On Intolerance and Immigration: Understanding Perceptions of Intra- and Extradiversity in Denmark and Canada

Tasfia Sharif

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By: Tasfia Sharif

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

Signed by the final examining committee:

____ Dr. Elizabeth Teel _____Chair

_____Examiner

Dr Robert Kilgour

_____Examiner

Dr Kim Lavoie

_____ Thesis Supervisor(s)

Dr Simon Bacon

_____

Approved by Dr Geoff Dover _____

Chair of Department or Graduate Program Director

Dr Pascale Sicotte Dean of Faculty of arts and science

Date 02/09/2022

Abstract

Sex differences in physiological responses after acute electronic cigarette smoking

Tasfia Sharif

Electronic cigarettes (e-cig), were created as a "safe" new alternative to conventional cigarettes, and as a smoking cessation tool; however, the efficacy of e-cig as a smoking cessation tool in traditional smokers is still unclear**.** There is quite a good number of studies about human physiological responses to e-cigarette use; however, there's still a lack of information regarding these parameters altogether. Furthermore, there is no clear data if these parameters respond differently in males and females after acute e-cig smoking. There are studies which suggest that there is a different physiological response to smoking traditional cigarettes in males and females which are suggestive of cardiovascular complications being more common in male smokers whereas respiratory complications are prone to develop more in female smokers.

My thesis work focused on examining the acute cardio-respiratory physiological responses to e-cig smoking by reviewing the current literature and exploring sex differences in these physiological responses after active e-cig smoking in young healthy male and female adults. Acute e-cig consumption was associated with significant negative impact on human and female e-cig users and respiratory responses were more significnat in females compared to males.

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Systematic review

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Experimental study

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Dedication

To those who are working for the benevolent of mankind.

CONTRIBUTION OF AUTHORS

Systematic review

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- Tasfia Tasbih (co-1st author) performed the database searches, the data extraction, interpretation, writing of the current review, and interpreted the meta-analysis of the data with the aid of Simon Bacon and Paula Ribeiro.

- Florent Larue (1st co-author and reviewer) assessed study eligibility, study quality, performed data extractions, data organizations, conceptualization and writing of the review and meta-analysis result interpretation and contributed to tables and figures conception.

- Dr. Paula Ribeiro performed all the meta-analysis statistical analysis, sensitivity analysis and meta regression and helped in meta-analysis results interpretation.

- Dr. Kim Lavoie supervised and provided guidance in interpreting the observed findings and developing the manuscript.

- Dr. Simon Bacon supervised and reviewed and edited all the sections of the systematic review, from preparing the methodology to interpretation of the results, provided guidance and idea in structuring the discussion and clinical implication.

Experimental study

Tasfia Tasbih, Kim L. Lavoie, Esse Julien Atto, Mariam Atoui, Maximilien Dialufuma, Simon L. Bacon. Sex differences in physiological responses after acute electronic cigarette smoking (2).

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- Tasfia Tasbih organized the data to analysis and interpretation and writing of the study findings.

- Esse Julien Atto, Mariam Atoui, Dialufuma Maximillien performed the statistical analysis and provided feedback on the interpretation of the results.

- Dr. Kim Lavoie supervised and provided guidance in interpreting the observed findings and developing the manuscript and direction for future research.

- Dr. Simon Bacon contributed to planning and idea development and reviewed and edited all the sections of the manuscript.

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Chapter 1: Introduction

Sex and gender

To ensure proper healthcare for everyone, an appropriate sex and gender-based research approach as well as government policies and initiatives are helpful (3, 4). Sex is generally considered as male and female and consists of physical and physiological components including chromosomal patterns, hormone levels, and anatomical structure, where as gender is constructed on societal rules and behaviors and expressed as boys, girls, men, women and gender diverse people (5, 6). This thesis is ultimately focused on exploring the sex differences (between male and female) in acute cardio-respiratory physiological responses after acute electronic cigarette (e-cig) smoking.

Physiological differences in males and females

There are multiple differences between males and females in terms of physiological and pathophysiological process of diseases (7) and recognition of these differences permits appropriate disease diagnosis and the provision of proper treatments (8).

The size of female hearts is generally smaller and the cardiac chamber walls are thinner than male hearts. Female hearts pumps faster and ejects less blood with each beat than male hearts (5, 9). Under stressful conditions, e.g. acute laboratory stress tasks, males show more of a rise in blood pressure due to arterial constriction and females show a greater rise in pulse rate (9). The sympathetic nervous system (SNS) has predominant control over cardiac responses to smoking in males compared to females (10); for example, testosterone (male sex hormone) has a role in elevating blood pressure whereas estrogen (female sex hormone) protects against high blood pressure (8). Males tend to have obstructive coronary arterial disease and females tend to have microvascular, endothelial dysfunction and non-obstructive coronary disease and vascular spasm (11). This could be partly explained by the presence of sex-based atypical risk factors in females e.g. menopause, pregnancy, polycystic ovarian disease and higher tendency to develop chronic inflammatory disease compared to males (12, 13).

Male lung size, e.g., diameter of airways, as well as lung function, e.g., lung volumes, is greater than in females (14). Due to smaller airways and lower lung volume, women tend to develop smaller maximal volume-loop and increased work of breathing (14). Menstrual cycle-induced hormonal changes also seem to affect lung function in females (15). Some respiratory diseases, e.g. chronic

obstructive pulmonary disease (COPD) and lung cancer, seem to develop more often in females due to such physiological factors (14). In terms of autonomic innervation, although clear data regarding such sex differences over the nervous control of respiratory function is not yet available, several studies have documented predominant airway inflammation and pulmonary vasoconstriction in females in response to stimuli e.g. smoking; however, the exact mechanism behind such responses is not yet explicit in the current literature (16, 17).

Females tend to have a stronger innate and adaptive immune responses than males which allows the clearance of pathogens or chemical irritants, but also, increases the susceptibility of developing inflammatory diseases in female (18). Sex hormones, testosterone, estrogen, and progesterone, seem to be one of the main factors for such differences in immunological responses (18).

Smoking epidemiology and evaluation

Smoking, which is an important modifiable behaviour, is one of the most common preventable causes of premature death. The average life expectancy of a heavy smoker is reduced by 9 years in comparison to a non-smoker (19) and recent studies have estimated that 21% of all deaths over the past decade were due to smoking (19). Every year more than five million people die of smoking complications and among them 1.5 million are female (20). Unless urgent action is taken, tobacco use could kill up to 8 million people every year by 2030, of which 2.5 million would be female (20). According to Canadian statistics, each day 100 Canadians die of smoking related illness and more than 37,000 Canadians die each year. Smoking prevalence is much higher among adult males than females around the world (21). According to a 2019 statistic, in Canada, around 4.7 million people smoked cigarettes either daily or occasionally, with 17.3% of males and 12.3% of females who currently smoke (22). Although current smoking has been found to have declined between 2005 (20.9%) and 2019 (14%), smoking remains a serious public health issue and the risk of growing smoking rate in the future still remains high with an significant increase in female smokers from eight to twenty percent predicted by 2025 (23).

Regular or traditional cigarettes are made of dried tobacco leaves, flavours, and other substances that are added to make smoking more pleasant, all of which make chemical constituents when they are burned (24). Thousands of chemicals have been found in tobacco smoke e.g., nicotine, hydrogen cyanide, formaldehyde, benzene, tobacco specific nitrosamines etc., 70 of which are carcinogens and are related to cancer. Smoking affects multiple systems of the human body, including the cardiovascular and respiratory systems, and causes cancer in various organs (25). The risk of coronary disease, COPD, and lung cancer has been found to be increased several times due to smoking (25).

Pathophysiological responses of smoking according to sex

There are certain differences between male and female smokers in terms of their response to smoking including physiological aspects which impacts the development of smoking related complications. Smokers mostly die from cardiovascular and respiratory complications (26) with male smokers tending to suffer from cardiovascular complications such as coronary artery disease (7.9% in male vs 5.1% in female), myocardial infarction (4.2% in male vs 2.1% in female)(27-29), which is likely driven by changes in the sympathetic nervous system being more predominant in male (30). The nicotine content of cigarettes activates the nicotine acetylcholine receptors which are localized on peripheral postganglionic sympathetic nerve endings and the adrenal medulla (31). This activation increases the release of catecholamines (adrenaline, noradrenaline and dopamine) which increases several cardiac parameters, e.g. heart rate, blood pressure, myocardial contractility and leads to developing cardiovascular diseases (31). Studies have observed that the SNS has a greater effect on male cardiac function compared to female, for example, young females exhibit lower tonic autonomic nervous system support of arterial blood pressure compared with young males due to their lower basal sympathetic nerve activity and attenuated alpha-adrenergic sensitivity (32).

Chronic obstructive pulmonary disease (COPD), lung cancer, and acute respiratory distress syndrome (ARDS) are common smoking related respiratory complications (29, 33) and current studies are suggestive of females being more prone (more than 50% greater risk than males) to developing these respiratory complications(34, 35). It has been suggested that this is due to more inflammatory response in airway and pulmonary vessel endothelium to nicotine or smoking constituents in female, probably due to shorter airway passages and certain pro-inflammatory impacts of estrogen (35, 36) .

Smoking cessation

Considering the health related complications of smoking, most countries are trying to reduce its burden by introducing a myriad of smoking cessation tools such as behavioural counselling by healthcare providers, telephone- and print-based interventions, computer and text-messaging interventions, and pharmacologic agents (that is, nicotine replacement therapy [NRT], bupropion hydrochloride sustained release [bupropion], and varenicline) (37). ***Electronic cigarettes (e-cig),*** were created as a “safe” new alternative to conventional cigarettes, and as a smoking cessation tool (38); however, the efficacy of e-cig as a smoking cessation tool in traditional smokers is still unclear(39). Hajek et al found higher abstinence rate in e-cig users (18%) compared to NRT users (9.9%)(40). On the other hand, there is a risk of people using both traditional and e-cig devices (dual users) which could increase the risk of cardiopulmonary complications of smoking e.g.,

atherosclerosis, chronic obstructive pulmonary disease (COPD) (41).

E-cig and its growing popularity

E-cig has been taken up by millions of people around the world since they first appeared on the Chinese market in 2004 (42, 43). Currently the number of e-cig user is 68 million(44). According to Statistics Canada, between 2017- 2018, the number of vaping users, aged 15-24 years, increased around 74%, and in 2020, it is the most common smoking device among this age group (45, 46). A similar percentage of males (19%) and females (18%), aged ≥15 years reported ever trying e-cig in the past 30 days (45).

Components of e-cig and how they work?

A typical e-cig device is usually composed of the following components: a rechargeable lithium battery; vaporizing chamber; and a cartridge that contains the e-liquid (47). The battery activates the device to charge the atomizer inside the cartridge (47). An airflow sensor activates a battery when the user inahles into the e-cig device nad it powers an atomizer to produce an aerosol from e- liquid that contains various chemical consitiuents e.g., nicotine, glycerol, propylene glycol (48). The e-cig aerosol (mixtures of chemical constituents) simulates cigarette smoke and produce vapour (49). When the user inhales a puff, the aerosol enters into the user's mouth and lungs by inhalation and the remaining aerosol is exhaled into the environment (49).

There are 4 generations of e-cig devices currently on the market (50). They are usually different in their structural components and battery voltage (50). New e-cig users use first-generation e-cigs which conatins cartomizer (cartridge and an atomizer) and low-voltage battery (3.7 V) (50). Second-generation e-cigs contains refillable tank and adjustable battery voltage (3–6 V) (51) and commonly used by more-experienced users. The third-generation devices/ mods have the largest size batteries, with higher voltages (up to 8 V) (52). Most recent generation/ fourth generation e-cig devices allows the vapers to inhale large volume of puffs with high e-liquid consumption as it conatins temperature control devices, which allow temperature controlling during vaping (53).

Approximately 60 to 70 identified and unidentified compounds of e-liquid has been found in several toxicology study and one study identified 113 chemicals in 50 brands of liquids, several of these components are also present in regular cigarette (54). Following compounds are identified in e-cig liquids; nicotine, solvent carriers (PG and glycerol), tobacco-specific nitrosamines (TSNAs), aldehydes, metals, volatile organic compounds (VOCs), phenolic compounds, polycyclic aromatic hydrocarbons (PAHs), flavorings, tobacco alkaloids, most of these substances have been documented

as harmful for human health (55). Even more chemicals are generated when the e-liquid/ aerosol is heated during vaping (56). One study reported an aerosol heated in a single e-cig device produced 18 additional compounds like acrolein, formaldehyde, acid aldehyde are produced from propylene glycol and glycerin when they are heated which likely have negative impact on lungs (54). Beside that, e-cig manufacturers often do not provide true information regarding the chemicals/ nicotine level used in the manufacturing process or synthesised during the aerosol generation process and hence safety concern exists on this regard (38).

Pathophysiological effects of e-cig

E-cig consumption is likely associated with long-term health effects, such as a 42% increase in the odds of myocardial infarctions (57), as well as negative short-term effects (58). There were 2,807 hospitalizations and 68 deaths due to EVALI (electronic cigarette or vapor associated lung injury), most of which were in young adults and reflects the potential acute negative health impacts of e-cigs (59). Vitamin E acetate was strongly linked to the EVALI outbreak (60), however, it is not documented clearly which component of e-cigs, such as flavors, heavy metals, carbonyls, acrolein or free radicals were respoinsible behind these EVALI cases (61-64). Studies have suggested that e-cigs have negative impacts on the cardiorespiratory system, central nervous system, and immune system (65). Some studies have suggested that the non-nicotine ingredients might be more toxic than nicotine alone and they might cause potential negative health effects (65). This thesis does not explore the specific physiological responses of specific e-cig constituents, and only focused on the overall effects of e-cig. However, the following sections provide some information on the potential effects of individuals components.

Nicotine: Nicotine activates the nicotine acetylcholine receptors on peripheral postganglionic sympathetic nerve endings and the adrenal medulla (31). This activation increases the release of catecholamines (adrenaline, noradrenaline and dopamine) which increases heart rate, blood pressure, myocardial contractility as well as oxygen demand (66). A continuous mismatch between myocardial oxygen supply and demand can result in myocardial ischemia or infarction (66). Nicotine also acts on dopaminergic receptors and within 8 seconds of inhalation, nicotine activates the dopamine receptors in the brain. Ultimately dopamine is released which gives the user a feeling of relaxation which could lead to smoking addiction (31).

Propylene glycol and glycerin: According to current literature, non-nicotine constituents of e-cig could cause negative health effects (67). For example, Propylene glycol (PG), also known as 1,2-propanediol, methyl glycol, and trimethyl glycol, has been found to cause allergic reaction, dry mouth

and throat, respiratory irritation (68). The short term effect of aerosolized PG has been documented in the studies e.g., upper respiratory tract irritation within 1 minute of inhalation though the longer-term health effect is not well documented (68). Beside that, a patient developed signs of exogenous lipoid pneumonia (e.g., fever, productive cough, and labored breathing) after using e-cig for half a year, and symptoms improved following e-cig smoking cessation (69). Two other components of e-cig, glycerin and ethylene glycol has been reported to cause petechial hemorrhage and respiratory tract irritation respectively (70).

Exploring sex differences in acute physiological responses to e-cig smoking and potential disease prevalence

Several studies have found e-cig have an association with significant cardio-respiratory and inflammatory responses (1, 71) and majority of EVALI cases were presented with tachypnea, shortness of breath, acute respiratory distress (ARDS) in both males and females, who were mostly young adults(72, 73). Complications derived from e-cig have shown similarities with traditional cigarette smoking in terms of physiological and pathological responses(74). Although we have information regarding complications and disease prevalence in male vs. female traditional cigarette smokers, we do not have any data regarding such sex differences in e-cig users. Moreover, e-cig contains some similar components that are also found in regular cigarette such as nicotine and formaldehyde(75). Considering all of these, there are a number of reasons to explore the physiological effects of acute e-cig smoking in general, as well as how males and females respond to acute e-cig smoking which might be helpful in providing data on sex-based response to e-cig smoking that we currently lack.

Chapter 2. Objectives and Hypotheses

There is quite a good number of studies about human physiological responses to e-cigarette use; however, there's still a lack of information regarding these parameters altogether. Furthermore, there is no clear data if these parameters respond differently in males and females after acute e-cig smoking. There are studies which suggest that there is a different physiological response to smoking traditional cigarettes in males and females which are suggestive of cardiovascular complications being more common in male smokers whereas respiratory complications are prone to develop more in female smokers.

My thesis work focused on examining the acute cardio-respiratory physiological responses to e-cig smoking by reviewing the current literature and exploring sex differences in these physiological responses after active e-cigarette smoking in young healthy male and female adults.

Objectives

1. Summarise, using a systematic review, the current literature assessing the acute physiological impacts of e-cig in humans.
2. Explore sex differences in physiological responses after acute e-cig smoking in an experimental study.

Hypothesis

1. Systematic review
    - Acute e-cig smoking has negative impacts on human cardio-respiratory and inflammatory responses.
2. Experimental study
    - Males would exhibit larger changes in cardiac responses, and females would exhibit larger changes in respiratory responses after acute e-cig smoking.

Chapter 3: Systematic review

Manuscript word count: 2997 words

Abstract word count: 293 words

Immediate physiological effects of acute Electronic Cigarette use in humans: a systematic review and Meta-Analysis

Florent Larue MD MSc,[1,2,3] Tasfia Tasbih MBBS MSc,[1,2] Paula A B Ribeiro PhD,[1] Kim L. Lavoie PhD,[1,4], Emilie Dolan Msc,[1,2] Simon L. Bacon PhD,[1,2]

1 Montreal Behavioural Medicine Centre, Centre integrée universitaire de santé et services sociaux du Nord de l'Ile de Montréal (CIUSSS-NIM), Montreal, QC, H4J 1C5, Canada
2 Department of Health, Kinesiology, and Applied Physiology, Concordia University, 7141 Sherbrooke St West, Montreal, H4B 1R6, Canada
3 Faculty of Medicine of Montpellier, Montpellier, France.
4 Department of Psychology, University of Quebec at Montreal, CP 8888, Succursale Centre-Ville, Montreal, QC, H3C 3P8, Canada

Address for correspondence:
Simon L. Bacon, PhD, FTOS, FCCS, FABMR
Department of Health, Kinesiology, and Applied Physiology
Concordia University
Email: simon.bacon@concordia.ca
Twitter: @sbacon20, @mbmc_cmcm

Key points

Question: What are the immediate physiological effects, i.e., cardiovascular, respiratory, and blood-based responses, associated with acute electronic cigarette (e-cig) usage in humans?

Findings: This systematic review included 45 articles, 27 of which (n= 919 patients, 8 outcomes) were included in meta-analyses. Acute use of e-cigs significantly impacted the cardiovascular system (heart rate, blood pressure, arterial stiffness), and airway inflammation (FeNO) but not spirometry results (FEV1, FVC).

Meaning: Consistent with the recent EVALI epidemic, the acute consumption of e-cig has a physiological impact on the cardiovascular and inflammatory systems.

Highlights:

- Meta-analysis of 27 studies assessing a wide range of physiological acute effect of e-cig and gathering 919 participants
- Acute e-cig consumption led to increases in heart rate, blood pressure and arterial stiffness
- FeNO decreased after acute e-cig use whereas spirometry measures did not change
- The acute changes observed have been associated with long term cardiovascular risk, but this is yet to be demonstrated with e-cig usage

Abstract (293 words)

Background: Electronic cigarettes (e-cigs) 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 reported.

Research question: What are the immediate physiological effects (i.e., cardiovascular, respiratory or blood-based responses) of acute e-cig usage in humans?

Study Design and Methods: PubMed, Web of Science, Cochrane and Scopus databases were searched for English or French peer-reviewed articles published until 20th May 2021 and measuring at least one physiological parameter before and after using an e-cig. The 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-regressions were 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 19823 articles screened, 45 articles were included for the qualitative synthesis, and 27 articles (919 patients) were included in meta-analyses. Acute use of nicotine e-cig was associated with increased heart rate (SMD=0.71; 95%CI 0.46-0.95), systolic blood pressure (SMD=0.38; 95%CI 0.18-0.57), diastolic blood pressure (SMD=0.52; 95%CI 0.33-0.70), and augmentation index AIx75 (SMD=0.580; 95%CI 0.220- 0.941), along with decreased FeNO (SMD=-0.26; 95%CI -0.49- -0.04). E-cig exposure wasn't associated with significant changes in any spirometry measure.

Interpretation: Acute use of nicotine e-cigs was associated with statistically significant cardiovascular and respiratory responses. These devices have a physiological impact that could be clinically relevant, especially in terms of cardiovascular morbidity. However, the direct consequences of long-term e-cig use needs to be further explored.

Registration: the protocol was registered in PROSPERO(CRD42017062693).

Background

Tobacco consumption is a major public health issue with an estimated 8 million global deaths per year attributed to tobacco (76). The numerous toxic substances released from the combustion process of tobacco leaves are known to lead to serious negative health outcomes such as cancer, COPD, and cardiovascular disease, impairing not only life expectancy but also the quality of life (77, 78). At present, with 1.1 billion smokers worldwide (76), smoking cessation continues to be a key public health focus.

Electronic cigarettes (e-cigs) were invented in 2003 as a potential smoking cessation aid (79). They use a battery to heat a metallic coil, turning 'e-liquids' into a smoke-like vapor (79). This e-liquid is usually a mixture of propylene glycol, glycerol, various flavoring, and quite often nicotine (79). Despite the lack of evidence of its innocuity (80-82) and the inconsistent results concerning its efficacy for smoking cessation (83), these devices have attracted a lot of consumers including both smokers and non-smokers (84). The popularity of these devices is especially concerning among youth. In the USA, the proportion of high school students ‘vaping’ increased significantly over 3 years going from 11.7% in 2017 to 19.6% in 2020 (85). The number of e-cig users worldwide is rising considerably and was already over 41 million as of 2018 (86).

E-cigs are likely to be less toxic than combustible cigarettes, but there are insufficient data to quantify the precise level of risk associated with them (87). Based on recent systematic reviews about e-cig’s health effect or physiological impact (88-90), as well as evidence concerning e-cig’s effect on brain development (91), the WHO stated in 2021 that e-cigs are harmful and should therefore be subject to regulation (92). Consistent with this, the US’s Food and Drug Administration (FDA) recently approved a tobacco flavored e-cig for smoking cessation (93) and Australia became the first country in the world where e-cig require a medical prescription(92). In contrast, the identification and rapid rise of Electronic-cigarette or Vapor Associated Lung Injury (EVALI) provide a stark warning about the potential negative health impacts of e-cigs (94). As of April 2020, there were 2,807 hospitalizations and 68 deaths due to EVALI, most of which were in young adults (95). Although vitamin E acetate was strongly linked to the EVALI outbreak (60), it is impossible to rule out other aspects of e-cigs such as flavors, heavy metals, carbonyls, acrolein or free radicals (61-64). As a consequence of these discoveries, evidence of negative physiological effects has been increasingly observed among e-cig users (96-98). Despite this growing evidence, this is, to our knowledge, the first systematic review and meta-analyses to

assess cardiovascular, respiratory, and hematological 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 (99) and the protocol was registered in PROSPERO (CRD42017062693). We selected English and French peer-reviewed studies that reported physiological data on cardiovascular, respiratory, and blood-based markers both before and after active e-cig vaping among human participants. Data on combustible cigarette comparison arms were also included if they were reported in the e-cig studies.

Study search and Screening

Four databases (PubMed, Web of Science, Scopus and Cochrane Library) were searched. The search terms and the detailed search strategy used for each database can be found in the supplementary material. An initial search was conducted up to the end of January 2019 and was then updated up to May 20th 2021. Reviewers were not blinded to the journal of publication, author names, or their institutions. The screening and full-text assessment were 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 and analysis

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 (cardiovascular, respiratory, and hematological). In cases of missing data, authors were contacted by e-mail with up to two reminders sent one week apart.

A minimum of four 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 (100). 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 ranges. 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), was calculated as post- minus pre-

smoking values. According to Cohen's recommendation (101), 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 the first 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 (102-104). Funnel plot asymmetry was evaluated using Begg and Egger's test and a significant publication bias was considered if *P* value was <0.10 (103).

Quality assessment

Study quality was evaluated independently by two reviewers using the Downs and Black Checklist (105) which was adapted for acute laboratory study design. A total of 13/27 items with the following subscales were assessed: reporting; external validity; and internal validity. The inter-reviewer agreement was 90% and discrepancies were resolved by consensus.

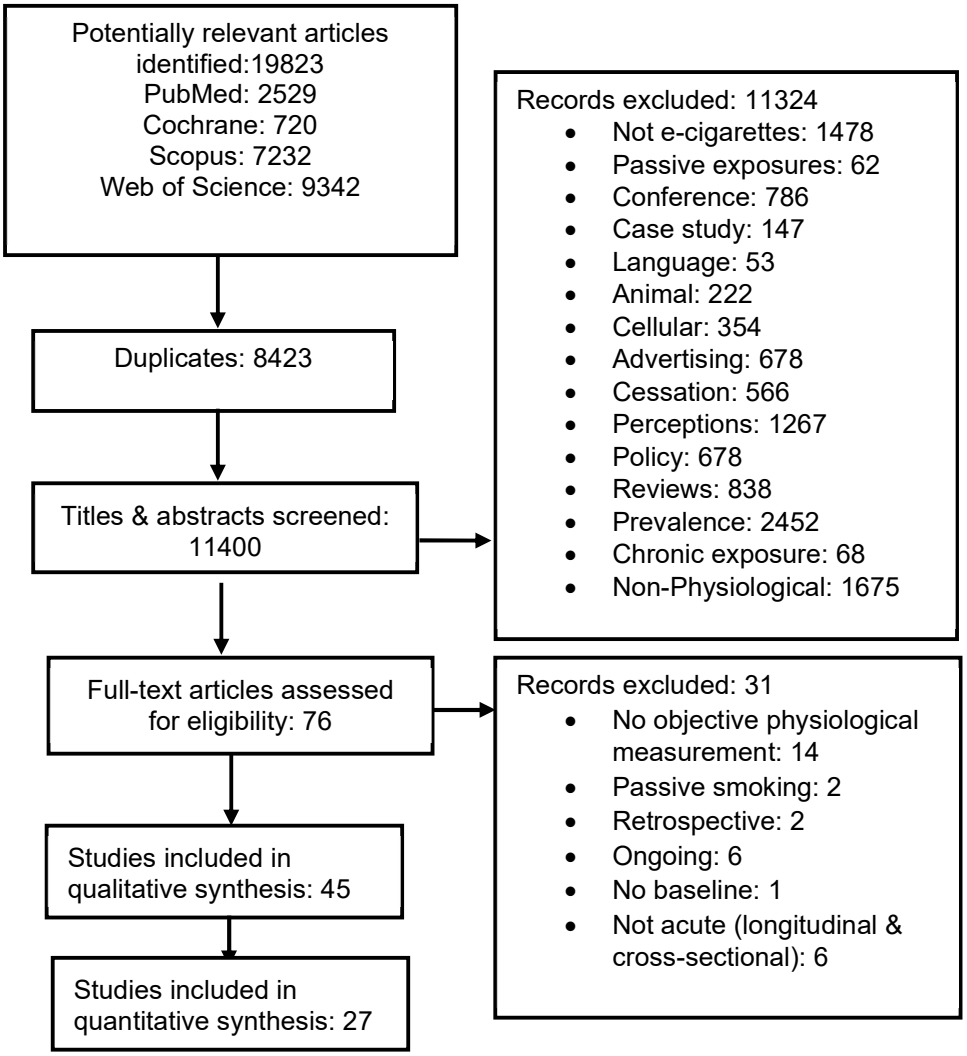
RESULTS

Of 19,823 articles, after removing duplicates 11,400 articles were screened, of which 76 eligible articles were extracted for full-text review. Most of the excluded articles were about e-cig prevalence, policy, perceptions, efficiency for tobacco cessation, or they did not assess physiological parameters (see eFigure1 for detailed flow diagram). From those articles, 45 were included in the qualitative analysis. Finally, a total of 27 articles (919 research participants) were eligible to be included in meta-analyses. Fourteen authors were contacted for missing data and seven provided us with useable data.

Study characteristics and smoking protocols

Among the 27 studies included in our meta-analyses there were 619 participants exposed to EC+, 432 to EC- and 339 to combustible cigarettes. As indicated in eTable1, 80% of the studies were cross-over studies and the rest 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 asthma and one including patients with COPD. The majority of studies only included current smokers (60%). However, seven studies included non-smokers only and seven

Figure 1: Diagram for the study selection process for the systematic review and meta-analysis



included both smokers and non-smokers.

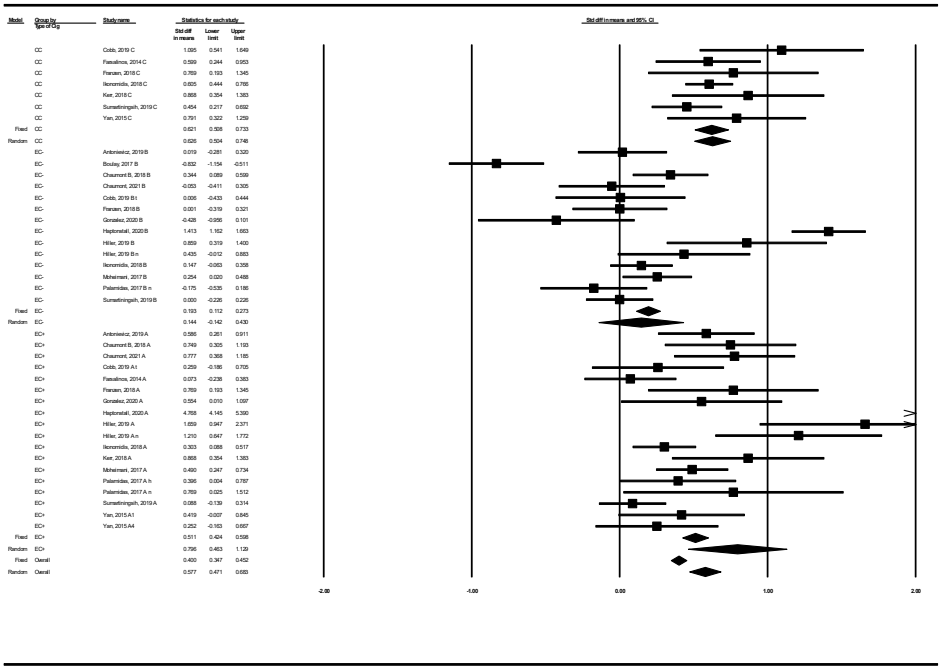
Included studies used different brands of e-cigs with different nicotine concentrations (0mg/ml to 36mg/ml). Variations in terms of propylene glycol/glycerol ratio (PG/GLY) as well as flavors of e-liquid were observed, the most frequently used e-liquids being 70/30 (PG/GLY) with tobacco flavor**.** This was consistent with the most frequently used e-liquids among adults (106). 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 min. The first post-inhalation assessment of the physiological outcome of interest occurred between 1- and 30-minutes post-smoking. Some studies compared the effects of e-cigs to combustible cigarettes, or sham vaping (e-cig turned off). Details of the smoking protocols can be found in eTable2.

Cardiovascular results

A total of 22 studies measured different cardiovascular responses to e-cigs (see eTable3, 4 and 5). From all outcomes reported by the authors, there were enough data to conduct meta-analyses for heart rate (HR); blood pressure (systolic (SBP) and diastolic (DBP)); and augmentation index adjusted for heart rate (AIx75).

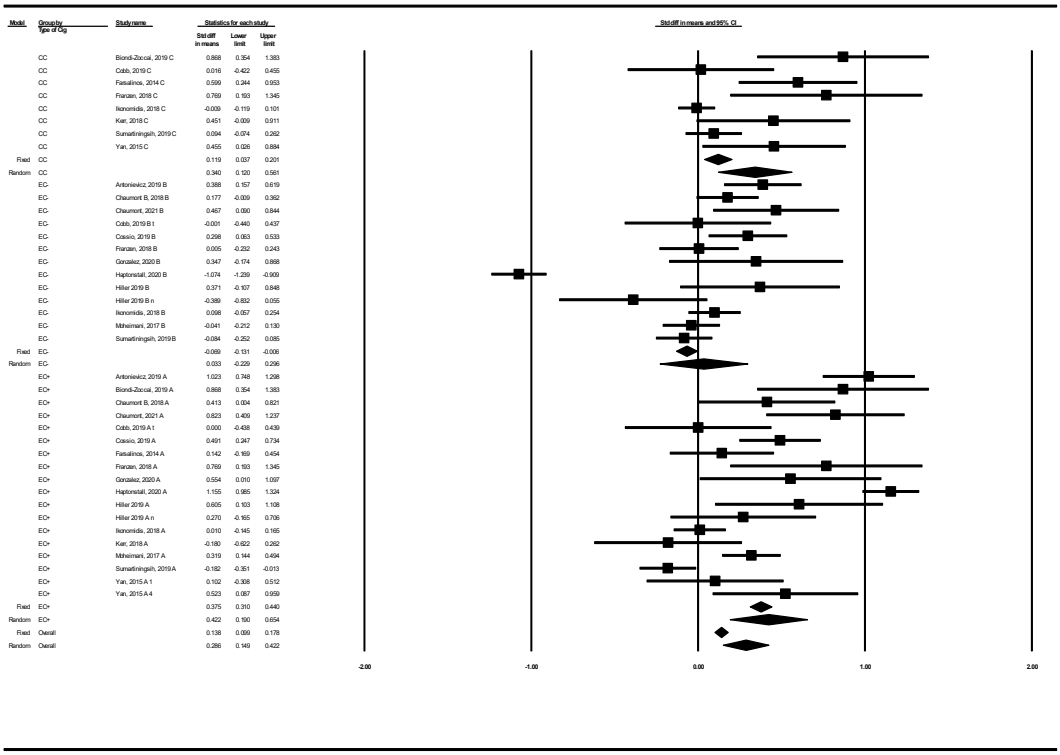
There was a significant increase in HR following acute smoking of EC+, with an average moderate effect-size (SMD=0.71; 95%CI 0.46-0.95) which was similar to acute combustible cigarette smoking (SMD=0.63; 95%CI 0.50-0.75) (107-118), see Figure2. Significant increases in SBP (SMD=0.38; 95%CI 0.18-0.57) and DBP (SMD=0.52; 95%CI 0.33-0.70) 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. HR, SBP, and DBP did not change in response to EC-. AIx75, 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. In addition, a number of other cardiovascular changes were identified in qualitative synthesis though none had enough data for meta-analyses. (see eTable4 and 5 for details)

Figure 2. Forest plot reporting standardized mean difference (SMD) and 95% confidence interval (CI) for each study measuring heart rate (HR)



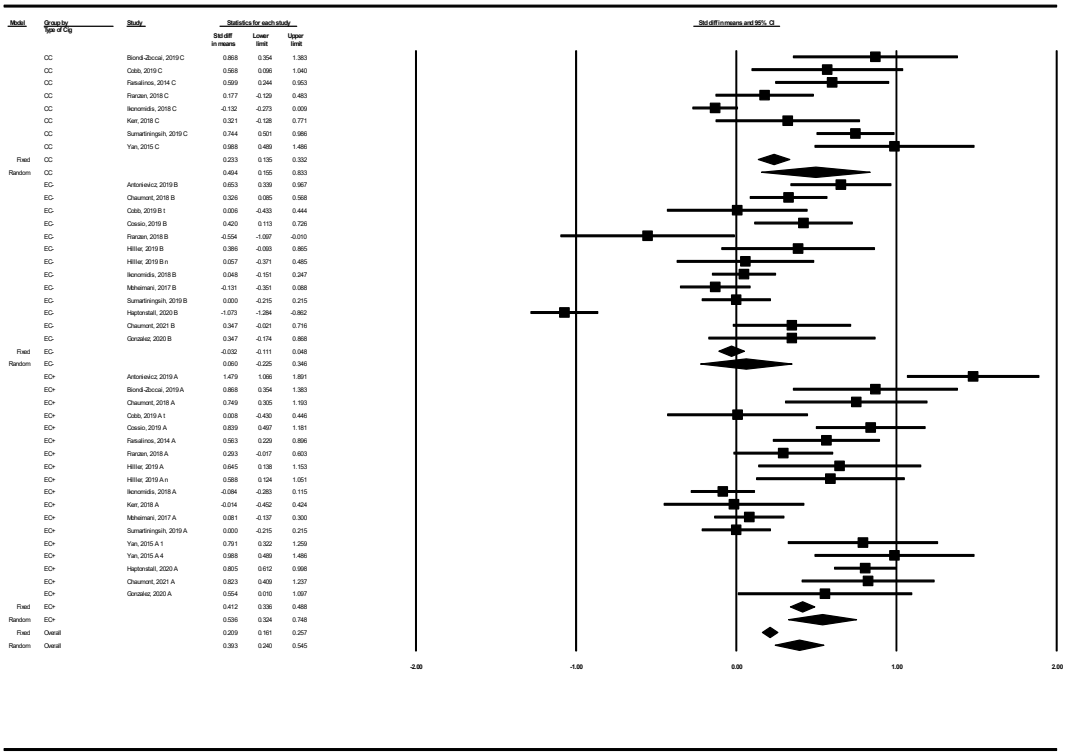
Overall test for heterogeneity: I^2= 91%; p= <0.001; Q-value = 11.1
((Note: The black diamond at the bottom of the page indicates the average effect size of the studies. Type of Cig= cigarette device type; std diff= standard difference; CI= confidence interval
A= EC+ (electronic cigarette with nicotine; B= EC- (electronic cigarette without nicotine); C= CC (combustible cigarette); h= healthy smoker group; n= nonsmoker group; t= tobacco flavored electronic cigarette; YAN 2015 A1, A4= different nicotine and PG/GLY concentration of electronic cigarette))

Figure 3. Forest plot reporting standardized mean difference (SMD) and 95% confidence interval (CI) for each study measuring systolic blood pressure (SBP)



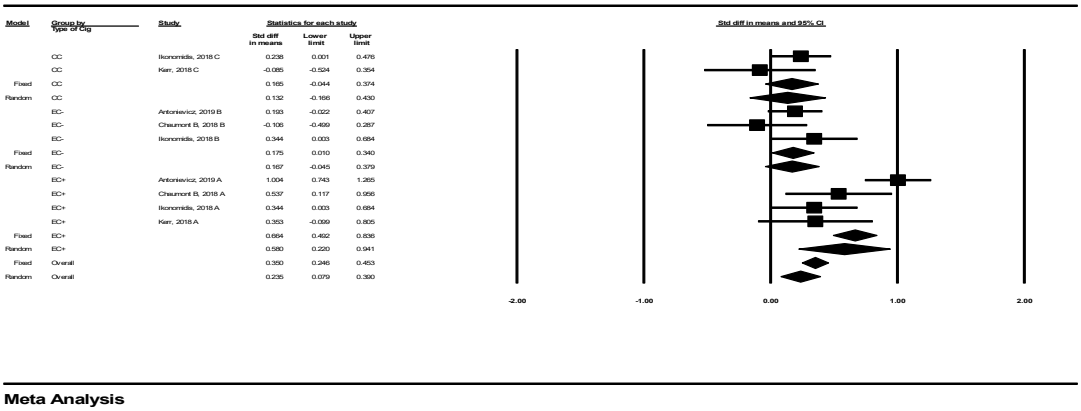
Overall test for heterogeneity: I^2= 92%; p= <0.001; Q-value = 5.11
((Note: The black diamond at the bottom of the page indicates the average effect size of the studies. Type of cig= cigarette device type; std diff= standard difference; CI= confidence interval
A= EC+ (electronic cigarette with nicotine; B= EC- (electronic cigarette without nicotine); C= CC (combustible cigarette); h= healthy smoker group; n= nonsmoker group; t= tobacco flavored electronic cigarette; YAN 2015 A1, A4= different nicotine and PG/GLY concentration of electronic cigarette))

Figure 4. Forest plot reporting standardized mean difference (SMD) and 95% confidence interval (CI) for each study measuring diastolic blood pressure (DBP)



Overall test for heterogeneity: I^2= 90%; p= <0.001; Q-value = 7.32
((Note: The black diamond at the bottom of the page indicates the average effect size of the studies.
Type of cig= cigarette device type; std diff= standard difference; CI= confidence interval.
A= EC+ (electronic cigarette with nicotine; B= EC- (electronic cigarette without nicotine); C= CC (combustible cigarette); n= nonsmoker group; t= tobacco flavored electronic cigarette.
YAN 2015 A1, A4= different nicotine and PG/GLY concentration of electronic cigarette))

Figure 5. Forest plot reporting standardized mean difference (SMD) and 95% confidence interval (CI) for each study measuring augmentation index adjusted for heart rate (AIx 75)



Overall test for heterogeneity: I^2= 78%; p= <0.001; Q-value = 4.37
((Note: The black diamond at the bottom of the page indicates the average effect size of the studies.
Type of cig= cigarette device type; std diff= standard difference; CI= confidence interval
A= EC+ (electronic cigarette with nicotine; B= EC- (electronic cigarette without nicotine); C= CC (combustible cigarette))

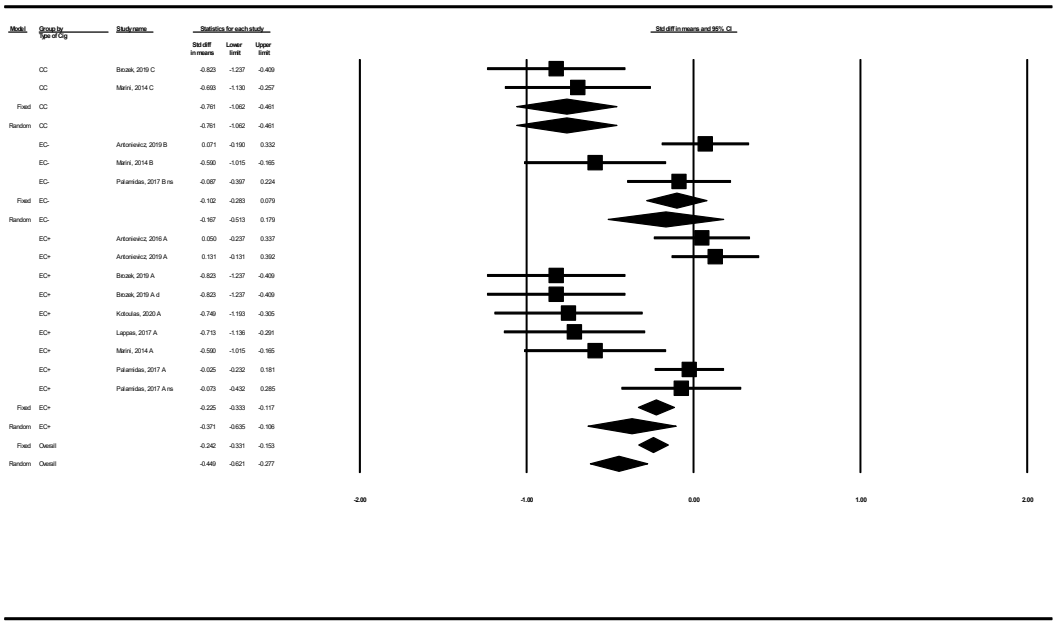
Respiratory results

A total of 17 studies measured different respiratory responses (eTable6 and 7). From these, there were 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 in FEV1 (SMD=-0.15; 95%CI -0.32- +0.01), FVC (SMD=-0.06, 95%CI -0.22- +0.10), nor FEV1/FVC ((SMD=-0.10 95%CI -0.35- +0.15) in response to EC+. Likewise, there were no changes in these measures to EC-, see eTable8 for all meta-analysis results. 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). As seen in Figure 6, FeNO decreased in response to EC+ (SMD=-0.26; 95%CI -0.49- -0.04) and CC (SMD=-0.76; 95%CI -1.06- -0.46) with no changes seen in response to EC- (SMD=-0.13; 95%CI= -0.37-+0.12). Heterogeneity concerning e-cig's results was low for FEV1 and FVC but high for FeNO and FEV1/FVC (see eTable8 for overall heterogeneity results).

A number of other respiratory changes were identified in qualitative synthesis such as increased respiratory resistance(116, 119, 120) and decreased oxygen saturation (121) though none had

enough data for meta-analyses (see eTable7 for details).

Figure 6. Forest plot reporting standardized mean difference (SMD) and 95% confidence interval (CI) for each study measuring fractional exhaled nitric oxide (FeNO)



Overall test for heterogeneity: I^2= 83%; p= <0.001; Q-value = 8.04
((Note: The black diamond at the bottom of the page indicates the average effect size of the studies. Type of cig= cigarette device type; std diff= standard difference; CI= confidence interval; A= EC+ (electronic cigarette with nicotine; B= EC- (electronic cigarette without nicotine); C= CC (combustible cigarette); d= dual smoker group (both EC & CC); ns=naive/ nonsmoker group))

Blood-based responses

Eleven studies looked at hematological responses to smoking e-cigs. EC+ seemed to induce hematological changes in measures indicative of worse endothelial function (109, 114, 121-123), greater oxidative stress (109, 113, 115, 122-124) as well as an increase in pro-thrombotic state (125, 126) and inflammatory levels (124), though there weren't enough studies to conduct meta-analyses. The detail of the hematological impact of e-cigs can be found in eTable9.

Sensitivity analyses and meta-regression

Sensitivity analysis focusing on healthy volunteers and standard e-cigs (i.e., removing

populations who were defined as having a disease and analyses conducted on flavored e-liquid) didn't impact the physiological changes previously observed.

We performed meta-regression to explore heterogeneity for HR, SBP and DBP to investigate the impact of time before first outcome measurement (eFigure4 (A)) and the e-liquid's nicotine concentration (eFigure4 (B)). These outcomes were chosen due to the higher number of studies included (statistical power). We could not include other parameters also due to a lack of adequate information. No correlation was found between e-liquid nicotine concentration nor time to first outcome measurement and these cardiovascular parameters.

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 36 studies scoring 10 or above, which is considered as good/excellent quality of the studies (see eTable1). The three reporting areas of greatest concern were: if the individual measuring the outcomes was blinded or not (68%); if there were probable adverse events during the studies (60%); and the description of the population that the participants were selected from (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 (A); Egger's regression two-tailed p=.13) but this wasn't the case for FeNO (eFigure5 (B): Egger's regression two-tailed p<.001). Nevertheless, fewer studies were included for FeNO than for HR and the authors agreed that visual analysis was symmetrical. The risk of publication bias in this meta-analysis is likely low for cardiovascular measures and probably low for respiratory measures.

DISCUSSION

This review found that acute exposure to e-cigs did 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 HR, BP and arterial stiffness (AIx75). There was also a significant decrease in FeNO although less pronounced than the one following combustible cigarettes. 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 endothelial dysfunction and increases in 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 found a linear relation between resting HR and cardiovascular mortality over 14.5 years of follow-up, with a 13% increase in death for each 10 bpm increase among patients not taking any heart rate lowering medication (127). The average blood pressure changes observed in our study correspond to a 3mmHg and 4mmHg increase for DBP and SBP respectively. Although this may seem low, a recent meta-analysis published on 24 prospective cohort studies found that a 10 mmHg increase in SBP was associated with a 10% increase in cardiovascular (CV) events over a 5.9-year follow-up (128). This same study also found that a 10% increase in AIx was associated with an 18% increase in CV events (128). Of note, our meta-analysis found a 5.8% increase in AIx75 following acute e-cig use. Based on the magnitude of changes seen in the current meta-analyses and the above-mentioned study, the aggregated acute physiological changes seen in our review could relate on the long term to a 3 to 10% increase in CV risk. This could be clinically meaningful especially considering the growing popularity of e-cig. Although longitudinal studies are lacking, two National Health Interview Surveys (2014 and 2016) have already found a significant cross-sectional association in risk of myocardial infarction after chronic e-cig use (OR:1.79 (95% CI=1.20-2.60) compared to a never smoker group (129). Nevertheless, this review did not directly examine the impact of chronic e-cig use on resting HR and BP level nor long-term CV outcomes. Moreover, our interpretation of the potential impacts of e-cigs on long-term outcomes is predicated on there being a linear relationship. However, as with other stimulants, like caffeine (130)t is possible that the relationship between e-cig consumption and health risk could follow a J or U curve. As such, we can only infer potential long-term health consequences from chronic e-cig use and this is clearly an area where further work is needed.

Our meta-regression analyses suggested that e-cigs 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 (131). Nicotine could therefore be responsible for the cardiovascular modifications observed following EC+ through sympathetic activation. Our qualitative synthesis also supports this idea (115, 132), as heart rate variability (HRV), one of the most widely used indicators of autonomic activation, has been shown to decrease after acute use of EC+ (115).

Immediately after EC+, there was a significant average FeNO reduction of 7%. Nitric oxide (NO)

is a potent vasodilator, playing an important role in regulating airway and vascular function (133), it is correlated with eosinophilic lung inflammation and oxidative stress in the airways (134) and has been widely studied as a marker of respiratory diseases (120, 134). For example, lower FeNO levels have been associated with decreased respiratory function and more severe COPD (133, 135). The FeNO decrease observed in our study suggests that e-cig aerosols disturb pulmonary homeostasis. It has been suggested that vaping creates oxidative stress and introduces toxic or irritant substances from thermal degradation of the e-liquid into the lungs (64), leading to bronchoconstriction, spirometric changes, and potentially FeNO decrease (136, 137). In addition, there was a trend for a reduction in FEV_1 to both e-cig with and without nicotine, 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 (68, 138). Moreover, a recent observational study found a 31% increase in the risk of respiratory disease among e-cig users compared to never users independent of past cigarette smoking (139). However, it is unclear if these effects are driven by the chemical content of the vapor or its mechanical action on the respiratory tract (120, 140, 141)

Clinical implications

The relatively recent epidemic of EVALI cases in the USA has highlighted the potential acute negative physiological impacts and clinical consequences of e-cigs. 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 14% of the patients reported using non-THC e-cigs, and vitamin E acetate use was only confirmed in about half of the cases (142). Our study provides details of other possible acute pathophysiological pathways that may account for some of the non-THC and/or non-vitamin E acetate cases.

It is clear that regular combustion cigarettes are worse for people than e-cigs, which is also supported to some degree by the current 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) (143). Although one 2019 trial found that e-cigs 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 were still using it at follow-up (144). Furthermore, cross-sectional data suggest that individuals who use e-cigs over the long-term

have an increased risk of myocardial infarction, relative to nonsmokers (129), but that NRT doesn't seem to increase the risk of major cardiovascular events compared to placebo (145). Moreover, e-liquids contain various flavoring, some of which have potential carcinogenic properties that could have a long-term health impact (146, 147). This data coupled with the acute negative changes seen in this review raises important questions about the appropriateness of e-cig as a smoking cessation strategy.

Limitation and Strengths

Methodological factors such as variability in 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 effect-sizes. We were not able to explore all of these aspects due to lack of sufficient data reporting. Moreover, average sample size was small with around 34 participants per study which not only adds to the result's heterogeneity but also limited our capacity to explore the above mentioned methodological factors. Larger and more consistent studies would be needed in the future. 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 as well. Despite these limitations, this systematic review was able to analyze data from e-cigs with and without nicotine. Furthermore, the quality of the methods and the use of meta-regression and sensitivity analysis for this review offer results that add to our capacity to understand how e-cigs might impact human health, as well as providing a strong base for further studies.

Conclusion

Our results suggest that acute use of e-cigs is not benign, as they seem to elicit several acute physiological responses. Our meta-analyses revealed that the cardiovascular impact, in terms of HR, BP 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 endothelial dysfunction, increased oxidative stress and sympathetic activation. The acute effects of e-cig are concerning and, extrapolating from other related studies and reviews, could potentially lead to a 3-10% increase in long-term CV risk. These data coupled with the EVALI epidemic means that better longitudinal studies are needed to assess long-term impacts.

Contributors

The manuscript was initially drafted by FL, TT, and SLB. All authors contributed to critical conceptual input, data interpretation, and revision of the manuscript.

Role of the funding source

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Data sharing

Information on all studies is provided in the paper. Access to data for the analyses can be provided upon request.

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Declaration of interests

Dr. Bacon has received consultancy fees from Merck for the development of behavior change continuing education modules, speaker fees from Novartis, Janssen, and Respiplus, and has served on advisory boards for Bayer, Sanofi, and Sojecci Inc none of which are related to the current article.

Dr Lavoie has served on the advisory board for Schering-Plough, Takeda, AbbVie, Almirall, Janssen, GSK, Boehringer Ingelheim (BI), and Sojecci Inc, and received sponsorship for investigator-generated research grants from GlaxoSmithKline (GSK) and AbbVie, speaker fees from GSK, Astra-Zeneca, Astellas, Novartis, Takeda, AbbVie, Merck, Boehringer Ingelheim, Bayer, Pfizer, Air Liquide, and Respiplus, and support for educational materials from Merck,

none of which are related to the current article.

Drs. Larue, Tasbih and Ribeiro have nothing to declare.

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
Arastoo, 2020	USA	Cross-over	100	21-45	NR[a]	Healthy smokers	EC-, CC and sham vaping	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
Chaumont, 2021	Belgium	Cross-over	30	38 (2)	0	Healthy Smokers	EC- and sham vaping	10
Chatterjee, 2019	USA	Pre-post	16	28.7 (5.5)	NR	Healthy smokers and non-smokers	No control	9
Chatterjee, 2021	USA	Pre-post	31	24.3 (4.3)	14 (45)	Healthy 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
Demir, 2020	Turkey	Pre-post	76	40.08 (10)	18 (23)	smokers and healthy non-smokers	EC	9
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
Gonzalez, 2021	USA	Cross-over	15	21 (1)	6 (66)	Healthy non-smokers	EC-	10
Haptonstall, 2020	USA	Cross-over	49	21-45	NR[a]	Healthy smokers and non-smokers	EC-, CC and sham vaping	11
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
Kotoulas, 2020	Greece	Pre-post	50	40.26 (11)	21 (42)	Healthy smokers and asthmatic smokers	No control	10
Kuntic, 2019	USA	Pre-post	20	34.7 (10.2)	10 (50)	Healthy Smokers	No control	10
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,	USA	Cross-over	29	26.3 (0.9)	20 (60)	Healthy former	EC- and sham	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)
2017						smokers	vaping	
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)

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[b]	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
Arastoo, 2020	Greensmoke, eGo-one	Own brand	0 & 12	NA	NR; tobacco & strawberry flavored	30	60	5
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
Chaumont, 2021	Alien 220 box mod	NA	12	NA	50/50	10	20	Immediately
Chatterjee, 2019	e-puffer	NA	0	NA	70/30; NR	3	16-17	30
Chatterjee, 2021	e-puffer	NA	0	NA	70/30; tobacco flavored	3	16	60-90
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
Cooke, 2015	Clean E-CIGarettes;	NA	18	NA	NR	5	10	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)
	Green Smart Living							
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	18	Immediately
Demir, 2020	NR	NA	16-21	NA	NR	5	25	~10
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
Fogt, 2016	Green smart living	NA	18	NA	NR	10	20	10
Gonzalez, 2021	SMOK FIT KIT	NA	0 & 59	NA	30/70; mango flavored	10	20	~10
Haptonstall, 2020	eGo-one	Own brand	0 & 12	NA	NR; strawberry flavored	30	60	5
Hiller, 2017	eGo, smoktech	NA	0, 8, 18, 36	NA	70/30; Menthol or tobacco	5 min (x2)	10 (x2)	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)
					flavored			
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
Kotoulas, 2020	NOBACCO, Hilandri	NA	15	NA	NR	5	10	15
Kuntic, 2019	Joyetech eGo C	NA	18	NA	NR; tobacco flavored	20	40	15
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
Palamidas, 2017	First generation of E-CIG	NA	11	NA	NR	10	Ad lib; 32;43;38;33;52	0
Ruther,2017	Cigarlike (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

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)
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
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)

eTable 3. Acute cardiovascular responses to EC+ and EC-

Study	Heart rate		Systolic blood pressure		Diastolic blood pressure		Augmentation Index (AIx 75) [a]	
	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
Chaumont, 2021	increase	NS	increase	NS	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	-	
Gonzalez, 2021	-	increase	-	increase	-	increase	-	
Haptonstall, 2020	increase	NS	increase	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	-	-	

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

eTable 4. Other acute cardiovascular responses to EC+ and EC-

Parameter	Study	Outcome	
		EC+	EC-
Ach mediated vasodilation	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	-
Ventricular repolarization parameters	Demir, 2020	increase	NS

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

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

eTable 6. Acute respiratory responses to EC+ and 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	-	-	
Kotoulas, 2020	decrease	-	-	-	decrease	-	decrease	-
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)

eTable 7. Other acute respiratory responses to EC+ and 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
	Kotoulas, 2019	decrease	-				
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	-
	Kerr, 2018	NS	-	Respiratory Resistance	Antoniewicz, 2019	increase	NS
					Boulay ,2017	-	NS
					Chaumont, 2018	-	NS
	Vansickel, 2010	NS	-		Lappas ,2017	increase	NS

Parameter	Study	Outcome		Parameter	Study	Outcome	
		EC+	EC-			EC+	EC-
	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	-			Kotoulas, 2019	decrease	-
	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)

eTable 8. 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	964	39	0.58	0.47 - 0.68	<0.01	91.34	11.11	<0.01
EC+	436	18	0.80	0.46 – 1.13	<0.01	92.60	229.41	<0.01
EC-	319	14	0.14	-0.14 - 0.43	0.32	91.68	156.27	<0.01
CC	209	7	0.63	0.50 - 0.75	<0.01	6.20	6.40	0.38
SBP								
Overall	987	39	0.29	0.20 – 0.42	<0.01	92.53	5.12	0.08
EC+	436	18	0.42	0.19 -0.65	<0.01	91.10	194.32	<0.01
EC-	319	13	0.03	-0.23- 0.30	0.81	93.83	191.05	<0.01
CC	232	8	0.34	0.12- 0.56	<0.01	76.62	29.94	<0.01
DBP								
Overall	987	39	0.39	0.24- 0.55	<0.01	90.26	7.32	0.03
EC+	436	18	0.54	0.32- 0.75	<0.01	85.93	120.82	<0.01
EC-	319	13	0.06	-0.23 – 0.35	0.68	91.60	142.94	<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	270	10	-0.08	-0.20- 0.03	0.16	<0.01	0.51	0.85

Outcomes & smoking conditions	Sample size (*n*)	No. of studies	SMD	95 % CI	p	Heterogeneity		
						I^2(%)	Q	p
EC+	147	5	-0.05	-0.22- 0.12	0.56	<0.01	1.56	0.82
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	333	14	-0.23	-0.38- -0.07	<0.01	68.52	2.99	0.22
EC+	167	6	-0.05	-0.31- 0.22	0.74	64.80	14.21	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	400	15	-0.42	-0.59- -0.24	<0.01	83.24	8.04	0.02
EC+	257	10	-0.27	-0.56- -0.01	0.06	85.43	61.75	<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

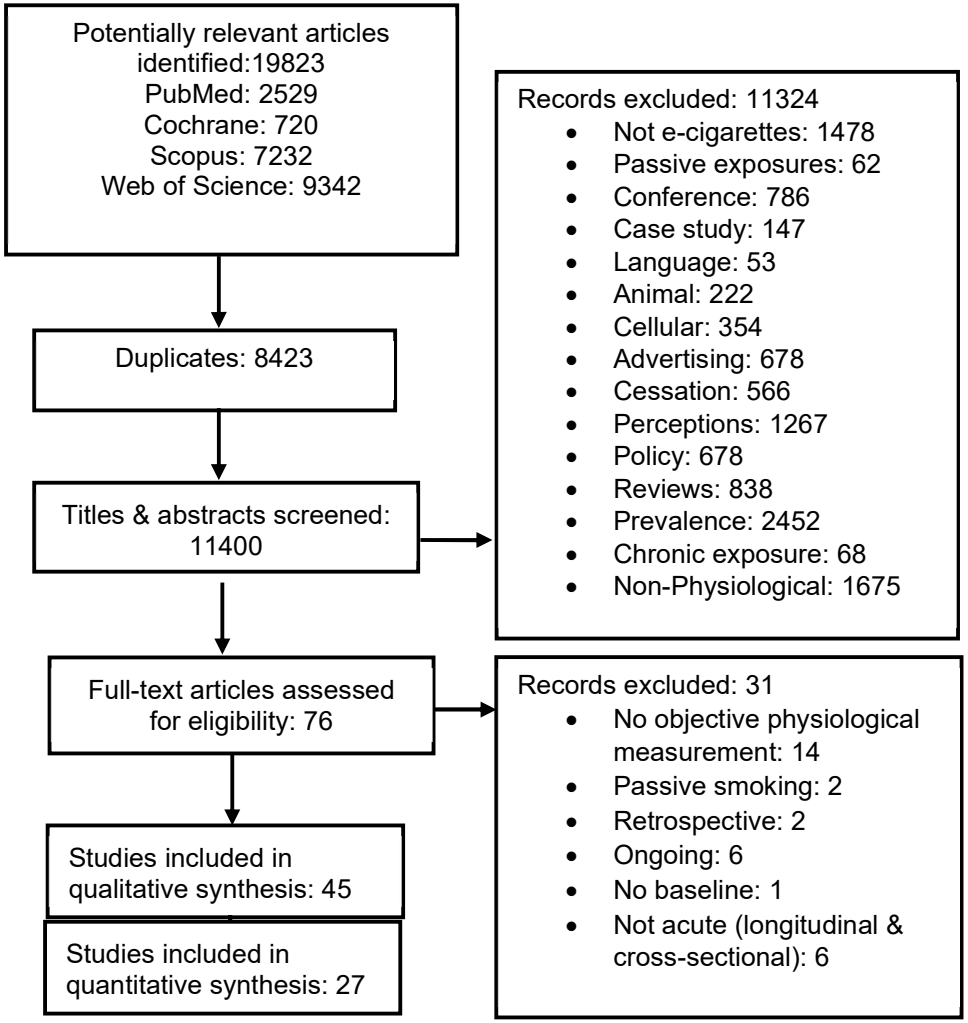
eTable 9. Endothelial, Platelet, Oxidative markers responses to EC+ and EC-

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
	Kuntic, 2020	decrease	-
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	-

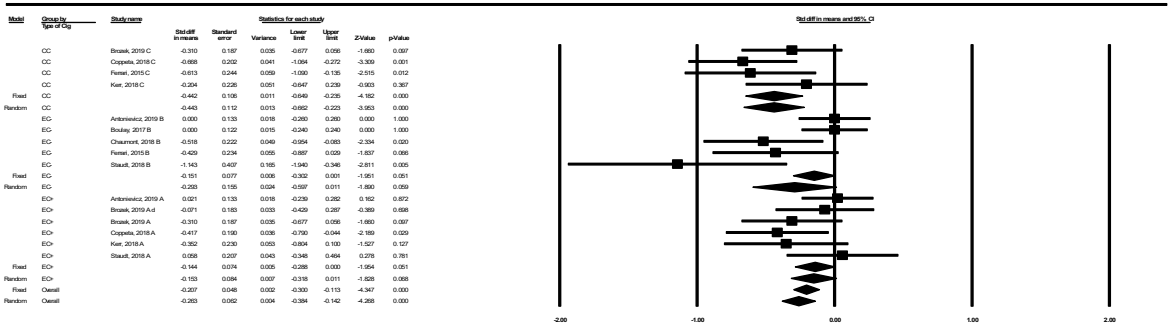
Parameter	Study	Outcome	
		EC+	EC-
	Mobarrez, 2020	increase	NS
Oxidative markers responses to e-cig			
8-iso-PGF2a	Biondi-Zoccai, 2019	increase	-
	Carnevale,2016	increase	-
HBA (H2O2 Breakdown activity)	Biondi-Zoccai, 2019	decrease	-
Hcit/lys (homocitrulline/ lysine ratio)	Chaumont B, 2018	NS	NS
HOI, 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)

eFigure 1. Diagram for the study selection process for the systematic review and meta-analysis



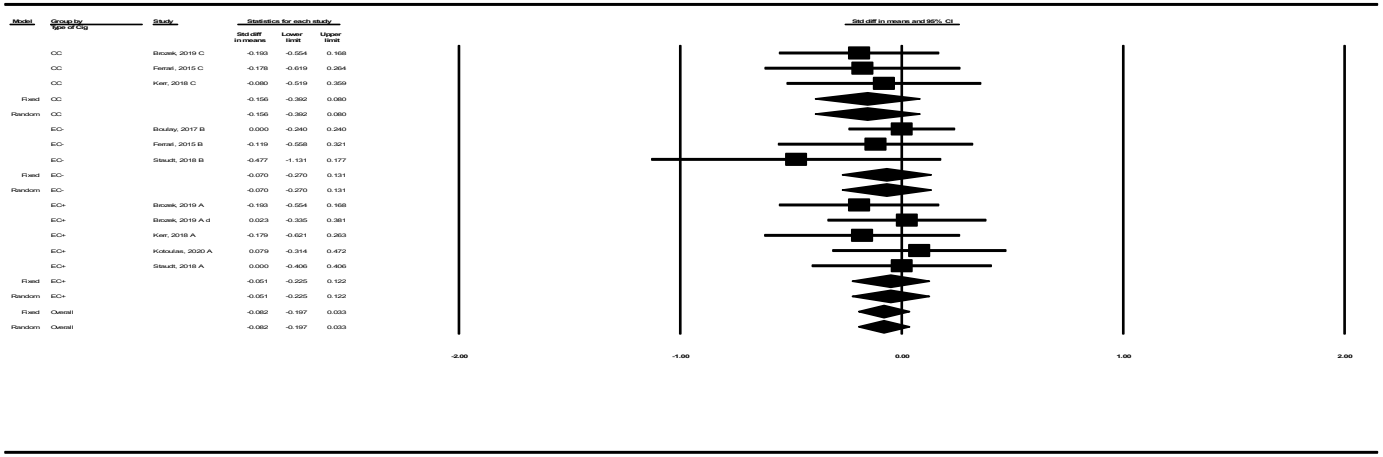
eFigure 2. Forest plot reporting standardized mean difference (SMD) and 95% confidence interval (CI) for each study measuring Forced expiratory volume in one second (FEV1)



Meta Analysis

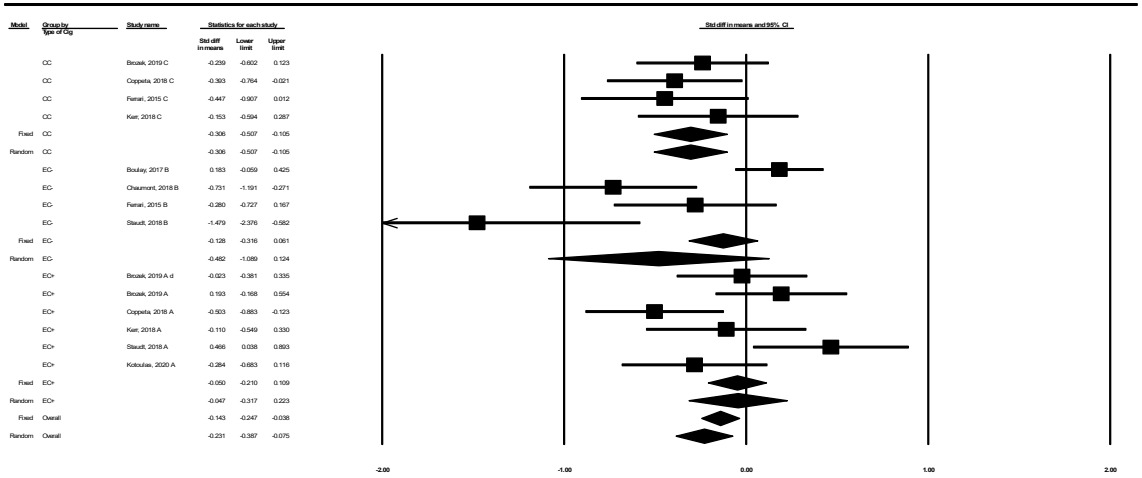
(Note: The black diamond at the bottom of the page indicates the average effect size of the studies. Type of cig= cigarette device type; std diff= standard difference; CI= confidence interval. A= EC+ (electronic cigarette with nicotine; B= EC- (electronic cigarette without nicotine); C= CC (combustible cigarette); d= dual smokers (both EC and CC)

eFigure 3. Forest plot reporting standardized mean difference (SMD) and 95% confidence interval (CI)for each study measuring Forced vital capacity (FVC)



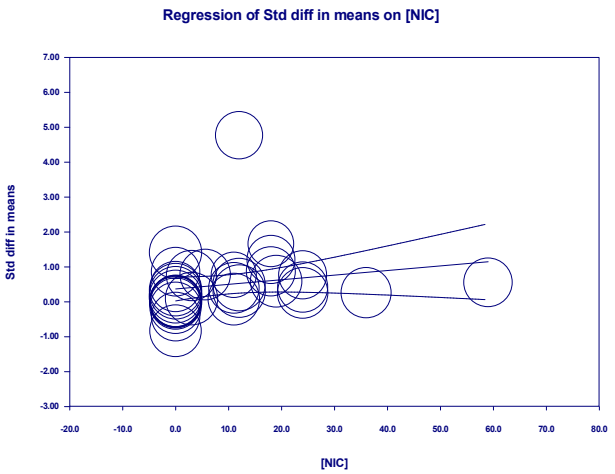
(Note: The black diamond at the bottom of the page indicates the average effect size of the studies. Type of cig= cigarette device type; std diff= standard difference; CI= confidence interval. A= EC+ (electronic cigarette with nicotine; B= EC- (electronic cigarette without nicotine); C= CC (combustible cigarette); d= dual smokers (both EC and CC)

eFigure 4. Forest plot reporting standardized mean difference (SMD) and 95% confidence interval (CI) for each study measuring Tiffeneau's ratio (FEV1/FVC)

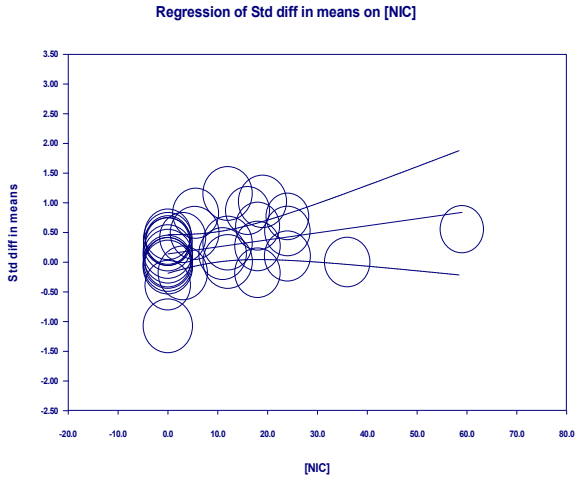


(Note: The black diamond at the bottom of the page indicates the average effect size of the studies. Type of cig= cigarette device type; std diff= standard difference; CI= confidence interval. A= EC+ (electronic cigarette with nicotine; B= EC- (electronic cigarette without nicotine); C= CC (combustible cigarette); d= dual smokers (both EC and CC)

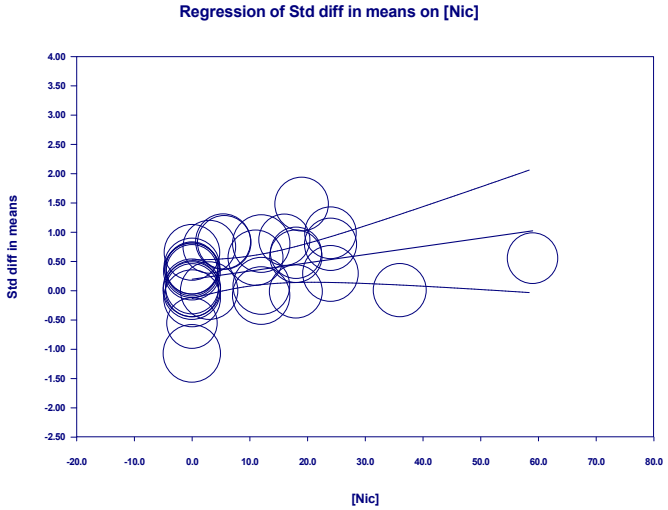
eFigure5. Meta regression of effect of nicotine concentration of e-cig on heart rate, systolic and diastolic blood pressure



eFigure 5 (A)

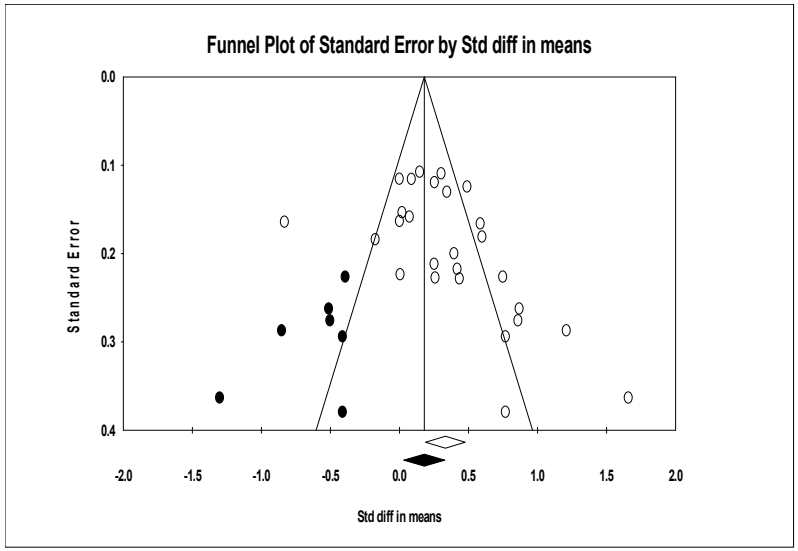


eFigure 5 (B)

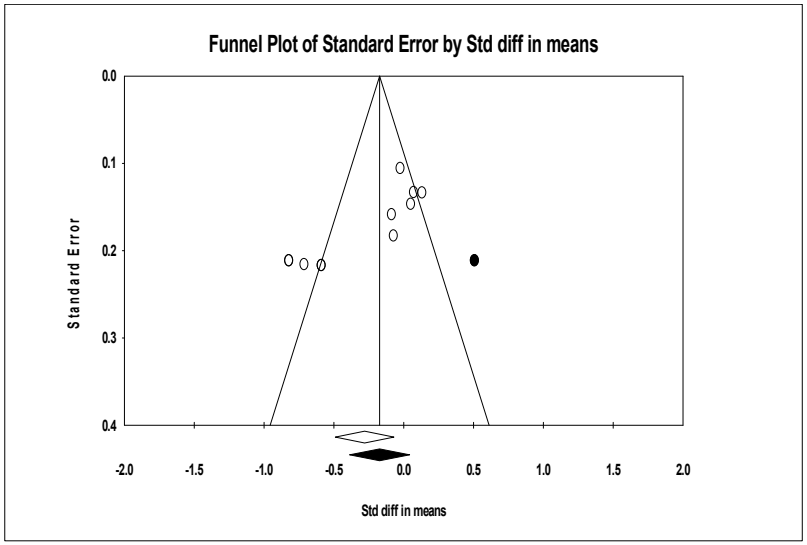


eFigure 5 (C)

eFigure 6. Funnel plot for publication bias (Heart rate and FeNO)



eFigure 6 (A). Funnel plot (Heart rate)



eFigure 6 (B). Funnel Plot (FeNO)

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 Vaporizer /Vaping /Vape

Physiological terms

Acute physiological response / Cardiovascular / Exercise / Health /Lung /Physiological /Physiological stress / Respiratory /Toxicity /Vapor /Vapor / 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 Vaporizer[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 Vapor[Title/Abstract] OR Safety[Title/Abstract])) Filters: Publication date from 2017/03/01 to 2021/04/20

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 Vapor OR Safety)

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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 vaporizer or vaping or vape) and (Acute physiological response or acute cardiovascular responses or acute respiratory responses or exercise or physiological stress)

Chapter 4: Experimental study

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Sex differences in physiological responses after acute electronic cigarette smoking

Tasfia Tasbih MBBS MSc,[1,2], Kim L. Lavoie PhD,[1,3], Esse Julien Atto PhD[1], Mariam Atoui BSc[1], Maximilien Dialufuma MSc[1], Simon L. Bacon PhD,[1,2]

1 Montreal Behavioural Medicine Centre, Centre integrée universitaire de santé et services sociaux du Nord de l'Ile de Montréal (CIUSSS-NIM), Montreal, QC, H4J 1C5, Canada
2 Department of Health, Kinesiology, and Applied Physiology, Concordia University, 7141 Sherbrooke St West, Montreal, H4B 1R6, Canada
3 Department of Psychology, University of Quebec at Montreal, CP 8888, Succursale Centre-Ville, Montreal, QC, H3C 3P8, Canada

Address for correspondence:
Simon L. Bacon, PhD, FTOS, FCCS, FABMR
Department of Health, Kinesiology, and Applied Physiology
Concordia University
Email: simon.bacon@concordia.ca
Twitter: @sbacon20, @mbmc_cmcm

Key points

Question: What are the differences in physiological effects (i.e., cardiovascular, respiratory) in males and females after acute e-cig usage?

Findings: This experimental study included 9 participants (4 male, 5 female) who were healthy young adult smokers. Acute e-cig consumption had significant impacts on respiratory parameters (e.g., respiratory exchange ratio (RER), breathing frequency (BF) in female participants compared to males where female smokers RER decreased and BF increased in post e-cig smoking period. Cardiovascular measures did not change in response to e-cig smoking.

Meaning: The respiratory physiological responses after acute e-cig smoking differed between males and females which might cause different sex-based respiratory complications and disease prevalence's. We did not observe cardiovascular responses to e-cig in either sex which is inconsistent with current literature and warrants further observation.

Highlights:

- Acute e-cig consumption was associated with decreases in respiratory exchange ratio (RER) and increases in breathing frequency (BF) in female smokers compared to male smokers.
- Acute e-cig consumption was not associated with significant cardiovascular responses in male or female smokers.
- Acute e-cig consumption has been associated with long-term respiratory effects in female which needs further observation.

Abstract (291 words)

Currently the number of electronic cigarettes (e-cig) user is 68 million. In Canada, in 2020, it was the most common smoking device among young adults (aged 15-24 years). Several studies have observed sex differences in adverse effects of regular cigarette smoking on cardio-respiratory health; however, no data is available regarding sex differences in physiological responses to acute e-cig smoking.

Research question: What are the differences in physiological responses (i.e., cardiovascular, respiratory) in males vs. females after acute e-cig usage.

Methods: We included 9 White healthy young adult smokers (4 male, 5 female). The smoking protocol was 10 puffs from a nicotine containing (6mg/ml) e-cig over 5 minutes. We used generalized mixed model to analyze the available data.

Main outcomes: We assessed systolic (SBP) and diastolic (DBP) blood pressure, heart rate (HR), forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), expired oxygen (VO_2), expired carbon di-oxide (VCO_2), respiratory exchange ratio (RER), breathing frequency (BF), tidal volume (VTex), and minute volume (VE) in pre- and post e-cig smoking.

Results: E-cig usage decreased RER and increased BF in females compared to males (RER: females, mean± SE 0.78±0.01 (pre-smoking) and 0.71±0.01 (post-smoking) vs. males, 0.80±0.01 (pre-smoking) and 0.80±0.01 (post-smoking); BF: females, 15.12±0.24 (pre-smoking) and 16.57±0.31 (post-smoking) vs. males, 18.68±0.24 (pre-smoking) and 18.65±0.30 (post-smoking)). Other cardiovascular and respiratory measures after acute e-cig smoking were not significant in any sex groups.

Interpretation: Acute consumption of e-cigs was associated with significant decrease in RER and increase in BF in female smokers compared to male. These responses might result in alterations in pulmonary surfactant function and impaired pulmonary gas exchange. Studies with long-term effects of e-cig involving larger participants and novel techniques, e.g., stress tasks could be effective in exploring the impacts of these physiological differences.

Background

The number of electronic cigarette (e-cig) user at the present time is 68 million across the world (148). E-cig is the most popular smoking device among young adults, including in Canada (46). According to Statistics Canada, between 2017- 2018 , the number of e-cig users, aged 15-24 years, increased around 74%, and in 2020, it was the most common smoking device among this age group (22, 46). A similar percentage of males (19%) and females (18%), aged ≥15 years reported ever trying e-cig in the past 30 days (149). E-cig smoking is associated with significant physiological responses such as cardio-respiratory, inflammatory as well as severe adverse effects in both male and female smokers (1). In 2019 and 2020, there were a number of e-cig or vaping associated lung injury (EVALI) events in USA with 2,807 hospitalizations and 68 deaths, and 20 EVALI events in Canada, most of which were in young adults and included both male (60%-70%) and female (30%-40%) smokers(150-152). EVALI has been defined as the presence of an acute or subacute respiratory illness, such as diffuse alveolar hemorrhage, bronchitis, or pneumonia, presenting with the following respiratory symptoms, e.g., cough, shortness of breath, respiratory distress, following the use of e-cig(153).

Acute e-cig consumption has an impact on human cardio-respiratory physiological responses and these changes are found to be quite similar to, although to a lesser extent, regular cigarette smoking(1). The cardiovascular (CVS) responses are usually associated with the activation of the sympathetic nervous system (SNS) by the smoking constituents, such as, nicotine, which increases several CVS measures such as, systolic (SBP) and diastolic blood pressure (DBP), and heart rate (HR) (154). Respiratory changes in response to e-cig consumption are mostly driven by less pulmonary gaseous exchange (poor oxygenation (VO_2) and carbon dioxide retention (VCO_2)), and changes in breathing frequency (BF), etc. (155, 156). These responses are mostly likely due to bronchoconstriction and poor pulmonary blood flow due to vasoconstriction and an association of both SNS and parasympathetic nervous system (PNS) have been suggested for such responses(74, 157).

Current literature suggests that there is a predominance of CVS physiological changes, e.g., increases in blood pressure, in males and a predominance of respiratory changes, e.g., airway damage and pulmonary vasoconstriction, in females in response to traditional cigarette smoking(10, 29). Hence cardiovascular complications, such as coronary artery disease (7.9% in male vs 5.1% in female), due to traditional smoking are commonly seen in males and respiratory complications, such as COPD, are more common in female smokers (50% more

risk)(29, 36). Several factors, e.g., predominance of SNS control over male cardiac function compared to females, anatomical differences in airway passages, and effects of sex hormones, are some reported possible mechanisms behind such differences in smoking related CVS-respiratory outcomes in male and female smokers (158, 159). Current studies have observed these physiological measures in response to e-cig(1), although there is no clear data available if there is any differences in these responses to e-cig smoking between male and female smokers.

Our study aimed to look into possible differences in cardio-respiratory physiological responses in young healthy adult male and female smokers after acute e-cig smoking which could pave a way to understanding possible outcomes / complications of e-cig usage in males vs. females. It was hypothesized that, males would exhibit larger changes in cardiovascular responses, and females would exhibit larger changes in respiratory responses after acute e-cig smoking.

Methodology

Participants

A total of nine English or French-speaking participants who currently smoked traditional cigarettes and were aged between 18 and 45 years old were recruited. The study exclusion criteria included: smoking only e-cigs (due to ethical concerns); BMI ≥ 30 kg/m^2; known or suspected chronic disease (e.g., such as CVD, diabetes, hypertension, COPD, or physician diagnosed asthma in adulthood); use of prescribed medications, apart from oral contraceptives; a currently diagnosed drug or alcohol abuse; cognitive or language deficit that affect the ability to provide consent; any diagnosed anxiety or mood disorder; current major or minor infection; and any trauma or surgery within the previous six months. In addition, females were excluded if they were currently pregnant or actively breast-feeding. Recruitment was achieved via promotion of the study through presentations, e-mails, and information sheets posted and sent within the CIUSSS-NIM medical community, and at Concordia University and UQAM.

Procedure

The study consisted of a screening and a laboratory session.

Screening session

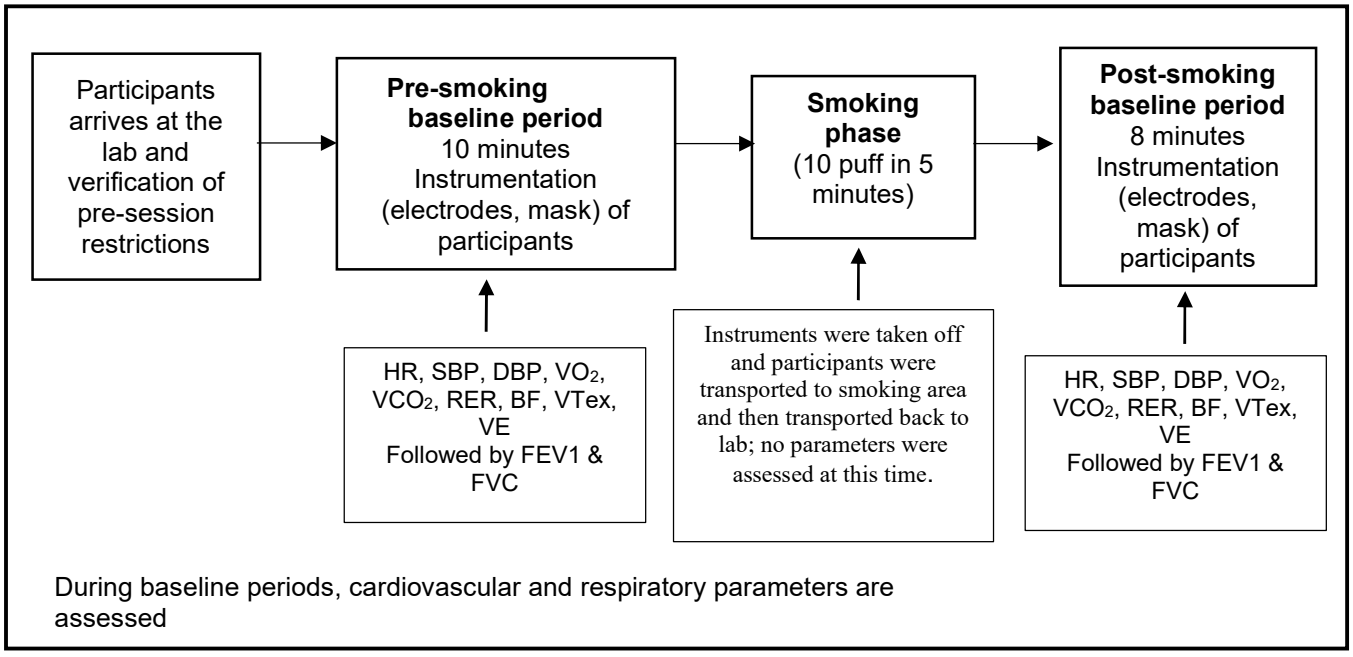
Screening was conducted by telephone and consisted of the following: 1) Full description of the

study and completion of informed consent/assent; 2) General health screening to determine smoking status and eligibility; and 3) Scheduling for laboratory session. Each participant was given pre-testing adherence criteria to follow (described below).

Laboratory session

All measurements were performed at the MBMC Psychophysiology laboratory, CIUSSS-NIM. All tests were performed in the morning. The participants were advised beforehand to dress appropriately for the tests. Upon arrival to the laboratory, verification of pre-session restrictions was made, including a) no alcohol consumption nor exercise for 24 hours; b) no eating nor consuming caffeine for 12 hours; c) no analgesics for 6 hours; and d) no use of non-steroidal anti-inflammatory agents, within 5 days prior to the test. Height, weight, and waist circumference were measured using standard protocols, followed by spirometry measures which assessed respiratory function and volume (to detect any possible respiratory disease). Electrode bands for cardiovascular assessment (impedance cardiography) and a brachial cuff for BP assessment and a well-fitted mask for respiratory assessment (ventilatory/ metabolic measures) were placed on the participant. Carbon Monoxide levels were taken before the smoking protocol to confirm 12- hour abstinence. Participants were asked to sit quietly with minimal movement for 10 minutes (baseline period), see figure1 for details.

Figure 1: Experimental study Laboratory session timeline



Smoking phase: After this, participants were escorted to a designated smoking area. Participants smoked an e-cig matched for the nicotine concentration of a traditional cigarette (6mg/ml). To verify the contents of the vapor, we tested the e-liquid (e-juice) using Gas Chromatography-Mass Spectrometry at McGill University. We used Gentlemen e-liquid which contained 6.26 mg/ml nicotine. We used an “Aspire’ e-cigarette with disposable, changeable filters to ensure sterilization and hygiene for each smoking participant. The e-cigarette was cleaned thoroughly after each use in line with hospital procedures. Each e-cig was smoked by taking 1 puff every 30 secs (totaling about 10 puffs) over a span of 5 mins (160). After returning, measurement of cardio-respiratory parameters was taken. During this time participants were asked to sit quietly with minimal movement for 8 minutes.

Physiological measures

Cardiovascular measures

We assessed Systolic (SBP) and diastolic blood pressure (DBP), Heart rate (HR). SBP and DBP were obtained using Suntech Tango system, which required a brachial cuff. Electrocardiograms using 4 bands and 6 spots electrodes were placed on neck and thorax to measure heart rate (HR).

Respiratory measures

To assess respiratory parameters, we used spirometry and a metabolic cart (Jaegar Oxycon Pro). During the spirometry assessment we asked participants to inhale and exhale (3 times) over a short period so that we can determine their Forced Vital Capacity (FVC), which consisted of breathing in as much as possible followed by maximal exhalation until the participant could not exhale anymore, and their Forced Expiratory Volume (FEV1) in one second, which is the volume delivered in the first second of an FVC maneuver. During the metabolic cart assessment, the participant was asked to wear a mask and the measures were taken during the baseline period (10 minutes) and the post smoking period (8 minutes). The metabolic cart provided the following breath-by-breath data: breathing frequency (BF); expired oxygen (VO_2); expired carbon dioxide (VCO_2); respiratory exchange ratio (RER); minute volume (VE); and tidal volume (VTex).

Demographic and descriptive information

Standard questionnaires were used to assess basic demographic information, including: sex; age; ethnicity; marital status; and socioeconomic status (years of education, income, occupation), as well as, general health behaviours (e.g., physical activity using the Canadian Health Measures Survey (161)).

Statistical analyses

All statistical analyses were performed using SAS statistical software (SAS Institute Inc, Cary, NC). We used repeated measures generalized mixed models (Proc Mixed) to explore the main effects of sex (male and female) and period (repeated measure: pre- and post-smoking) and their interaction. The analysis included age and length of smoking history as covariates.

Results

Participants characteristics

Our study included nine white young adult participants (see table1): four males (mean age ± SD = 27.09 ±10.97yrs) and five females (mean age ± SD = 28.91 ± 6.6 yrs), who were active smokers (years of smoking – male: 6-16 years, female; 5-20 years) which indicates a very early stage of smoking initiation, more specifically, during adolescent period. 50% of males completed secondary and 50% CEGEP (publicly funded college in Quebec education system) (162) level education and 40% of females had a CEGEP and 60% had a university level education. Their participation in physical activity per week were almost similar between male and female participants (see table1). The majority of participants were unmarried (male100% and female 60%) and female participants were more likely to be employed than the male participants (80 vs 50%), see Table 1 for details.

Table 1: Basic information of participants

Contents	Male	Female
Participants	4	5
Age(yrs)(mean ± SD)	27.09 ± 10.97	28.91 ± 6.6
BMI (kg/ m^2)	20.4 ± 4.3 (50%)	24.4 ± 5.17 (90%)
Ethnicity	100% White	100% White
Education level	Secondary (50%) College (50%)	Secondary (40%) University (60%)
Length of smoking (yrs)	11.5 ± 10.11	13.5 ± 6.98
Physical activity/ week	Rarely/Never (20%) Occasionally (20%) Often (50%)	Rarely/Never (40%) Occasionally (20%) Often (40%)
Marital status	Never married (100%)	Married (40%) Never married (60%)
Socio-economic status	Employed (50%) Unemployed (50%)	Employed (80%) Unemployed (20%)

Physiological measures during pre to post e-cig smoking period

Cardiovascular measures

Heart rate (HR)

The main effect of sex, period and their interaction were not significant for heart rate (see Tables 2 and 3).

Systolic (SBP) and diastolic blood pressure (DBP)

There was a main effect of sex for SBP and DBP; however, there were no main effects of period nor a sex*period interaction (see Table 3). Overall, SBP was higher in males and DBP was higher in females (see Table 2 and 3).

Table 2: Adjusted mean ± SE CVS parameters during the pre-smoking and post-smoking period in males and females

Parameters	Males		Females	
	Pre-smoking	Post-smoking	Pre-smoking	Post-smoking
HR (beats/min)	72.58±2.43	68.29±2.78	73.85±2.43	70.37±2.79
SBP (mmHg)	109.55±1.52	110.39±1.74	104.20±1.52	105.28±1.74
DBP (mmHg)	62.94± 1.15	63.48±1.31	64.93±1.15	68.85±1.31

Table 3: main effect of sex, period, and sex*period interactions of cardiovascular parameters of e-cig smoking

Parameters	Sex		Period		Sex*Period	
	F	P	F	P	F	P
HR	0.35	0.555	2.33	0.133	0.03	0.874
SBP	8.81	0.005	0.36	0.550	0.01	0.938
DBP	7.65	0.008	3.42	0.070	1.96	0.167

Respiratory measures

Expired oxygen (VO_2)

The main effect of sex was significant for VO_2, but there was no significant main effect of period nor a sex*period interaction, where males had an overall high VO_2 than females (see Tables 4 and 5).

Table 4: Adjusted mean ± SE of respiratory parameters during the pre-smoking and post-smoking period in males and females

Parameters	Males		Females	
	Pre-smoking	Post-smoking	Pre-smoking	Post-smoking
VO_2 (ml/min)	333.64±5.68	324.54±7.08	247.94±5.71	240.33±7.21
VCO_2(ml/min)	272.12±4.86	265.22±6.05	195.59±4.88	174.60±6.16
RER	0.80±0.005	0.80±0.007	0.78±0.005	0.71±0.006
BF (breaths/min)	18.68±0.24	18.65± 0.30	15.12±0.24	16.57±0.31
VE (L/min)	12.14±0.17	12.11±0.22	8.05±0.17	7.59±0.22
VTex (L/min)	0.72± 0.01	0.67 ±0.01	0.55±0.01	0.46±0.01
FEV1 (L)	3.75± 0.17	3.64±0.17	2.91± 0.15	2.92± 0.15
FVC (L)	5.01±0.16	5.14± 0.16	3.83± 0.14	3.92± 0.14

Table 5: main effect of sex, period, and sex*period interactions of respiratory parameters of e-cig smoking

Parameters	Sex		Period		Sex*Period	
	F	P	F	P	F	P
VO_2	143.21	<.0001	1.79	0.181	0.01	0.905
VCO_2	189.82	<.0001	6.83	0.009	1.74	0.187
RER	68.71	<.0001	44.24	<.0001	26.75	<.0001
BF	84.21	<.0001	6.90	0.009	7.53	0.006
VE	380.78	<.0001	1.65	0.199	1.31	0.252
VTex	108.94	<.0001	19.37	<.0001	3.01	0.083
FEV1	17.03	<.0001	0.07	0.797	0.16	0.694
FVC	48.73	<.0001	0.76	0.388	0.00	0.974

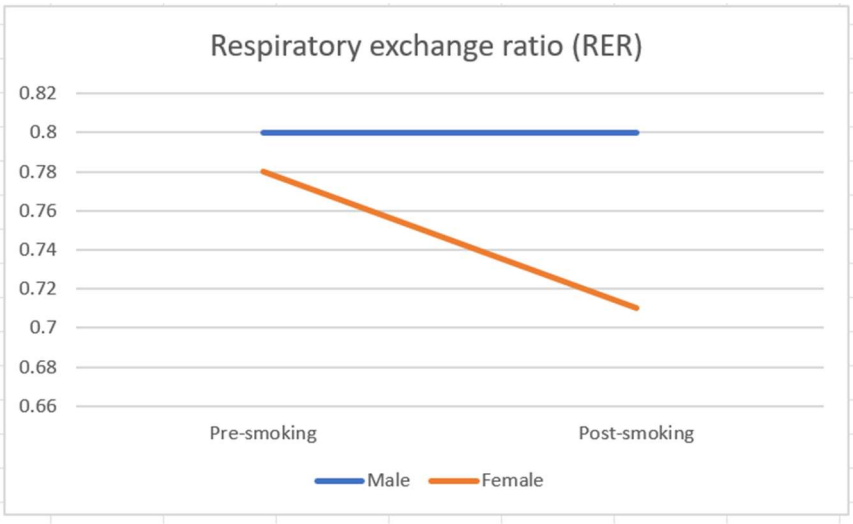
Expired Carbon dioxide (VCO_2)

There were significant main effects of sex and period for VCO_2; however, the sex*period interactions for VCO_2 were not significant. There was an overall reduction in VCO_2 post smoking and males had overall high VCO_2 than females (see Tables 4 and 5).

Respiratory exchange ratio (RER)

There were significant main effects of sex and period, as well as a significant sex*period interaction for RER (see Table 4 and 5). As seen in Figure 2, there was no change in RER from pre- to post-smoking in males, but post-smoking RER was decreased in females relative to pre-smoking. With regards to the main effects, there was an overall reduction in RER post smoking (mostly driven by the females) and males had overall high RERs than females (see Tables 4 and 5)

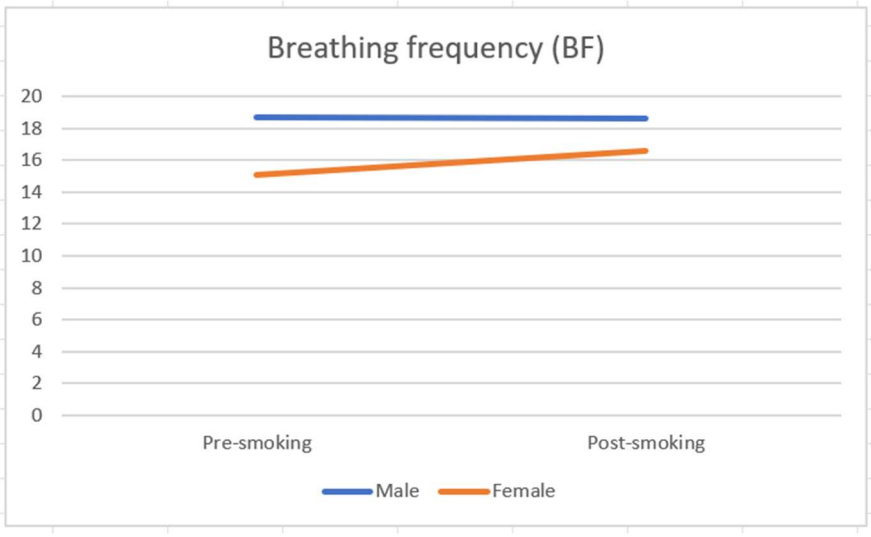
Figure 2: Significant interaction of sex*period (pre and post e-cig smoking) on RER in males and females



Breathing frequency (BF)

The main effect of sex and the sex*period interactions was significant for BF. As seen in Figure 3, there was no change in BF from pre- to post-smoking in males, but post-smoking BF was increased in females relative to pre-smoking. With regards to the main effect, males had an overall high BF than females (see Tables 4 and 5)

Figure 3: Significant interaction of sex*period (pre and post e-cig smoking) on BF in males and females



Minute volume (VE)

The main effect of sex was significant on VE. There was no significant main effect of period and sex*period interactions on VE. With regards to the main effect, males had overall high VEs than females (see Tables 4 and 5).

Tidal volume (VTex)

The main effect of sex and period was significant on VTex; however, the sex*period interactions was not significant. With regards to the main effects, there was an overall reduction in VTex post smoking and males had overall high VTexs than females (see Tables 4 and 5).

Forced expiratory volume in one second (FEV1)

The main effect of sex was significant on FEV1; however, the main effect of period and sex*period interaction were not significant. With regards to the main effect, males had overall high FEV1s than females (see Tables 4 and 5).

Forced vital capacity (FVC)

The main effect of sex was significant on FVC; however, the main effect of period and sex*period interaction were not significant. With regards to the main effect, males had overall high FVCs than females (see Tables 4 and 5).

Discussion

In our study, we found that after acute e-cig smoking female smokers' RER was decreased and their BF was increased compared to male smokers. RER (respiratory exchange ratio) is the ratio of production of CO_2 to consumption of O_2 during metabolism and any changes of these two components might result in alterations in RER (163). It is measured by exhaled gases, i.e., expired CO_2 (VCO_2) and expired O_2 (VO_2); RER= VCO_2 / VO_2) (164). E-cig smoking has previously been associated with changes in pulmonary gaseous exchange, i.e., changes in VO_2 and VCO_2, possibly through the inflammatory impacts of e-cig components such as nicotine, propylene glycol, and glycerin on airway epithelium(39, 74). Current literature suggests that these components might dehydrate the surfactant (airway surface liquid) and disrupts mucociliary clearance (155, 165). These could eventually result in airway inflammation and bronchoconstriction (165). Beside that, this alteration in airway surface liquid could also increase surface tension that could further impair pulmonary gas exchange (155, 166).

Several possible mechanisms might be the driving factors behind the significant sex differences we found in the respiratory changes. One mechanism might be via lipid composition. Middlekauff et al reported an association between e-cig smoking and decreases in plasmalogen (a lipid component in the lungs with is essential for normal lung function) in females, but not in males (167). As plasmalogen plays a role in surfactant synthesis and the oxidative stress response, this alteration has been suggested to cause impairment in pulmonary surfactant function which, as detailed above, is important in maintaining pulmonary gas exchange and RER (167-169). Alternatively, traditional smoking has been found to impair the estrogen signaling pathway on airway smooth muscle tone, causing inflammation, bronchoconstriction, and impaired gas exchange (170). Due to some similarity of traditional smoking constituents and e-cig, for example, nicotine, there might be a possibility of observing such responses to e-cig smoking in females vs. males, though, this would need to be explored further(75). On top of these, female airway passages are smaller than males which makes them more prone to smoking constituent exposure compared to males and hence exaggerated responses and airflow limitations could occur in females in response to e-cig smoking (171).

Though the findings of our study might be explained by adaptions in females it is also possible that male physiology plays a key role in the observed sex differences. Vasodilatory and anti-inflammatory effects of male sex hormone or androgens (e.g., testosterone, dihydro-epiandrosterone or DHEA) might be a possible factor behind such responses (172, 173). Jones et al reported a vasodilatory effect of androgens on the pulmonary vascular bed which might be independent of other vasodilatory components e.g., nitric oxide (NO) (173). Also, the potential anti-inflammatory properties of testosterone have been documented in several studies where there has been association of chronic obstructive pulmonary disease (COPD – a respiratory inflammatory condition) with low level of testosterone, and testosterone therapy has been found to decrease inflammatory responses, although the exact mechanism is not yet well-defined (174, 175).

The changes we observed in RER are likely to activate chemoreceptors and the PNS, which could result in the increase in BF that we observed in females (176, 177). Of note, one of the most common presenting symptoms of EVALI cases were rapid breathing or an increase in BF during hospitalization (178).

Differences in some basic characteristics between male and female participants such as, BMI, smoking length, and marital status and their possible association with inflammatory markers

might have some impact on the observed respiratory responses. The following features in the female participants were higher compared to male participants; BMI (24.4 vs. 20.4 kg/ m^2), and length of smoking history (13.5 vs. 10.1 years). Generally overweight (BMI 25-29 kg/ m^2) and obesity (BMI ≥30 kg/ m^2) have been suggested to have some pro-inflammatory or chronic inflammatory impacts on health in general, as well as the pulmonary airways (179, 180). The BMI for female participants in the study was within the normal range (18.5-24.9 kg/ m^2) but also near to overweight and this was not the case for males. As weight increases there can be a greater strain on respiratory function, such as increased breathing effort and frequency (181, 182), which may partially explain the respiratory differences between sexes seen in our study. Smoking usually causes airway damage and bronchoconstriction by inflammation and alteration of smooth muscle hyperplasia and around 15-20 years of smoking might exacerbate these changes (183, 184). In our study, female participants had a longer history of smoking compared to males, with an average length of 13.5 years which is near to the damaging range of smoking. There is a possibility that their airways were likely damaged more than the males. However, we did not measure the interaction of the smoking length and sex differences in physiological responses on the context of e-cig smoking. Also, we included length of smoking as a co-variate in the analysis and as such, the observed responses to e-cig in the study in male and female were not impacted by this variable, so though smoking length may have a potential impact, it is unlikely to account for the results seen.

Marital status, which was different between our populations (40% females were married vs. 0% of males), may also have some indirect pro-inflammatory effects related to factors like increased stress and negative effects on smoking behaviors (185). For example, studies have found that being married is associated with lower quit attempts and a greater length of smoking, with this being more pronounced in females compared to males (186). Regarding stress, it is commonly seen that married females tend to be impacted by this more than married males (185, 187). Of note, both an increase in stress and a greater length of smoking leads to chronic inflammation (188, 189), which may partially account for some of the physiological sex-differences we observed in our study. Unfortunately, due to the small sample size, we weren't able to explore these potential indirect impacts of marital status, hence, the impact of marital status on the observed responses in this study warrant further research.

In the experimental study, there was a decrease in RER in females after acute e-cig smoking. This decrease in RER could also have some association with anxiety during the laboratory session as females tend have higher anxiety symptoms than males (190). Anxiety could result

in shortness of breath, e.g., decrease in VCO_2 / hypercapnia (accumulation of excess CO_2 in the blood) (191, 192), resulting in an increase in BF to adapt to these changes, as we observed in this study. Unfortunately, we did not assess anxiety and, as such, future studies should explore the potential impact anxiety may have on the sex-differences we observed. The increase in BF after acute e-cig smoking in female might have occurred as an adaptive response to decrease in RER and impaired gas exchange (decreased in VCO_2). An increase in BF can translate to either hyperventilation (rapid and deep breathing, BF above normal levels of 12-20 breaths/min) or tachypnea (rapid and shallow breathing with a BF above normal levels) (157), something that is often associated with anxiety. However, it is quite unlikely that our results would be explained by either of these mechanisms. Hyperventilation is associated with an increase in exhaled CO_2 (VCO_2), with little effect on exhaled O_2 (193). In this experimental study, BF in females increased from 15 breaths/min to 16 breaths/min, which is within normal levels, and there was a decrease in both VCO_2 and RER (RER= VCO_2 / VO_2) (see table 4). Unfortunately, in our study we did not measure the depth of breathing frequency, i.e., to be able to determine deep or shallow breaths. Hence future studies should measure this to help understand if there are any impacts of not only the frequency, but the depth of breathing on the observed sex-different responses.

Our study did not find any significant cardiovascular responses to e-cig smoking in males or females. According to our previous systematic review (1) and other current literature (194), e-cig smoking has significant impacts on SBP, DBP and HR, which is in contrast to our study findings. On the other hand, some studies reported no significant SBP, DBP and HR responses after acute e-cig smoking (195). Considering our study limitations (see limitation section) such as few participants (4 male, 5 female), smoking protocol (10 puffs in 5 minutes), old e-cig device (second generation), our CVS findings could be inconclusive. Beside that, studies suggest that physiological responses to traditional smoking in basal/resting condition are not that evident in young healthy adults, hence utilizing some novel techniques such as stress task might be helpful to observe any sex differences in CVS responses to e-cig smoking (196, 197).

Considering the above discussion of respiratory physiological mechanisms, our data is suggestive of the start of persistent bronchoconstriction and poor oxygenation, with more negative respiratory impacts of e-cig in female smokers compared to males. This is consistent with the current literature where it was demonstrated that females have a greater tendency to develop negative respiratory responses, such as, airway inflammation and impairment in surfactant function compared to males(198-200).

Limitations

We observed the acute physiological responses of e-cig on only nine young healthy adult smokers, which lowers our statistical power (201). Due to the COVID-19 pandemic, we could not recruit further participants. We used a second-generation e-cig device, and there are various new e-cig generation devices whose mechanics could differ in producing chemical constituents as well as impacts on human physiological markers, as such, our results may not translate to these new devices. Our study was focused on acute smoking (10 puffs of e-cig in 5 minutes), as such the physiological effects of long-term e-cig need to be explored.

Clinical implications

Our observations of decreased RER and increased BF in females compared to males might be informative in understanding the possible sex differences in physiological responses to acute e-cig smoking. These observations are suggestive of altered pulmonary surfactant function and impaired gas exchange in females vs. males. Several possible complications could arise due to such responses such as hypoxemic respiratory failure and respiratory distress, with a greater prevalence in females. Also, there is possible indications for the development of chronic inflammation disorders, such as COPD, in female due to e-cig smoking related alterations in airway lipid composition and oxidative stress which can disrupt inflammation (202, 203). However, longitudinal studies with larger participants are needed to explore these physiological responses and long-term outcomes in males and females.

Contributors

The manuscript was initially drafted by TT and SLB. All authors contributed to critical conceptual input, data interpretation, and revision of the manuscript.

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Data sharing

Due to the restrictions from the local ethics committee, there is no available data that can be shared.

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Declaration of interests

Dr. Bacon has received consultancy fees from Merck for the development of behavior change continuing education modules, speaker fees from Novartis, Janssen, and Respiplus, and has served on advisory boards for Bayer, Sanofi, and Sojecci Inc none of which are related to the current article.

Dr Lavoie has served on the advisory board for Schering-Plough, Takeda, AbbVie, Almirall, Janssen, GSK, Boehringer Ingelheim (BI), and Sojecci Inc, and received sponsorship for investigator-generated research grants from GlaxoSmithKline (GSK) and AbbVie, speaker fees from GSK, Astra-Zeneca, Astellas, Novartis, Takeda, AbbVie, Merck, Boehringer Ingelheim, Bayer, Pfizer, Air Liquide, and Respiplus, and support for educational materials from Merck,

none of which are related to the current article.

Dr. Tasbih, Ms. Atoui, Dr. Esso, and Mr. Dialufuma have nothing to declare.

Chapter 5: General discussion

This thesis found that, acute e-cig consumption has negative impacts on human cardio-respiratory and inflammatory responses in the general population and it has negative impacts on the respiratory physiology of young adult females who smoke compared to their male counterparts. According to our systematic review (chapter 3), acute e-cig smoking could cause significant increases in systolic and diastolic blood pressure, heart rate and arterial stiffness which is suggestive of an increased risk of CVD such as coronary artery disease (1). In terms of respiratory measures, we found a decrease in FeNO which is suggestive of an increased risk of vasoconstriction and inflammatory conditions, such as COPD (1). Our experimental study (chapter 4) found that acute e-cig consumption decreases RER significantly in females which could have possible associations with altered lipid composition, impaired surfactant function (164, 167) impaired pulmonary gas exchange, and respiratory distress (39, 204). This further supports the potential links of e-cig with chronic inflammation diseases such as COPD. We also observed a significant increase in BF in female smokers compared to males, which may reflect the impaired gas exchange detailed above (205).

The observed sex-differences in respiratory responses could possibly be due to a number of factors, such as: the presence of estrogen (female sex hormone) which has stimulatory effect on inflammatory responses to smoking (170); absence of androgens (male sex hormone) which are is vasodilatory (35, 206); smaller airway passages and lung volumes which put females at increased e-cig smoking constituent exposure compared to males (171); and alterations of lipid composition in lung which impairs surfactant function and pulmonary gas exchange (167).

Differences in participants characteristics, e.g., BMI, length of smoking history, and marital status between male and female might also have some impact on the observed respiratory responses because of their possible association with pro-inflammatory / chronic inflammatory impacts on female health and airways (179, 180, 187, 207). The following characteristics in females: a BMI near to overweight range; and being married might have played some role in the differential physiological responses to e-cig smoking in females compared to males (as discussed above). Beside that, there is a possibility that the airways of the females in our study were more likely to have greater damage, e.g., airway inflammation, than the males as females had a longer history of smoking, with an average length of 13.5 years which is near to the damaging range of smoking (15-20 years) (183, 184). However, we did not measure the interaction of the smoking length and sex differences in physiological responses but we did

include smoking length as a covariate in our models, so though smoking length may have a potential impact, it is unlikely to account for the results seen.

Anxiety could be another possible driving factor behind such observations in females since females tend to be more anxious than males (208). Anxiety could result in both shortness of breathing, e.g., decreases in VCO_2 / hypercapnia and/ or increase in BF (191, 192, 209). The increase in BF might also be explained by the concept of hyperventilation; however, the impact is quite unlikely in the experiment study as hyperventilation usually causes increase in CO_2 exhalation (VCO_2) (210) and BF goes above normal level 12-20 breaths/min (211) which is not consistent with our results.

Future research

According to our systematic review and other current literature, there is association between e-cig smoking and negative CVS responses, our experimental study did not find significant CVS impacts of e-cig in males nor females (1). Hence, such observations could be inconclusive. Utilizing some novel techniques such as stress tasks might be helpful to observe any sex differences in cardiac responses to acute e-cig smoking in young adults (197, 212). Since the number of e-cig smokers are increasing and there has been documented EVALI cases, there is a need for more research to explore the impacts of e-cig usage in males and females separately, such as longitudinal studies with a larger number of participants and using currently available e-cig devices, e.g., fourth generation e-cig. Analyzing participants basic characteristics e.g., BMI, smoking length, marital status and the potential impact of anxiety and hyperventilation on e-cig smoking responses might also be helpful to understand their possible association on the physiological responses in males vs. females.

Clinical implication

Acute e-cig smoking has negative impacts on human cardio-respiratory and inflammatory system and hence, we could say, it is not completely harmless. The data from this thesis are indicative of acute alterations of normal physiological mechanisms, that could lead to possible long-term cardiovascular and respiratory complications due to e-cig smoking. The findings of this thesis question the potential usage of e-cig as a smoking cessation aid in the general population. According to current data, the role of e-cig as a smoking cessation aid are still inconclusive. It has been suggested that nicotine e-cig has some efficacy in smoking cessation compared to non-nicotine e-cig or NRT (nicotine replacement therapy) (213). On the other hand,

Hanewinkel et al, in their systematic review and meta-analysis reported that, permanent nicotine dependence could occur due to e-cig usage as a smoking cessation tool (214). Hence, these collective considerations, the acute physiological impact and unclear use as a smoking cessation aid, necessitate further thought regarding regulations around e-cig, for example, the inclusion of warnings/information about the potential impacts of e-cigs on health on packaging (215, 216).

CHAPTER 6. References

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