Heart

The cardiovascular health effects of vaping e-cigarettes: A systematic review and meta-analysis.

Journal:	*Heart*
Manuscript ID	heartjnl-2024-325030.R3
Article Type:	Systematic review
Date Submitted by the Author:	n/a
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Keywords:	

Abstract:	Background There is substantial interest in the cardiovascular effects of e-cigarette use, highlighting the need to update our knowledge on the subject. We conducted this review to analyze whether e-cigarette use increases cardiovascular health risks and how these risks vary among different populations. Methods We searched six databases and included peer-reviewed human, animal, cell/in vitro original studies but excluded qualitative studies, which were published between July 2021 and December 2023. Three types of e-cigarette exposure were examined: acute, short-to-medium term, and long-term. Different risk of bias tools were used for assessing quality of the included human studies and we conducted meta-analysis when possible. Results We included 63 studies in the main analysis, 12 studies in the meta-analysis, and 32 studies in the socio-demographic factor-based subgroup analysis. Over half of the human studies had low risk of bias. Acute exposure to e-cigarette was associated with increased heart rate (HR) (MD 11.329, $p<0.01$) and blood pressure (BP) (MD 12.856, $p<0.01$ for systolic; MD 7.676, $p<0.01$ for diastolic) compared to non-use. While HR was lower after acute exposure to e-cigarettes compared to cigarettes (MD -5.415, $p<0.01$), no significant difference in systolic or diastolic BP was observed. Non-smoker current vapers had no significant differences in resting HR and BP compared to non-users, but lower resting HR (MD -

	2.608, p<0.01) and diastolic BP (MD -3.226, p<0.01) compared to non-vaper current smokers. Despite some association between e-cigarette and endothelial dysfunction, short-to-medium term transition from cigarettes to e-cigarettes may improve blood flow and BP, particularly among females and younger individuals. There is lack of evidence supporting any association of e-cigarette use with cardiovascular diseases, and cardiac dysfunction or remodelling. Conclusions This review highlighted several important cardiovascular impacts of e-cigarette use compared to non-use and cigarette smoking. However, the evidence is still limited and requires future research.

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Title: The cardiovascular health effects of vaping e-cigarettes: A systematic review and meta-analysis.

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ABSTRACT

Background

There is substantial interest in the cardiovascular effects of e-cigarette use, highlighting the need to update our knowledge on the subject. We conducted this review to analyze whether e-cigarette use increases cardiovascular health risks and how these risks vary among different populations.

Methods

We searched six databases and included peer-reviewed human, animal, cell/*in vitro* original studies but excluded qualitative studies, which were published between July 2021 and December 2023. Three types of e-cigarette exposure were examined: acute, short-to-medium term, and long-term. Different risk of bias tools were used for assessing quality of the included human studies and we conducted meta-analysis when possible.

Results

We included 63 studies in the main analysis, 12 studies in the meta-analysis, and 32 studies in the socio-demographic factor-based subgroup analysis. Over half of the human studies had low risk of bias. Acute exposure to e-cigarette was associated with increased heart rate (HR) (MD 11.329, $p<0.01$) and blood pressure (BP) (MD 12.856, $p<0.01$ for systolic; MD 7.676, $p<0.01$ for diastolic) compared to non-use. While HR was lower after acute exposure to e-cigarettes compared to cigarettes (MD -5.415, $p<0.01$), no significant difference in systolic or diastolic BP was observed. Non-smoker current vapers had no significant differences in resting HR and BP compared to non-users, but lower resting HR (MD -2.608, $p<0.01$) and diastolic BP (MD -3.226, $p<0.01$) compared to non-vaper current smokers. Despite some association between e-cigarette and endothelial dysfunction, short-to-medium term transition from cigarettes to e-cigarettes may

improve blood flow and BP, particularly among females and younger individuals. There is lack of evidence supporting any association of e-cigarette use with cardiovascular diseases, and cardiac dysfunction or remodelling.

Conclusions

This review highlighted several important cardiovascular impacts of e-cigarette use compared to non-use and cigarette smoking. However, the evidence is still limited and requires future research.

PROSPERO registration: CRD42023385632

Keywords: Blood vessels, Heart, Electronic nicotine delivery systems, Vaping, Meta-analysis.

INTRODUCTION

The popularity of electronic cigarette or e-cigarette increased significantly among youth and young adults in the past decade.[1,2] From 2013 to 2020, the prevalence of e-cigarette use in the past 30 days increased across all Canadians, with youth and young adults experiencing more than a fourfold increase.[2] A similar increase in e-cigarette use was also observed in the United States (US),[1] raising questions about the potential impact of e-cigarettes on cardiovascular health.

It is well known that smoking cigarettes is one of the principal risk factors of atherosclerosis, coronary heart disease, stroke and peripheral vascular disease.[3] Several reviews have been published in the recent years summarizing different cardiovascular health effects of e-cigarette use.[4–6] The 2018 National Academics of Science, Engineering, and Medicine review concluded that e-cigarette use results in acute endothelial cell dysfunction and acute increase in heart rate (HR).[4] While acute increase in HR and blood pressure (BP) was also showed in a meta-analysis, it also suggested that switching from cigarette to e-cigarette might improve BP.[6] The recently published 2022 McNeill et al. review focused on biomarker-based assessment of cardiovascular health impacts of vaping e-cigarettes with special attention to effects on HR, BP, and vascular blood flow.[5] Another recent review reported association of e-cigarette use with increased HR, BP, and oxidative stress in healthy individuals.[7] As the research on the health effects of vaping are still emerging, findings are constantly being updated and given the new findings, there is a need for conducting an updated review. Besides, in addition to looking into overall cardiovascular effects, it is also important to compare these effects between different subgroups, which was not explored by previous reviews.[4,5] Hence, we conducted this review with the purpose of providing insights into both the immediate and long-term impacts of e-cigarette exposure, and whether these changes varied in magnitude by different population subgroups.

METHODS

This review was conducted as a part of the "Vaping and Electronic Cigarette Toxicity Overview and Recommendations (VECTOR)" project aimed to evaluate various health risks of e-cigarette use. The protocol of this review was prospectively registered on the PROSPERO (CRD42023385632) and we followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline.[8] We formulated three research questions:

1. Does e-cigarette use increase cardiovascular health risk?
2. How does this risk differ in different e-cigarette users (people who vape, but do not smoke; people who quit smoking, but have continued vaping; and people who are both smoking and vaping (dual use)) compared to people who neither smoke or vape; and people who smoke, but do not vape?
3. Do the risks differ by age groups, sex, gender, sexual orientation, race, ethnicity, indigenous identity, pregnant/postpartum, education level, individual or household income, employment status, and occupation?

Search strategy and selection criteria

We searched CINAHL, Embase, MEDLINE, PsycINFO, PubMed and Cochrane library databases in Jan 2023 and updated it in Jan 2024. As the 2022 McNeill et al. review[5] included studies until June 2021, we limited our search between July 2021 and December 2023. Detailed search strategies are presented in the Supplementary File 1. However, for updating several meta-analyses of the 2022 McNeill et al. review,[5] we collected the studies (n=8)[9–16] that were included in those meta-analyses.[5] As the 2022 McNeill et al. review did not conduct any socio-

demographic factor-based subgroup analysis, we reviewed the 427 original studies of that review[5] to assess their eligibility for subgroup analysis.

We included studies that assessed the cardiovascular health effects from nicotine e-cigarette exposure in either humans, cell/*in vitro* (i.e., human or animal), or animals. Only peer-reviewed studies published in English or French language were included. We excluded qualitative studies, literature reviews, studies evaluating effects of cannabis vapour exposure or exposure to heated or other tobacco products. From the 427 studies of the 2022 McNeill et al. review,[5] we included studies if they assessed cardiovascular health effects in different subgroups under research question 3. We also included single-sex studies, or any case reports in the sex-based subgroup analysis. Title and abstract screening and full text screening were conducted by two independent reviewers and disagreements were resolved by discussion.

Data collection, synthesis and meta-analysis

A custom-made data extraction form was developed, and the detailed data items are presented in Supplementary File 2 and 3. We assessed the health effects of 3 types of e-cigarette exposure: acute (one-off exposure to 7 days), short to medium term (8 days to 12 months), and long-term exposure (more than 12 months). No exposure type was determined for cross-sectional studies. For consistency, we categorized the comparison groups according to their frequency of exposure. For example, current vaping was defined as any use within the past 30 days. The comparison groups were non-smoker current vapers, never smoker current vapers, former smoker current vapers, dual users of cigarettes and e-cigarettes, non-vaper current smokers, never vaper current smokers, former vaper current smokers, non-users, and never users. One reviewer extracted data, and another reviewer checked for accuracy for all finally included studies.

We conducted meta-analyses of the human studies if the studies had consistent comparison groups, same study design, and clear definition of the exposure received. Otherwise, we followed a narrative synthesis approach. Supplementary File 4 shows the list of the studies that were included in the meta-analyses. We tried to contact the authors of four studies[17–20] for additional data. Although we received a response from the authors of one study,[17] due to non-response from other authors we could not include the study in the meta-analysis. Detailed methodology of the meta-analysis is presented in Supplementary File 5. As part of patient and public involvement, we planned to share our findings with the stakeholders at the end of the review.

Quality Assessment

Various risk of bias assessment tools for quality assessment of individual human studies were applied independently by two reviewers and any disagreements were resolved by discussion. We did not assess the quality of the cell/*in vitro* and animal studies. For different tools, we assigned a final rating of 'low', 'moderate'/'some concerns', 'serious'/'high', or 'critical'/'very high' risk of bias to each individual study. Detail quality assessment methodology is presented in Supplementary File 6.

RESULTS

As part of the VECTOR systematic review, we retrieved a total of 5,125 articles from the databases following removing the duplicates. From these articles we finally included 63 studies[17–79] in this review. Additionally, from the 427 studies of the 2022 McNeill et al. review,[5] we selected 7 studies[80–86] for the subgroup analysis and 8 studies for meta-analyses.[9–16] The detailed study selection process is presented in the PRISMA flow diagrams (Figure 1).

We categorized the cardiovascular health outcomes into 5 main categories: effect on heart rate, blood pressure and hypertension, cardiovascular diseases, endothelial/vascular dysfunction, and

cardiac dysfunction and remodelling, of which endothelial/vascular dysfunction was the most investigated outcome (n=24, 38%) (Table 1). We included 12 studies in meta-analyses to assess effect on HR and BP, combining studies from our review (n=4)[25,39,66,70] and those from the 2022 McNeill et al. review[5] (n=8).[9–16] A total of 32 studies[21,29,33,35,37–40,42,44,45,47,51–55,57,59–61,63,69,74,76,80–86] were included in the subgroup analysis, of which 94% (n=30) assessed sex-based differences. Characteristics of individual studies are presented in Supplementary File 2 and 3.

Table 1. Summary statistics of included studies examining cardiovascular effects of vaping e-cigarettes (N=63).

Characteristics	No. of studies, n (%)
Outcomes/health condition(s)	
Effect on heart rate	12 (19)
Effect on blood pressure and hypertension	20 (32)
Cardiovascular disease	23 (37)
Endothelial/vascular dysfunction	24 (38)
Cardiac dysfunction and remodelling	10 (16)
Country	
The United States	45 (71)
Canada	1 (2)
European countries	12 (19)
Others	5 (8)
Type of exposure[a]	
Acute	26 (41)
Short-to-medium	12 (19)
Long	7 (11)
Study design[b]	
RCT/cross-over trials	6 (10)
Non-randomized experimental	6 (10)
Longitudinal observational	6 (10)
Cross-sectional	18 (29)
Case reports	2 (3)
Animal studies	21 (33)
In vitro/cell studies	9 (14)
No. of participants (human studies only, n= 38)	
<100	14 (37)
100-1000	8 (21)

1001-10,000	4 (11)
>10,000	12 (32)
Age of the participants (human studies only, n=38)	
≤18 years	1 (3)
>18 years	37 (98)
Risk of bias (human studies only, n=38)	
Low	21 (55)
Moderate/Some Concerns	12 (32)
High/Serious/Critical	5 (13)
Association with Tobacco companies	
Yes	2 (3)
No	57 (91)
Not Specified	4 (6)
Subgroup analysis (N=32) [c]	
Age	5 (16)
Sex	30 (94)
Race/Ethnicity	2 (6)
Income	2 (6)
Education	1 (3)
Occupation	1 (3)
Pregnancy (embryonic)	1 (3)

[a] For cross-sectional studies, no type of exposure was determined.
[b] Several studies (n=5) had used multiple study designs.
[c] Subgroup analysis included studies from both this review (n= 25) and the 2022 McNeill et al. review (n=7).

Quality assessment

Of the 38 human studies,[17–45,65–73] 21 (55.3%) had low risk of bias,[19,21–23,26,30,33–35,37–40,43–45,67,69,70,72,73] (Table 1, Supplementary File 7). Of the studies that had high risk of bias (n=5), one was a cross-over trial examining effect on heart rate and blood pressure,[25] and four were non-randomized experimental studies.[27–29,32] Two studies were funded by tobacco comapnies,[48,72] while any association with tobacco industries could not be determined for four studies[19,36,40,42].

Effect on heart rate

3 cross-over trials,[23–25] 4 non-randomized experimental studies,[26,27,32,66] 3 cross-sectional studies,[39,42,70] and 2 animal studies[51,62,76] addressed the impacts e-cigarette exposure on HR. All trial studies found that acute exposure to e-cigarettes significantly (p<0.01) increased HR compared to non-use.[23–27,32,66] The increase in HR following acute exposure to e-cigarettes was often similar to that of smoking cigarettes.[25,27,32]

We conducted meta-analyses comparing first HR following acute exposure of e-cigarette and non-use based on 5 studies[9,12,13,25,66] and acute exposure of e-cigarettes and cigarettes based on 5 studies.[9–11,25,66] Acute exposure to e-cigarette raised HR significantly compared to that of non-use (mean difference (MD) 11.329; 95% CI 5.528, 17.130; p <0.01; I^2 97%; N=286) (Fig 2). However, this increase in HR was lower than that of cigarettes (MD -5.415; 95% CI -9.094, -1.737; p <0.01; I^2 52%; N=264). Sensitivity analyses findings were insignificant, and details are provided in Supplementary File 8.

The pooled analysis of 4 studies,[14,15,39,70] showed that non-smoker current vapers had lower resting HR than non-users, although there was no statistically significant difference (MD -2.232; 95% CI -7.733, 3.269; p =0.43; I^2 96%; N=286) (Fig 3). However, we found statistically significant lower resting HR in non-smoker current vapers compared to non-vaper current smokers (MD -2.608; 95% CI -4.423, -0.794; p <0.01; I^2 0%; N=409) in an analysis of 3 studies.[14,15,39] Sensitivity analyses findings were insignificant (Supplementary File 8).

Effect on blood pressure and hypertension

Two RCTs,[21,22] 2 cross over trials,[23,25] 3 nonrandomized experimental studies,[27,32,66] 5 cross-sectional studies[35,39,42,67,70], and 3 animal studies[47,53,76] investigated the association between e-cigarette exposure and BP. The RCTs found that transitioning from cigarette to e-cigarette use

was associated with significant improvements in BP following both acute (F=4.24, p<0.001)[22] and short-to-medium-term (β=1.74, p=0.001)[21] exposure. Among other human studies, six studies[25,27,32,35,66,70] found significant (p<0.05) increases in BP following acute exposure or increases in resting BP among non-smoker current vapers. Additionally, 3 longitudinal observational studies,[20,33,34] and 3 cross-sectional studies[19,37,67] assessed the risk of HTN in e-cigarette users. The findings were widely variable between studies.

The pooled analysis of 5 studies[9,12,13,25,66] showed significantly increased systolic and diastolic BP following acute exposure to e-cigarette compared to non-use (MD 12.856; 95% CI 7.413, 18.300; p <0.01; I^2 88%; N=286 and MD 7.676; 95% CI 5.156, 10.197; p <0.01; I^2 89%; N=286 respectively) (Fig 4). However, no statistically significant differences in systolic or diastolic BP were found when compared to acute exposure to cigarettes (MD 0.677; 95% CI -2.111, 3.465; p =0.63; I^2 14%; N=256 and MD -0.691; 95% CI -3.419, 2.037; p =0.62; I^2 54%; N=256 respectively) in an analysis of 5 studies.[9,10,16,25,66] Sensitivity analyses findings were insignificant (Supplementary File 8).

In case of resting BP, no statistically significant difference was seen in either systolic or diastolic BP between non-smoker current vapers and non-users (MD 1.101; 95% CI -3.236, 5.438; p =0.62; I^2 64%; N=286 and MD 0.131; 95% CI -1.431, 1.692; p =0.87; I^2 0%; N=286 respectively) in the pooled analysis of 4 studies[14,15,39,70] (Fig 5). When compared to non-vaper current smokers, the pooled analysis of 3 studies[14,15,39] showed that non-smoker current vapers had slightly lower resting systolic and diastolic BP, (MD -3.059; 95% CI -8.947, 2.829; p =0.31; I^2 76%; N=409 and MD -3.226; 95% CI -5.593, -0.858; p <0.01; I^2 43%; N=409 respectively), although only the difference in diastolic BP was statistically significant. Details of the sensitivity analyses are provided in Supplementary File 8.

The narrative review findings on cardiovascular diseases (CVDs), endothelial/vascular dysfunction, and cardiac dysfunction and remodelling, and subgroup findings are presented in Supplementary File 9.

DISCUSSION

This review highlighted several important findings on the cardiovascular health impacts of e-cigarette exposure. First, we found that acute exposure to e-cigarette increased HR and BP compared to non-use (Fig 2 and 4). Similar to cigarettes, e-cigarettes mostly contain nicotine, which was found to be responsible for increasing sympathetic activity, hence causing an increase in heart rate and blood pressure in several studies.[87,88] It is worth noting that the 2022 McNeill et al. meta-analyses[5] which only included 3 studies[9,12,13] did not find these effects. Adding 2 more studies[25,66] for a total of 5 studies[9,12,13,25,66] in our meta-analyses revealed that acute exposure to e-cigarettes does increase HR and BP. These updated results are supported by several other studies[23,24,26,27,32] and previous meta-analysis evidence.[89] Additionally, compared to cigarettes, acute exposure to e-cigarette was associated with significantly lower HR but similar BP effects (Fig 2 and 4), aligning with the 2022 McNeill et al.[5] and other previous meta-analyses.[90] Second, while non-smoker current vapers showed no significant difference in resting HR and BP compared to non-users, they had lower resting HR and diastolic BP compared to non-vaper current smokers (Fig 3 and 5). Although not statistically significant, the difference in systolic BP was nearly the same as that of diastolic BP in non-smoker current vapers compared to non-vaper current smokers (Fig 5). These findings align with the 2022 McNeill et al. meta-analyses.[5] Our findings were also supported by a recently published systematic review which concluded that acute exposure to e-cigarettes increases HR and BP, however switching from cigarettes to e-cigarettes might reduce both measures.[7] Furthermore, none of the included studies in the meta-

analyses showed resting HR and BP within the range of clinical HTN or tachycardia (Fig 3 and 5). Findings from the longitudinal data[20,33,34] also did not support any incident risk of HTN among non-smoker current vapers. Hence, it seems that e-cigarette use might increase HR and BP only transiently, but apparently have no lasting effect on resting measures. This finding was also reflected in one of the non-randomized experimental studies.[66] Still, future meta-analyses should be conducted to explore long-term effects of e-cigarette use on the risk of HTN.

Third, although we did not find any significant risk of CVDs among non-smoker current vapers (Supplementary File 9), a meta-analysis to assess the relative and absolute risk in this group was not possible, highlighting the need for future longitudinal studies. Additionally, the studies on CVDs were highly heterogeneous, and the limited number of studies for each outcome and population (e.g., dual users, former smoker current vapers) prevented us from reaching a definitive conclusion. Fourth, switching from cigarettes to e-cigarettes was found to have significant cardiovascular benefits by improving blood flow and BP following short-to-medium term exposure, particularly among females and younger people (Supplementary File 9). Although these findings came from a single RCT,[21] it matches with another RCT[80] included in the 2022 McNeill et al. review.[5] Fifth, there is evidence that e-cigarette exposure is associated with endothelial/vascular dysfunction, and some evidence of association with cardiac dysfunction and remodelling (Supplementary File 9). A previous review suggested that e-cigarette aerosol contains acrolein metabolites, which can cause oxidative stress, endothelial dysfunction, and inflammatory responses.[91] Although acrolein metabolite levels are lower in e-cigarette users than in cigarette smokers,[92] the association between e-cigarette use and endothelial or cardiac dysfunction requires thorough investigation through RCTs and longitudinal studies.

We observed several methodological challenges and research gaps in the included studies, which need further attention. Several studies defined their population as current vapers,[38,40–42,67,69] without clearly distinguishing their smoking status. It might be inappropriate and misinformative to the audience to indicate cardiovascular risk in current vapers, whereas these effects might be from smoking cigarettes rather than e-cigarettes. In addition, to get a comprehensive idea about cardiovascular effects, it is important to examine the risks not only in non-smoker current vapers, but in former smoker current vapers and dual users compared to both non-users and non-vaper current smokers. These findings will inform whether e-cigarettes could be suggested as a safer alternative to smoking cigarettes. Furthermore, we detected only 7 studies[17,20,30,31,33,34,45] assessing long-term e-cigarette use, with the longest follow-up being 6 years,[30,31] which is insufficient to observe long-term cardiovascular complications like CVDs.[93] Therefore, more longitudinal observational and experimental studies with extended follow-ups are needed to assess early signs of cardiac or vascular malfunctions. Finally, most studies did not account for the impact of socio-demographic determinants on health effects. Aside from finding that switching from cigarettes to e-cigarettes in the short-to-medium term provided greater cardiovascular benefits for females and younger adults, our subgroup analysis was inconclusive. Future research should focus on assessing the cardiovascular effects of e-cigarette use in diverse socio-demographic populations.

Our review has limitations. First, several of our meta-analyses were limited by high heterogeneity, which is probably due to low number of the included studies (n=3-5).[94] As heterogeneity is important for the reliability and interpretability,[95] the findings of our meta-analyses should be updated in the future by adding similar studies and examining impact on heterogeneity. Second, we could not assess publication bias in our meta-analyses because each

analysis included fewer than 10 studies.[96] Third, while we aimed to examine cardiovascular risks in dual users and former smoker current vapers, we were unable to conduct any meta-analysis in these groups, which should be explored by future reviews. Fourth, we limited our academic database search strategy for papers published following the 2022 McNeill et al. review.[5] However, we also included studies from their review into meta-analyses (n=8) and subgroup analyses (n=7). It allowed us to update their findings[5] instead of conducting a full cumulative review. Although there are some methodological differences, for example, the 2022 McNeill et al. review[5] mostly defined non-use as not using cigarettes or e-cigarettes in the past 6 months, and daily or almost daily use as current use, while we defined our comparison groups differently to reflect the definition of current use (use in the past 30 days) that were used in the majority of the studies. Hence, these differences should be kept in mind while comparing our findings with the 2022 McNeill et al. review.[5]

CONCLUSIONS

This review found some evidence of cardiovascular health risk of e-cigarette use, particularly increase in HR and BP, and some evidence of endothelial dysfunction. Although some of these risks from acute exposure to e-cigarettes were similar to that of cigarettes, the resting measures were often lower than resulting from smoking cigarettes. However, long-term evidence of impact of e-cigarette exposure on cardiovascular health, particularly different cardiovascular conditions and functions is still limited. Hence, future researchers should conduct rigorously designed clinical trials and longitudinal studies in diverse populations and varied global contexts. Additionally, guidance to clinicians should encourage screening e-cigarette users for early signs of cardiovascular conditions, and public health campaigns are needed to raise awareness of cardiovascular risks among younger populations.

Acknowledgements: We thank Dr. Peter Selby and his Nicotine Dependence Services team at Centre for Addiction and Mental Health, Toronto, Canada for their assistance in funding acquisition, reviewing protocol of the review, and knowledge translation. We also acknowledge Karolina Urbanovich, Bayley Levy, Albana Isai, Rachel Foy, Chang Gao for their assistance in data extraction.

Author contributions: AK, AF, NAZ, MS, KS, SiS contributed to the collection and/or assembly of data. AK conducted data analysis and interpretation, drafting of the manuscript, and project administration. RS and MC were responsible for research concept and design, and supervision. All authors contributed to the critical revision of the manuscript. AK is responsible for the overall content as guarantor.

Competing interests: The authors have no conflicts of interest to declare.

Funding: This research was funded by the Health Canada's Substance Use and Addiction Program (Arrangement # 2223-HQ-000150). The views expressed herein do not necessarily represent the views of Health Canada.

Data sharing statements: Search strategies, data extraction tables, and citations of individual studies are provided in the references and the online supplementary materials.

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References 51-96 are included in the Supplementary File 10.

Figure Legends

Fig 1. PRISMA flow diagram showing study selection process (A) for main analysis and (B) from the 2022 McNeill et al. review for the subgroup analysis.

Fig 2. Meta-analysis comparing heart rate following acute exposure to e-cigarettes vs non-use[9,12,13,25,66] (upper graph) and e-cigarettes vs cigarettes[9–11,25,66] (bottom graph) in cross-over trials.

Fig 3. Meta-analysis comparing resting heart rates of non-smoker current vapers with resting heart rates of non-users[14,15,39,70] (upper graph) and non-vaper current smokers[14,15,39] (bottom graph) in cross-sectional studies.

Fig 4. Meta-analysis comparing A) systolic blood pressure and B) diastolic blood pressure following acute exposure to e-cigarettes vs non-use[9,12,13,25,66] and e-cigarettes vs cigarettes[9,10,16,25,66] in cross-over trials.

Fig 5. Meta-analysis comparing resting A) systolic and B) diastolic blood pressure among non-smoker current vapers vs non-users[14,15,39,70] and non-smoker current vapers vs non-vaper current smokers[14,15,39] in cross-sectional studies.

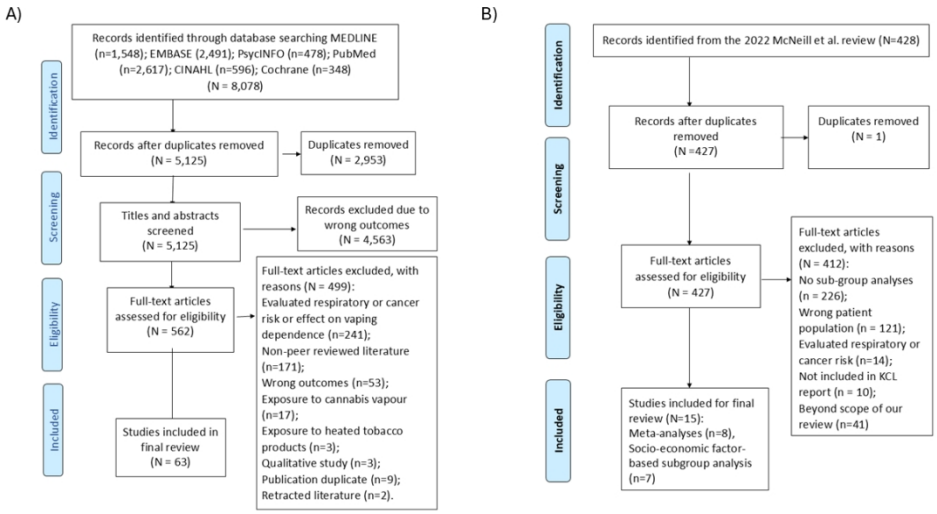


Fig 1. PRISMA flow diagram showing study selection process (A) for main analysis and (B) from the 2022 McNeill et al. review for the subgroup analysis.

108x60mm (300 x 300 DPI)

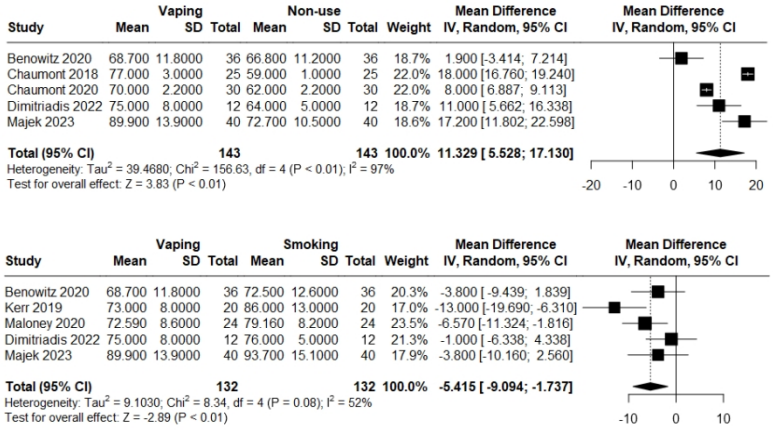


Fig 2. Meta-analysis comparing heart rate following acute exposure to e-cigarettes vs non-use11,14,15,27,68 (upper graph) and e-cigarettes vs cigarettes11–13,27,68 (bottom graph) in cross-over trials.

102x48mm (300 x 300 DPI)

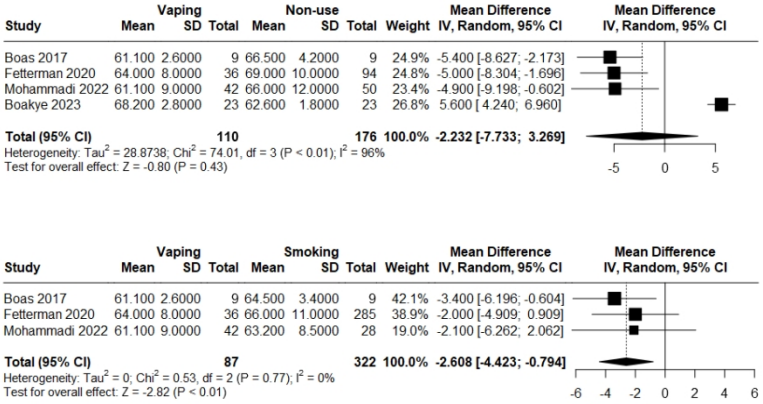
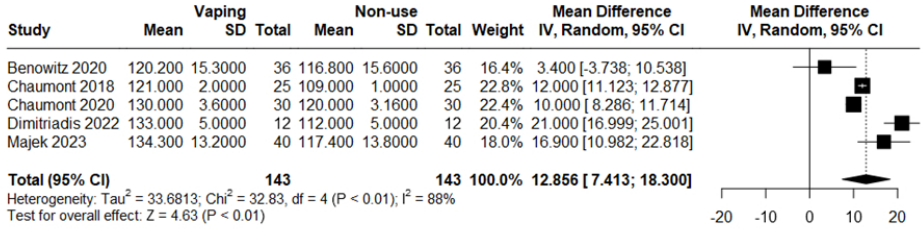
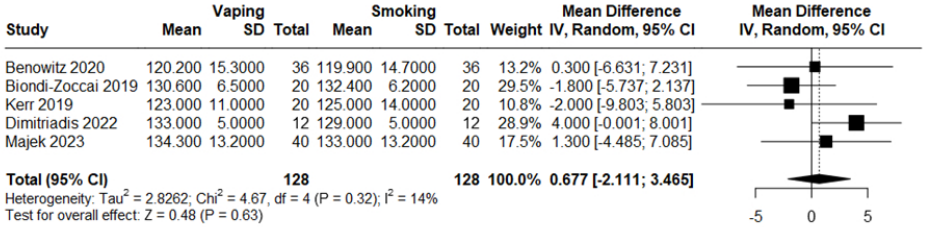


Fig 3. Meta-analysis comparing resting heart rates of non-smoker current vapers with resting heart rates of non-users16,17,41,72 (upper graph) and non-vaper current smokers16,17,41 (bottom graph) in cross-sectional studies.

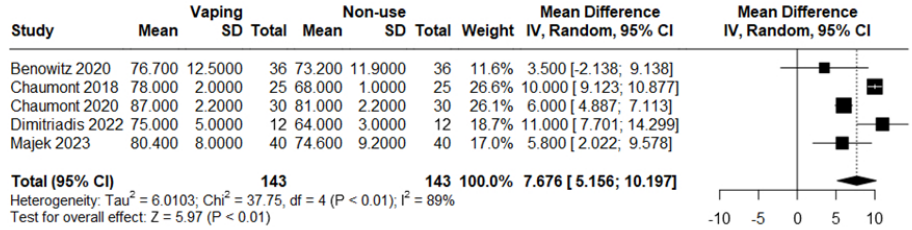
102x48mm (300 x 300 DPI)

A) Systolic BP





B) Diastolic BP



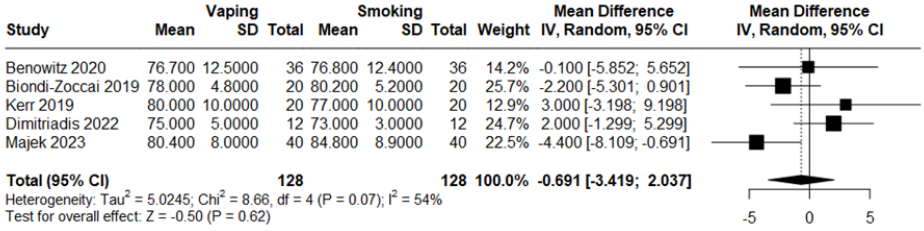
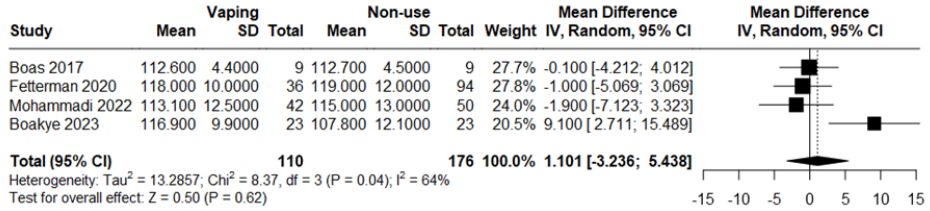
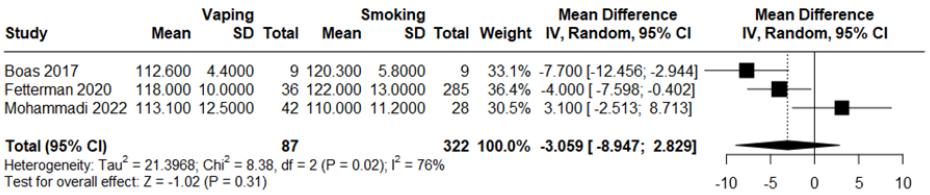


Fig 4. Meta-analysis comparing A) systolic blood pressure and B) diastolic blood pressure following acute exposure to e-cigarettes vs non-use11,14,15,27,68 and e-cigarettes vs cigarettes11,12,18,27,68 in cross-over trials.

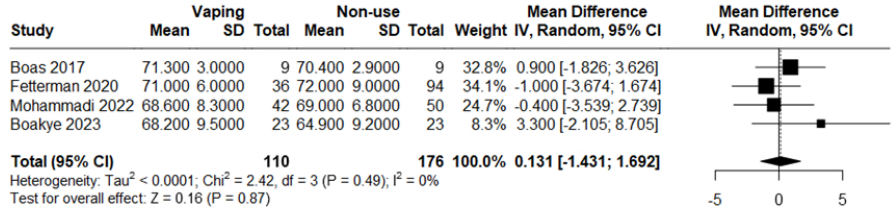
81x97mm (300 x 300 DPI)

A) Systolic BP





B) Diastolic BP



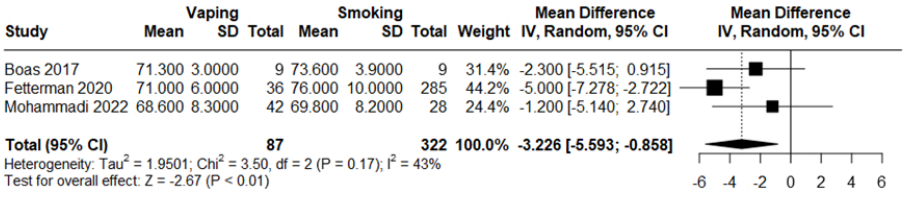


Fig 5. Meta-analysis comparing resting A) systolic and B) diastolic blood pressure among non-smoker current vapers vs non-users16,17,41,72 and non-smoker current vapers vs non-vaper current smokers16,17,41 in cross-sectional studies.

81x97mm (300 x 300 DPI)

Online Supplementary Materials

The cardiovascular health effects of vaping e-cigarettes: A systematic review and meta-analysis.

Supplementary File 1. Database search strategy

Date	Serial	Searches		Results
MEDLINE				
Jan 31, 2023	1.	1.	exp Electronic Nicotine Delivery Systems/	359
		2.	exp Vaping/	
		3.	e-cig*.tw,kw.	
		4.	electronic cig*.tw,kw.	
		5.	(ENDS and nicotine).tw,kw.	
		6.	electronic nicotine delivery system*.tw,kw.	
		7.	vaping.tw,kw.	
		8.	vape*.tw,kw.	
		9.	(nicotine and (vapor* or vapouris*)).tw,kw.	
		10.	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9	
		11.	exp Lung/	
		12.	((respiratory or lung) adj2 effect*).tw,kw.	
		13.	exp Cardiovascular Diseases/	
		14.	((heart or cardiac or cardiovascular or vascular) adj2 effect*).tw,kw.	
		15.	exp Neoplasms/	
		16.	(neoplas* or cancer* or carcinoma* or malignan* or tumor*).tw,kw.	
		17.	11 or 12 or 13 or 14 or 15 or 16	
		18.	10 and 17	
		19.	limit 18 to yr="2021 -Current"	
Jan 31, 2023	2.	1.	exp Electronic Nicotine Delivery Systems/	891
		2.	exp Vaping/	
		3.	exp "Tobacco Use Disorder"/	
		4.	(e-cig* or (electronic adj2 cig*) or ENDS or vaping or vape*).tw,kw.	
		5.	((e-cig* or vaping or nicotine) adj2 (dependen* or addict*)).tw,kw.	
		6.	1 or 2 or 4	

		7. 3 or 5 8. 6 and 7 9. limit 8 to yr="2017 -Current"	
Jan 02, 2024	3.	Updated search 1 limit 18 to dt=20230201-20231231	152
Jan 02, 2024	4.	Updated search 2 limit 8 to dt=20230201-20231231	146
EMBASE			
Jan 31, 2023	1.2	1. exp Electronic Nicotine Delivery Systems/ 2. exp Vaping/ 3. e-cig*.tw,kw. 4. electronic cig*.tw,kw. 5. (ENDS and nicotine).tw,kw. 6. electronic nicotine delivery system*.tw,kw. 7. vaping.tw,kw. 8. vape*.tw,kw. 9. (nicotine and (vapor* or vapouris*)).tw,kw. 10. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 11. exp Lung/ 12. ((respiratory or lung) adj2 effect*).tw,kw. 13. exp Cardiovascular Diseases/ 14. ((heart or cardiac or cardiovascular or vascular) adj2 effect*).tw,kw. 15. exp Neoplasms/ 16. (neoplas* or cancer* or carcinoma* or malignan* or tumor*).tw,kw. 17. 11 or 12 or 13 or 14 or 15 or 16 18. 10 and 17 19. limit 18 to yr="2021 -Current"	907
Jan 31, 2023	2.	1. exp Electronic Nicotine Delivery Systems/ 2. exp Vaping/	1362

		3. exp "Tobacco Use Disorder"/ 4. (e-cig* or (electronic adj2 cig*) or ENDS or vaping or vape*).tw,kw. 5. ((e-cig* or vaping or nicotine) adj2 (dependen* or addict*)).tw,kw. 6. 1 or 2 or 4 7. 3 or 5 8. 6 and 7 9. limit 8 to yr="2017 -Current"	
Jan 02, 2024	3.	Updated search 1 limit 18 to dd=20230201-20231231	170
Jan 02, 2024	4.	Updated search 2 limit 8 to dd=20230201-20231231	52
PsycINFO			
Jan 31, 2023	1.	1. exp Electronic Cigarettes/ 2. e-cig*.tw. 3. electronic cig*.tw. 4. (ENDS and nicotine).tw. 5. electronic nicotine delivery system*.tw. 6. vaping.tw. 7. vape*.tw. 8. (nicotine and (vapor* or vapouris*)).tw. 9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 10 exp lung disorders/ 11 ((respiratory or lung) adj2 effect*).tw. 12 exp Cardiovascular Disorders/ 13 ((heart or cardiac or cardiovascular or vascular) adj2 effect*).tw. 14 exp Neoplasms/ 15 (neoplas* or cancer* or carcinoma* or malignan* or tumor*).tw. 16 10 or 11 or 12 or 13 or 14 or 15 17 9 and 16	49

		18 limit 17 to yr="2021 -Current"	
Jan 31, 2023	2,	1. exp Electronic Cigarettes/ 2. "tobacco use disorder"/ 3. (e-cig* or (electronic adj2 cig*) or ENDS or vaping or vape*).tw. 4. ((e-cig* or vaping or nicotine) adj2 (dependen* or addict*)).tw. 5. 1 or 3 6. 2 or 4 7. 5 and 6 8. limit 7 to yr="2017 -Current"	336
Jan 02, 2024	3.	Updated search 1 limit 17 to up =20230201-20231231	28
Jan 02, 2024	4.	Updated search 2 limit 7 to up =20230201-20231231	65
CINAHL			
Jan 31, 2023	1.	S1. (MH "Electronic Cigarettes") S2. (MH "Vaping") S3. TI (e-cig* or (electronic N2 cig*) or ENDS or vaping or vape*) S4. S1 OR S2 OR S3 S5. (MH "Lung Diseases") S6. TI ((respiratory or lung) N2 effect*) S7. (MH "Cardiovascular Diseases") S8. TI ((heart or cardiac or cardiovascular or vascular) N2 effect*) S9. (MH "Neoplasms") S10. TI (neoplas* or cancer* or carcinoma* or malignan* or tumor*) S11. S5 OR S6 OR S7 OR S8 OR S9 OR S10 S12. S4 AND S11 S13. S12 ((Limiters - Published Date: 20210701-20221231)	339
Jan 31, 2023	2.	S1. (MH "Electronic Cigarettes") S2. (MH "Vaping") S3. TI (e-cig* or (electronic N2 cig*) or ENDS or vaping or vape*) S4. S1 OR S2 OR S3 S5. TI (e-cig* or vaping or nicotine) N2 (dependen* or addict*) S6. S4 AND S5 S7.S6 (Limiters - Published Date: 20170101-20221231)	73
Jan 02, 2024	3	Updated search 1 S14. S12 ((Limiters - Published Date: 20230201-20231231)	171
Jan 02, 2024	4.	Updated search 2 S8. S6 ((Limiters - Published Date: 20230201-20231231)	13

PubMED			
Jan 31, 2023	1.	1. "electronic nicotine delivery systems"[MeSH Terms] OR ("electronic"[All Fields] AND "nicotine"[All Fields] AND "delivery"[All Fields] AND "systems"[All Fields]) OR "electronic nicotine delivery systems"[All Fields] OR ("electronic"[All Fields] AND "cigarettes"[All Fields]) OR "electronic cigarettes"[All Fields] 2. "vaped"[All Fields] OR "vaping"[MeSH Terms] OR "vaping"[All Fields] OR "vapes"[All Fields] 3. #1 OR #2 4. "lung diseases"[MeSH Terms] OR ("lung"[All Fields] AND "diseases"[All Fields]) OR "lung diseases"[All Fields] 5. "cardiovascular diseases"[MeSH Terms] OR ("cardiovascular"[All Fields] AND "diseases"[All Fields]) OR "cardiovascular diseases"[All Fields] 6. "cancer s"[All Fields] OR "cancerated"[All Fields] OR "canceration"[All Fields] OR "cancerization"[All Fields] OR "cancerized"[All Fields] OR "cancerous"[All Fields] OR "neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "cancer"[All Fields] OR "cancers"[All Fields] 7. #4 OR #5 OR #6 8. #3 AND #7 9. #8 Filters: from 2021/7/1 - 2022/11/28	937
Jan 31, 2023	2.	1. "electronic nicotine delivery systems"[MeSH Terms] OR ("electronic"[All Fields] AND "nicotine"[All Fields] AND "delivery"[All Fields] AND "systems"[All Fields]) OR "electronic nicotine delivery systems"[All Fields] OR ("electronic"[All Fields] AND "cigarettes"[All Fields]) OR "electronic cigarettes"[All Fields] 2. "vaped"[All Fields] OR "vaping"[MeSH Terms] OR "vaping"[All Fields] OR "vapes"[All Fields] 3. #1 OR #2 4. "tobacco use disorder"[MeSH Terms] OR ("tobacco"[All Fields] AND "disorder"[All Fields]) OR "tobacco use disorder"[All Fields] OR ("nicotine"[All Fields] AND "dependence"[All Fields]) OR "nicotine dependence"[All Fields] 5. #3 AND #4 6. #5 Filters: from 2017/1/1 - 2022/11/28	998
Jan 02, 2024	3.	Updated search 1 9. #8 Filters: from 2023/02/01 - 2023/12/31	520
Jan 02, 2024	4.	Updated search 2 7. #5 Filters: from 2023/02/01 - 2023/12/31	162
Cochrane			
Jan 31, 2023	1.	#1 [mh "Electronic Nicotine Delivery Systems"] #2 [mh vaping] #3 (e-cig* or (electronic NEAR/2 cig*) or ENDS or vaping or vape*):ti,ab,kw #4 [mh "lung diseases"] #5 ((respiratory or lung) NEAR/2 effect*):ti,ab,kw #6 [mh "Cardiovascular Diseases"] #7 ((heart or cardiac or cardiovascular or vascular) NEAR/2 effect*):ti,ab,kw #8 [mh Neoplasms] #9 (neoplas* or cancer* or carcinoma* or malignan* or tumor*):ti,ab,kw #10 #1 or #2 or #3 #11 #4 or #5 or #6 or #7 or #8 or #9 #12 #10 and #11 with Cochrane Library publication date Between Jul 2021 and Nov 2022	92
Jan 31, 2023	2.	#1 [mh "Electronic Nicotine Delivery Systems"] #2 [mh vaping] #3 (e-cig* or (electronic NEAR/2 cig*) or ENDS or vaping or vape*):ti,ab,kw #4 [mh "Tobacco Use Disorder"]	185

		#5 ((e-cig* or vaping or nicotine) NEAR/2 (dependen* or addict*)):ti,ab,kw #6 #1 or #2 or #3 #7 #4 or #5 #8 #6 and #7 with Cochrane Library publication date Between Jan 2017 and Nov 2022	
Jan 02, 2024	3.	Updated search 1 #12 #10 and #11 with Cochrane Library publication date Between Feb 2023 and Dec 2023	51
Jan 02, 2024	4.	Updated search 2 #8 #6 and #7 with Cochrane Library publication date Between Feb 2023 and Dec 20231	20

Supplementary File 2. Summary of studies assessing risk of cardiovascular outcomes from exposure to e-cigarettes (n=63).

Author and year; countries	Funding source; conflict of interest'	Type of exposure (exposure length/follow-up duration)	Total Participants; characteristics	Intervention/ grouping(s)	Health condition/ Outcome (reversibility of health condition)	Study findings	Subgroup characteristics	Subgroup findings	Risk of bias (critical appraisal score)
Randomized Control Trial									
Klonizakis et al., 2022,[21] and Klonizakis et al., 2021;[22] UK	Independent funding organizations; no COI	Acute (3 days); Short to medium term (6 months)	N=248; mean age 44 years; 50% male; all were daily smokers	Randomized into: Behavioral support + EC with nicotine (n=84): 55% male, received behavioural support with 18 mg/mL nicotine in either ice menthol or tobacco flavour for 3 months. Behavioral support + EC without nicotine (n = 82): 50% male, received behavioural support with 0 mg/mL nicotine in either ice menthol or tobacco flavour for 3 months. Behavioral support + NRT (n=82): 44% male, received behavioural support and NRT prescription support for 3 months.	Cardiovascular impact of quitting smoking by vaping (FMD, CVC response, MAP, TC/HDL ratio, cardiometabolic risk (%QRISK)) (Not measured)	%FMD and CVC responses: improved significantly ($p<0.01$) in response to ACh following both acute and short-to-medium term exposure. In response to SNP, improved significantly ($p<0.01$) following short-to-medium term exposures. NS difference was seen between groups. Mean arterial pressure (MAP): improved significantly ($p<0.05$) following both acute and short-to-medium term exposure. NS difference was seen between groups. TC/HDL ratio: NS changes was seen for all groups following short-to-medium term exposure Reduction in %Q-Risk: was significant ($p<0.01$) following short-to-medium term exposure of EC with or without nicotine. NS	Age: Mean age 44 years for all groups. Sex: 55% male in Behavioural support + EC with nicotine, 50% male in Behavioural support + EC without nicotine, 44% male in Behavioural support + NRT group.	Age: Higher age group had higher risk of high MAP ($p=0.001$) than lower age groups following short-to-medium term exposure, but NS difference in %FMD, CVC responses between age groups. Sex: Males had lower improvement in %FMD ($p=0.005$) and higher risk of high MAP ($p=0.001$) than females following short-to-medium term exposure, but NS difference in CVC responses between males and females. Interpretation: Females and lower age groups had higher CV	Low

						changes was seen at 6 months follow-up in the NRT group. Interpretation: Switching from smoking to vaping following acute and short-to-medium term exposure was associated with positive CV benefits irrespective of presence of nicotine. The benefits was similar to those of NRT.		benefits following short-to-medium term exposure.	
Cross-over Trial									
Maclean et al., 2021;[23] US	Independent funding organizations; no COI	Acute (24 hrs)	N=24; 18-30 years old; 62.5% male, 37.5% female; 62.5% AA, 29.2% Caucasian, 16.6% other race, 25% Hispanic; all were non treatment seeking non-vaper daily smokers.	All participants crossed over between 3 groups: Menthol (n=24); Green apple (n=24); Green apple + menthol (n=24). Participants inhaled EC aerosol with respective flavors + PG:VG (1:1) + 0% nicotine followed by received IV infusion of saline (0 mg nicotine), lower dose (0.25 mg nicotine/70 kg), and higher dose nicotine (0.5 mg nicotine/70 kg) at 1 hr. apart. Wash-out period: 1 hr between IV nicotine, 24 hrs between flavour inhalations.	HR, BP (Reversible)	HR: Changes in HR were dose-dependent on nicotine ($p<0.0001$). Lower dose nicotine infusion significantly increased HR than saline infusion ($p<0.05$) and higher dose nicotine infusion significantly increased HR compared to both saline and lower dose nicotine infusion ($p<0.001$). NS effect of flavour or nicotine by flavour interaction was seen. BP: NS effect on SBP or DBP. Interpretation: Increase in HR following acute exposure to e-cigarette is mainly nicotine dose dependent, but no association with flavors.	N/A	N/A	Low

Gueorguieva et al., 2022;[24] US	Independent funding organizations; no COI	Acute (Single exposure-10 min)	N=45; 18-30 years age; male (n=36), female (n=9); White (n=23), Black (n=20), other races (n=2); all were daily smokers, menthol cigarette smokers (n=24), non-menthol smokers (n=21).	Randomized and cross-overed between 3 groups: 0% menthol (n=45); 0.5% menthol (n=45); 3.2% menthol (n=45). Participants received 6 inhalations of respective concentration of menthol+ PG/VG 75:25 tobacco flavoured EC followed by IV infusion of 0 mg, 0.25 mg/70 kg, and 0.5 mg/70 kg nicotine at 1 hr. apart. Wash-out period: 24 hrs. between crossovers.	HR (Reversible)	HR: There was a main effect of nicotine [$F(2,73) = 8.6$, $p < 0.001$], and pairwise comparisons showed a dose-dependent increase in heart rate [0.5 mg > 0.25 mg > saline]. NS difference in changes in heart rate between different menthol concentrations. Interpretation: HR increase following acute exposure to e-cigarette is mainly dependent on nicotine content, but not on menthol flavor.	N/A	N/A	Some concern
Dimitriadis et al., 2022;[25] Greece	None; no COI	Acute (Single exposure)	N=12; age 25-45 years; 100% male, all were healthy and normotensives non vaper current smokers.	Randomized and crossed over between 3 group: Sham smoker group (n=12): simulated smoking with a drinking straw with a filter to provide resistance. Cigarettes group (n=12): Smoked 2 cigarettes containing 1.1mg of nicotine. EC group (n=12): Vaped EC with tobacco-flavoured, PG/VG solvents, and 1.2% nicotine containing e-liquid.	BP, HR (Reversible)	SBP, DBP, MAP, HR: At 5 min and 30 min following acute exposure to EC, there was a significant increase in SBP (by 8 and 14 mm of Hg, $p<0.001$), DBP (by 4 and 7 mm of Hg, $p<0.001$), MAP (by 6 and 10 mmHg, respectively, overall $p< 0.001$) and HR (by 5 and 9 beats/minute, respectively, overall $p< 0.001$). These changes were higher than sham smoker group, but similar to those of cigarette group. Interpretation: The	N/A	N/A	High

				Wash-out period: 24 hrs. between crossovers.		impact of acute exposure to EC on BP and HR (increased) are similar to those elicited by smoking in healthy habitual smokers.			
Belkin et al., 2023;[65] Switzerland	Independent funding organization; no COI	Acute (4 days)	N=40, age 21.9 +/- 2.6 years for 1st approach group, age 25.2 +/- 0.9 years for 2nd approach group; 50% male; all were active smokers	Randomized and cross-overed between 4 groups: HTP (n=40): exposed to IQOS containing 0.5mg nicotine per hit, Cig (n=40): Exposed to a commercial tobacco cigarette containing 0.5mg nicotine, Nic EC/JUUL (n=40): Exposed to tobacco flavored 20 mg/ml nicotine containing EC in 1st approach (n=20) or JUUL (n=20) in 2nd approach, Non-nic EC (n=40): Exposed to tobacco flavored 0 mg/ml nicotine containing EC. Washout period: 48 hrs between cross-overs.	Endothelial/vascular dysfunction	PWV and augmentation index to measure arterial stiffness: Significantly increased in 20 mins. post-exposure for both Nic EC/JUUL ($p<0.05$) and Non-nic EC ($p<0.05$) exposure compared to baseline. However, the effect was lower than that seen in Cig exposure. Interpretation: Acute exposure to EC induced significant arterial stiffness among active smokers.	N/A	N/A	Some concerns
Nonrandomized experimental studies									
Felicione et al., 2022;[26] US	Independent funding organizations; no COI	Acute (3hrs)	N=15; mean age 20.1 (SD 2.0) years; 53.3% females; 73.7% White; all were never smoker current vapers.	Participants were split into 2 groups and crossed-over between: Abstinence condition: could not vape for 3 hrs, Ad lib condition: used their own EC for 3 hrs.	HR (Reversible)	HR: was significantly higher for the ad lib use than abstinent condition ($F = 12.60$, $p < .01$). HR increased from pre- to post exposure, and then decreased at 60 min and 180 post-exposure ($p < .01$).	N/A	N/A	Moderate

				Wash-out period: >48 hrs.		Interpretation: Exposure to EC increases HR immediately following exposure and returns back to normal over time.			
Shahin et al., 2022;[27] Canada	Independent funding organizations; no COI	Acute (Single exposure 2 min)	N=16; 18-25 years age; 44% male, 56% female; healthy participants	Current EC users (n=9): used EC for average 1.7 years; instructed to vape 5% nicotine for 2 mins. Current TC users (n=7): used cigarette for average 4.7 years; instructed to smoke their normal cigarette for 5 mins. Not all participants were exclusive users. NS difference in baseline characteristics between groups.	BP, HR (Reversible)	HR, SBP, DBP, MAP, RPP: All parameters significantly increased following acute exposure (ps<0.001). NS difference in parameters between smoking and vaping exposure. Interpretation: Acute exposure to EC induces similar effects on HR and BP as cigarette smoking.	N/A	N/A	Serious
Majid et al., 2023;[28] US	Independent funding organization; no COI	Acute (Single exposure 10 min)	N=23; 21-45 years old; female (n=10); White (n=11), Black/AA (n=3), Asian (n=6), other race (n=3).	Never users (n=7): were not exposed to any tobacco products. Current pod-based EC users (n=10): used pod-based EC for at least 6 months 5 days a week; included dual users n=3 (30%), former smoker current vaper n=4 (40%); were instructed to use their own product for 10 mins Non vaper current smokers (n=6): used cigarette for at least 6 months 5 days a week	Endothelial dysfunction (Not measured)	ACh-induced eNOS activation in cells: Was impaired in current pod-based EC users compared to never users (p=0.01) and the degree of impairment was similar to non-vaper current smokers. Interpretation: Acute exposure to EC may impair endothelial cell function similar to cigarettes.	N/A	N/A	Serious

				without concurrent usage of e-cigarettes; were instructed to use their own product for 10 mins.					
Lorkiewicz et al., 2022;[29] US	Independent funding organizations; no COI	Acute (single exposure-15 min)	N=9	Current EC users (n=9): used 1 or fewer times/day; instructed to avoid smoking, vaping or tobacco use 12 hr. before study; used own vaping device for at least 15 puffs.	Cardiovascular dysfunction (Not measured)	Urinary 3HPMA and 23HPMA levels: NS change in urine 3HPMA level, but both the absolute and relative (approx. 10%) concentration of urinary 23HPMA level increased 155 min following exposure ($p<0.05$). Interpretation: Acute exposure to EC increased acrolein metabolites in urine and thus increases risk of CV dysfunction	N/A	N/A	Serious
Mueller et al., 2021;[32] US	Independent funding organization; no COI	Acute (24 hrs)	N=31; 18-80 years old.	Vapers (n=17, 55%): continued ad lib vaping. Smokers (n=14, 45%): continued ad lib smoking. NS difference between groups in gender, ethnicity, educational attainment. Duration and frequency of EC or cigarette use was not specified.	HR, BP (Reversible)	BP,MAP, HR: Vapers had significant relative increase in DBP ($p=0.03$), MAP ($p=0.02$) and HR ($p<0.001$) following acute exposure to EC. NS difference was found between vapers and smokers following acute exposure. Interpretation: Acute exposure to EC was associated with increase in HR and BP similar to smoking cigarettes.	N/A	N/A	Critical
Majek et al., 2023;[66] UK	None; None	Acute (single exposure)	N=160; 18-30 years old; 53.1% male, 46.9% female.	EC (n=40): participants were non-smoker current vapers; instructed to vape non-	HR, BP; reversible	HR: Significantly increased 5 min post-exposure compared to baseline	N/A	N/A	Moderate

				flavored EC containing 12 mg/ml nicotine for 5 min. Cig (n=40): participants were non-vaper current smokers; instructed to smoke one Cig- non-flavored containing 0.5 mg nicotine per Cig. HTP (n=40): participants were exclusive HTP users; Instructed to use one non-flavored tobacco stick of IQOS 2.4 Control (n=40): participants never smoked or vaped in their lifetime, instructed to simulate smoking for 5 min. Participants were instructed to not use their products for 6 hrs. before the intervention.		(p<0.01) in EC group. NS difference was seen between baseline and 5-min post-exposure measures in EC group. HR significantly decreased in 30 min post-exposure compared to 5-min post-exposure measures in EC group. SBP, DBP: Significantly increased 5 min post-exposure compared to baseline (p=0.01 for both) in EC group. NS difference was seen between baseline and 5-min post-exposure or 5 min and 30 min post-exposure measures in EC group. Interpretation: Acute exposure to EC was associated with significant acute increase in HR and BP which became normal 30 min post-exposure.			
Longitudinal observational studies									
Mahoney et al., 2022;[30] US	Independent funding organization; some (no pro-tobacco association)	Long-term (6 years)	N=7,820 participants, 10,548 observations; 47.1% 55 years old or older; males (n=4,707), 16-30% attrition rate.	Depending on the tobacco use status in each follow-up, participants were categorized into 5 groups: Continuing exclusive smoking (n=6263). Exclusive smokers switched to exclusive vapers (n=53).	CVD (including heart failure, stroke, heart attack/MI, other heart conditions) (Irreversible)	Self-reported incidence of CVD in past 12 months: There were 0 incidence of CVD among Exclusive smokers switched to exclusive vapers. NS difference was seen in any tobacco user groups when compared to continuing never use	N/A	N/A	Low

				Exclusive smokers switched to dual use (n=564). Exclusive smokers who quit tobacco use (n=654). Continuing never use (n=3,014). Exclusive use was indicated by use in past 30-days.		group. Interpretation: Long-term exposure to EC did not change risk of CVD among former smokers or current smokers.			
Berlowitz et al., 2022;[31] US	Independent funding organization; some (no pro-tobacco association)	Long-term (6 years)	N=24,027; 18+ years age; 50% younger than age 35; 51% females.	Non-smoker current vapers: n=822. Non vaper current smokers: n=6,515 Dual users: n=1858, Nonusers: n=14,832. Current use was not defined by time-period.	CVD (MI or bypass surgery, HF, stroke, other heart conditions); MI, HF, stroke (Irreversible)	Self-reported incident CVD in past 12 months: Non-smoker current vapers had significantly lower ($p<0.05$) risk compared to non-vaper current smokers. Current dual users had significantly higher ($p<0.05$) risk compared to nonusers. NS difference between non-smoker current vapers vs non-users and current dual users vs non vaper current smokers. Self-reported incident cases of MI, HF or stroke in past 12 months: Current dual users had significantly higher ($p<0.05$) risk compared to nonusers. NS difference between non-smoker current vapers vs non-users or	N/A	N/A	Some concerns

						non-vaper current smokers, and current dual users vs non vaper current smokers. Interpretation: Long-term exposure to only EC might not increase risk of CVD in non-users, but had lower risk when compared to non-vaper current smokers. Long-term dual use increase risk of CVD, which is similar to non-vaper current smokers.			
Hirschtick et al., 2022;[17] US	Independent funding organization; no COI	Long-term (4 years)	N= 11,031 for MI and N=11,076 for stroke; Mean age 57.5 years; ~55% females and ~45% males; ~71% NH White, ~11% Hispanic, ~11% NH Black, ~6% Other race/ethnicity.	MI: Non-users (n= 6798), Non-smoker current vapers (n=3785), Non vaper current smokers (n=174), Dual users (n=274). Stroke: Non users (n= 6813), Non-smoker current vapers (n=3810), Non vaper current smokers (n=172), Dual users (n=281). Current use was defined by everyday or someday use.	MI, Stroke (Irreversible)	Self-reported incidence of MI in past 12 months: NS risk was seen among non-smoker current vapers and dual users compared to non-users. Self-reported incidence of stroke in past 12 months: NS risk was seen among non-smoker current vapers and dual users compared to non-users. Interpretation: Long-term exposure to EC did not increase risk of MI and stroke in non-smoker current vapers and dual users compared to non-users.	N/A	N/A	Some concerns
Shi et al., 2022;[33] US	Independent funding	Long-term (3 years, 3 follow-ups at	N=16,434; ≥18 years age; females	Current dual users (n=488): used both EC and cigarette everyday	HTN (Irreversible)	Incidence of self-reported HTN:	Sex: same as entire population	Same as findings of entire population	Low

	organizations; no COI	1 year interval)	(n=8792), males (n=7642).	or some days. Current exclusive vapers (n=300): used EC everyday or some days. Current exclusive smokers (n=4977): used cigarette everyday or some days. Non-users (n=10,606): Did not use either product everyday or some days. N.B: did not define current use by using product within last 30 days.		NS risk was found among male or female non-smoker current vapers and current dual users compared to nonusers. Interpretation: Long-term exposure to e-cigarette was found to not increase incident risk of HTN among male or female non-smoker current vapers and dual users.			
Goldberg Scott et al., 2023;[34] US	Independent funding organization; no COI	Long-term (Prospective: Median days 504-713 days. Retrospective: EHR data)	N=119,593; 18+ years age, 22% >70 years; 60% female, 40% male; heterosexual (n=109,222), gay or lesbian (n=8023) and other sexual orientation (n=1218); 70% NH White, 10% Hispanic, 10% NH Asian, 6% NH Black, 2% American Indian/Alaska Native, 2% NH Native Hawaiian/Other race/ethnicity.	ENDS never user (n=112396, 94%): Never used EC in lifetime. ENDS former user (n=5603, 5%): Used EC >30 days ago. ENDS current user (n=1594, 1%): Used EC in the past 30 days; included both dual users and non-smoker current vapers	HTN, hyperlipidemia, heart attack, stroke, non-stroke cerebral vascular disease (Irreversible)	HTN, heart attack, and stroke: Former ENDS users had significantly higher ($p<0.05$) odds of prevalence of HTN, heart attack and stroke compared to never users; but NS risk in current ENDS users and NS incident risk of heart attack and stroke was seen among either group. Non-stroke cerebrovascular disease: Significantly higher ($p<0.05$) odds of prevalence was seen among former and current ENDS users, but NS incident risk was seen among either	N/A	N/A	Low

						group. ER visits and death: Significantly higher ($p<0.05$) incident risk was seen among former and current ENDS users for both outcomes. Hyperlipidemia: NS prevalent risk was seen among either group. Interpretation: Long-term current exposure to e-cigarette was associated with increased ER visits and death, but no significant risk was found for developing heart attack or stroke or non-stroke cerebrovascular disease.			
Cook et al., 2023;[20] UK	Independent Funding Organization; no COI	Long term (4 years)	N = 17,539; mean age 38.97 (SD 15.42) years; 46.1% male, 53.9% female, 46.1% male; 63% NH White, 17.6% Hispanic, 11% NH Black, 5.8% NH Asian, 2.6% NH other race.	Non-smoker current vapers (N = 336): Used EC everyday or somedays. Non-vaper current smokers (N = 5570): Smoked cigarette everyday or somedays. Dual user (N = 570): used both EC and cigarettes everyday or somedays. Non users (N = 11 063): Did not use either products currently, including never users.	HTN; irreversible	Self reported incidence of HTN: NS difference in risk was seen between non-smoker current vapers or dual users compared to non-users. Interpretation: Long-term use of EC did not increase risk of developing HTN among non-smoker current vapers and dual users.	N/A	N/A	Some concerns
Cross-Sectional Studies									

Bricknell et al., 2021;[18] US	Not specified; no COI	N/A (N/A)	N=465,594; 18-65+ years old; 56.7% female, 43.3% male, 76.2% NH White, 22.1% other race/ethnicity.	Never vapers (n=391,581), Current daily vapers (n=5010), Current frequent/non-daily vapers (n=10,169), Former vapers (n=58,834), Never smokers (n=260,997), Current daily smokers (n=48,755), Current frequent/non-daily smokers (n=19542), Former smokers (133,795). N.B. ENDS included EC, e-hookahs, vape pen, e-cigars.	Stroke (Irreversible)	Self-reported stroke: Significantly higher odds of prevalence was seen in current daily vapers and current frequent vapers (p=0.01 and p=0.03 respectively) compared to never vapers; but NS risk was seen in former vapers. The odds were lower than that seen among current daily and frequent smokers respectively. Interpretation: Current vaping was associated with higher probability of prevalence of stroke compared to never vaping.	N/A	N/A	Moderate (5/8)
Okafor et al., 2022;[35] US	Independent funding organization; no COI	N/A (N/A)	N=8,688; mean age 45.2 +/- 0.39 years; 47% male; 53% female; 63.1% NH White, 11.1% NH Black, 6.1% NH Asian, 15.9% Hispanic, 3.8% other race/ethnicity	Never users, n=6862, Non-smoker current vapers, n=187, Non vaper current smokers, n=1389, Dual users, n=250.	Cardiometabolic risk, BP (Reversible)	BP: Non-smoker current vapers had significantly higher odds of high BP ($p<0.05$) compared to both never users and non-vaper current smokers. NS risk was seen in dual users compared to never users or non-vaper current smokers. HDL-C, LDL-C, TG: Dual users had significantly higher	Age groups: ≤30 years of age and > 30 years of age	≤30 years: Non-smoker current vapers (vs never users) had increased odds of reduced HDL-C ($p<0.05$). >30 years: Current dual users (vs never users) were associated with increased odds of reduced HDL-C ($p<0.05$).	Low (15/20)

						odds of reduced HDL-C ($p<0.05$) and elevated TG ($p<0.05$) compared to never users; but NS difference compared to non-vaper current smokers. NS difference was seen in non-smoker current vapers compared to never users or non-vaper current smokers. NS difference in LDL-C between groups. FBG: NS difference was seen between groups. Interpretation: Non-smoker current vapers had higher odds of high BP compared to never users and non-vaper current smokers. Dual users had higher odds of low HDL-C and high TG compared to never users, which was not different from those in non-vaper current smokers.			
Critcher and Siegel, 2021;[36] US	None; not specified	N/A (N/A)	N=175,546; average age 51 (SD 18.46) years; 46% males; 14% Hispanic, 67% White, 12% Black, 5.21% Asian, 3% Other race/ethnicity.	Current dual users: (n=3191), used EC and cigarette everyday or some days, Former smoker current vapers: (n=1933), former smokers who used EC everyday or some days, Former vaper current smokers: (n=10,445),	MI (Irreversible)	Self-reported prevalence of MI: daily dual users and frequent dual users had the highest risk of lifetime MI compared to never vaper daily smokers and never vaper frequent smokers respectively ($p<0.05$ and $p<0.001$ respectively). Former smoker daily	N/A	N/A	Moderate (5/8)

				former vapers who used Cig everyday or some days, Former users: (n=4,444), ever users currently not using either products, Never-smoker current vapers: (n=702), used EC everyday or some days, but no lifetime Cig Never-vaper current smokers: (n=13,969), used Cig everyday or some days, but no lifetime EC Never users: (n=100,321), did not use EC or Cig in their lifetime.		vapers had higher risk compared to never vaper former smokers ($p<0.05$). NS association between MI and EC use among never smokers. Interpretation: Dual users had higher prevalent risk of MI than never vaper current smokers. EC use increased prevalent risk of MI among former smoker current vapers, but not among never smoker current vapers.			
Kim et al., 2022;[37] South Korea	Not specified; no COI	N/A (N/A)	N=275,762; 19+ years; male n= 20,766 (44%) and female n= 154,996 (56%); sample taken from people who were not using any HTN medication.	Current dual users: (n=3268), using both Cig and EC currently, Non-smoker current vapers: (n=1192), currently using EC, but not Cig, Non vaper current smokers: (n=45,888), currently using Cig, but not EC, Former smokers or vapers: (n=48,642), Were past users of either Cig or EC, Never users:	HTN (Irreversible)	Male current dual users, and male non-smoker current vapers had significantly higher odds of HTN compared to never users ($p<0.05$); but NS association was seen among females. Interpretation: Vaping was associated with higher risk of prevalence of HTN among current dual users and non-smoker current vapers compared to never users.	Sex: Male: (n=120,766) Female: (n=154,996) Age groups: Among males: 19-29 years n=16,206; 30-39 years n=18,704; 40-49 years n=23,298; 50-59 years n=23,700; 60+ years n=38,858. Among females: 19-	Sex: Same as main findings. Age groups: Among males, current dual users 19-29 Y and non-smoker current vapers 30-39 Y and 50-59 Y had significantly higher odds ($p<0.05$) compared to never smokers. Education: Among males with college or	Low (7/8)

				(n=176,772), did not ever use either products.			29 years n=19,816; 30-39 years n=23,576; 40-49 years n= 29, 694; 50-59 years: n=33,180; 60+ years: n= 49,730. Education: Among males: Middle school or less (n=26,230), high school (n=37,784), college or over (n=56,752). Among females: Middle school or less (n=47,602), high school (n=46,182), college or over (n=61,212). Income: Among males: low (n=27,102), mid-low (n=21,040), mid-high (n=34,386), high (n=38,238). Among females: low (n=39,128)),	over education, both dual users and non-smoker current vapers had significant risk ($p<0.05$) compared to never smokers. Income: Both male and female dual users and male non-smoker current vapers with high income had significant risk ($p<0.05$) compared to never smokers. Occupation and employment: Male dual users with White and pink occupational category and female dual users with pink occupational category had higher risk ($p<0.05$) compared to never smokers.	

							mid-low (n=25,956), mid-high (n=41,216), high (n=48,696). Occupation category and employment: Among males: White (n=29,380), Pink (n=13,618), Blue (n=49,330), unemployed (n=24,438). Among females: White (n=32,588), Pink (n=27,156), Blue (n=28,596), unemployed (n=66,656).		
Liu et al., 2022;[38] US	Independent funding organization; no COI	N/A (N/A)	N=253,561; 41.4% ≥ 55 years old; 50.7% females; 66.2% White, 12.6% Black, 21.2% other race.	Never vapers (n=192,268), Former vapers (n=47,843): Ever vapers who currently not using EC at all. Current vapers (n=13,450): using EC everyday or some days. Never smokers (n=151,450), Former smokers	CVD (including CHD, stroke) (Irreversible)	Self-reported prevalence of CVD: Former vapers had significantly higher risk than never vapers ($p<0.05$). Dual users had significantly higher risk than never users ($p<0.05$). NS difference between current vapers vs never vapers; never smoker current vaper vs never users; former smoker current vapers vs never	Age groups: <35 Y: n=951, 35-55 Y: n=3,831, ≥55 Y: n=18,126. Sex: Male: n=13,093, Female: n= 9,815 Race: White: n=17,144, Black:	Age groups: Current vaping with insufficient sleep increased risk significantly ($p=0.04$) in all age groups. 35-55 Y and ≥55 Y Former vapers had higher risk than never vapers ($p<0.05$). Sex: Both male and female current vapers	Low (6/8)

				(n=62,823): Ever smokers who currently not smoking at all, Current smokers (n=39,288): using Cig everyday or some days.		users Interpretation: Dual use was associated with higher prevalent risk of CVD compared to never users. No such risk was seen among never smoker current vapers or former smoker current vapers.	n=2,697, other race: 3,067.	with insufficient sleep had higher risk ($p<0.05$) compared to never vapers. Race: White and Black current vapers with insufficient sleep had higher risk ($p<0.05$) compared to never vapers.	
Falk et al., 2022;[19] US	Not specified; not specified	N/A (N/A)	N=84,533; 18+ years old.	Non-smoker current vapers (n= 2,619): using e-cigarettes everyday or some days, Non-vaper current smokers (n=6,459): used Cig everyday or some days, Former-smoker current vapers (n=3,169): Current vapers who are also ever smokers but not using Cig at all. Former-smoker non vapers (n=17,788): Ever smokers who not using either products at all. Current dual users (n=6,581): used both Cig and EC everyday or some days, Nonusers (n=47,937): not using either products at all.	HTN, stroke, DM, CHD, MI (Irreversible)	Self-reported prevalence of HTN: All groups had significantly higher risk of HTN compared to non-users ($p<0.05$). Self-reported prevalence of DM: Current dual users had higher risk compared to non-users ($p<0.05$), NS risk was seen among non-smoker current vapers and former-smoker current vapers Self-reported prevalence of CHD, MI and stroke: All groups except non-smoker current vapers had higher risk compared to non-users ($p<0.05$) for each outcomes. Interpretation: Non-smoker current vapers had only higher risk of prevalence of HTN	N/A	N/A	Low (7/8)

						compared to never users, while dual users and former smoker current vapers had higher risk of prevalence of HTN, CHD, MI and stroke. Dual users had also higher risk of prevalence of DM.			
Mohammadi et al., 2022;[39] US	Independent funding organizations; no COI	N/A (N/A)	N=120; 21-50 years old; 39.2% female, 60.8% male; all were free of CVD, no dual users.	Non-smoker current vapers (n=42): used EC at least 5 times/week for 3 months. Non vaper current smokers (n=28): used at least 5 cigarettes/day for ≥1 pack year. Nonusers (n=50): Did not use either product in last 1 year.	HR, BP, endothelial dysfunction (Reversible)	SBP, DBP and HR: NS difference in SBP, DBP and HR between groups. FMD: Non-smoker current vapers had lower FMD than nonusers ($p<0.001$). NS difference in FMD was seen between vapers and smokers. Circulating biomarkers: Non-smoker current vapers had increased level of inflammatory biomarkers (HMGB1, S100A8, IFN-β, MPO) and cell adhesion biomarkers (vWF, sICAM-1) than non-users ($p<0.05$). Non-smoker current vapers had decreased level of inflammatory biomarkers (RAGE, IL-1β) and cell adhesion biomarkers (E-selectin, PECAM-1) and increased level of inflammatory biomarker (IFN-β) than non-vaper current	Sex: female (n=47), male (n=73)	NS difference in FMD between males and females.	Low (13/20)

						smokers (p<0.05). Interpretation: Non-smoker current vapers had low FMD and increased endothelial biomarkers compared to non-users. The effect on FMD was similar to smokers. NS effect on HR and BP was seen among vapers.			
Patel et al., 2022;[40] US	None; not specified	N/A (N/A)	N=78,825; >18 years old.	Current vapers (n=7756): Used EC in past 30 days, mean age 50 years, male 63.64%, NH White 37.88%. Current smokers (n=48,625): used Cig in past 30 days, mean age 69 years, male 66.09%, NH White 42.77%. Dual users (n=23,444): Used both EC and Cig in past 30 days, mean age 55 years, male 48.07%, NH White 47.13%.	Stroke (Irreversible)	Self-reported prevalence of stroke: Current vapers had higher risk of stroke in comparison with current smokers (p< 0.0001) and non-vapers (p< 0.0001). Dual users had higher risk of stroke in comparison with current smokers (p< 0.0001). Interpretation: Current vapers and dual users had higher risk of prevalence of stroke compared to current smokers.	Age: Median age of onset among current vapers 48 Y, current smokers 59 Y and dual users 50 Y. Sex: Male (62.37%), female (37.63%) Race: Mexican-American (7.39%), Other Hispanic (7.44%), NH White (43.59%), NH Black (29.33%), NH Asian (2.96%), Other race-including multi-racial (9.30%) Annual	Age: Current vapers have an early onset of stroke compared to dual and current smokers (p< 0.0001). Sex: female dual users and male current vapers had significantly higher prevalence of stroke (p<0.0001). Race/ethnicity: Non-Hispanic White current vapers and dual users had higher prevalence of stroke (p< 0.0001). Income: Current vapers and dual users with very low income ($0--$25,000) had higher prevalence of stroke (p<0.0001).	Low (6/8)

							Household Income: <$25,000 (52.44%), $25,000-$65,000 (32.16%), $65,000-$100,000 (7.57%), >$100,000 (7.83%).		
Metzen et al., 2021;[41] Germany	Independent funding organization; no COI	N/A (N/A)	N=212; 18+ years age	Non-smokers (n=37): no smoking in last 1 year. Current vapers (n=102): used EC consistently in last 1 year. Current smokers (n=73): used cigarette consistently in last 1 year.	Platelet aggregation (Not measured)	Collagen- induced platelet aggregation: Current vapers vs current smokers: p<0.0001 Current vapers vs non-smokers: p =0.002 ADP-induced platelet aggregation: Current vapers vs current smokers: NS Current vapers vs non-smokers: p =0.001 Interpretation: Current vapers had enhanced platelet reactivity compared to current smokers and non-smokers, indicating higher risk of CV events.	N/A	N/A	Moderate (12/20)
Podzolkov et al., 2021;[42] Russia	Independent funding organizations; Not specified	N/A (N/A)	N=369; median age 21 years; 43.1% males, 56.9% females.	Nonusers (n=196, 53.1%): Did not use either cigarettes or EC in past 12 months. Current smokers (n=83, 22.5%): smoked cigarette for (median) 4 years; used nicotine in cigarette 2.05 mg/day	Vascular wall damage, SBP, DBP, HR (Not measured)	hsCRP: Current vapers had higher hsCRP level than nonusers (p<0.001). NS difference between current vapers and smokers. Albuminuria: Current	Age: all groups median age 21 years Sex: Male: Nonusers (n= 73, 37.2%), current	NS correlation of age or sex with hsCRP, Albuminuria or ABI among current vapers, current smokers, or nonusers was observed.	Moderate (12/20)

				(daily smokers) Current vapers (n=90, 24.4%): Used EC for (median) 4 years; used nicotine in EC 3.3mg/day (daily vapers).		vapers had higher albuminuria (p<0.001) than non-users and current smokers (p<0.001). ABI: Current vapers had lower ABI (p<0.001) than non-users and current smokers (p<0.001). SBP and DBP: Current vapers had higher SBP than nonusers (p<0.05). NS difference between current vapers and smokers. NS difference in DBP between groups. HR: Current vapers had higher HR (p<0.05) than non-users, but lower than current smokers (p<0.05). Interpretation: Current vapers had higher hsCRP level, albuminuria, SBP, HR and lower ABI than non-users. These effects were almost similar or sometimes higher than current smokers, except HR.	smokers (n=55, 66.3%), current vapers (n=39, 43.3%). Female: Nonusers (n=123, 62.8%), current smokers (n=28, 33.7%), current vapers (n=51, 56.7%).		
Amraotkar et al., 2023;[43] US	Independent funding organization; no COI	N/A (N/A)	N=324; 21-45 years age; female 47%, male 53%; 1% American Indian/Alaskan, 3% Asian, 51% Black/AA, 42%	Never users: (n=65), used less than 100 cigarettes in lifetime with no use of other tobacco products, urinary cotinine <10 ng/ml.	Level of circulating angiogenic cells (CACs) (Reversible)	Blood level of CACs: CD146+ (endothelial) CACs significantly (p<0.05) increased in all groups compared to never users. CD34+ (stem) positive CACs increased	N/A	N/A	Low (16/20)

			White/Caucasian, 6% Other race; 9% Hispanic/Latino, 91% NH,	Non-smokers current vapers (n= 19): currently used EC 5 days/week with no cigarette use in ≥past 3 months. Non vaper current smokers (n=212): currently smoked cigarette 5 days/week with no EC use in ≥past 3 months. Current dual users (n=28): currently used both cigarette and EC 5 days/week		significantly ($p<0.05$) in current dual users compared to never users. CD45+ (leukocyte) CACs increased significantly ($p<0.05$) in non-smoker current vapers and current dual users compared to never users. NS difference between non-smoker current vapers and non-vaper current smokers. Interpretation: Dual users were associated with higher levels of endothelial origin CACs, while non-smoker current vapers had higher endothelial and inflammatory CACs compared to never users, suggesting ongoing systemic injury.			

April-Sanders et al., 2023;[67] US	Independent funding organization; some COI (no pro-tobacco association)	N/A (N/A)	N=11,623; age > 18 years, mean age 47 ± 0.3 years; 52% women; all were Hispanic/Latino adults	Current vapers (n=136): used EC in past 30 days; Ever vapers (n=932): used EC in their lifetime; Non-vaper current smokers (n=866): Used Cig daily or somedays; Non-users (n=6057): Used neither products in past 30 days	BP; HTN, Cardiometabolic risk, CVD (non-specific), HF	BP: Current vapers had significantly lower SBP than non-vaper current smokers ($p<0.001$). NS difference in DBP between current vapers and non-vaper current smokers seen. NS difference in SBP or DBP seen between current vapers and non-users. TG, HDL-C, LDL-C, Hypercholesterolemia: Current vapers had significantly lower TG and LDL-C levels than both non-users and non-vaper current smokers ($p<0.05$). NS difference in HDL-C between current vapers and non-users or non-vaper current smokers. Ever vapers had significant association with hypercholesterolemia compared to non-smokers (OR 1.3); but NS association found with current vapers. CVD (non-specific), HF: Ever vapers had significant association with prevalent CVD and HF compared to non-smokers (OR 2.33 and 2.98 respectively); but NS association	N/A	N/A	Low (7/8)

						found with current vapers. HTN: NS prevalent risk of HTN seen in current vapers or ever vapers compared to non-smokers. Interpretation: Ever vapers had significantly higher cardiometabolic risk, and higher probabilities of CVD (non-specific) compared to non-smokers, but NS risk was seen in current vapers. Current vapers had significantly lower SBP, TG and LDL-C levels than non-vaper current smokers.			
Austin-Datta et al., 2023;[68] US	Independent funding organization; no COI	N/A (N/A)	N=7,253; ≥18 years age; 36.9% male, 63.1% female; 48.4% Black/AA, 44.4% White, 7.2% other races, 92% non-Hispanic, 8% Hispanic.	Never vapers (n=6076): Never used EC in lifetime. Ever vapers (n=1,177): Used EC in their lifetime.	CVDs (non-specific) (Arrythmia, CHD, MI, HTN, DVT, hypercholesterolemia, HF); irreversible	Compared to those not having CVDs (non-specific), those with Non-specific CVDs had significantly higher odds of being ever vapers (aOR 1.1). Interpretation: Ever vapers had higher probability of prevalence of CVDs (non-specific).	N/A	N/A	Moderate (5/8)

Halstead et al., 2023;[69] US	Independent funding organization; no COI	N/A (N/A)	N=40; 18-24 years old; 50% male, 50% female.	Current vapers (N = 20): history of chronic EC use lasting ≥6 months Non-users (N = 20): adults without a history of EC use.	Endothelial/vascular dysfunction	CVC/ endothelium dependent vasodilatation: Significantly decreased in current vapers compared to non-users (*p*=0.001). NO/endothelium non-dependent vasodilatation: Significantly decreased in current vapers compared to non-users (p=0.01). Interpretation: Current vapers had significant impairment of vasodilatation compared non-users.	Sex: Male (n=20); female (n=20)	CVC/ endothelium dependent vasodilatation: Significantly decreased in female current vapers compared to female non-users (p=0.002). NS difference was seen between male current vaper and male non-users. NO/endothelium non-dependent vasodilatation: Significantly decreased in female current vapers compared to female non-users (p=0.005). NS difference was seen between male current vaper and male non-users.	Low (16/20)

Boakye et al., 2023;[70] US	Independent funding organization; no COI	N/A (N/A)	N=46; mean Age 24.3 (SD 4.0) years; 78.3% male; 89.1% NH, 10.9% Hispanic; 58.7% White, 10.9% Black/AA, 10.9% Asian, 19.5% American Indian/Alaskan Native.	Non-smoker current vapers (N=23): Used EC for at least 6 consecutive past months and did not use cigarettes or any other tobacco products. Non-users (N=23): Used EC <5 times in lifetime, and had not used an EC in the past 90 days, did not use cigarettes or any other tobacco products.	HR, BP, Endothelial/vascular dysfunction; Not measured	HR: NS difference in HR was seen between groups. BP: Non-smoker current vapers had significantly higher SBP (p=0.01) compared to non-users. NS difference in DBP was seen between groups. FMD: NS difference in co-efficient was seen between groups. RHI: NS difference in co-efficient was seen between groups. Inflammatory markers: Non-smoker current vapers had significantly increased probability of high IL-6 levels compared to non-users. Otherwise, NS difference in hsCRP, fibrinogen, P-Selectin, MPO level was seen between groups. Interpretation: Other than having higher SBP, non-smoker current vapers and non-users did not differ in HR and BP. Non-smoker current vapers did not have any significant risk of	N/A	N/A	Low (15/20)

						impaired vasodilatation and endothelial dysfunction.			
Kelesidis et al., 2023;[71] US	Independent funding organization; no COI	N/A (N/A)	N=60; Median age of 24.0 years old; male (n=29), females (n=31).	Non-smoker current vapers (N=21): used only EC for >1 year. Non-vaper current smokers (N=18): Smoked only cigarette for >1 year. Non-users (N=21): Did not use either products for >1 year	Atherosclerosis Risk; not measured	Monocyte transendothelial migration: Significantly increased in non-smoker current vapers compared to non-users ($p<0.01$). But the level was significantly lower than that of non-vaper current smokers ($p<0.01$). Monocyte-derived foam cell formation: Significantly increased in non-smoker current vapers compared to non-users ($p<0.001$). But the level was significantly lower than that of non-vaper current smokers ($p<0.01$). Interpretation: Non-	N/A	N/A	Moderate (10/20)

						smoker current vapers had significant proatherogenic changes compared to non-users, but this change was significantly lower than that of non-vaper current smokers.			
Shiffman et al., 2023;[72] UK	JUUL Labs, many (pro-tobacco association)	N/A (N/A)	N=264; mean age ~ 45-years; 42.4% Male; 87.9% White.	Former smoker current vapers (N= 140): former smokers who switched completely to JUUL 5.0% nicotine ENDS for ≥ 6 months, and did not use cigarette or OTPs. Non-vaper current smokers (N=124): Smoked ≥10 cigarettes per day for ≥10 years and had not used other tobacco or nicotine-containing products in the past 30 days.	Endothelial dysfunction, cardiometabolic risk; not measured	Biomarkers of endothelial inflammation and oxidative stress: sICAM-1, total WBC count, IL-6, MCP-1, fibrinogen, CRP, PF2A8EP level were significantly lower in former smoker current vapers compared to non-vaper current smokers. HDL-C, LDL-C, total Chol, TG: Former smoker current vapers had significantly higher HDL-C and lower TG level compared to non-vaper current smokers ($p<0.0001$, $p<0.05$ respectively). NS difference in LDL-C and total cholesterol	N/A	N/A	Low (15/20)

						level was seen between groups. HbA1C or DM: Former smoker current vapers had significantly lower HbA1C level or prevalence of DM compared to non-vaper current smokers ($p<0.001$). Interpretation: Former smoker current vapers had significant lower prevalence of endothelial dysfunction and cardiometabolic risk compared to non-vaper current smokers.			
Shi et al., 2023;[73] China	Independent funding organization; no COI	N/A (N/A)	N=4,022; median age 55 years; 48.3% male; 32% NH white, 24.3% NH black, 13.5% Mexican American, 9.9% other Hispanic, 20.3% other races.	Non-users (74.9%): Did not use either cigarette or EC currently. Non-smoker ever vapers (5.8%): used EC even once, but did not use cigarettes currently Never-vaper current smokers (9.5%): Smoked cigarettes everyday or somedays, but never used EC. Dual users (9.8%): Used both cigarettes everyday or somedays currently and ever used EC.	Stroke; irreversible	Prevalence of stroke: Non-smoker ever vapers and dual users had significantly higher odds compared to non-users ($p=0.027$, $p<0.001$ respectively) Interpretation: EC use among non-smokers and dual users was associated with higher prevalent risk of stroke compared to non-users.	N/A	N/A	Low (8/8)
Case reports									

Glenski et al., 2021;[44] US	Not specified; no COI	Not specified (N/A)	N=1; 13 years old male; had Anomalous LCA originating from right sinus of Valsalva; vaped nicotine 2-3 times during the day of the event and just before starting exercise.	N/A	Cardiac arrest (Reversible)	EKG: Ventricular fibrillation and polymorphic ventricular tachycardia. Echo and CT angiogram: Anomalous left coronary artery (LCA) originating from the right sinus of Valsalva. Urine drug screen: Positive for nicotine and cotinine.	Sex: male (n=1)	Same as findings of the entire population	Low (7/8)
Grech et al., 2022;[45] Australia	None; no COI	Long-term (1 year)	N=1; 52 years old female; used one bottle EC with nicotine 6 mg/ml per fortnight for over 1 year and 3 pack of cigarettes/day since age over 36 years; had significant second-hand vape exposure prior to own use; had multiple comorbidities including CHD and COPD. Had no abnormal environmental exposure of CO at home.	N/A	Pulmonary arterial HTN and heart failure resulting from CO poisoning. (Irreversible)	ABG: Carboxyhaemoglobin (COHb) was grossly elevated, four times greater than are seen with cigarette smoking. COHb levels returned to normal within an average of 47 h using targeted oxygen therapy. Hypercapnia (partial pressure of carbon dioxide [PaCO2] range: 51-60 mmHg) without lactic acidosis Others: Elevated BNP and pulmonary arterial hypertension (mean pulmonary artery pressures of 26-45 mmHg) with high cardiac output (7.4-9.8 L/min).	Sex: Female (n=1)	Same as findings of entire population	Low (8/8)
Cell/*in Vitro* Studies									
Le et al., 2021;[46] US	Independent funding	Acute (48hrs)	Human induced pluripotent stem cell-derived	Control: untreated cells.	Endothelial dysfunction (Not measured)	ROS production after 48 hr exposure: increased significantly	N/A	N/A	

	organization; no COI		endothelial cells (iPSC-ECs)	E-cigarette aerosol Extract (EAE): EAE was made from menthol flavored e-liquid with PG:VG (50:50) + 24mg/ml nicotine, 2s puff duration, every 30s, with a 55-ml puff volume. Cells were incubated with diluted EAE for 48 h.		following EAE exposure in a concentration-dependent manner ($p<0.05$). Caspase 3/7 activity (apoptosis): was significantly increased in EAE exposure ($p<0.05$). Gene expression: 183 lncRNAs and 132 mRNAs were found to be upregulated, whereas 297 lncRNAs and 413 mRNAs were found to be downregulated with EAE exposure. Others: FAO activity assay increased ($p<0.05$), and glycolysis assay, glucose uptake assay decreased ($p<0.01$) in EAE exposure. The knockdown of LUCAT1($p<0.05$) (upregulated following EAE exposure) increased cell permeability. Interpretation: Acute EC exposure caused significant endothelial dysfunction.			
Mohammadi et al., 2022;[39] US	Independent funding organizations; no COI	N/A (N/A)	HUVECs culture was exposed to human sera and e-liquid aerosol condensates	Serum from-Non-smoker current vapers (n=42): used EC at least 5 times/week for 3 months.	Endothelial dysfunction (Not measured)	NO production, VEGF-induced NO secretion: reduced significantly ($p<0.05$ and $p<0.01$ respectively) on exposure to vapers sera	N/A	N/A	

			without and with nicotine and flavours (menthol, ethyl maltol, vanillin, cinnamaldehyde).	Non vaper current smokers (n=28): used at least 5 cigarettes/day for ≥1 pack year. Nonusers (n=50): did not use either e-cigarette or cigarette for 1 year.		compared to non-user sera. Endothelial H2O2 secretion and microvascular permeability: increased significantly on exposure to vapers sera ($p<0.05$) compared to nonuser sera. RAGE ligands: Vapers sera had higher concentrations of the receptor for RAGE ligands (S100A8 and HMGB1) than smoker ($p<0.05$) and nonuser sera ($p<0.05$). Interpretation: Vaping EC causes oxidative stress and RAGE has role in EC induced endothelial dysfunction.			
Mulorz et al., 2022;[47] US	Independent funding organization; no COI	Acute (24hrs)	Human aortic smooth muscle cells (AoSMC)	IL-6: Exposed to recombinant IL-6 for 24 hrs. IL-6 +10 nM nicotine: Exposed to recombinant IL-6 +10 nM nicotine for 24 hrs. IL-6 + 100 nM nicotine: Exposed to recombinant IL-6 +100 nM nicotine for 24 hrs.	AAA related inflammation (Irreversible)	Nicotine in IL-6+ 10nM Nicotine and IL-6 + 100nM nicotine groups increased inflammation, increased ROS and augments the effects of IL-6 in down-regulating pri-miR-24-1 in macrophages on human AoSMCs. Interpretation: EC induces changes which are crucial for mediating inflammation in AAA.	N/A	N/A	
Caruso et al., 2022;[48] Italy	Funded by tobacco company;	Acute (Single	HUVEC	Negative control: AqE capture media 0.1% FBS,	Endothelial wound healing (Not measured)	HUVEC migration/ wound area closure: NS reduction in wound	N/A	N/A	

	many (association with pro-tobacco company)	exposure- 48 hrs.)		Cigarette exposure (1R6F): 5-30% AqE concentration representing 0.64-3.84µg/ml of nicotine, Vype ePen 3: 40 to 100% concentration, 1.68- 4.2µg/ml nicotine, Glo™Pro: 40 to 100% concentration, 1.8-4.5µg/ml nicotine, Exposure was given at 55 ml puff volume, 30 s puff frequency, and 2s puff duration.		area on exposure to Vype ePen 3 or Glo™Pro compared with negative control. EC aerosol showed no effect on endothelial cells until 80%-100% concentrations. Interpretation: Vaping does not affect endothelial wound healing, unless in high nicotine concentration.			
Majid et al., 2023;[28] US	Independent funding organization; no COI	Acute (Single exposure-90 mins)	Human aortic endothelial cells (HAECs)	Control HAECs: Not exposed. Mango-flavoured JUUL: exposed to 5% nicotine JUUL in "Mango" flavour. Mint-flavoured JUUL: exposed to 5% nicotine JUUL in "Mint" flavour. Menthol- flavoured JUUL: exposed to 5% nicotine JUUL in "Menthol" flavour. Tobacco-flavoured JUUL: exposed to 5% nicotine JUUL in "Virginia Tobacco" flavour. PG:VG vehicle only:	Endothelial damage (Not measured)	Cell death in HAECs: A progressive increase in cell death with JUUL e-liquid exposure was observed across 0.0001–1% dilutions. PG:VG solvent alone induced a similar loss of cell viability as JUUL e-liquids and nicotine salts in PG:VG. A23187-stimulated NO production: Was decreased with all flavored JUUL e-liquids, PG:VG and nicotine salt exposures. IL-6 expression: Only mint flavored JUUL e-liquids had increased level at 0.0001 dilution; NS changes for other	N/A	N/A	

				exposed to 30:70 PG:VG PG:VG + nicotine salt: exposed to 30:70 PG:VG + nicotine salt 60 mg/ml. Cigarette: exposed to standard cigarette (3R4F) and low yield cigarette (1R5F).		groups. Oxidative stress/ROS production: Relative to control HAECs, menthol-flavoured JUUL e-liquid increased ROS production. Interpretation: Pod-based EC exposure can cause oxidative stress, inflammation and endothelial damage.			
Michon et al., 2022;[49] France	None; no COI	Acute (24hrs)	Human aortic smooth muscle cells (AoSMC)	E-liquid: exposed to 50/50 PG/VG without nicotine and flavour e-liquid. E-liquid + nicotine (18 mg/mL): same as previous group with added 18 mg/ml nicotine in e-liquid. EC aerosol condensate (low power, high power): Exposed to aerosol condensate generated from 40 puffs of e-liquid at 8W power (low) or 25W power (high). EC aerosol condensate (high power) +nicotine (18 mg/mL): Exposed to EC aerosol condensate with 18 mg/ml nicotine at 25 W power. EC aerosol condensate	Cardiovascular inflammation (Not measured)	Relative cytotoxicity (LDH release) and relative ROS production: NS difference between groups compared to control (unexposed) cells. IL-8 production: significantly increased in EC aerosol condensate (high power-25W, high power-25W+nicotine, high power-25W+nicotine+cinnamon flavour) compared to control cells. ($p<0.01$). Interpretation: Vaping increased vascular inflammation in high power settings, irrespective of presence of nicotine and cinnamon flavour.	N/A	N/A	

				(high power) +nicotine(18 mg/mL)+cinnamon flavour: Same as previous group with added cinnamon flavor in e-liquid.					
Liu et al., 2023;[50] US	Independent funding organizations; no COI	Acute (48hrs)	Induced pluripotent stem cell-derived endothelial cells (iPSC-ECs) from healthy individuals and PAH patients	Healthy iPSC-ECs: differentiated from 2 healthy individuals; PAH iPSCs-ECs: differentiated from 2 PAH patient-derived iPSCs. Both group of cells were exposed to EC AqE at varying concentrations (0, 0.2, 0.6, 0.8, 1, and 2 total puff equivalents (TPE)) for 48 hours.	PAH (Irreversible)	Cytotoxicity: PAH iPSCs-ECs had dose-dependent decrease in cell viability by apoptosis and necrosis and significantly higher ($p<0.05$) intracellular ROS levels than in healthy iPSC-ECs with 0.6 or 1 TPE EC treatment, while only the highest e-cig dose (1 TPE) affected healthy iPSC-ECs. Gene expression: differential expression of Akt3 may be responsible for increased autophagic flux impairment in PAH iPSC-ECs. Interpretation: PAH iPSC-ECs are more susceptible to ECs than healthy iPSC-ECs, vaping might have worsening effect on PAH.	N/A	N/A	

Chhor et al., 2023;[74] Australia	Independent funding organizations; no COI	Acute (24 hrs)	Human coronary artery endothelial cells	Control: exposed to air. PG/VG: Exposed to non-flavored EC aerosol condensate containing 80%/20% PG/VG. Non-nic EC: Exposed to tobacco flavored non-nicotine EC aerosol condensate containing 80%/20% PG/VG. Nic EC: Exposed to tobacco flavored EC aerosol condensate containing 80%/20% PG/VG and 18 mg/ml nicotine.	Endothelial dysfunction (Not measured)	Cell viability was significantly reduced following all 3 types of EC exposure ($p<0.05$ for all) compared to control. ROS production: Significantly increased following PG/Vg and Nic EC exposure compared to control ($p<0.01$ for both). NS changes seen in Non-nic EC exposure. Other biomarker expression: ICAM-1 protein expression significantly increased following Nic EC exposure compared to control ($p<0.01$). NS changes seen on PG/VG and Non-nic EC exposure. Interpretation: EC exposure, both nicotine or non-nicotine, induced significant endothelial dysfunction.	N/A	N/A	
Wölkart et al., 2023;[78] UK	None; None	Acute (24 hours)	Porcine aortic endothelial cells	Control: exposed to Cig: Exposed to cigarette smoke extract containing 0.8 mg. nicotine and 10 mg. tar. EC: Exposed to EC vapour extract from unflavored e-liquid containing 20 mg/ml nicotine and 50/50	Endothelial/vascular dysfunction (not measured)	Endothelial vasodilatation in response to bradykinin: NS changes seen in EC exposure compared to control. Metabolic activity/cytotoxicity: NS changes seen in EC exposure compared to control.	N/A	N/A	

				PG/VG. HTP: Exposed to IQOS extract containing 0.5 mg. nicotine.		Endothelial NO/cGMP signaling: NS changes seen in EC exposure compared to control. Interpretation: EC exposure did not affect vascular relaxation or endothelial function.			
Animal Studies									
Goto et al., 2022;[51] US	Independent funding organizations; no COI	Acute (Single exposure 1hr)	N=48; 12-14 weeks old C57BL/6J male mice	Control: exposed to air, 0 puff aged coil: Exposed to non-nicotine EC aerosol with a new coil, 900 puff aged coil: Exposed to non-nicotine EC aerosol with a 900 puff aged coil, 1800 puff aged coil: Exposed to non-nicotine EC aerosol with a 1800 puff aged coil. E-liquid was a mixture of PG/VG 50:50 ratio, no nicotine or flavour added. Puffs were given at 2 puffs/min, 100 ml/puff for 1 hour.	HR (Not measured)	Significant decrease ($p<0.001$) in HR was observed in 1800 puff aged coil exposure compared to control and 0puff aged coil exposure.	Sex: Male mice (n=48)	Same as study findings of entire population.	
Mills et al., 2022l;[52] US	Independent funding organizations; no COI	Acute (Single exposure)	N=49; 4 months old male Sprague-Dawley rats	Air (n=5): Exposed to air, Ecig 20 puffs (n=16): given as 20 puffs over 1 hour,	Vascular reactivity/dysfunction in MCA (Reversible)	Endothelium dependent dilatation: The greatest effect was observed within 24 h of exposure (~50%) ($p<0.05$), and	Sex: Male (n=49)	Same as study findings of entire population.	

				Ecig 60 puff (n=12): given as 20 puffs over a 1h for 3 hrs total, Traditional cigarette (n=16): given as 20 puffs over a 1h. E-liquid contained 50/50 PG/VG non-nicotine non flavoured fluid.		impairment persisted with for up to 3 days. NS difference seen between EC and Cig groups. Endothelium independent dilatation: Changes were less severe (~27%) ($p<0.05$) and shorter lived (recovering by D2) compared with endothelium-dependent dilatation responses. NS difference seen between EC and Cig groups. Vasoconstriction in response to serotonin: Greatest impairment (~45%) at D0-D1 ($p<0.05$), returning to normal by D2. NS difference seen between EC and Cig groups. Interpretation: Vaping EC with or without nicotine may cause cerebrovascular dysfunction similar to smoking cigarettes.			
El Mahdy et al., 2022;[53] US	Independent funding organization; no COI	Short to medium term, and Long-term (16 weeks; 60 weeks)	N=24; 16 weeks old male C57/BL6 mice.	Control: Exposed to air. EC-0: Exposed to EC aerosol with no nicotine. EC-6: Exposed to EC aerosol with nicotine 6 mg/ml.	Endothelial dysfunction (Not measured)	Endothelial dependent vascular relaxation: Following 16 week and 60-week of exposure, significant ($p<0.05$) impairment was observed in EC-0, EC-6 and EC-24 groups compared to control. Endothelial	Sex: Male mice (n=24)	Same as study findings of entire population.	

				EC-24: Exposed to EC aerosol with nicotine 24 mg/ml. Mice were given 20 cycles each day, each cycle consisting of 3.2 min of e-cig aerosol, followed by 2 min of fresh air purge and 5s of rest; 5 days per week for 16 or 60 weeks.		independent vascular relaxation: Following 16 week and 60-week exposure, significant ($p<0.05$) impairment was observed in EC-0, EC-6 and EC-24 groups compared to control. SBP, DBP, MAP and SVR: Significant increase ($p<0.05$) were seen in an exposure time (60 weeks >16 weeks) and nicotine dependent (EC-24> EC-6> EC-0 > control) manner. Superoxide, NADPH oxidase 2 generation and NT release in aorta: Significant increase ($p<0.05$) occurred in an exposure time and nicotine-dependent manner. Others: Significant reduction ($p<0.05$) in NO level, eNOS and p-AKT level in aorta and increase in eNOS uncoupling in an exposure time and nicotine dependent manner. Interpretation: EC exposure starts a vicious cycle of vascular oxidative stress that triggers endothelial dysfunction			

						and hypertension with predisposition to other cardiovascular disease.			
Sifat et al., 2022;[54] US	Independent funding organizations; no COI	Short to medium term (14 days)	N=~64; male C57BL/6 mice	JUUL: (n=31) Exposed to JUUL vapor 30 mg/ml nicotine (27.5 ml puff depth volume, 3 s puff duration, 2 puffs per 60 s, 32 puffs/cycle) 6 cycles/day for 14 days. TS: (n=23) Exposed to 3R4F standardized research cigarettes 9.4 mg tar and 0.726 mg nicotine/cigarette equivalent to full flavor commercial products (27.5 ml puff depth volume, 2 s puff duration, 2 puffs per 60 s, 32 puffs/cycle) for 14 days. Control: (n=10) After 14 days exposure, all groups including control underwent transient middle cerebral artery occlusion surgery followed by reperfusion to mimic ischemic stroke.	Outcome of ischemic stroke (Irreversible)	Brain histology: % infract area in the ischemic brain hemisphere was significantly higher in JUUL group ($p<0.01$) compared to control. NS difference in brain swelling ratio between JUUL and control. Blood inflammatory markers: Post-infarction, plasma thrombomodulin was significantly lower ($P<0.01$) in JUUL group compared to control. Brain Nrf2 and ICAM-1 expression: Significant decrease ($P<0.05$) in brain Nrf-2 expression was observed in JUUL group compared to control. The decrease in Nrf2 was not as much as that seen in TS group ($p<0.001$). Interpretation: JUUL exposure could negatively impact the cerebrovascular system, although to a lesser extent than TS exposure.	Sex: Male (n=~64)	Same as study findings of entire population.	
Fried et al., 2022a;[55] US	Independent funding	Short to medium term (12 weeks)	N=40; 10 weeks old female C57BL6/J mice	Intact air: Mice with intact ovaries exposed to room air.	PAH, and cardiac remodeling, cardiac	LV plus septal and RV weights: reduced by nicotine exposure and	Sex: female mice (n=40)	Same as study findings of entire population.	

	organization; no COI			OVX air: mice underwent bilateral ovariectomy (OVX) were exposed to room air. Intact Nicotine: Mice with intact ovaries exposed to nicotine vapour created from ≥99% free base e-liquid. OVX-nicotine: mice underwent bilateral OVX 1 week before nicotine exposure followed by exposed to nicotine vapour created from ≥99% free base e-liquid.	function (Not measured)	are unaffected by OVX. Fulton index, a marker of RV hypertrophy: was unaffected by both nicotine exposure and OVX. RV free wall thickness and RV internal diameter during diastole: Not affected by OVX or nicotine exposure. Cardiac function (RV systolic pressure, pulmonary vascular resistance, cardiac output, ejection fraction, and fractional shortening): Not affected by OVX or nicotine exposure. Interpretation: EC vapor was not associated with cardiac remodelling, cardiac function or PAH.			
Carll et al., 2022; [56]US	Independent funding organizations; no COI	Acute (90 minutes)	N=80; 12-30 weeks old male and female C57BL6/J mice.	Control: Exposed to HEPA or charcoal-filtered air MCS 3R4F or MCS 1R5F: Exposed to mainstream cigarette smoke 2s puff, 35 ml puff, 1 puff/min, 9 puffs/cigarette, 1 cigarette/session, 18 min washout between sessions, 2 sessions. EC sessions: were 4-s	Cardiac arrhythmia and conductivity (Reversible)	Cardiac conduction abnormality: EC-PG, EC-VG, EC-PG:VG, E-menthol and E-tobacco induced bradycardia, bradyarrhythmia, and elevations in heart rate variability (greatest change in EC-PG:VG) during inhalation exposure, with inverse post-exposure effects similar to Cig smoke. Significantly prolonged	Sex: male mice, female mice (sample no. by sex not specified).	Cardiac conduction abnormality: was lower in Female mice than male mice ($p<0.05$).	

				puffs, 91 mL puff, 2 puffs/min, 18 puffs/session, 9 min washout between sessions, 3 sessions. Following EC sessions were provided: EC-PG: exposed to 100% PG, EC-VG: Exposed to 100% VG, EC-PG:VG: Exposed to PG:VG at 50/50 v/v E-Tobacco: Exposed to 2.4% freebase nicotine with Classic Tobacco flavour, E-menthol: Exposed to 2.4% freebase nicotine with Magnificent Menthol flavour, E-cig solvents: 100% PG, 100% VG, and equal ratio PG:VG at 50/50 v/v. (three 9-min puff sessions), Acrolein: exposed to acrolein- biproduct of VG.		atrial conduction, increased ventricular arrhythmias and augmented early ventricular repolarization, and high-grade supraventricular blocks were seen in all EC session, highest effect seen in EC-PG:VG. Interpretation: PG or VG or flavors in EC could contribute to cardiac risk by provoking pro-arrhythmic changes and stimulating autonomic reflexes.			
Fried et al., 2022;[57] US	Independent funding organization; no COI	Short to medium term (8 weeks)	N=46; 8-12 weeks old male mice	Air (n=19-23): exposed to room air, Nicotine (n=19-23): exposed to inhaled nicotine for 12 h on/12 h off schedule. After 4 weeks of exposure, a subset of mice was implanted with subcutaneous osmotic mini-pumps containing angiotensin-	Cardiac remodelling (Irreversible)	LV posterior wall thickness at systole: was lower in Nicotine+ Ang-II group compared to air +Ang-II group LV posterior wall thickness at diastole: NS difference was seen. LV internal diameter at systole and LV internal diameter at diastole: NS differences observed.	Sex: male mice (n=46)	Same as study findings of entire population.	

				II (Ang II) for infusion at a dose of 450 ng/kg per min for a duration of 4 weeks while maintaining either nicotine- or air-exposure.		LV mass index (LVMI): Ang II significantly increased LVMI ($p < 0.0001$) in both air and nicotine exposed mice. Nicotine caused significant reduction of LVMI ($P < 0.05$). Relative wall thickness (RWT): NS difference was seen. Interpretation: Nicotine EC exposure is possibly associated with cardiac remodeling.			
Getiye et al., 2022;[58] US	Independent funding organizations; no COI	Short to medium term (6 months)	N=39; 2 months old male, C57BL/6 wild type (WT), caspase recruitment domain containing protein 9 (CARD9)-/-, and NOD-like receptor family pyrin domain containing 3 (NLRP3)-/- mice	Control: Air exposed. EwH: Exposed to 6 mg/ml nicotine, PG/VG 7.5:17.5 ratio, raspberry flavoured EC aerosol by heating the e-liquid for 3 h/day, 5 days/week for 6 months. EwoH: Exposed to 6 mg/ml nicotine, PG/VG 7.5:17.5, raspberry flavoured EC aerosol without heating the e-liquid for 3 h/day, 5 days/week for 6 months.	Cardiac remodelling (Not measured)	Transthoracic echocardiography: EwH exposure had significantly increased ($p<0.01$) RV free wall thickness at systole and diastole. But, EwoH exposure had significantly ($p<0.05$) decreased wall thickness at systole compared to control in WT mice, but not in CARD9-/- and NLRP3-/- mice. RV fractional shortening was also markedly reduced ($p<0.01$) in EwH exposure compared to control in WT mice and NLRP3-/- mice. Pulmonary artery peak velocity decreased significantly ($p<0.01$) in EwH exposure but increased significantly	N/A	N/A	

						(p<0.05) in EwoH exposure compared to control in WT mice. Interpretation: EC aerosol exposure induced significant cardiac remodelling.			
Rao et al., 2022;[59] US	Independent funding organizations; no COI	Acute (Single exposure)	N=88; 9-11 weeks old Sprague-Dawley rats; 50% male, 50% female rats.	Control Group: n = 8; exposed to room air. PG exposed: n = 8; 100% PG. VG exposed: n = 8, 100% VG . PG+VG (no nicotine) exposed: n = 8; 100% PG and 100% VG. Previous Gen e-cigarette exposed: n = 8, exposed to 1st generation EC. USONICIG exposed: n = 8; exposed to unflavored e-liquid consisting of 60%:40% PG:VG with 12 mg/mL freebase nicotine. JUUL Virginia Tobacco/menthol/mango exposed: n = 24; exposed to 5% nicotine, 60%:30% VG:PG e-liquid, IQOS exposed: n = 8, . Marlboro Red exposed: n = 8,	Endothelial dysfunction (Not measured)	FMD: was impaired in all groups except controls (P<0.05). NS difference in FMD impairment between groups. Platelet aggregation: NS effect was seen in any groups. Serum NO levels: NS change in in any groups. Interpretation: Vaping increases risk of endothelial dysfunction like smoking.	Sex: Male (n=44), female (n=44).	NS difference in FMD, platelet aggregation and serum NO level between males and females.	

				Exposure was given in 10 cycles, each cycle was 5 second exposure, followed by 25 seconds of clean air, for 5 minutes.					
Moshensky et al., 2022;[60] US	Independent funding organizations; no COI	Short to medium term (4-12 weeks)	6-8 weeks old female C57BL/6 mice	Randomized to- Air (control) (room air only), JUUL Mint (5% nicotinic salts in mint flavour), JUUL Mango (5% nicotinic salts in mango flavour), Exposure was given 20 mins at a time, three times daily, for a total of 60 min per day, for 4-12 weeks; harvest occurred 30 minutes after the last exposure.	Cardiac inflammation (Not measured)	Cardiac tissue gene expression: No pro-inflammatory cytokines or chemokines examined were upregulated by JUUL exposure. Mechanic scan for physiology: NS changes in cardiac physiology. at 1 or 3 months. Cardiac histology: did not induce cardiac fibrosis. Interpretation: JUUL aerosol did not cause cardiac inflammation directly.	Sex: female mice	Same as study findings of entire population.	
Piechowski and Bagatto, 2021;[61] US	Independent funding organization; no COI	Acute (Single exposure 24hrs)	(N~223); Zebrafish embryos	Untreated control (n~85) Chocolate flavoured EC (n~78): Exposed to 'Chocolate Delight' EC vapor containing 0 nicotine and 70 : 30 PG/VG ratio at t 0.6, 12, and 25 puffs/L exposure concentration. Cinnamon flavoured EC.: (n~61) exposed to 'Red hot cinnamon" vapor containing 0	Embryonic cardiovascular development and function (Not measured)	Embryonic end systolic volume, end diastolic volume, stroke volume, HR, mean cardiac output, red blood cell density, and arterial and venous blood vessel diameters: Cinnamon flavoured EC significantly decreased ($P<0.05$) all these parameters at 25 puffs/L exposure compared to untreated control, with the exception of blood vessel diameter.	Pregnant/post-partum: Embryo	Same as study findings of entire population.	

				nicotine and 70 : 30 PG/VG ratio at t 0.6, 12, and 25 puffs/L exposure concentration. EC used was a second-generation vape pen with 25W max output		NS effect was seen on exposure to 0.6 or 12 puffs/L cinnamon flavored EC. NS effect on any of the parameters was seen with chocolate flavoured EC irrespective of exposure concentration. Interpretation: Cinnamon flavored EC vapor can affect cardiovascular function during early development, even in the absence of nicotine, particularly at elevated exposure concentrations.			
Mulorz et al., 2022;[47] US	Independent funding organization; no COI	Short to medium term (6 weeks)	N~29-52; 8weeks old male and female C57BL/6J and Apo (Etm1Unc) mice.	Control: Exposed to room air for 6 weeks. EC: Exposed to PG/VG 50%/50% and 24 mg/mL nicotine for 6 weeks; puff duration of 9s per minute for a total of 60 min at the same time each day. After 2 weeks of exposure, AAA was surgically induced in the infrarenal segment with PPE infusion (or saline for sham-operation)	AAA, BP (Irreversible)	BP: NS change on EC exposure. Inflammatory cytokines: Expression of pro-inflammatory (IL-6, Ccl2) and extracellular matrix remodelling genes (Mmp9) known to be crucial for AAA development were increased and elastin decreased in mice exposed to EC (vs. controls) by 7 days after surgery ($p<0.05$). Aortic expression of the novel cytokine Chil1 was significantly upregulated ($p<0.05$) at both 7 days and 28 days follow-ups post-surgery and miR-24 expression	Sex: male (n=5-13) and female mice (n=5-13).	Growth of AAA: Both male and female C57BL/6J mice in the EC group developed larger AAA when compared to controls after AAA induction. NS difference in aortic expression of cytokine Chil1 between male and female mice.	

						(p<0.05) downregulated at 7 days follow-up in mice exposed to EC (vs. controls). Inflammatory cytosis: Increased F4/80 marker expression in the aneurysms of EC (vs. controls) animals after 28 days post-surgery, indicating enhanced macrophage infiltration when mice were exposed to EC vapour. Interpretation: EC promotes growth of AAA.			
Yu et al., 2021;[62] US	Independent funding organizations; no COI	Short to medium term (10 days)	N=80; ALDH2 mice and ALDH2*2 knock-in mouse	Room air exposed wild type ALDH2 mice (n=20), Room air exposed homozygous ALDH2*2 mice (n=20), EC exposed wild type ALDH2 mice (n=20), EC exposed ALDH2*2 mice (n=20). 3 brands of EC were used: JUUL (30/70 PG/VG, 50 mg/ml), Halo (50/50 PG/VG, 25 mg/ml), Blu (60/40 PG/VG, 25 mg/ml).	HR, Cardiovascular inflammation (Not measured)	Oxidative stress: in EC exposed ALDH2*2 cardiomyocytes, there were 4-fold greater peak calcium influx, 2-fold increase in ROS production and 2-fold increase in 4-HNE-induced protein adducts relative to wild-type ALDH2 cardiomyocytes. HR: In ALDH2*2 mice increased ~200 beats/min, while HR in ALDH2 mice increased ~150 beats/min after 10 days of e-cigarette exposure, relative to air-exposed mice. Interpretation: people carrying an ALDH2*2 genetic	N/A	N/A	

						variant may be more susceptible to increases in HR and cardiovascular oxidative stress from EC aerosol exposure.			
Whitehead et al, 2022;[63] US	Independent funding organization; no COI	Short to medium term (12 weeks)	57BL6/J Wild-type (WT) and α7-nAChR knockout (α7-nAChR−/−) mice	Control: Exposed to room air Nicotine exposure: (7-8 L/min) The nicotine vapor exposure was set on a 12h on/12h off schedule that overlapped with the dark cycle	Cardiac remodelling, PAH and vascular dysfunction (Not measured)	Echocardiography: Male WT mice developed increased RV systolic pressure with RV hypertrophy and dilatation following 12-week nicotine vapor exposure. NS changes in α7-nAChR−/−mice regardless of genotype. ACh induced vasodilation in aorta and pulmonary arteries: was impaired on nicotine exposure in both type of mice eNOS release: Altered eNOS phosphorylation and reduced plasma nitrite levels was seen in WT but not α7-nAChR−/−mice. Gene expression: Upregulation of multiple inflammatory pathways in thoracic aortas was seen in WT but not α7-nAChR−/−mice. Interpretation: α7-nAChR mediates chronic nicotine inhalation-induced PAH, RV remodeling	Sex: male and female mice	Echocardiography: Male WT mice developed increased RV systolic pressure with RV hypertrophy and dilatation following 12-week nicotine vapor exposure. These effects were not seen in female WT mice. NS changes in male α7-nAChR−/−mice or female mice regardless of genotype. Interpretation: Females appear protected from nicotine-induced PAH and RV remodelling following exposure to nicotine.	

						and vascular dysfunction.			
Lorkiewicz et al., 2022;[29] US	Independent funding organizations; no COI	Acute (6hrs)	N=28; C57BL/6J wild type male mice	Control group: filtered air exposure, PG:VG exposed mice: Exposed to PG:VG mixture (50:50 or 30:70ratio, v:v) for 6 hrs. JUUL-exposed mice (JUUL-Virginia Tobacco/JUUL-V, JUUL Mango, JUUL Menthol): Exposed to JUUL aerosol over 6 hrs in 20 evenly spaced 9 min sessions. Mainstream cigarette smoke (MCS) exposed mice: exposed to either 6 or 12 cigarettes over 6 hrs.	Cardiovascular dysfunction (Not measured)	Urinary 3HPMA and 23HPMA levels: PG:VG, JUUL-V exposed mice had higher levels within 0-3 h of exposure than controls ($p<0.05$). JUUL-V and JUUL Mango exposed mice had higher urine 3HPMA level than MCS exposed mice ($p<0.05$). JUUL-Menthol exposed mice had higher urinary 23HPMA levels than controls ($p<0.05$) and MCS exposed mice ($p<0.05$). