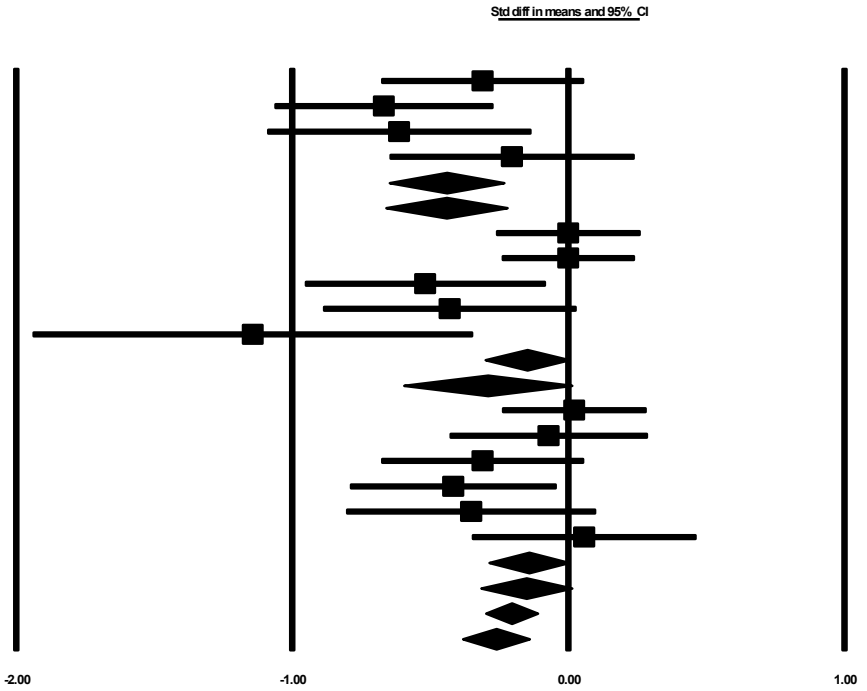
Parameter	Study	Outcome	
		EC+	EC-
Endothelial function in response to e-cig			
Endothelial Progenitor Cell (EPC)	Antoniewicz, 2016	increase	-
Endothelial Microvesicles (EMV)	Staudt ,2018	increase	NS
	Mobarrez, 2020	increase	NS
Endothelial Microvesicles (EMV)+ E selectin	Antoniewicz, 2016	increase	-
Flow mediated dilation (FMD)	Biondi-Zoccai, 2019	decrease	-
	Caporale, 2019	-	decrease
	Carnevale, 2016	decrease	-
	Cossio, 2019	NS	NS
PECAM-1(Platelet Endothelial Cell Adhesion Molecules)	Kerr, 2018	NS	-
sICAM-1 (Inter Cellular Adhesion Molecules)	Chatterjee, 2019	increase	-
	Kerr, 2018	NS	-
sVCAM-1(Vascular Adhesion Molecules)	Kerr, 2018	NS	-
Soluble Endothelial selectin (sE selectin)	Kerr, 2018	NS	-
Total Microvesicles (MVs)	Antoniewicz, 2016	NS	-
	Kerr, 2018	NS	-
NO Bioavailability	Biondi-Zoccai, 2019	decrease	-
	Carnevale, 2016	decrease	-
	Chaumont B, 2018	NS	NS
Platelet function in response to e-cig			
Platelet Microvesicles	Kerr, 2018	increase	-
	Mobarrez, 2020	increase	NS
sCD40L	Biondi-Zoccai, 2019	increase	-
	Mobarrez, 2020	increase	increase
sP selectin (soluble platelet selectin)	Biondi-Zoccai, 2019	increase	-
	Kerr, 2018	decrease	-

