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

Emilie Dolan

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

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

March 2020

CONCORDIA UNIVERSITY
School of Graduate Studies

This is to certify that the thesis prepared

By: Emilie Dolan

Entitled: The Physiological Effects of Electronic Cigarettes: A Systematic Review and Meta-Analysis

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

Master of Science (Exercise Science)

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. Richard Courtemanche Chair

Dr. Robert Kilgour Examiner

Dr. Kim Lavoie Examiner

Dr. Simon Bacon Supervisor

Approved by Dr. Veronique Pépin
Chair of Department or Graduate Program Director

André Roy
Dean of Faculty

Date July 26, 2017

# ABSTRACT


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

Emilie Dolan

**Background:** Electronic cigarettes represent a new phenomenon in the fight against smoking. While they continue to be marketed both as safer than traditional cigarettes and as potential smoking cessation tools, little is known about their potential physiological effects.

**Objectives:** The purpose of this systematic review was to provide an analysis of the physiological effects of e-cigarettes in humans.

**Methods:** A search was conducted by two independent authors using PubMed, SCOPUS, Web of Science and the Cochrane Library electronic databases (until July 24, 2017 ). Inclusion criteria consisted of: English and French language peer-reviewed articles; studies including human participants; objective measurements of physiological responses to active e-cigarette smoking; physiological measures obtained during or post-smoking and compared to baseline measures.

Results: Of the 3101 studies investigated, fourteen studies met the inclusion criteria. These studies indicated that the short-term (4-20 minutes) use of e-cigarettes resulted in decreases in measures of respiratory function such as forced expiratory volume in one second ($FEV_1$), forced vital capacity (FVC), forced expiratory flow (FEF) and exhaled carbon monoxide (eCO); as well as increases in cardiovascular measures such as heart rate and blood pressure. Exposure to e-cigarettes was found to be less harmful than exposure to combustible cigarettes, though not entirely benign.

**Conclusions:** Based on the current literature, e-cigarettes do not appear to be as harmful as traditional cigarettes. As these devices have only recently become available, it has been impossible to conduct any long-term studies into their repercussions. Further studies are needed to gain an understanding of potential long-term effects.

# ACKNOWLEDGEMENTS

First and foremost, I would like to thank my supervisor, Dr. Simon L. Bacon, for his constant support and guidance throughout my graduate studies. His patience and steadfast determination challenged me to push my academic boundaries.

I would also like to thank my co-supervisor, Dr. Kim L. Lavoie for her support and meaningful input throughout this process.

To Dr. Robert D. Kilgour, thank you; your encouragement, support, and humor were so greatly appreciated.

To Dr. Nicola Paine, for never hesitating to answer a question, no matter how simple and for your patience and guidance, thank you.

To Mélanie Béland, your statistical prowess was invaluable.

To Paula Ribeiro, for your tireless help with final statistical analyses.

To my lab-mate, class-mate and friend, Candace Bell; I am forever grateful for your partnership and friendship throughout this process.

# CONTRIBUTION OF AUTHORS

Emilie Dolan performed the background research, developed the main criteria for the review as well as performed the database searches, the data extraction, interpretation and writing of the current review.

Dr. Simon Bacon contributed to all phases of idea development, interpretation and writing.

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

Candace Raddatz performed the secondary database search, exclusions/inclusions and data extractions.

Mélanie Béland, Paula Ribeiro and Emilie Dolan performed and interpreted the meta-analysis of the data with the aid of Simon Bacon.

# TABLE OF CONTENTS

# List of Tables

# List of Figures

# GLOSSARY

A: Peak late velocity

Am: Late diastolic peak velocity

DBP: Diastolic blood pressure

DT: E wave deceleration time

E: Peak early velocity

E/A: Peak ratio

eCO: exhaled carbon monoxide

Em: Early diastolic peak velocity

eNo: exhaled nitric oxide

FEF: forced expiratory flow

FeCO: fraction of exhaled carbon monoxide

FeNO: Fraction of exhaled nitric oxide

$FEV_1$: Forced expiratory volume in 1 second

$FEV_1$/FVC:

FVC: forced vital capacity

IVRT: isovolumetric relaxation time

IVRTc: corrected-to-heart rate IVRT

GS: End-systolic global strain

HR: Heart rate

M: Mean

MEF: Maximal expiratory flow

MeSH: Medical subject headings

MMEF: Maximal mid-expiratory flow

MPI: Myocardial performance index (Doppler flow)

MPIt: Myocardial performance index (Doppler tissue)

MSNA: muscle sympathetic nerve activity

PEF: peak expiratory flow

SBP: Systolic blood pressure

SD: Standard deviation

Sm: Systolic peak velocity

SRa: Late diastolic strain rate

SRe: Early diastolic strain rate

SRs: Global peak longitudinal systolic strain rate

# 1.0 INTRODUCTION

## 1.1 Smoking

Cigarette smoking is one of the most important modifiable risk factors for a number of chronic diseases. Despite this knowledge, the World Health Organization estimates that there are over 1 billion smokers worldwide [1]. When lit, conventional tobacco cigarettes rapidly deliver nicotine, a highly addictive substance, along with a number of other toxic and carcinogenic chemicals to the body and brain [2, 3]. Traditional cigarettes release over 7,000 different compounds into the air; a great many of which have been linked to the diseases and premature deaths of over 7 million people each year [1, 3, 4]. It is this knowledge of the dangers of cigarette smoking that has led to the decrease in smokers since the early 1980's [5, 6]. In fact, 2015 marked the lowest prevalence of cigarette smokers in Canada, 3.9 million, since it first started being monitored [7].

## 1.2 Electronic Cigarettes

The year 2004 saw the advent of the modern electronic cigarette (also known as e-cigarette, e-cig, electronic nicotine delivery system (ENDS), electronic vaping device or personal vapourizer) [8]. Since the inception of the e-cigarette, the number of young adults, aged 20-24, reporting the use of these devices has seen a steady increase [5, 9]. According to the Centre for Disease Control (CDC), in 2015, e-cigarettes were the most commonly used tobacco product among youth in the United States [10, 11]. In Canada, a 2013 survey reported that 20.1% of young adults had tried e-cigarettes at least once [12], and today, almost 4 million Canadians have tried e-cigarettes [7].

E-cigarettes deliver an aerosol by heating a chemical solution containing glycerol or propylene glycol, flavouring, and optionally, nicotine. E-cigarettes have been marketed as a healthier alternative to traditional cigarettes and, prior to new regulation, provided a means for smokers to evade many 'no smoking' laws [13]. In addition, some professionals advocate their use as potential smoking cessation tools [14]. There are preliminary studies indicating that the success rate of permanent smoking cessation with the use of e-cigarettes can be quite low (1%) and that most people who use e-cigarettes remain addicted to nicotine [15]. In addition, some systematic reviews on the use of these devices as smoking cessation tools have found that e-cigarettes lead to worse odds of quitting smoking when compared to

traditional cessation methods [16, 17]. In contrast, there are other reviews that report that using e-cigarettes results in equal, if not greater, rates of smoking cessation when compared to nicotine replacement therapy (NRT), varenicline or bupropion [18-21].

The suggestion of using e-cigarettes to aid in smoking cessation is based on claims that the device user has the ability to choose how much nicotine they will smoke, and therefore allows for the gradual weaning off of their nicotine addiction [15, 16, 22]. Despite giving users the ability to choose their nicotine usage, nearly 20% of surveyed users were unsure as to the nicotine content of their e-cigarette [5]. In addition, it is estimated that nearly half of all e-cigarettes contain nicotine despite being marketed as non-nicotine containing products [5, 23]. These claims have sparked major debates as to the potential harms and benefits of e-cigarettes. Often times the argument in favour of e-cigarettes is based on the fact that some do not contain tobacco. The US Food and Drug Administration (FDA), though, has made it clear that while these e-cigarettes may not contain tobacco, they do contain a number of carcinogens that may be dangerous to humans [24]. Yet, as there has been little to no regulation, the levels of toxicants found in e-cigarettes varies, sometimes reaching levels higher than those found in traditional cigarettes [25]. The FDA is now in the process of imposing regulations on the manufacturing and distribution of e-cigarettes [26]. By the end of 2017, in the United States, e-cigarette manufacturers will have to submit health documents and ingredient lists prior to selling them, and by 2019, they will have to submit documents specifying the quantities of harmful and potentially harmful constituents [26]. Currently, in Canada, eight provinces have put in place regulations to restrict the sale, promotion and use of e-cigarettes, though no federal regulation exists at this time [27-30].

In addition to the carcinogens found in e-cigarettes, there is also a major concern regarding the vast number (approximately 7,750) of unregulated flavouring agents that can be added to the device [31]. In the early 2000's, strong evidence indicated that certain flavouring agents used in the production of popcorn flavouring, when inhaled, were linked to a phenomenon known as *bronchitis obliterans* in factory workers [32]. Bronchitis obliterans, also known as Popcorn Lung, is a non-reversible obstructive lung disease causing a dry cough, wheezing and shortening of breath [33]. This disease is thought to be caused by the chemical Diacetyl, which has also been found to be present in 75% of e-cigarette flavour additives. Consistent with this, recent studies that have found increases in respiratory impedance, flow

respiratory resistance, and overall peripheral airway resistance immediately after smoking an e-cigarette [24]. Given this information, the need to better understand their effects on health is critical.

At this time, there is little in the way of firm evidence in support of, or against, the use of e-cigarettes. Due to this lack of evidence, the majority of organizations are recommending the strict regulation of e-cigarettes (often adopting combustible cigarette regulations) until further information becomes available. In fact, The Forum of International Respiratory Societies released a position statement in which they recommend that e-cigarettes be banned or, at the very least, be heavily restricted until more is known about the potential dangers of these devices [22]. Their main concerns rest in the levels of nicotine, propylene glycol and trace chemicals like quinoline, benzoic acid, and diethylcarbonate in these devices and their potential long-term health effects.

There remain many gaps in the knowledge base about e-cigarettes and their physiological effects. The aim of this document is to provide a systematic review and meta-analysis of the current literature on the effects of smoking electronic cigarettes on physiological parameters in comparison to not smoking e-cigarettes (e.g. traditional cigarettes, placebos and controls). We hypothesized that: 1) e-cigarettes would have deleterious effects on physiological responses, and 2) those effects would be less pronounced than those seen when smoking traditional cigarettes.

# 2.0 METHODS

This systematic review was conducted in accordance with the preferred reporting items for systematic reviews and meta-analysis protocol (PRISMA-P) guidelines (PROSPERO ID: CRD42017062693) [34].

## 2.1 Literature Search

Systematic literature searches were conducted until July 24 2017 to identify research related to e-cigarettes and their effects on all physiological parameters in human subjects. The following electronic databases were used: PubMed, Scopus, The Cochrane Library and Web of Science. The search terms used as well as the detailed search strategy used for each database can be found in **Appendices A and B**. Additional articles were identified using the reference sections of eligible articles.

## 2.2 Study Selection and Data Extraction

Potential studies were selected in accordance with the following inclusion criteria: 1) English and French language peer-reviewed articles; 2) studies including only human participants; 3) studies that objectively measured physiological responses to active e-cigarette smoking; 4) physiological measures obtained during or post-smoking and compared to baseline or pre-smoking. For this review, only studies that measured the effects of the active smoking of e-cigarettes were included. Human studies were defined as those with effects being measured in human beings; in vitro, ex vivo and animal studies were not included. Passive smoking or exposure to second-hand smoke were not included.

Two reviewers (ED and CR) independently screened all articles returned by the databases. Initial screening of titles and abstracts was conducted. Once the initial abstract screening was completed, the full-text of the remaining articles were independently assessed by the two reviewers (ED and CR). Any discrepancies were discussed with a third reviewer (SLB). Reviewers then performed an independent data extraction of the selected studies. Data extraction was performed using Excel.

The quality of the chosen studies was evaluated using the Downs and Black Checklist [35]. This checklist was adapted to only include those questions relevant to the acute laboratory study design, so that a total of 13 of the 27 items (reporting subscale: 1- 4, 6, 8, 10; external validity subscale: 11; internal validity subscale: 15, 16, 18, 20, 21) were considered.

## 2.3 Assessment of Publication Bias

To identify potential publication bias, a funnel plot was examined. Symmetrical funnel plots indicate a low risk of publication bias, while asymmetrical plots represent greater risk of publication bias, often resulting in overestimates of effect size. While symmetry can be indicative of low risk of publication bias, it can also indicate heterogeneity among the selected studies or small-study effects.

## 2.4 Statistical Analysis

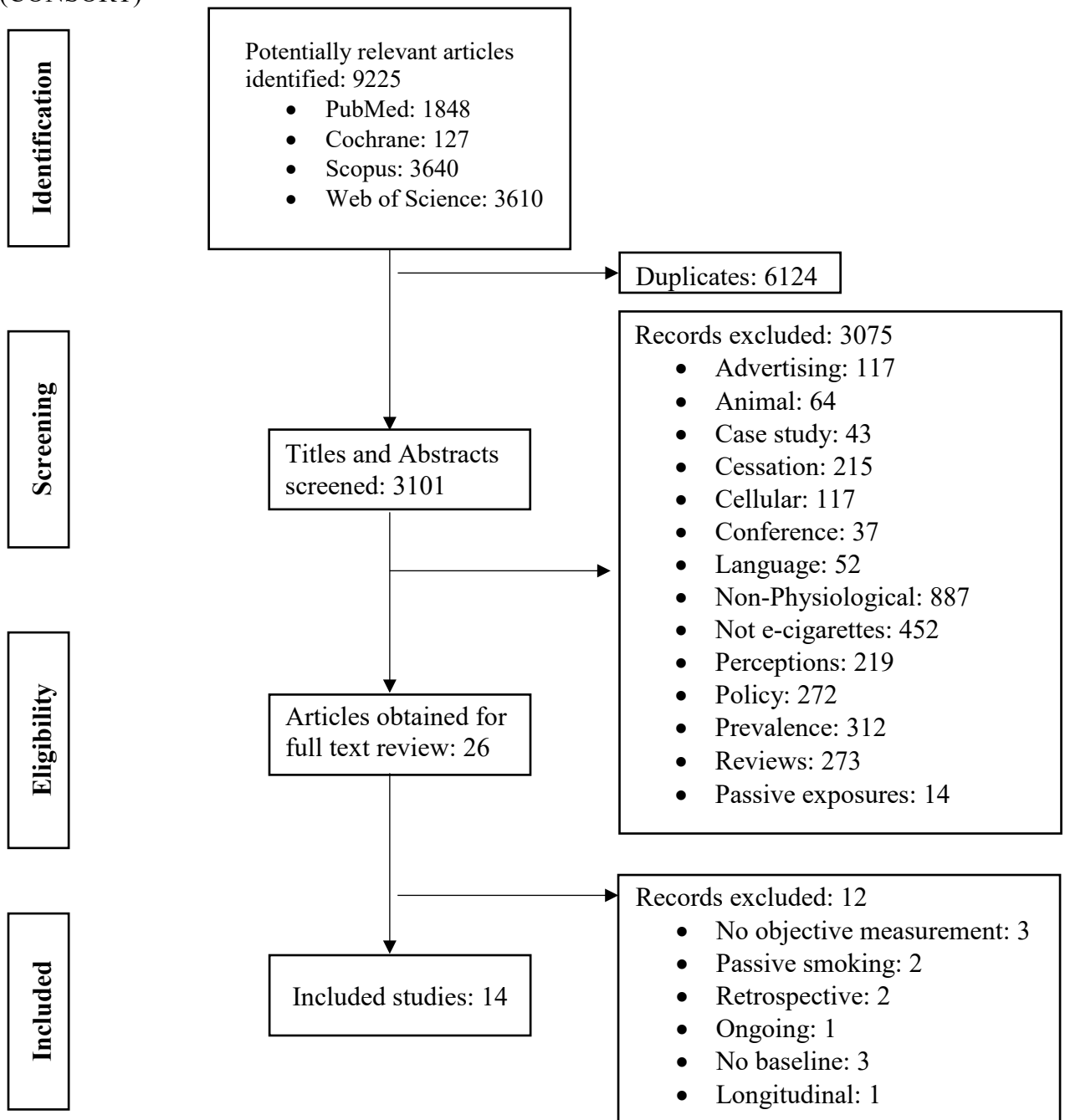
Data were analyzed using Comprehensive Meta-Analysis software (CMA) [36]. A minimum of two studies reporting means and standard deviations for the same response were needed in order to perform the meta-analysis. Standardized difference in means (SMD) with 95% confidence intervals (CI)

were calculated for each response to e-cigarettes. SMDs were evaluated based on the following categories: between 0.2 and 0.5 were considered a small effect size, between 0.5 and 0.8 were considered moderate, and 0.8 and above was a large effect [37]. The effect size (ES) representing the difference in physiological response (heart rate, systolic and diastolic blood pressure) between pre and post cigarette smoking was computed using mean changes and p-values. High levels of homogeneity were expected, therefore, the fixed effects model was used. Secondary analyses were performed to assess differences between e-cigarettes and traditional cigarettes on physiological responses. The moderators used were e-cigarette and traditional cigarette. Of note: the six unique smoking arms of the Yan et al. study were included as separate entries in the meta-analysis and risk of bias assessments.

# 3.0 RESULTS

The initial search yielded 9255 articles (see **Figure 1**); 6124 of which were duplicates or descriptions of the same study. After article titles and abstracts were reviewed for adherence to the inclusion and exclusion criteria, 26 articles were reviewed in full. A total of 12 studies were excluded after full-text review: two studied passive smoking [38, 39]; three lacked objective physiological measurements [40-42]; three lacked baseline measures [43-45]; two were retrospective reviews of past medical charts [46, 47]; one was an ongoing protocol with no results at this time [48]; and one was longitudinal (not experimental) [49]. A total of 14 studies met the inclusion criteria and were retained for this review [22, 24, 50-61].

**Figure 1.** Flow chart of article screening based on Consolidated Standards of Reporting Trials (CONSORT)



## 3.1 Study Characteristics

**Table 1** describes the characteristics of the selected studies. All studies reported the sex of the participants; two of the studies included only men [54, 56]. The overall percentage of women was 34.68%. The mean age of the populations was 32.35 years old with a range of 18 [61] to 65 [56, 61]. Smoking status of participants was objectively measured through serum and/or urine cotinine tests in 11 of the 14 studies [22, 50, 51, 53-60]. The remaining three articles either used self-report [52, 61] or did not report how smoking status was verified [24].

**Table 1.** Characteristics of the studies

| First author (year) | Location | No. of participants | Age M(SD) | % Women | Smoking Assessment | Comparator | D&B Score |
|---|---|---|---|---|---|---|---|
| **Antoniewicz (2016)** | Sweden | 14 | 27(5) | 35.7 | Objective | Smoking Cessation | 10 |
| **Carnevale (2016)** | Italy | 40 | 28(5.3) | 52.5 | Objective | Traditional cigarette | 11 |
| **Cooke (2015)** | USA | 20 | 23(1) | 50.0 | Objective or Self-report | Response in non-smokers | 12 |
| **D'Ruiz (2017)** | USA | 105 | 37.8(11.1) | 35 | Objective | Traditional cigarettes & non-smoking | 12 |
| **Farsalinos (2014)** | Greece | 76 | 35.5 (5) | 7.8 | Self-report | Traditional cigarette | 12 |
| **Ferrari (2015)** | Italy | 20 | 39.3(12.6) | 45.0 | Objective | Traditional cigarette | 11 |
| **Marini (2014)** | Italy | 25 | 28(9) | 44.0 | Objective | Traditional cigarette & other nicotine concentrations | 12 |
| **O'Connell (2016)** | USA | 105 | 37.8(11.1) | 35 | Objective | Traditional cigarettes & non-smoking | 12 |
| **Schober (2014)** | Germany | 9 | 24.7(4.2) | 0.0 | Objective | Other nicotine concentrations | 12 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Vansikel (2010)** | USA | 32 | 33.6(12) | 40.6 | Objective or Self-report | Traditional cigarette & other nicotine concentrations or placebo | 11 |
| **Vardavas (2012)** | USA | 30 | 34.8(11) | 53.3 | Not Mentioned | Other nicotine concentrations or placebo | 12 |
| **Wadia (2016)** | England | 20 | 18-65 | | Self-report | Traditional cigarette | 10 |
| **Walele (2016)** | Netherlands | 24 | 21-65 | 0.0 | Objective or Self-report | Other nicotine concentrations | 11 |
| **Yan (2015)** | USA | 30 | 38.7(10.77) | 52.0 | Objective | Traditional cigarette & other nicotine concentrations | 13 |

*Note:* D&B, Downs and Black Checklist [35] (Maximum total score = 13).

## 3.2 Cigarette Consumption

Smoking session duration ranged from 5 minutes [22, 24, 53, 62] to 2 weeks [61]. Four studies had two arms, comparing an e-cigarette with a traditional cigarette [22, 50, 52, 61]. Two studies, with 2 arms, compared e-cigarettes at different nicotine concentrations [51, 54]. Three studies compared e-cigarettes of differing nicotine concentrations with traditional cigarettes [53, 56, 57]. One study compared e-cigarettes to both traditional cigarettes as well as a sham cigarette or non-smoking condition [55]; and four studies compared e-cigarettes to a sham e-cigarette or non-smoking condition only [24, 58-60]. Details on smoking protocol and devices used can be found in **Table 2.**

**Table 2.** Study Protocols

| First author (year) | Products Used (e-cigarette) | Products Used (traditional cigarette) | Nicotine Concentration E-cigarette | Nicotine Concentration Traditional Cig | Duration of Smoking Protocol | Smoking protocol |
|---|---|---|---|---|---|---|
| **Antoniewicz (2016)** | eGO XL | NA | 12mg | N/A | 10 min | 10 puffs |
| **Carnevale (2016)** | Unspecified | Unspecified | 0.6mg | 0.6mg | - | 9 puffs |
| **Cooke (2015)** | Clean E-Cigarettes | N/A | 0mg<br>18mg | N/A | 5 min | 1 puff/30s interval |

| | | | | | | |
|---|---|---|---|---|---|---|
| | Green Smart Living | | | | | |
| **D'Ruiz (2017)** | Blu Tobacco rechargeable<br>Blu Cherry rechargeable<br>Blu Cherry disposable | Participants preferred brand | 24mg<br>24mg<br>24mg | Participants own brand | 16 hours (x 5 days) | Ad lib |
| **Farsalinos (2014)** | eGo-T battery & eGo-C atomizer | Unspecified | 11mg | 1.0mg | 7 min | Ad lib |
| **Ferrari (2015)** | ELIPS C Series | Marlboro Red Label Box | 0mg | 0.8mg | 5 min | Ad lib |
| **Marini (2014)** | Unspecified | Unspecified | 0mg<br>18mg | 0.8mg | 5 min | Ad lib |
| **O'Connell (2016)** | Blu Tobacco<br>Blu Cherry | Participants preferred brand | 24mg | Participants own brand | 16 hours (x 5 days) | Ad lib |
| **Schober (2014)** | Unspecified | N/A | 0mg<br>18mg | N/A | 120 min (x 5) | Ad lib |
| **Vansikel (2010)** | NPRO EC<br>Hydro EC | Participants preferred brand | 16mg<br>18mg | Participants own brand | 5 min | 1 puff/30s interval |
| **Vardavas (2012)** | NOBACCO black line | N/A | 11mg | N/A | 5 min | Ad lib |
| **Wadia (2016)** | Blu PRO | Participants preferred brand | 18mg | Participants own brand | 2 weeks | Ad lib |
| **Walele (2016)** | EVP Fontem Ventures B.V. | JPS Silver King Size CC | 0mg<br>0.54mg<br>1.22mg<br>2.7mg | 0.6mg | 5 min (x 4) | 1 puff/30s interval |
| **Yan (2015)** | Blu Classic Tobacco<br>Blu Magnificent Menthol | Marlboro Gold King Size | 16mg<br>24mg | 0.8mg | 60 min<br>30 min | Ad lib<br>1 puff/30s interval |

## 3.3 Physiological Stress Responses

Below are the detailed results for each physiological measure reported.

### 3.3.1 Cardiovascular Responses

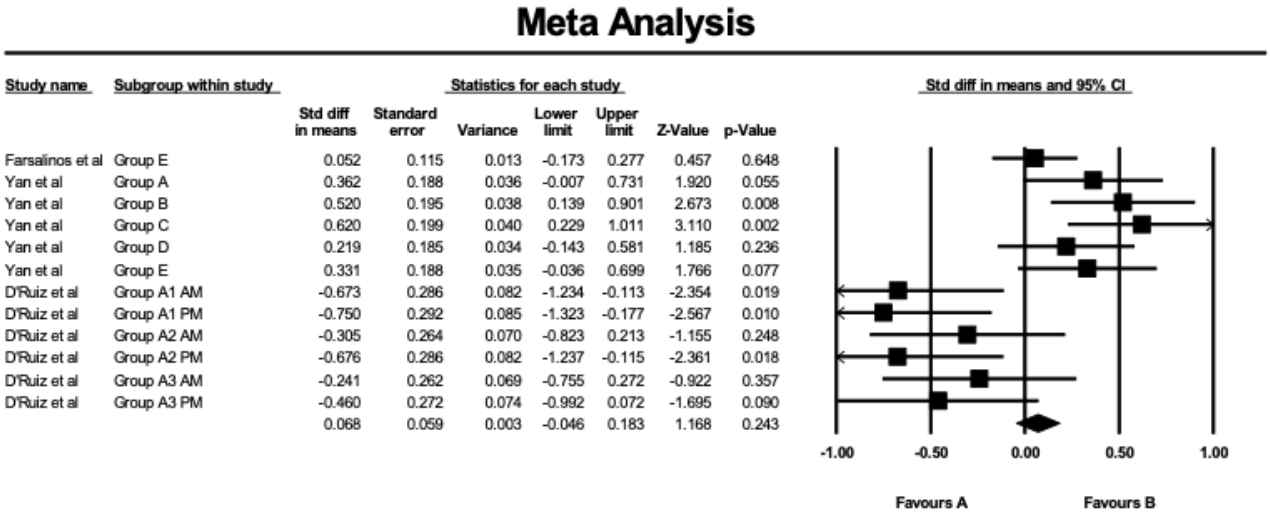
A total of 5 studies measured cardiovascular responses to e-cigarettes [51, 52, 55, 57, 59]. These details can be found in **Table 3.**

Overall, e-cigarettes were found to cause minimal cardiovascular responses. Of the five studies that measured heart rate, two found that smoking e-cigarettes caused an increase in heart rate, regardless of nicotine concentration [51, 57]. One study found heart rate to decrease when smoking e-cigarettes, compared to traditional cigarettes [59]. Only these three studies were meta-analyzed, as neither Cooke et al. nor Vansickel et al. provided the necessary information for quantitative analysis [51, 62]. A very minor, non-significant effect size was found for the increases in heart rate following the smoking of e-cigarettes (SMD=0.068; 95% CI -0.046-0.183) [52, 57, 59] (**Figure 2a**).

Four studies measured blood pressure [51, 52, 57, 59]; three of these studies provided the information required for meta-analysis [52, 57, 59]. This found e-cigarettes to increase systolic blood pressure (SMD = 0.064; 95% CI -0.049-0.177), though the effect size was minimal and not significant (**Figure 2b**). For diastolic blood pressure, a small, but statistically significant, effect size was found for its increase after smoking e-cigarettes (SMD = 0.303; 95% CI 0.181- 0.425) (**Figure 2c)**. Overall, minor variations in the length of smoking session did not appear to have an effect on the results obtained.

**Figure 2.** Forrest plots for studies reporting means and standard deviations; a: heart rate; b: systolic blood pressure; c: diastolic blood pressure.

*a. Heart rate*

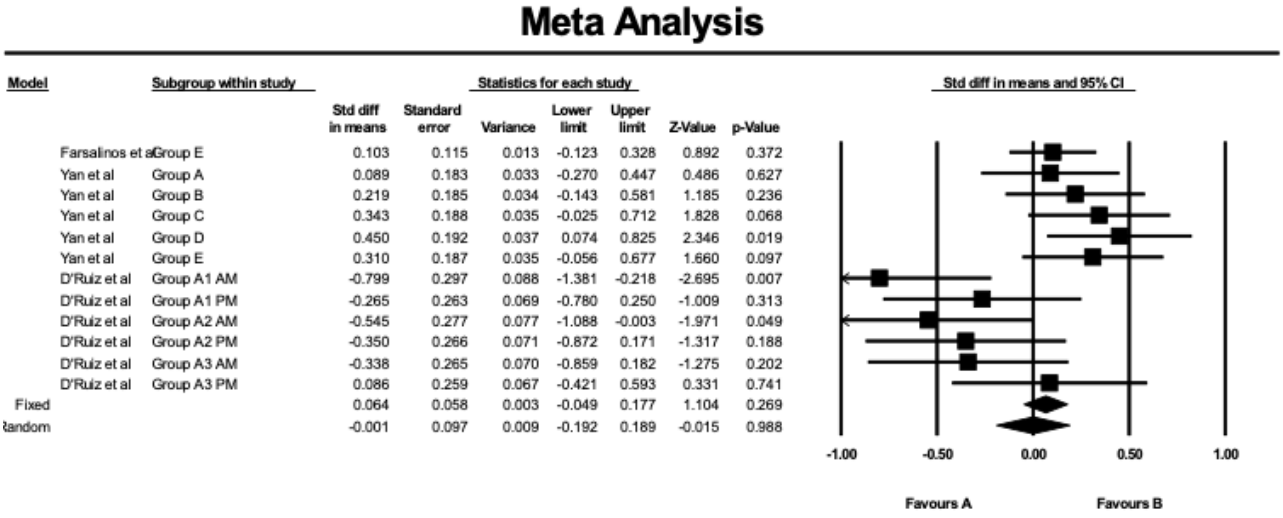



**Meta Analysis**

*Note:* The black diamond at the bottom of the plot indicates the average effect size of the studies. Conditions of Yan et al. are as follows: E-Cig A, Classic 2.4% nicotine, ~75% glycerin; E-cig B, Classic 2.4% nicotine, ~50%

glycerin, ~20% propylene glycol; E-cig C, Menthol 2.4% nicotine, ~75% glycerin; E-cig D, Classic 1.6% nicotine, ~75% glycerin; E-cig E, Classic 1.6% nicotine, ~50% glycerin, ~20% propylene glycol. D'Ruiz et el. are: A1, blu tobacco rechargeable 24mg; A2, blu cherry rechargeable 24mg; A3, blu cherry disposable 24mg.

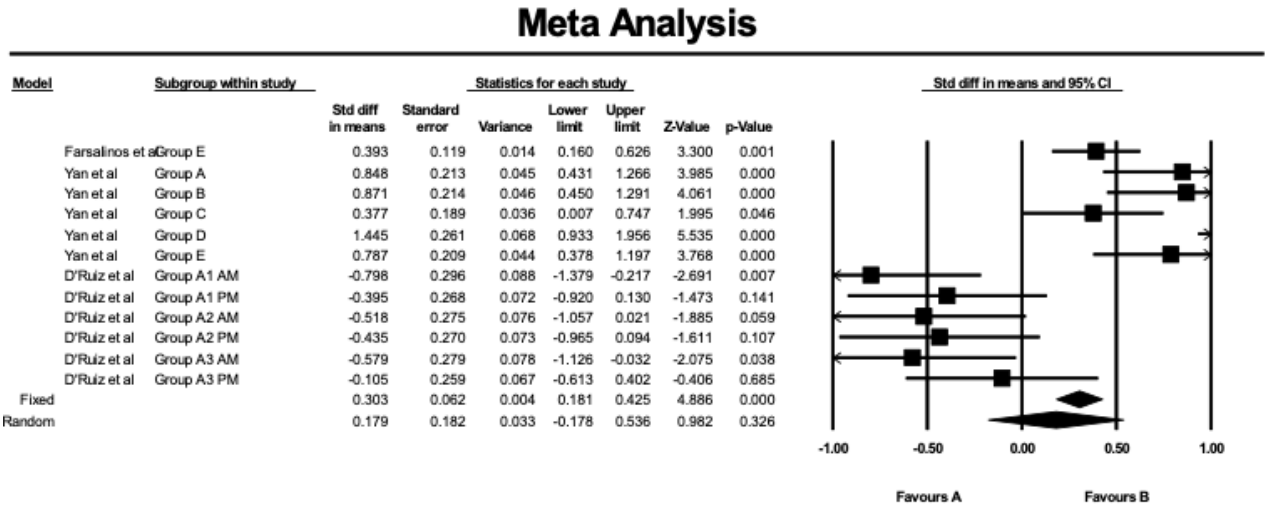
*b. Systolic blood pressure*




**Meta Analysis**

*Note:* The black diamond at the bottom of the plot indicates the average effect size of the studies. Conditions of Yan et al. are as follows: E-Cig A, Classic 2.4% nicotine, ~75% glycerin; E-cig B, Classic 2.4% nicotine, ~50% glycerin, ~20% propylene glycol; E-cig C, Menthol 2.4% nicotine, ~75% glycerin; E-cig D, Classic 1.6% nicotine, ~75% glycerin; E-cig E, Classic 1.6% nicotine, ~50% glycerin, ~20% propylene glycol. D'Ruiz et el. are: A1, blu tobacco rechargeable 24mg; A2, blu cherry rechargeable 24mg; A3, blu cherry disposable 24mg.

*c. Diastolic blood pressure*




**Meta Analysis**

*Note:* The black diamond at the bottom of the plot indicates the average effect size of the studies. Conditions of Yan et al. are as follows: E-Cig A, Classic 2.4% nicotine, ~75% glycerin; E-cig B, Classic 2.4% nicotine, ~50% glycerin, ~20% propylene glycol; E-cig C, Menthol 2.4% nicotine, ~75% glycerin; E-cig D, Classic 1.6% nicotine,

~75% glycerin; E-cig E, Classic 1.6% nicotine, ~50% glycerin, ~20% propylene glycol. D'Ruiz et el. are: A1, blu tobacco rechargeable 24mg; A2, blu cherry rechargeable 24mg; A3, blu cherry disposable 24mg.

Measures of myocardial function were also assessed [52], see **Appendix C**. Pressure rate product, peak late velocity, E wave deceleration time, late diastolic peak velocity, E/Em, late diastolic strain rate, peak early velocity, early diastolic peak velocity, early diastolic strain rate and systolic peak velocity were all found to increase, though not significantly, after smoking e-cigarettes. Meanwhile, peak ratio, E/Am, global peak longitudinal systolic strain rate, myocardial performance index Doppler flow (IVRT), myocardial performance index Doppler tissue (IVRTc) and end-systolic global strain were found to decrease after use of e-cigarettes. As with the other markers of myocardial function, changes in values after smoking e-cigarettes were not found to be significant. Though not significant, the pattern of these results suggest that long term use of e-cigarettes may alter myocardial function in similar ways to traditional cigarettes, potentially leading to the development of atherosclerosis and cardiovascular disease [52].

One study assessed muscle sympathetic nerve activity (MSNA) and vagal cardiac control [51] (Appendix C). The authors found that MSNA increased, though not significantly, after use of an e-cigarette with nicotine. Vagal cardiac control was shown to decrease non-significantly after both nicotine free and nicotine testing conditions. The pattern of these results suggests that e-cigarettes induce mild sympathoexcitatory responses.

**Table 3.** Cardiovascular Responses

| Marker | Studies | Nicotine Content | Outcome |
|---|---|---|---|
| **Heart Rate** | Cooke et al. 2015 | 18mg | ↑ |
| | Cooke et al. 2015 | 0mg | ↓ |
| | D'Ruiz et al. 2017, E-Cig A1 | 24mg | ↓* |
| | D'Ruiz et al. 2017, E-Cig A2 | 24mg | ↓ |
| | D'Ruiz et al. 2017, E-Cig A3 | 24mg | ↓ |
| | Farsalinos et al. 2014 | 11mg | ↔ |
| | Vansickel et al. 2010 | 16mg | ↔ |
| | Vansickel et al. 2010 | 18mg | ↑ |
| | Yan et al. 2015, E-Cig A | 2.4% | ↑ |
| | Yan et al. 2015, E-Cig B | 2.4% | ↑* |

| | | | |
|---|---|---|---|
| | Yan et al. 2015, E-Cig C | 2.4% | ↑* |
| | Yan et al. 2015, E-Cig D | 1.6% | ↑ |
| | Yan et al. 2015, E-Cig E | 1.6% | ↑ |
| **Systolic Blood** | Cooke et al. 2015 | 18mg | ↑ |
| **Pressure** | Cooke et al. 2015 | 0mg | ↓ |
| | D'Ruiz et al. 2017 | 24mg | ↓* |
| | D'Ruiz et al. 2017 | 24mg | ↓ |
| | D'Ruiz et al. 2017 | 24mg | ↓ |
| | Farsalinos et al. 2014 | 11mg | ↑ |
| | Yan et al. 2015, E-Cig A | 2.4% | ↑ |
| | Yan et al. 2015, E-Cig B | 2.4% | ↑ |
| | Yan et al. 2015, E-Cig C | 2.4% | ↑ |
| | Yan et al. 2015, E-Cig D | 1.6% | ↑* |
| | Yan et al. 2015, E-Cig E | 1.6% | ↑ |
| **Diastolic Blood** | Cooke et al. 2015 | 18mg | ↑* |
| **Pressure** | Cooke et al. 2015 | 0mg | ↓* |
| | D'Ruiz et al. 2017 | 24mg | ↓* |
| | D'Ruiz et al. 2017 | 24mg | ↓ |
| | D'Ruiz et al. 2017 | | |
| | Farsalinos et al. 2014 | 24mg | ↑ |
| | Yan et al. 2015, E-Cig A | 11mg | ↑* |
| | Yan et al. 2015, E-Cig B | 2.4% | ↑* |
| | Yan et al. 2015, E-Cig C | 2.4% | ↑* |
| | Yan et al. 2015, E-Cig D | 2.4% | ↑* |
| | Yan et al. 2015, E-Cig E | 1.6% | ↑* |
| | | 1.6% | ↑* |

*Note:* Conditions of Yan et al. are as follows: E-Cig A, Classic 2.4% nicotine, ~75% glycerin ; E-cig B, Classic 2.4% nicotine, ~50% glycerin, ~20% propylene glycol; E-cig C, Menthol 2.4% nicotine, ~75% glycerin; E-cig D, Classic 1.6% nicotine, ~75% glycerin; E-cig E, Classic 1.6% nicotine, ~50% glycerin, ~20% propylene glycol. Conditions of D'Ruiz et al.: A1, blu tobacco rechargeable 24mg; A2, blu cherry rechargeable 24mg; A3, blu cherry disposable 24mg.
↑, Increase; ↓, Decrease; ↔, No change; *, change was statistically significant.

### 3.3.2 Respiratory Responses

A total of eight studies [22, 24, 54-59] assessed the effects of e-cigarettes on respiratory responses. Details of the main measurements and outcomes can be found in **Table 4.**

Insufficient data was provided on respiratory measures to perform a meta-analysis. As seen in Table 4, fractional exhaled nitric oxide (FeNO) was found to increase slightly (p=0.03) after smoking e-cigarettes in one study [54], remain unchanged in two studies [22, 58], and decrease (p=0.005 and 0.007) in two other studies [24, 53]. No meta-analysis was performed on FeNO as neither means nor standard deviations were reported in three of the five studies. Fractional expired carbon monoxide (FeCO) and expired carbon monoxide (eCO) were not affected by e-cigarettes [22, 54-57], regardless of nicotine content in all except one study, which found a decrease in eCO when using e-cigarettes [59].

As shown in Appendix C, both forced expiratory volume in 1 second ($FEV_1$)– the maximum amount of air one can exhale in the first second of a forced vital capacity (FVC) test – and forced expiratory flow at 25% ($FEF_{25}$) – the average forced expiratory flow during the mid-portion of the FVC – showed conflicting results among studies measuring them [22, 59]. One study evaluated the effects of e-cigarettes on respiratory mechanics, finding that respiratory impedance (Z5Hz), respiratory resistance (R5Hz, R10Hz and R20Hz), respiratory reactance (X20Hz), peripheral resistance and central resistance increased after smoking e-cigarettes [24]. Respiratory reactance measures (X5Hz and X10Hz) and resonant frequency showed decreases after smoking e-cigarettes [24]. Qualitative evaluation of the collective data suggests that smoking e-cigarettes decreased respiratory measures.

**Table 4.** Respiratory Responses

| Marker | Studies | Nicotine Concentration | Outcomes |
|---|---|---|---|
| **FeNO** | Antoniewicz et al. 2016 | 12mg | ↔ |
| | Ferrari et al. 2015 | 0mg | ↔ |
| | Schober et al. 2014 | 0mg | ↔ |
| | Schober et al. 2014 | 18mg | ↑* |
| | Vardavas et al. 2012 | 11mg | ↓* |
| | Marini et al. 2014 | 0% | ↓ |
| | Marini et al. 2014 | 18% | ↓ |
| **eCO** | D'Ruiz et al. 2017, E-Cig A1 | 24mg | ↓* |
| | D'Ruiz et al. 2017, E-Cig A2 | 24mg | ↓* |
| | D'Ruiz et al. 2017, E-Cig A3 | 24mg | ↓* |
| | Ferrari et al. 2015 | 0mg | ↔ |
| | Schober et al. 2014 | 0mg | ↔ |
| | Schober et al. 2014 | 18mg | ↔ |

| | | |
|---|---|---|
| Vansickel et al. 2010 | 16mg | ↔ |
| Vansickel et al. 2010 | 18mg | ↔ |
| Walele et al.2016 | 2% | ↔ |
| Yan et al. 2015, E-Cig A | 2.4% | ↔ |
| Yan et al. 2015, E-Cig B | 2.4% | ↔ |
| Yan et al. 2015, E-Cig C | 2.4% | ↔ |
| Yan et al. 2015, E-Cig D | 1.6% | ↔ |
| Yan et al. 2015, E-Cig E | 1.6% | ↔ |

*Note:* FeNO, fractional exhaled nitric oxide; eNO, exhaled nitric oxide; eCO, exhaled carbon monoxide. Conditions of Yan et al. are as follows: E-Cig A, Classic 2.4% nicotine, ~75% glycerin ; E-cig B, Classic 2.4% nicotine, ~50% glycerin, ~20% propylene glycol; E-cig C, Menthol 2.4% nicotine, ~75% glycerin; E-cig D, Classic 1.6% nicotine, ~75% glycerin; E-cig E, Classic 1.6% nicotine, ~50% glycerin, ~20% propylene glycol. Conditions of D'Ruiz et el. are: A1, blu tobacco rechargeable 24mg; A2, blu cherry rechargeable 24mg; A3, blu cherry disposable 24mg.
↑, Increase; ↓, Decrease; ↔, No change.

### 3.3.3 Other Responses

One study looked at both immune and hematological responses to smoking e-cigarettes [56]. There was found to be no significant acute effects of e-cigarettes on any of the responses measured. Endothelial progenitor cell (EPC) and microvesicle levels were measured in one study, finding significant increases in EPC levels ($p=0.003$) as well as CD144+CD62E ($p=0.038$) following exposure to e-cigarettes [58]. One study looked at the effects of smoking e-cigarettes on oxidative stress [50]; serum soluble NOX2-derived peptide (sNOX2-dp), a marker of NADPH oxidase activation, increased significantly after smoking e-cigarettes ($p<0.001$). The same was found for 8-iso-prostaglandin F2α, which also showed a significant increase ($p<0.001$) after exposure to e-cigarettes. Furthermore, nitric oxide bioavailability and vitamin E significantly decreased after participants smoked e-cigarettes [50]. This study also evaluated the effects of e-cigarettes on endothelial function. Flow-mediated dilation (FMD), a marker used to assess endothelial function, was found to decrease after smoking e-cigarettes ($p<0.001$) [50]. One study, analyzing a number of biomarkers of exposure to harmful or potentially harmful constituents, found significant decreases in all markers following e-cigarette use [60]. Gingival crevicular fluid and gum bleeding upon probing were found to increase post e-cigarette exposure [61]. Further details on other responses reported in these studies can be found in Appendix C.

### 3.3.4 Physiological Effects of Traditional Cigarettes

Traditional cigarettes were, generally, found to have greater effects on physiological responses than e-cigarettes. In general, exposure to traditional cigarettes resulted in greater increases in cardiovascular measures, more significant changes in myocardial function, greater decreases in respiratory measures such as FEV1 and FEF25, as well as increases in CO production and markers of oxidative stress.

Traditional cigarettes were found to increase heart rate a small amount (SMD=0.290; 95% CI 0.123-0.458) [52, 57, 59]. The difference between e-cigarettes and traditional cigarettes for heart rate was statistically significant with a p-value of 0.032. Of the three studies that measured blood pressure [52, 57, 59], two found traditional cigarettes to increase systolic blood pressure to a greater degree than e-cigarettes, while one found traditional cigarettes to decrease systolic blood pressure (SMD = -0.110; 95% CI -0.283-0.063) with a non-significant difference between groups (p=0.100). With regards to diastolic blood pressure, a moderate effect size was found for its increase when smoking traditional cigarettes (SMD = 0.336; 95%CI 0.163-0.508), though the difference between groups was non-significant (p=.760).

Traditional cigarette use resulted in larger negative changes in myocardial function than did e-cigarettes [52]. E-wave deceleration time, peak ratio, E/Am, peak early velocity, early diastolic peak velocity, early diastolic strain rate and global peak longitudinal systolic strain rate were found to decrease after use of traditional cigarettes [52]. Other measures were found to produce opposite effects for traditional cigarettes compared to e-cigarettes: myocardial performance index Doppler flow (IVRT), myocardial performance index Doppler tissue (IVRTc) and end-systolic global strain increased after smoking traditional cigarettes. Finally, systolic peak velocity remained unchanged by traditional cigarettes.

FeNO and eNO were shown to decrease after the use of traditional cigarettes though these changes were comparable to those found after smoking e-cigarettes [22, 53]. In contrast to e-cigarettes, measures of fractional and expired carbon monoxide (eCO) were increased after smoking traditional cigarettes [22, 54-56]. $FEV_1$ and $FEF_{25}$ decreased significantly for traditional cigarettes (p=.037 for all) in smokers but did not show significant decreases in non-smokers [22].

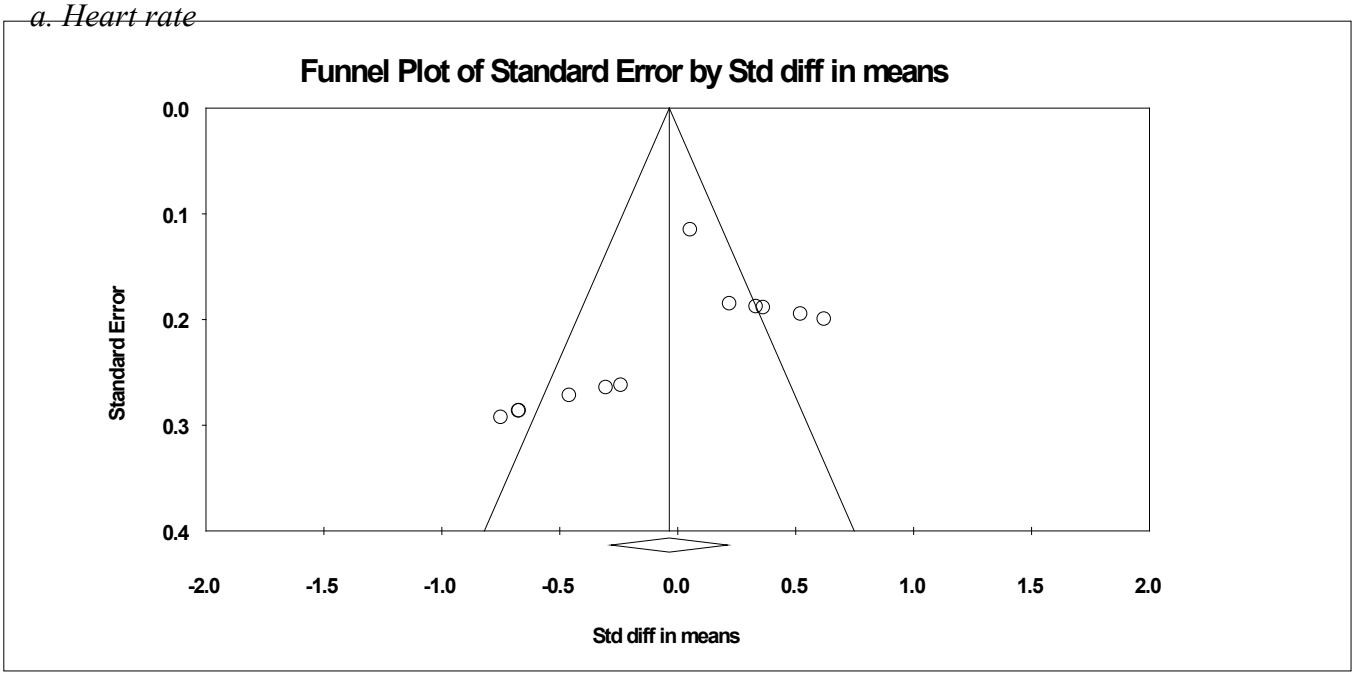
A single study evaluated oxidative stress markers [50]. Serum Soluble NOX2-derived peptide (sNOX2-dp), a marker of NADPH oxidase activation, increased significantly after smoking traditional cigarettes ($p<.001$). The same was found for 8-iso-prostaglandin F2α, which also showed a significant increase ($p<.001$) after exposure to traditional cigarettes. Both nitric oxide bioavailability and vitamin E significantly decreased after smoking traditional cigarettes [50]. Overall, e-cigarettes showed a significantly less detrimental impact on levels of sNOX2-dp ($p=.001$), 8-iso-prostaglandin F2α ($p=.046$), and NO bioavailability ($p=.001$) compared to traditional cigarettes. Flow-mediated dilation (FMD), a marker used to assess endothelial function, was found to decrease significantly in smokers of both traditional cigarettes and e-cigarettes($p<.001$) [50]. Meta-analysis of, and further details on, responses to traditional cigarettes can be found in **Appendices D and E**.

### 3.4 Publication Bias and Assessment of Study Quality

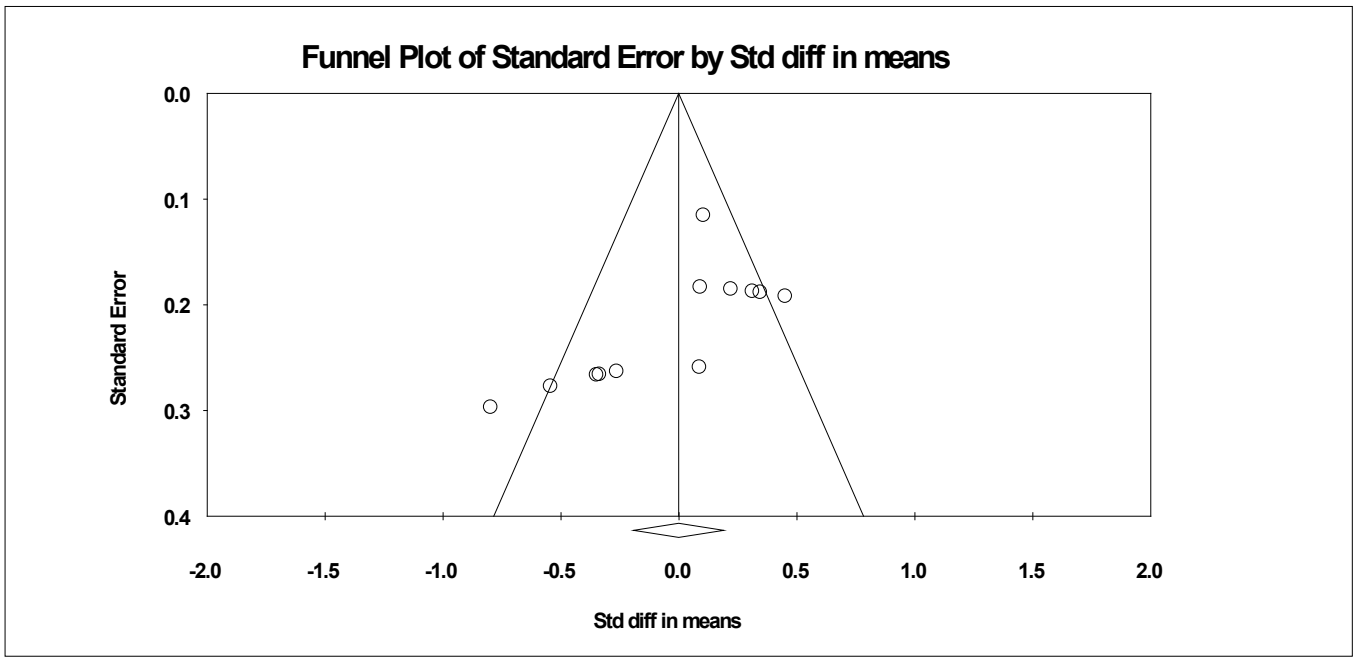
**Figure 3** represents the funnel plot of the SMDs and standard errors for all studies evaluating heart rate, systolic blood pressure and diastolic blood pressure for electronic cigarettes. Funnel plots for the evaluation of traditional cigarettes can be found in **Appendix F**. Assessment of the funnel plots suggests risk of publication bias.

**Figure 3.** Funnel plot for studies assessing publication bias; heart rate; systolic blood pressure; and diastolic blood pressure

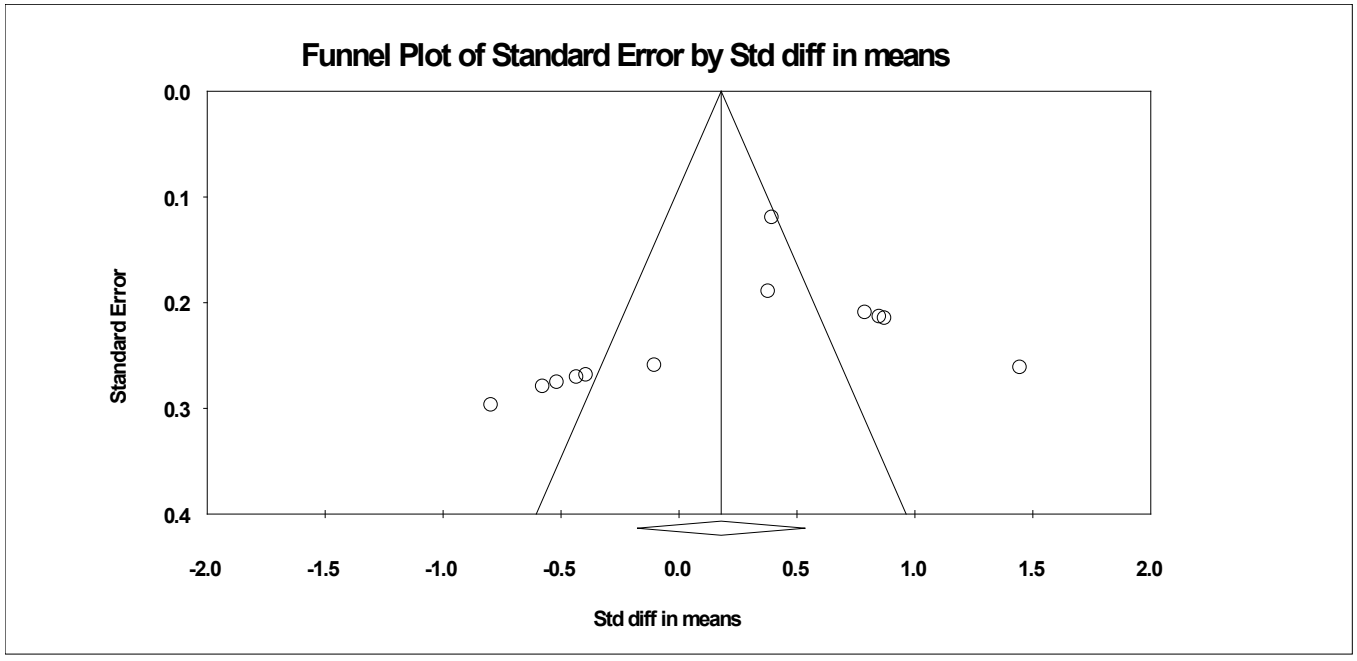
*a. Heart rate*



*b. Systolic blood pressure*




*c. Diastolic blood pressure*




Study quality was rated using a modified Downs and Black Checklist. Final scores ranged from 11 to 13 (mean [M] ± standard deviation [SD] = 11.5 ± 0.85) and are reported in **Table 1**. All studies

received high scores, with two receiving 10/13 [58, 61], four receiving 11/13 [22, 50, 55, 56], seven receiving 12/13 [24, 51-54, 59, 60], and one receiving 13/13 [57]. Over half of the studies (8/14) did not comment on whether or not they were blinded [22, 24, 53-56, 59, 60]. Six out of ten studies did not provide information regarding the representativeness of their samples (ex. “Were the subjects asked to participate in the study representative of the entire population from which they were recruited?”) [22, 50, 52, 55, 58, 61].

# 4.0 DISCUSSION

The purpose of this systematic review was to provide a synthesis of the physiological effects of e-cigarettes in humans. An extensive literature search performed by two independent researchers resulted in fourteen studies assessing the physiological effects of e-cigarettes. As hypothesized, it was found e-cigarettes are not benign and exposure to their vapour does affect numerous physiological systems warranting further research. Also as expected, the physiological effects of e-cigarettes were less severe than those of traditional cigarettes.

## 4.1 Physiological Effects of E-cigarettes

Findings suggest that the effects of e-cigarettes, while not as severe as those from conventional cigarettes, can trigger harmful physiological reactions. E-cigarettes were shown to lead to an immediate, though not statistically significant, increase in heart rate and blood pressure. The consequences of these increases in heart rate and blood pressure are potentially significant when considering long-term use of e-cigarettes. Increased blood pressure reactivity is associated with changes in alpha and beta-adrenoceptor sensitivity, endothelial dysfunction, higher vascular resistance and vascular remodeling [63]. These associations may explain why long term increased blood pressure reactivity has been linked to incident hypertension, incident cardiovascular disease, myocardial infarction and stroke [63, 64]. Meanwhile, elevated heart rate over the long term has been linked to an increased risk of cardiovascular related death and all-cause mortality [65]. In fact, for every increase in heart rate of 10 bpm, the chances of cardiovascular related death increases by 25%, while all-cause mortality increases by 27%. While the heart rate increases presented in this review are not of this magnitude, this information is crucial in understanding the potential for increased disease risk over the long term as persistent elevated heart rate is also linked to the development of arthrosclerosis and arrhythmias [65].

When looking at the findings in Yan et al., it is clear that e-cigarettes B and C produced the largest changes in heart rate [57]. This may be due to the effects of nicotine, as it has been shown to cause an immediate increase in cardiovascular responses such as heart rate, blood pressure and myocardial contractility [66]. However, there were three products containing the highest level of nicotine concentration (2.4%: products A, B and C), suggesting there may be other explanations, in addition to nicotine, for the larger increases in heart rate. When comparing products B and C, device C has the most sizeable effect on heart rate (SMD=0.62); e-cigarette C was also the only menthol-flavoured cigarette. It is possible that the addition of menthol to the device played a role in the greater increases in heart rate. Currently the research regarding menthol and its effects on cardiovascular responses is inconclusive, with a number of studies presenting evidence that menthol flavouring in cigarettes leads to worse responses when compared to cigarettes without menthol [67, 68].

A slight decrease in FeNO was also shown as a result of nicotine-containing e-cigarette smoking. FeNO is known to be sensitive to eosinophilic inflammation, airway caliber, mucus production, oxidative stress and enzyme activity, all of which may be affected by smoking e-cigarettes. These short term reductions can be seen after as little as 5 minutes of smoking when the decrease in FeNO occurs in conjunction with increases in lung flow resistance at a number of different frequencies [24]. Nitric oxide plays a significant role in physiological processes such as vascular regulation, neurotransmission, host defense and cytotoxicity [69]. It has also been identified as a marker associated with airway diseases related to smoking [24]. The reduction in FeNO immediately after smoking e-cigarettes indicates that pulmonary homeostasis may be negatively affected [70-72]. The reduction in FeNO may be due to a common substance in e-cigarettes, propylene glycol. Past studies have shown that frequent exposure to inhalation of these vapours in other contexts (e.g., theatrical smoke), is associated with acute cough and decreased lung function [73-75]. Increases in the circulating markers of oxidative stress [50], s-NOX2-dp and 8-iso-prostaglandin F2α were also observed. This was in addition to a reduction in NO bioavailability and FMD. eCO measures remained relatively unchanged among e-cigarette users in most studies compared to the significant increases seen with traditional cigarettes [22, 54, 56, 57, 59, 62].

Taken together, these results suggest that smoking e-cigarettes may activate the sympathetic nervous system (SNS). The increases in heart rate and blood pressure is likely due, in part, to nicotine,

which causes vasoconstriction and stimulation of the adrenal medulla, releasing epinephrine and norepinephrine[57]. This release of norepinephrine induces a beta-adrenoceptor-mediated increase in heart rate as well as an alpha-adrenoceptor-mediated increase in vasomotor tone, and by consequence, blood pressure [66]. This upregulation of the SNS has previously been shown to last up to 24 hours after smoking traditional cigarettes [76], though it's length has not yet been studied in e-cigarettes. This is in line with the reduction in FeNO, which, when levels decrease, can cause an increase in levels of sympathetic nerve activity [77]. This reduction in NO has also been identified as a pathway through which oxidative stress increases blood pressure via the SNS [78]. Of note, the FeNO response to e-cigarettes seems to be almost comparable to that of traditional cigarettes [53]. The results presented here are concerning, as similar, though more prominent, activation of the SNS is seen when smoking traditional cigarettes [79]. While the magnitude of these changes may not be large at this time, the effects being seen warrant future research.

## 4.2 Methodological Implications and Recommendations

There are a number of inconsistencies among the articles assessing the impact of e-cigarettes on physiological responses. Methodological factors such as the relatively short smoking sessions, the small sample sizes, and standardization of smoking may have influenced the results and contributed to some of these inconsistencies. This section aims to account for some of these factors and make recommendations for future studies.

### 4.2.1 Length of Smoking Sessions

The smoking sessions in the studies assessed ranged from 5 minutes [22, 24, 53, 55] to two weeks [61]. When one considers the amount of time the average smoker spends smoking, it can be difficult to expect immediate health repercussions when exposing never-smokers to e-cigarettes for a short period of time. The use of more standardized lengths of e-cigarette exposure would be useful in creating consistency within the research, though, in the studies included here there was no major difference in response between the different lengths of interventions.

### 4.2.3 Standardization of Inhalations (vapes)

Many studies in this review used *ad lib* smoking during their interventions. While this method does provide a more realistic measure of one's day to day smoking, there is no way to ensure that

participants are inhaling the same, or even similar, amounts of the vapour. One study addressed this issue by having participants partake in both a controlled smoking session as well as an *ad lib* session [57]. This study found that, when smoking traditional cigarettes, only 1 cigarette was smoked during the controlled session compared to an average of 3.6 cigarettes during the ad lib session. The use of both controlled and ad lib smoking would be beneficial for future studies, as controlled use allows for exposure standardization while ad lib sessions allow for more generalizable results reflective of real-life use.

### 4.2.2 Sample Size

Most studies indicated their small sample sizes as being their main methodological limitation. Some studies were unsuccessful with recruitment and obtaining a representative sample, as many volunteers for e-cigarette studies, are, in fact, people with intentions to quit smoking [49]. It is important that future studies make use of larger sample sizes in order to obtain a more accurate and precise picture of the physiological effects of smoking e-cigarettes.

## 4.3 Limitations and Strengths of the Present Review

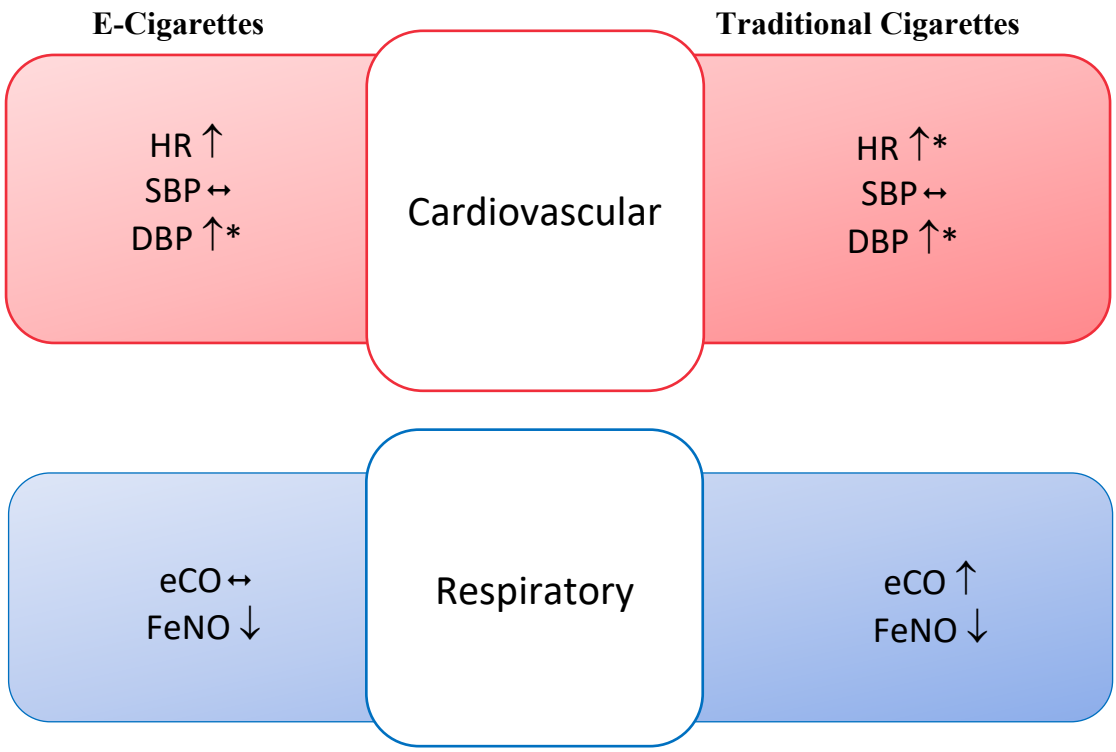
There are several limitations to this review that should be noted. First, and perhaps most obvious, is the limited number of studies eligible for this review. To date, there are not many published experimental studies looking at the physiological effects of e-cigarettes. While this number is on the rise, the results presented here may not be generalizable to the larger population of e-cigarette users. Second, this review makes use of proxy physiological measures and does not capture direct health changes. In order to capture these health changes, such as the development of cardiovascular disease, longitudinal studies would be necessary.

Despite these limitations, this systematic review also has important strengths. This review explored a wide range of physiological responses to e-cigarettes including respiratory, cardiovascular, hematological and immunological. Furthermore, the systematic process followed for this review offers results that provide a strong base for further study.

# 5.0 CONCLUSIONS

To date, though there are very few studies, e-cigarettes seemed to elicit negative physiological responses similar to, though of a lower magnitude, than traditional cigarettes (**Figure 4)**. It is likely that some of these responses, such as the increases in heart rate, are, in part, the result of nicotine consumption and in general, these responses seem to indicate a disruption in the SNS. Furthermore, the often toxic and unknown constituents of e-liquids could also be responsible for the effects seen here [80, 81]. E-cigarettes represent a major unknown to the fields of research and healthcare. The challenge is to build upon these first studies to learn more about the lasting effects of these devices.

**Figure 4.** Summary of the main physiological responses to e-cigarettes




Note: This summary of the physiological responses to e-cigarette use is based on at least two consistent studies. HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; eCO, exhaled carbon monoxide; FeNO, fraction exhaled nitric oxide.
↑, increase; ↓, decrease, ↔, no change. * indicates statistical significance.

## 5.1 Future Directions

This review highlights the need for research into the long term effects of e-cigarettes on physiological responses. It can take up to 20 years of exposure for the effects of traditional cigarettes to become apparent; it cannot be expected that the effects of e-cigarettes will be identifiable immediately. While the information presented here is vital, studies into the long term health effects would fill many gaps with regards to the health, safety and future uses of e-cigarettes.

## 5.2 Clinical Implications

In sum, short-term use of e-cigarettes appears to result in less severe physiological changes than those observed with traditional cigarettes. While this seems to indicate that e-cigarettes are a safer alternative to traditional cigarettes, they are certainly not benign and it is of the utmost importance that their long-term effects be examined. Based on these results, e-cigarettes may be a viable option for smoking cessation with the help of healthcare professionals though it is important the e-cigarettes do not simply become the new smoking, as their long-term effects do remain unknown.

# 6.0 REFERENCES


1. *Tobacco Factsheet*. 2017; Available from: http://www.who.int/mediacentre/factsheets/fs339/en/.
2. Messner, B. and D. Bernhard, *Smoking and Cardiovascular Disease: Mechanisms of Endothelial Dysfunction and Early Atherogenesis.* Arteriosclerosis, Thrombosis, and Vascular Biology, 2014. **34**(5): p. 509-515.
3. *How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease: A Report of the Surgeon General*. 2010, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health.
4. *The Health Consequences of Smoking—50 Years of Progress: A Report of the Surgeon General.* 2014, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health.
5. Lim, S., et al., *A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010.* The Lancet, 2012. **380**(9859): p. 2224-2260.
6. *Preventing Tobacco Use Among Youth and Young Adults: A Report of the Surgeon General.* 2012, U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health.
7. Reid, J., et al., *Tobacco Use in Canada: Patterns and Trends, 2017 Edition*. 2017, Propel Centre for Population Health Impact.
8. Sanford, Z. and L. Goebel, *E-cigarettes: an up to date review and discussion of the controversy.* The West Virginia medical journal, 2014. **110**(4): p. 10-5.
9. Arrazola, R.A., et al., *Tobacco use among middle and high school students - United States, 2011-2014.* MMWR. Morbidity and mortality weekly report, 2015. **64**(14): p. 381-5.
10. Singh, T., et al., *Tobacco use among middle and high school students—United States, 2011–2015.* Morbidity and Mortality Weekly Report 2016. **65**(14): p. 361-367.
11. Abuse, N.I.o.D., *Monitoring the Future Study: Trends in Prevalence of Various Drugs. National Institute on Drug Abuse*. 2016, National Institute on Drug Abuse.
12. *Canadian Tobacco Alcohol and Drugs (CTADS): 2013 summary*. 2013, Government of Canada: Canadian Tobacco, Alcohol and Drugs Survey.
13. Grana, R.A. and P.M. Ling, *"Smoking Revolution" A Content Analysis of Electronic Cigarette Retail Websites.* American Journal of Preventive Medicine, 2014. **46**(4): p. 395-403.
14. Grana, R., N. Benowitz, and S.A. Glantz, *E-Cigarettes A Scientific Review.* Circulation, 2014. **129**(19): p. 1972-1986.
15. Pisinger, C. and M. Dossing, *A systematic review of health effects of electronic cigarettes.* Preventive Medicine, 2014. **69**: p. 248-260.
16. Grana, R., L. Popova, and P. Ling, *A Longitudinal Analysis of Electronic Cigarette Use and Smoking Cessation.* JAMA Internal Medicine, 2014. **174**(5): p. 812-813.
17. Kalkhoran, S. and S.A. Glantz, *E-cigarettes and smoking cessation in real-world and clinical settings: a systematic review and meta-analysis.* Lancet Respiratory Medicine, 2016. **4**(2): p. 116-128.
18. Brown, J., et al., *Real-world effectiveness of e-cigarettes when used to aid smoking cessation: a cross-sectional population study.* Addiction, 2014. **109**(9): p. 1531-1540.

19. Kotz, D., J. Brown, and R. West, *Real-world effectiveness of e-cigarettes when used to aid smoking cessation: a population study.* Addiction, 2014. **109**(3): p. 491-499.
20. McRobbie, H., et al., *Electronic cigarettes for smoking cessation and reduction.* Cochrane Database of Systematic Reviews, 2014(12).
21. Rahman, M.A., et al., *E-Cigarettes and Smoking Cessation: Evidence from a Systematic Review and Meta-Analysis.* Plos One, 2015. **10**(3).
22. Ferrari, M., et al., *Short-term effects of a nicotine-free e-cigarette compared to a traditional cigarette in smokers and non-smokers.* BMC Pulm Med, 2015. **15**: p. 120.
23. McNeill, A., et al., *E-cigarettes: An evidence update. A report comissioned by Public Health England*. 2015, Public Health england.
24. Vardavas, C.I., et al., *Short-term Pulmonary Effects of Using an Electronic Cigarette Impact on Respiratory Flow Resistance, Impedance, and Exhaled Nitric Oxide.* Chest, 2012. **141**(6): p. 1400-1406.
25. Visser, W., et al., *The Health Risks of Using E-Cigarettes*. 2015, National Institute for Public Health and the Environment, Ministry of Health, Welfar and Sport.
26. *Manufacturing Regulations*. 2017.
27. *E-Cigarettes in Canada*. Heart and Stroke Foundation of Canada 2016.
28. *Vaping, e-cigarettes to be regulated by Health Canada: E-cigarettes offer possible benefits for harm reduction, but new rules aim to protect young people*. CBC News 2016.
29. *Vaping and e-cigarette regulations across Canada*. CBC News 2016.
30. *Electronic Cigarette Trade Association*. 2017.
31. Tierney, P.A., et al., *Flavour chemicals in electronic cigarette fluids.* Tobacco Control, 2016. **25**(E1): p. E10-E15.
32. Allen, J.G., et al., *Flavoring Chemicals in E-Cigarettes: Diacetyl, 2,3-Pentanedione, and Acetoin in a Sample of 51 Products, Including Fruit-, Candy-, and Cocktail-Flavored E-Cigarettes.* Environmental Health Perspectives, 2016. **124**(6): p. 733-739.
33. *Flavourings-related lung disease*. 2016, National Institute for Occupational Safety and Health: Respiratory Health Division, Centers for Disease Control and Prevention.
34. Shamseer, L., et al., *Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation.* British Medical Journal, 2015. **349**.
35. Downs, S. and N. Black, *The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions.* Journal of Epidemiology and Community Health, 1998. **52**: p. 377-384.
36. Biostat, *Comprehensive Meta-Analysis Software*. 2015.
37. Cohen, J., *Statistical Power Analysis for the Behavioural Sciences*, ed. 2nd. 1988, Hillsdale, NJ: Erlbaum.
38. Flouris, A.D., et al. *Acute impact of active and passive electronic cigarette smoking on serum cotinine and lung function*. Inhalation toxicology, 2013. **25**, 91-101 DOI: 10.3109/08958378.2012.758197.
39. Flouris, A.D., et al. *Acute effects of electronic and tobacco cigarette smoking on complete blood count*. Food and chemical toxicology : an international journal published for the British Industrial Biological Research Association, 2012. **50**, 3600-3 DOI: 10.1016/j.fct.2012.07.025.
40. Kumral, T.L., et al., *How does electronic cigarette smoking affect sinonasal symptoms and nasal mucociliary clearance?* B-Ent, 2016. **12**(1): p. 17-21.
41. Popa, C., *Infrared spectroscopy study of the influence of inhaled vapors/smoke produced by cigarettes of active smokers.* Journal of Biomedical Optics, 2015. **20**(5).

42. Popa, C., et al., *CO2 LASER-PHOTOACOUSTIC STUDY OF EXHALED BREATH PRODUCED BY ELECTRONIC vs. TRADITIONAL CIGARETTES.* Romanian Reports in Physics, 2015. **67**(3): p. 946-953.
43. Martin, E., et al., *E-cigarette use results in suppression of immune and inflammatory-response genes in nasal epithelial cells similar to cigarette smoke.* Am J Physiol Lung Cell Mol Physiol, 2016: p. ajplung.00170.2016.
44. Moheimani, R.S., et al., *Increased Cardiac Sympathetic Activity and Oxidative Stress in Habitual Electronic Cigarette Users: Implications for Cardiovascular Risk.* JAMA Cardiol, 2017. **2**(3): p. 278-284.
45. Franco, T., et al., *Electronic Cigarette: Role in the Primary Prevention of Oral Cavity Cancer.* Clin Med Insights Ear Nose Throat, 2016. **9**: p. 7-12.
46. Polosa, R., et al., *Effect of Smoking Abstinence and Reduction in Asthmatic Smokers Switching to Electronic Cigarettes: Evidence for Harm Reversal.* International Journal of Environmental Research and Public Health, 2014. **11**(5): p. 4965-4977.
47. Polosa, R., et al., *Persisting Long Term Benefits of Smoking Abstinence and Reduction in Asthmatic Smokers Who Have Switched to Electronic Cigarettes.* Discovery Medicine, 2016. **114**: p. 99-108.
48. Pearson, J.L., et al., *The Moment Study: Protocol for a mixed method observational cohort study of the Alternative Nicotine Delivery Systems (ANDS) initiation process among adult cigarette smokers.* BMJ Open, 2016. **6**(4).
49. Farsalinos, K., et al., *Effect of continuous smoking reduction and abstinence on blood pressure and heart rate in smokers switching to electronic cigarettes.* Internal and Emergency Medicine, 2016. **11**(1): p. 85-94.
50. Carnevale, R., et al., *Acute impact of tobacco versus electronic cigarette smoking on oxidative stress and vascular function.* Chest, 2016.
51. Cooke, W.H., et al., *Acute inhalation of vaporized nicotine increases arterial pressure in young non-smokers: a pilot study.* Clinical Autonomic Research, 2015. **25**(4): p. 267-270.
52. Farsalinos, K.E., et al., *Acute effects of using an electronic nicotine-delivery device (electronic cigarette) on myocardial function: comparison with the effects of regular cigarettes.* Bmc Cardiovascular Disorders, 2014. **14**.
53. Marini, S., et al. *Short-term effects of electronic and tobacco cigarettes on exhaled nitric oxide*. Toxicology and applied pharmacology, 2014. **278**, 9-15 DOI: 10.1016/j.taap.2014.04.004.
54. Schober, W., et al., *Use of electronic cigarettes (e-cigarettes) impairs indoor air quality and increases FeNO levels of e-cigarette consumers.* International Journal of Hygiene and Environmental Health, 2014. **217**(6): p. 628-637.
55. Vansickel, A.R., et al., *A Clinical Laboratory Model for Evaluating the Acute Effects of Electronic "Cigarettes": Nicotine Delivery Profile and Cardiovascular and Subjective Effects.* Cancer Epidemiology Biomarkers & Prevention, 2010. **19**(8): p. 1945-1953.
56. Walele, T., et al., *A randomised, crossover study on an electronic vapour product, a nicotine inhalator and a conventional cigarette. Part B: Safety and subjective effects.* Regulatory Toxicology and Pharmacology, 2016. **74**: p. 193-199.
57. Yan, X.S. and C. D'Ruiz *Effects of using electronic cigarettes on nicotine delivery and cardiovascular function in comparison with regular cigarettes*. Regulatory toxicology and pharmacology : RTP, 2015. **71**, 24-34 DOI: 10.1016/j.yrtph.2014.11.004.
58. Antoniewicz, L., et al., *Electronic cigarettes increase endothelial progenitor cells in the blood of healthy volunteers.* Atherosclerosis, 2016. **255**: p. 179-185.

59. D'Ruiz, C.D., et al., *Measurement of cardiovascular and pulmonary function endpoints and other physiological effects following partial or complete substitution of cigarettes with electronic cigarettes in adult smokers.* Regul Toxicol Pharmacol, 2017. **87**: p. 36-53.
60. O'Connell, G., D.W. Graff, and C.D. D'Ruiz, *Reductions in biomarkers of exposure (BoE) to harmful or potentially harmful constituents (HPHCs) following partial or complete substitution of cigarettes with electronic cigarettes in adult smokers.* Toxicology Mechanisms and Methods, 2016. **26**(6): p. 443-454.
61. Wadia, R., et al., *A pilot study of the gingival response when smokers switch from smoking to vaping.* British Dental Journal, 2016. **221**(11): p. 722-726.
62. Vansickel, A.R., M.F. Weaver, and T. Eissenberg, *Clinical laboratory assessment of the abuse liability of an electronic cigarette.* Addiction, 2012. **107**(8): p. 1493-1500.
63. Yano, Y., et al., *Blood Pressure Reactivity to Psychological Stress in Young Adults and Cognition in Midlife: The Coronary Artery Risk Development in Young Adults (CARDIA) Study.* Journal of the American Heart Association, 2016. **5**(1).
64. *Hearti-Facts: Can smoking harm your heart*. 2016.
65. Okin, P.M., et al., *All-cause and cardiovascular mortality in relation to changing heart rate during treatment of hypertensive patients with electrocardiographic left ventricular hypertrophy.* European Heart Journal, 2010. **31**(18): p. 2271-2279.
66. Haass, M. and W. Kübler, *Nicotine and Sympathetic Neurotransmission.* Cardiovascular Drugs Therapy, 1997. **10**(6): p. 657-665.
67. Pickworth, W., et al., *Sensory and physiologic effects of menthol and non-menthol cigarettes with differing nicotine delivery.* Pharmacology Biochemistry and Behavior, 2002. **7**(1-2): p. 55-61.
68. Hoffman, A., *The health effects of menthol cigarettes as compared to non-menthol cigarettes.* Tobacco Induced Diseases, 2011. **9**(Supplement): p. S7.
69. Moncada, S., R. Palmer, and E. Higgs, *Nitric oxide: physiology, pathophysiology, and pharmacology.* Parmacological Reviews, 1991. **43**(2): p. 109-142.
70. Rytilä, P., et al., *Increased oxidative stress in asymptomatic current chronic smokers and GOLD stage 0 COPD.* Respir Research, 2006. **7**(1): p. 69.
71. Kharitonov, S., et al., *Acute and chronic effects of cigarette smoking on exhaled nitric oxide.* American Journal of Critical Care Medicine, 1995. **152**(2): p. 609-612.
72. Hoyt, J., et al., *Cigarette smoke decreases inducible nitric oxide synthase in lung epithelial cells.* Experimental Lung Research, 2003. **29**(1): p. 17-28.
73. Varughese, S., et al., *Effects of theatrical smokes and fogs on respiratory health in the entertainment industry.* American Journal of Industrial Medicine, 2005. **47**(5): p. 411-418.
74. Wieslander, G., D. Norback, and T. Lindgren, *Experimental exposure to propylene glycol mist in aviation emergency training: acute ocular and respiratory effects. .* Occupational and Environmental Medicine, 2001. **58**(10): p. 649-655.
75. Moline, J., et al., *Health effects evaluation of theatrical smoke, haze and pyrotechnics*. 2000, Equity-League Pension and Health Trust Funds.
76. Benowitz, N.L. and P. Jacob Iii, *Daily intake of nicotine duing cigarette smoking.* Clinical Pharmacology and Therapeutics, 1984. **35**(4): p. 499-504.
77. Ramchandra, R., C. Barrett, and S. Malpas, *Nitric oxide and sympathetic nerve activity in the control of blood pressure.* Clinical and Experimental Pharmacology and Physiology, 2005. **32**(5-6): p. 440-446.
78. Ye, S., H. Zhong, and V. Campese, *Oxidative stress mediates the stimulation of sympathetic nerve activity in the phenol renal injury model of hypertension.* Hypertension, 2006. **48**: p. 309-315.

79. Niedermaier, O., et al., *Influence of cigarette smoking on human autonomic function.* Circulation, 1993. **88**(2): p. 562-571.
80. *E-cigarette flavours pose unknown harm risk*. 2017.
81. Medana, C., et al., *Analysis of nicotine alkaloids and impurities in liquids for e-cigarettes by LC-MS, GC-MS, and ICP-MS.* Spectroscopy, 2016. **14**(2): p. 20-28.

# 7.0 APPENDICES

## 7.1 Appendix A: Data search strategies presented by database

**PubMed**

Build a search library of the relevant search terms.

Create an advanced search, ADD search 1 (e-cigarette terms) with single physiological terms.

Example

Search: (((((((electronic cigarette[Title/Abstract]) OR e-cigarette[Title/Abstract]) OR e-cig[Title/Abstract]) OR electronic nicotine delivery system[Title/Abstract]) OR personal vaporizer[Title/Abstract]) OR personal vapourizer[Title/Abstract])) AND safety

**Web of Science**

Build a search library of e-cigarette terms (#1) using "Title, Abstracts, Keywords"

Create an advanced search combining #1 and single physiological search terms

**Scopus**

Build a search library of the relevant search terms.

Create an advanced search, ADD search 1 (e-cigarette terms) with single physiological terms.

Example

Search: (((((((electronic cigarette[Title/Abstract]) OR e-cigarette[Title/Abstract]) OR e-cig[Title/Abstract]) OR electronic nicotine delivery system[Title/Abstract]) OR personal vaporizer[Title/Abstract]) OR personal vapourizer[Title/Abstract])) AND safety

**The Cochrane Library**

Choose "Title, Abstracts, Keywords" and enter "acute mental stress" as the first set of keywords. Repeat this process

## 7.2 Appendix B: Comprehensive list of search terms

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

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

## 7.3 Appendix C: Additional responses to e-cigarettes

**Table S1.** Other cardiovascular responses to e-cigarettes

| First Author (year) | Nicotine Conc. | Markers | Outcome |
|---|---|---|---|
| **Cooke et al. (2015)** | 18mg | MSNA | ↑ |
| | | VCC | ↓ |
| **Faralinos et al. (2014)** | 11mg | PRP | ↑ |
| | | E | ↑ |
| | | A | ↑ |
| | | E/A | ↓ |
| | | DT | ↑ |
| | | IVRT | ↓ |
| | | IVRTc | ↓ |
| | | Sm | ↑ |
| | | Em | ↑ |
| | | Am | ↑ |
| | | E/Am | ↓ |
| | | E/Em | ↑ |
| | | MPI | ↓ |
| | | MPIt | ↓ |
| | | GS | ↓ |
| | | SRs | ↑ |
| | | SRe | ↑ |
| | | SRa | ↑ |

*Note:* MSNA, muscle sympathetic nerve activity; VCC, vagal cardiac control; LV, left ventricular; LAAD, left atrial antero-posterior diameter; PRP, pressure rate product; E, peak early velocity; A, peak late velocity; E/A, peak ratio; DT, E wave deceleration time; IVRT, isovolumetric relaxation time; IVRTc, corrected to heart IVRT; Sm, systolic peak velocity; Em, Early diastolic peak velocity; Am, late diastolic peak velocity; MPI, myocardial performance index (Doppler flow); MPIt, myocardial performance index (Doppler tissue); GS, end-systolic global strain; SRs, global peak longitudinal systolic strain rate; SRe, early diastolic strain rate; SRa, late diastolic strain rate.
↑, Increase; ↓, Decrease; ↔, No change.

**Table S2.** Other respiratory responses to e-cigarettes

| First Author (year) | Nicotine Conc. | Markers | Outcome |
|---|---|---|---|
| **D'Ruiz et el. (2017)** | 24mg | FEV1 | ↑ |
| | | FVC | ↑ |
| **Ferrari et al. (2015)** | 0mg | FEV1 | ↓ |
| | | FVC | ↓ |
| | | FEV1/FVC | ↓ |
| | | PEF | ↓ |
| | | FEF25 | ↓ |
| | | FEF50 | ↓ |
| | | FEF75 | ↓ |
| | | FeCO | ↔ |
| **Vardavas et al. (2012)** | 11mg | Z5Hz | ↓ |
| | | R5Hz | ↑ |
| | | R10Hz | ↑ |
| | | R20Hz | ↑ |
| | | X5Hz | ↓ |
| | | X10Hz | ↓ |
| | | X20Hz | ↓ |
| | | Peripheral resistance | ↑ |
| | | Central Resistance | ↑ |
| | | Resonant frequency | ↓ |

*Note:* FEV1, Forced expiratory volume in 1 second; FVC, Forced vital capacity; PEF, peak expiratory flow; FEF, forced expiratory flow; FeNO, fractional exhaled nitric oxide; FeCO, fractional exhaled carbon monoxide; eNO, exhaled nitric oxide; eCO, exhaled carbon monoxide; UF2, unflavoured liquid with 2% nicotine; FL2, flavoured liquid with 2% nicotine; Z5Hz, respiratory impedance; R5/10/20Hz, respiratory resistance; X5/10/20Hz, respiratory reactance, Fres., resonant frequency; res., resistance. ↑, Increase; ↓, Decrease; ↔, No change.

**Table S3.** Other responses to e-cigarettes

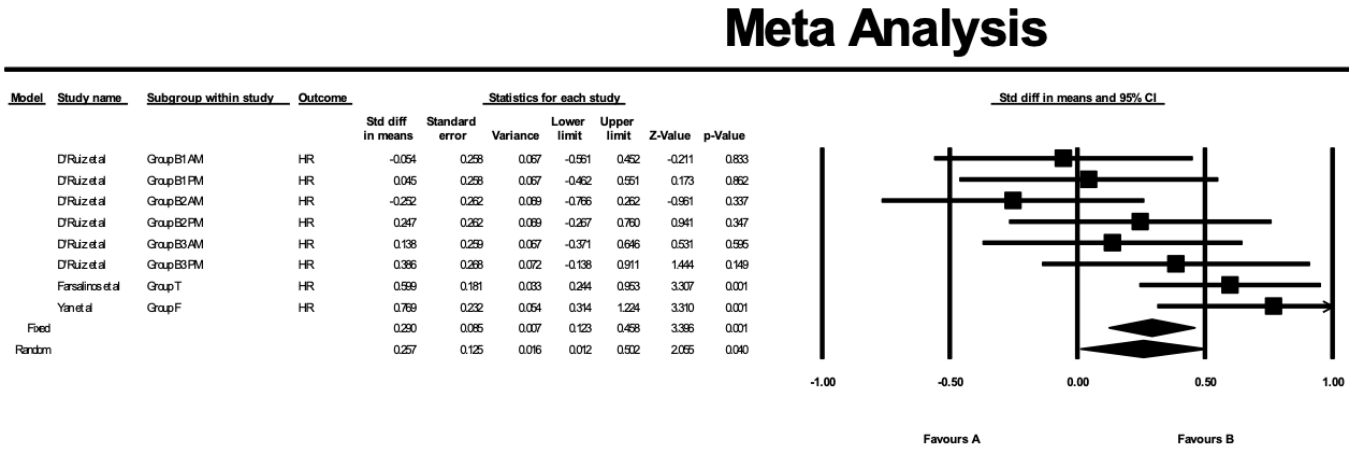
| First Author (year) | Nicotine Conc. | Markers | Outcome |
|---|---|---|---|
| **Antoniewicz et al. (2016)** | 12mg | EPC | ↑ |
| | | MV | ↑ |
| | | CD45 | ↑ |
| | | CD14 | ↑ |
| | | CD14+HMGB1 | ↑ |
| | | CD41 | ↓ |
| | | CD41+HMGB1 | ↑ |
| | | CD41+CD62P | ↑ |
| | | CD41+CD154 | ↑ |
| | | CD144 | ↔ |
| | | CD144+CD62E | ↑ |
| | | SYTO13 | ↓ |
| | | SYTO13+HMGB1 | ↑ |
| **Carnevale et al. (2016)** | 16mg | sNOX2-dp | ↑ |
| | | 8-iso-PGF2α | ↑ |
| | | NO bioavailability | ↓ |
| | | Vitamin E | ↓ |
| | | FMD | ↓ |
| **O'Connell et al. (2016)** | 24mg | NNAL | ↓ |
| | | 3_HPMA | ↓ |
| | | HMPMA | ↓ |
| | | CEMA | ↓ |
| | | 1-OHP | ↓ |
| | | NNN | ↓ |
| | | MHBMA | ↓ |
| | | S-PMA | ↓ |
| **Wadia et al. (2016)** | 18mg | BOP | ↑ |
| | | GCF | ↑ |
| **Walele et al. (2016)** | 2% | WBC | ↔ |
| | | RBC | ↔ |
| | | Hemoglobin | ↔ |
| | | Hematocrit | ↔ |
| | | MCV | ↔ |
| | | MCHC | ↔ |
| | | Lymphocytes | ↔ |
| | | Monocytes | ↔ |

*Note:* sNOX2-dp, serum soluble NOX2-derived peptide; 8-iso-PGF2α, 8-iso-prostaglandin F2α; FMD, flow-mediated dilation; WBC, White blood cells; RBC, red blood cells; MCV, mean corpuscular volume; MCHC, mean corpuscular hemoglobin concentration;
↑, Increase; ↓, Decrease; ↔, No change.

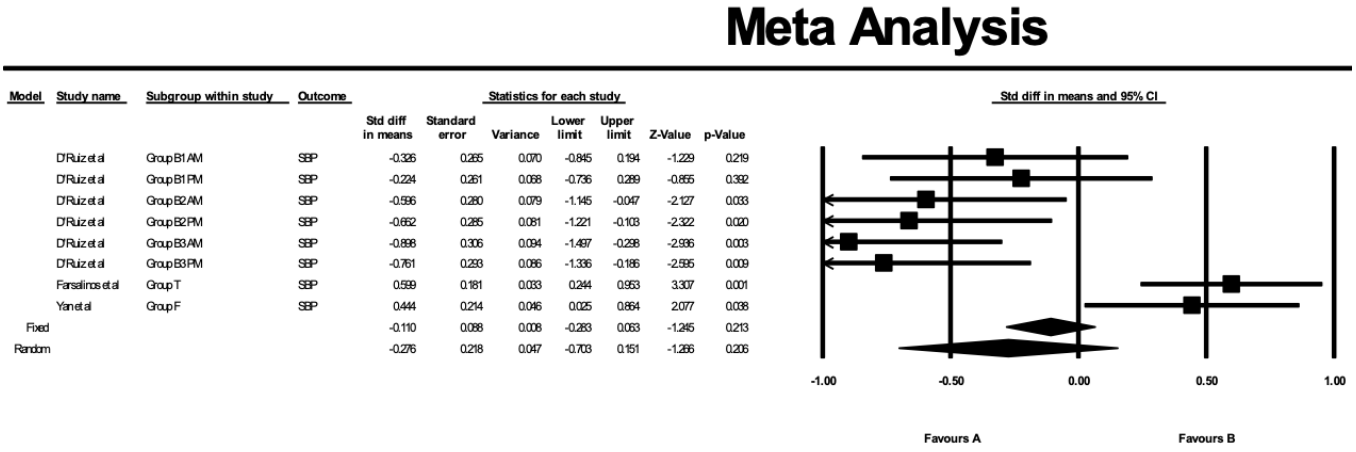
## 7.4 Appendix D: Meta-analysis of effects of traditional cigarettes

**Figure S1.** Cardiovascular effects of traditional cigarettes: a, heart rate; b, systolic blood pressure; c, diastolic blood pressure.

a.



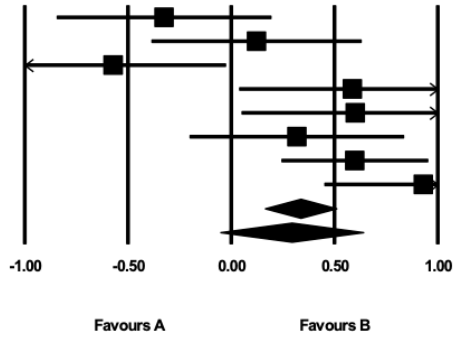

b.



c.

# Meta Analysis

| Model | | Subgroup within study | Std diff in means | Standard error | Variance | Lower limit | Upper limit | Z-Value | p-Value |
|---|---|---|---|---|---|---|---|---|---|
| | D'Ruiz et al | Group B1 AM | -0.325 | 0.265 | 0.070 | -0.844 | 0.194 | -1.227 | 0.220 |
| | D'Ruiz et al | Group B1 PM | 0.123 | 0.259 | 0.067 | -0.385 | 0.630 | 0.473 | 0.636 |
| | D'Ruiz et al | Group B2 AM | -0.572 | 0.279 | 0.078 | -1.118 | -0.026 | -2.053 | 0.040 |
| | D'Ruiz et al | Group B2 PM | 0.587 | 0.280 | 0.078 | 0.039 | 1.135 | 2.099 | 0.036 |
| | D'Ruiz et al | Group B3 AM | 0.601 | 0.281 | 0.079 | 0.051 | 1.151 | 2.142 | 0.032 |
| | D'Ruiz et al | Group B3 PM | 0.318 | 0.265 | 0.070 | -0.201 | 0.837 | 1.201 | 0.230 |
| | Farsalinos et a | Group T | 0.599 | 0.181 | 0.033 | 0.244 | 0.953 | 3.307 | 0.001 |
| | Yan et al | Group F | 0.930 | 0.244 | 0.060 | 0.452 | 1.409 | 3.808 | 0.000 |
| Fixed | | | 0.336 | 0.088 | 0.008 | 0.163 | 0.508 | 3.817 | 0.000 |
| Random | | | 0.293 | 0.176 | 0.031 | -0.052 | 0.638 | 1.664 | 0.096 |




**Meta Analysis**

## 7.5 Appendix E: Physiological effects of traditional cigarettes

**Table S4.** Cardiovascular effects of traditional cigarettes

| First Author (year) | Nicotine Conc. | Markers | Outcome |
|---|---|---|---|
| **Farsalinos et al. (2014)** | 1mg | HR | ↑ |
| | | SBP | ↑ |
| | | DBP | ↑ |
| | | PRP | ↑ |
| | | E | ↓ |
| | | A | ↑ |
| | | E/A | ↓ |
| | | DT | ↑ |
| | | IVRT | ↑ |
| | | IVRTc | ↑ |
| | | Sm | ↑ |
| | | Em | ↓ |
| | | Am | ↑ |
| | | E/Am | ↓ |
| | | E/Em | ↑ |
| | | MPI | ↑ |
| | | MPIt | ↑ |
| | | GS | ↑ |
| | | SRs | ↓ |
| | | SRe | ↓ |
| | | SRa | ↑ |
| **Vansickel et al. (2010)** | Own brand | HR | ↑ |
| **Yan et al. (2015)** | 0.8mg | HR | ↑ |
| | | SBP | ↑ |
| | | DBP | ↑ |

*Note:* HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; MSNA, muscle sympathetic nerve activity; VCC, vagal cardiac control; LV, left ventricular; LAAD, left atrial antero-posterior diameter; PRP, pressure rate product; E, peak early velocity; A, peak late velocity; E/A, peak ratio; DT, E wave deceleration time; IVRT, isovolumetric relaxation time; IVRTc, corrected to heart IVRT; Sm, systolic peak velocity; Em, Early diastolic peak velocity; Am, late diastolic peak velocity; MPI, myocardial performance index (Doppler flow); MPIt, myocardial performance index (Doppler tissue); GS, end-systolic global strain; SRs, global peak longitudinal systolic strain rate; SRe, early diastolic strain rate; SRa, late diastolic strain rate.
↑, Increase; ↓, Decrease; ↔, No change.

**Table S5.** Respiratory effects of traditional Cigarettes

| First Author (year) | Nicotine Conc. | Markers | Outcome |
|---|---|---|---|
| **Ferrari et al. (2015)** | 0.8mg | FEV1 | ↓ |
| | | FVC | ↓ |
| | | FEV1/FVC | ↓ |
| | | PEF | ↓ |
| | | FEF25 | ↓ |
| | | FEF50 | ↓ |
| | | FEF75 | ↓ |
| | | FeNO | ↔ |
| | | FeCO | ↑ |
| **Marini et al. (2014)** | Own brand | eNO | ↓ |
| **Vansickel et al. (2010)** | 1.06mg | eCO | ↑ |
| **Walele et al. (2016)** | 0.6mg | eCO | ↑ |
| **Yan et al. (2015)** | 0.8mg | eCO | ↑ |

*Note:* FEV1, Forced expiratory volume in 1 second; FVC, Forced vital capacity; PEF, peak expiratory flow; FEF, forced expiratory flow; FeNO, fractional exhaled nitric oxide; FeCO, fractional exhaled carbon monoxide; eNO, exhaled nitric oxide; eCO, exhaled carbon monoxide; UF2, unflavoured liquid with 2% nicotine; FL2, flavoured liquid with 2% nicotine; Z5Hz, respiratory impedance; R5/10/20Hz, respiratory resistance; X5/10/20Hz, respiratory reactance, Fres., resonant frequency; res., resistance.
↑, Increase; ↓, Decrease; ↔, No change.

**Table S6.** Other responses of traditional cigarettes

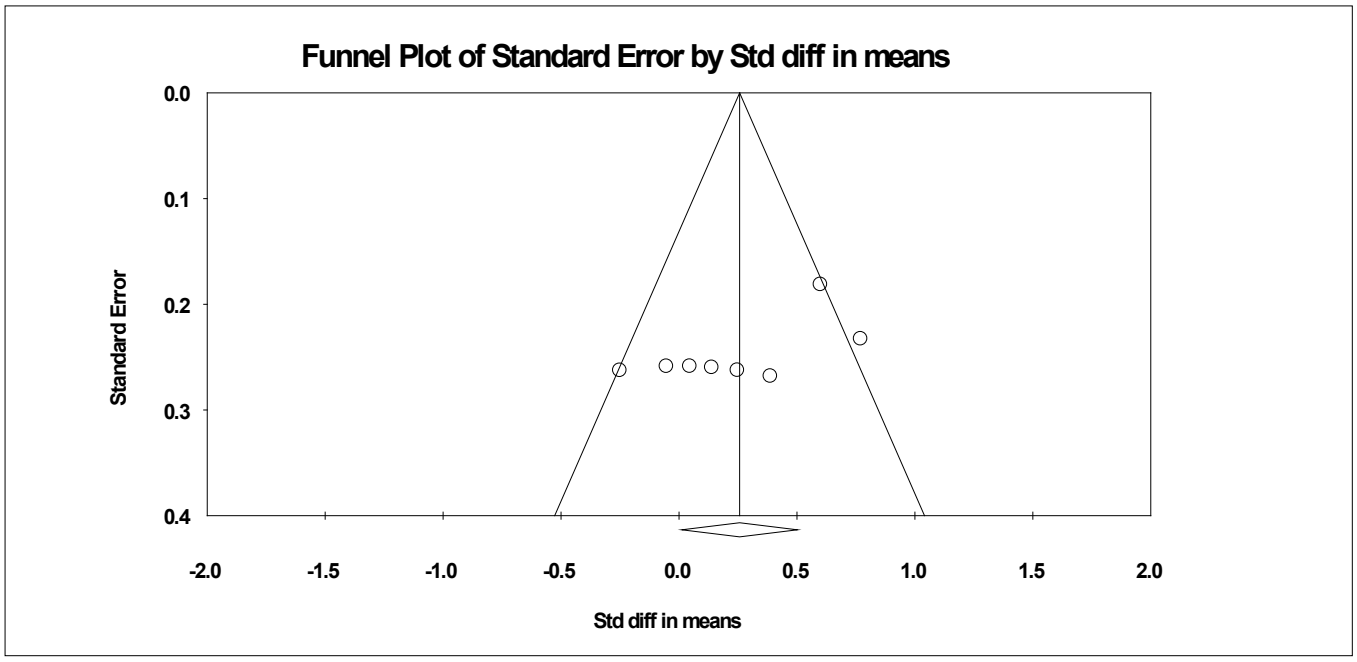
| First Author (year) | Nicotine Conc. | Markers | Outcome |
|---|---|---|---|
| **Carnevale et el. (2016)** | 0.6mg | sNOX2-dp | ↑ |
| | | 8-iso-PGF2α | ↑ |
| | | NO bioavailability | ↓ |
| | | Vitamin E | ↓ |
| | | FMD | ↓ |
| **Walele et al. (2016)** | 0.6mg | Lymphocytes | ↔ |
| | | Monocytes | ↔ |

*Note:* sNOX2-dp, serum soluble NOX2-derived peptide; 8-iso-PGF2α, 8-iso-prostaglandin F2α; FMD, flow-mediated dilation; WBC, White blood cells; RBC, red blood cells; MCV, mean corpuscular volume; MCHC, mean corpuscular hemoglobin concentration;
↑, Increase; ↓, Decrease; ↔, No change.

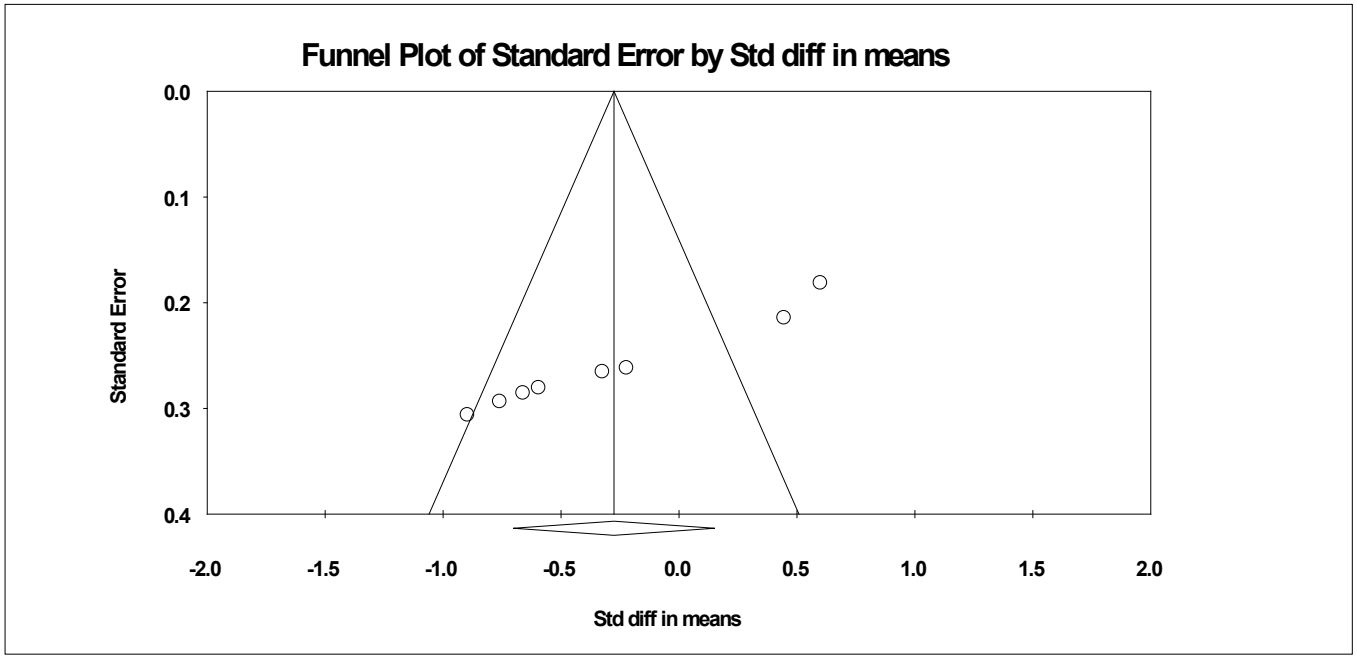
## 7.6 Appendix F: Funnel plots for traditional cigarettes

**Figure S2.** Funnel plots for traditional cigarettes: a, heart rate; b, systolic blood pressure; c, diastolic blood pressure.

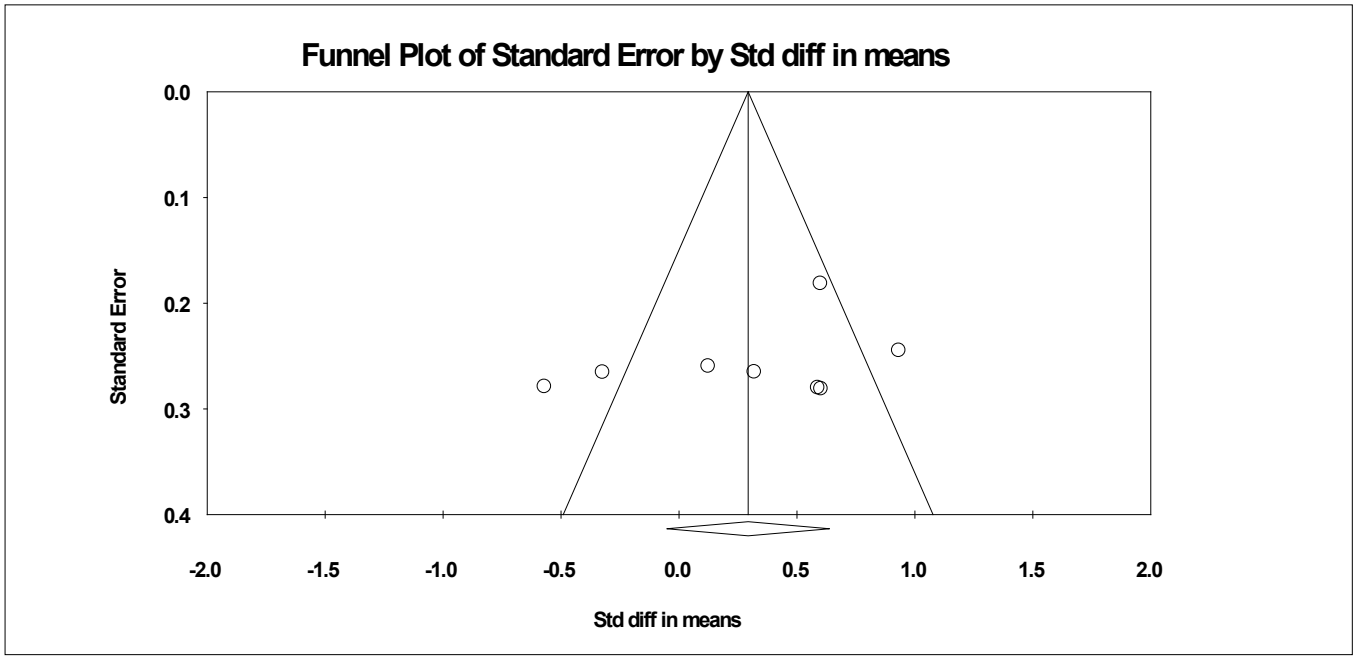
*a.*




*b.*



*c*.


Funnel Plot of Standard Error by Std diff in means
Standard Error
0.0
0.1
0.2
0.3
0.4
-2.0
-1.5
-1.0
-0.5
0.0
0.5
1.0
1.5
2.0
Std diff in means