Parameter	Study	Outcome	
		EC+	EC-
	Mobarrez, 2020	increase	NS
Oxidative markers responses to e-cig			
8-iso-PGF2a	Biondi-Zoccai, 2019	increase	-
	Carnevale,2016	increase	-
HBA (H2O2 Breakdown activity)	Biondi-Zoccai, 2019	decrease	-
Hcit/lys (homocitrulline/ lysine ratio)	Chaumont B, 2018	NS	NS
HOI, high-density lipoprotein antioxidant index	Moheimani, 2017	NS	NS
LDL-Ox low-density lipoprotein oxidizability	Moheimani, 2017	NS	NS
MDA (malondialdehyde)	Ikonomidis,2018	increase	increase
MPO (Myeloperoxydase)	Chaumont B, 2018	increase	NS
PB3 Cl-Tyr/Tyr (protein-bound3-chlorotyrosine/tyrosine ratio)	Chaumont B, 2018	NS	decrease
PON1 (paraxonomase 1 activity)	Moheimani, 2017	NS	NS
ROS (radical oxygen species)	Chatterjee, 2019	-	increase
sNOX2-dp	Biondi-Zoccai, 2019	increase	-
	Carnevale,2016	increase	-

[c](NS= not significant); (empty cells = studies did not measure those outcomes)

K. eFigure 1: Forest plot reporting SMD and 95%CI for each study measuring Forced expiratory volume in one second (FEV1)

Model	Group by Type of Cig	Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
	CC	Brozek, 2019 C	-0.310	0.187	0.035	-0.677	0.056	-1.660	0.097
	CC	Coppeta, 2018 C	-0.668	0.202	0.041	-1.064	-0.272	-3.309	0.001
	CC	Ferrari, 2015 C	-0.613	0.244	0.059	-1.090	-0.135	-2.515	0.012
	CC	Kerr, 2018 C	-0.204	0.226	0.051	-0.647	0.239	-0.903	0.367
Fixed	CC		-0.442	0.106	0.011	-0.649	-0.235	-4.182	0.000
Random	CC		-0.443	0.112	0.013	-0.662	-0.223	-3.953	0.000
	EC-	Antonievicz, 2019 B	0.000	0.133	0.018	-0.260	0.260	0.000	1.000
	EC-	Boulay, 2017 B	0.000	0.122	0.015	-0.240	0.240	0.000	1.000
	EC-	Chaumont, 2018 B	-0.518	0.222	0.049	-0.954	-0.083	-2.334	0.020
	EC-	Ferrari, 2015 B	-0.429	0.234	0.055	-0.887	0.029	-1.837	0.066
	EC-	Staudt, 2018 B	-1.143	0.407	0.165	-1.940	-0.346	-2.811	0.005
Fixed	EC-		-0.151	0.077	0.006	-0.302	0.001	-1.951	0.051
Random	EC-		-0.293	0.155	0.024	-0.597	0.011	-1.890	0.059
	EC+	Antonievicz, 2019 A	0.021	0.133	0.018	-0.239	0.282	0.162	0.872
	EC+	Brozek, 2019 A d	-0.071	0.183	0.033	-0.429	0.287	-0.389	0.698
	EC+	Brozek, 2019 A	-0.310	0.187	0.035	-0.677	0.056	-1.660	0.097
	EC+	Coppeta, 2018 A	-0.417	0.190	0.036	-0.790	-0.044	-2.189	0.029
	EC+	Kerr, 2018 A	-0.352	0.230	0.053	-0.804	0.100	-1.527	0.127
	EC+	Staudt, 2018 A	0.058	0.207	0.043	-0.348	0.464	0.278	0.781
Fixed	EC+		-0.144	0.074	0.005	-0.288	0.000	-1.954	0.051
Random	EC+		-0.153	0.084	0.007	-0.318	0.011	-1.828	0.068
Fixed	Overall		-0.207	0.048	0.002	-0.300	-0.113	-4.347	0.000
Random	Overall		-0.263	0.062	0.004	-0.384	-0.142	-4.268	0.000



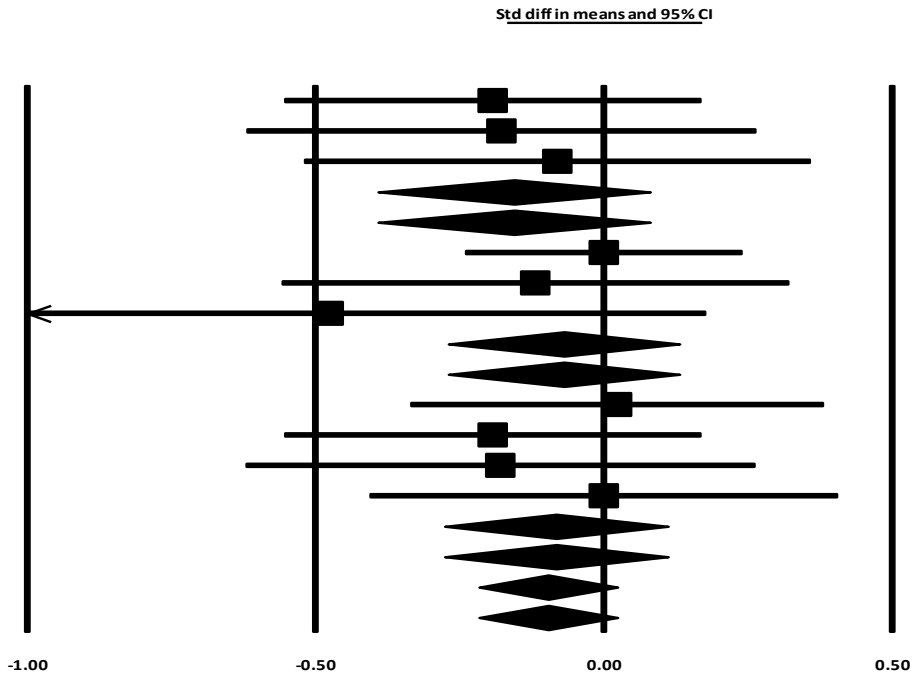
((Note: The black diamond at the bottom of the plot indicates the average effect size of the studies.

A= EC+ (electronic cigarette with nicotine); B= EC- (electronic cigarette without nicotine); C=CC (combustible cigarette);.

d= dual smokers (both CC and EC)).

L. eFigure 2: Forest plot reporting SMD and 95%CI for each study measuring Forced vital capacity (FVC)

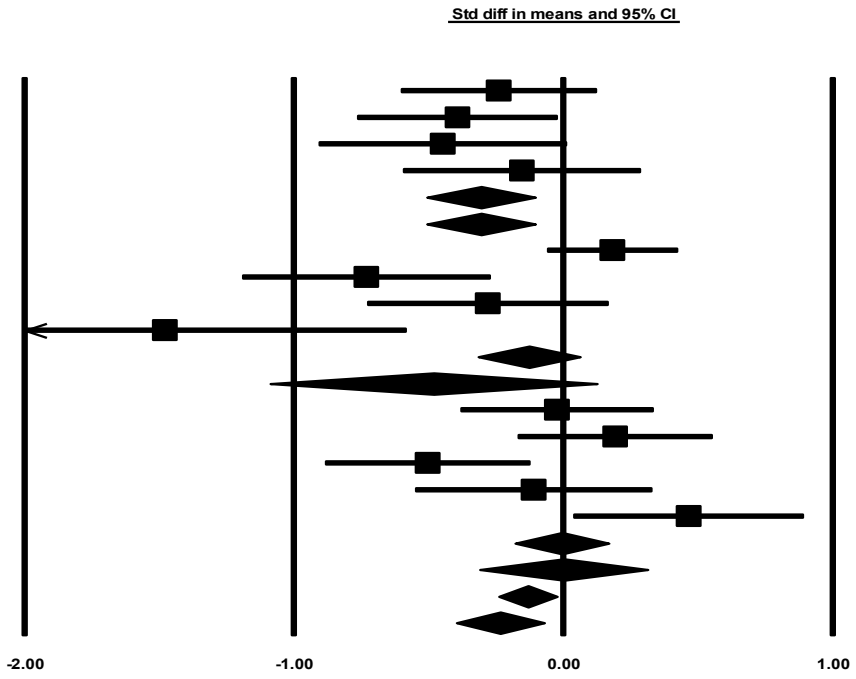
Model	Group by Type of Cig	Study	Statistics for each study: Std diff in means	Lower limit	Upper limit
	CC	Brozek, 2019 C	-0.193	-0.554	0.168
	CC	Ferrari, 2015 C	-0.178	-0.619	0.264
	CC	Kerr, 2018 C	-0.080	-0.519	0.359
Fixed	CC		-0.156	-0.392	0.080
Random	CC		-0.156	-0.392	0.080
	EC-	Boulay, 2017 B	0.000	-0.240	0.240
	EC-	Ferrari, 2015 B	-0.119	-0.558	0.321
	EC-	Staudt, 2018 B	-0.477	-1.131	0.177
Fixed	EC-		-0.070	-0.270	0.131
Random	EC-		-0.070	-0.270	0.131
	EC+	Brozek, 2019 A d	0.023	-0.335	0.381
	EC+	Brozek, 2019 A	-0.193	-0.554	0.168
	EC+	Kerr, 2018 A	-0.179	-0.621	0.263
	EC+	Staudt, 2018 A	0.000	-0.406	0.406
Fixed	EC+		-0.083	-0.277	0.111
Random	EC+		-0.083	-0.277	0.111
Fixed	Overall		-0.097	-0.217	0.023
Random	Overall		-0.097	-0.217	0.023



((Note: The black diamond at the bottom of the plot indicates the average effect size of the studies.
A= EC+ (electronic cigarette with nicotine); B= EC- (electronic cigarette without nicotine); C=CC (combustible cigarette);.
d= dual smokers (both CC and EC)).

M. eFigure 3 : Forest plot reporting SMD and 95%CI for each study measuring Tiffeneau's Ratio (FEV1/FVC).

Model	Group by Type of Cig	Study name	Std diff in means	Lower limit	Upper limit
	CC	Brozek, 2019 C	-0.239	-0.602	0.123
	CC	Coppeta, 2018 C	-0.393	-0.764	-0.021
	CC	Ferrari, 2015 C	-0.447	-0.907	0.012
	CC	Kerr, 2018 C	-0.153	-0.594	0.287
Fixed	CC		-0.306	-0.507	-0.105
Random	CC		-0.306	-0.507	-0.105
	EC-	Boulay, 2017 B	0.183	-0.059	0.425
	EC-	Chaumont, 2018 B	-0.731	-1.191	-0.271
	EC-	Ferrari, 2015 B	-0.280	-0.727	0.167
	EC-	Staudt, 2018 B	-1.479	-2.376	-0.582
Fixed	EC-		-0.128	-0.316	0.061
Random	EC-		-0.482	-1.089	0.124
	EC+	Brozek, 2019 A d	-0.023	-0.381	0.335
	EC+	Brozek, 2019 A	0.193	-0.168	0.554
	EC+	Coppeta, 2018 A	-0.503	-0.883	-0.123
	EC+	Kerr, 2018 A	-0.110	-0.549	0.330
	EC+	Staudt, 2018 A	0.466	0.038	0.893
Fixed	EC+		-0.006	-0.180	0.168
Random	EC+		0.001	-0.310	0.311
Fixed	Overall		-0.132	-0.240	-0.024
Random	Overall		-0.235	-0.398	-0.072

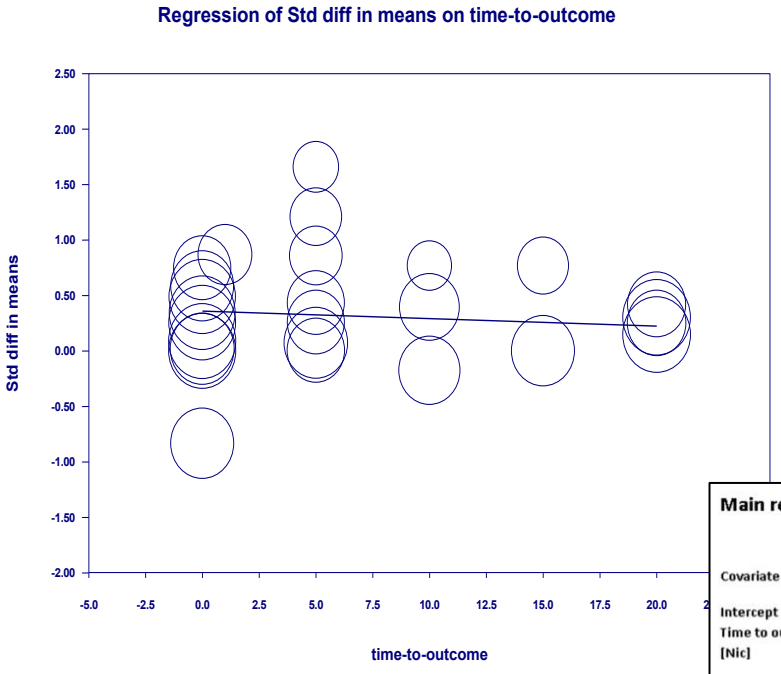


((Note: The black diamond at the bottom of the plot indicates the average effect size of the studies.

A= EC+ (electronic cigarette with nicotine); B= EC- (electronic cigarette without nicotine); C=CC (combustible cigarette);

d= dual smokers (both CC and EC))

N. eFigure 4 : Meta-regression of effect of time to outcome measure (A) and nicotine concentration (B) of e-cig on heart rate.



eFigure 4(A)

Main results for Model 3, Random effects (MM), Z-Distribution, Std diff in means

Covariate	Coefficient	Standard Error	95% Lower	95% Upper	Z-value	2-sided P-value
Intercept	0.0574	0.0775	-0.0944	0.2093	0.74	0.4586
Time to outcome	0.0013	0.0068	-0.0119	0.0146	0.20	0.8422
[Nic]	0.0159	0.0047	0.0066	0.0252	3.34	0.0008

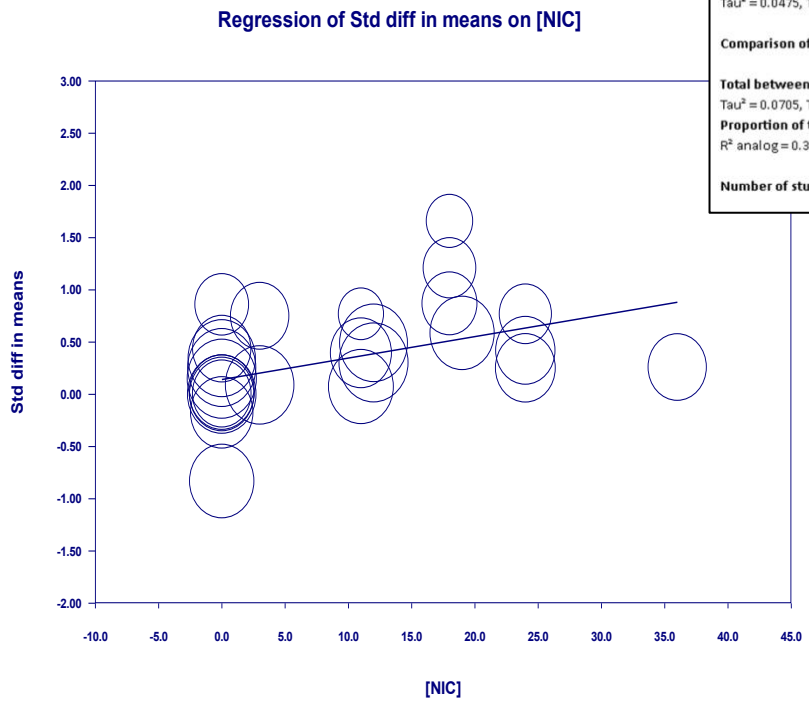
Statistics for Model 3

Test of the model: Simultaneous test that all coefficients (excluding intercept) are zero
Q = 13.25, df = 2, p = 0.0013
Goodness of fit: Test that unexplained variance is zero
Tau^2 = 0.0475, Tau = 0.2179, I^2 = 61.97%, Q = 76.25, df = 29, p = 0.0000

Comparison of Model 3 with the null model

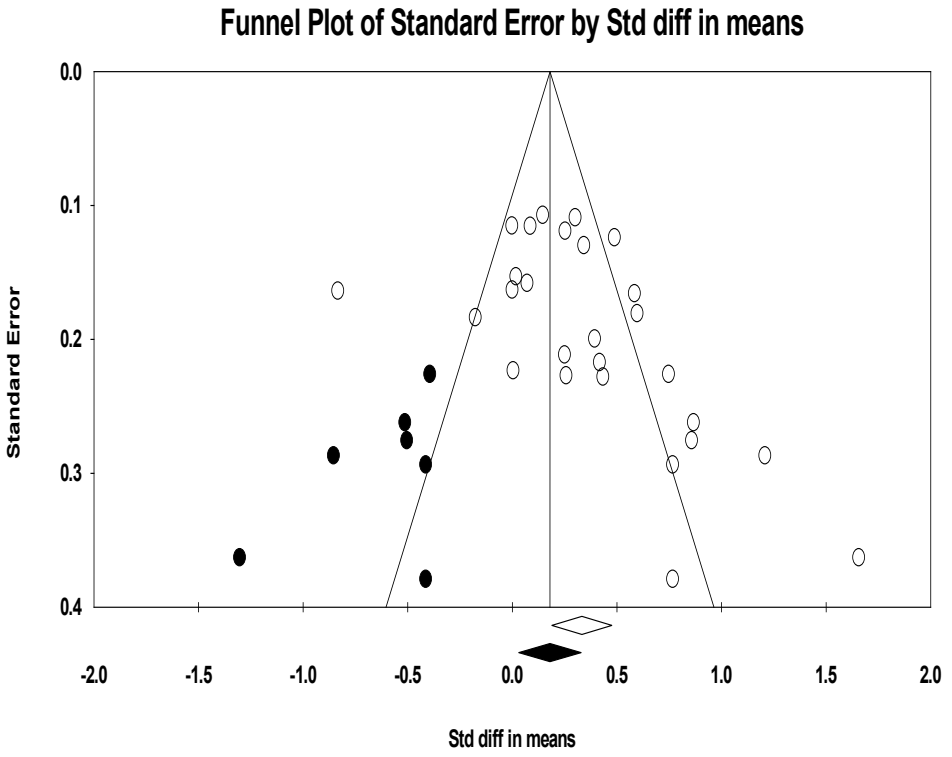
Total between-study variance (intercept only)
Tau^2 = 0.0705, Tau = 0.2656, I^2 = 71.25%, Q = 107.81, df = 31, p = 0.0000
Proportion of total between-study variance explained by Model 3
R^2 analog = 0.33

Number of studies in the analysis 32

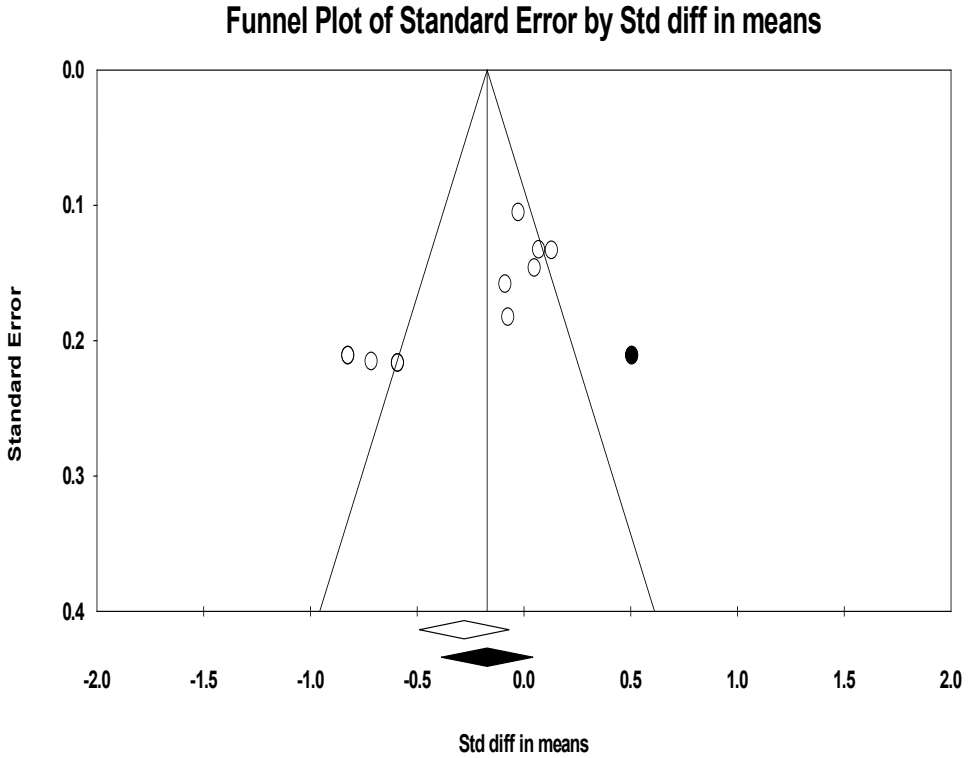


eFigure 4(B)

O. eFigure 5: Funnel plot for publication bias (Heart rate (A) and FeNO (B)).



Funnel plot A (Heart rate).



Funnel plot B (FeNO)

P. eBox: Data search strategies presented by databases

Search terms:

E-cig terms:

E-cig /E-cigarette /Electronic cigarette /Electronic nicotine delivery system /Personal Vaporizer /Personal Vapourizer /Vaping /Vape

Physiological terms

Acute physiological response / Cardiovascular / Exercise / Health /Lung /Physiological /Physiological stress / Respiratory /Toxicity /Vapor /Vapour / Safety

Search strategy:

PubMed

Search ((((E-cig[Title/Abstract] OR E-cigarette[Title/Abstract] OR Electronic cigarette[Title/Abstract] OR Electronic nicotine delivery system[Title/Abstract] OR Personal Vaporizer[Title/Abstract] OR Personal Vapourizer[Title/Abstract] OR Vaping[Title/Abstract] OR Vape[Title/Abstract])) AND (Acute physiological response[Title/Abstract] OR Cardiovascular[Title/Abstract] OR Exercise[Title/Abstract] OR Health[Title/Abstract] OR Lung[Title/Abstract] OR Physiological[Title/Abstract] OR Physiological stress[Title/Abstract] OR Respiratory[Title/Abstract] OR Toxicity[Title/Abstract] OR Vapor[Title/Abstract] OR Vapour[Title/Abstract] OR Safety[Title/Abstract])) Filters: Publication date from 2017/03/01 to 2020/05/20

Web of science

#1 TS= ((Acute physiological response) OR Cardiovascular OR Exercise OR Health OR Lung OR Physiological OR (Physiological stress) OR Respiratory OR Toxicity OR Vapor OR Vapour OR Safety)

#2 TS= ((E-cig) OR (E-cigarette) OR (Electronic cigarette) OR (Electronic nicotine delivery system) OR (Personal Vaporizer) OR (Personal Vapourizer) OR Vaping OR Vape)

Search = #1 AND #2

Scopus

TITLE-ABS-KEY (E-cig OR (E-cigarette) OR (Electronic cigarette) OR (Electronic nicotine delivery system) OR (Personal Vaporizer) OR Vaping OR Vape AND (Safety OR (Acute physiological response) OR Cardiovascular OR Exercise OR Health OR Lung OR Physiological))

Cochrane

(e-cig or e-cigarette or electronic cigarette or electronic nicotine delivery system or personal vaporizer or personal vapourizer or vaping or vape) and (Acute physiological response or acute cardiovascular responses or acute respiratory response or exercise or physiological stress or toxics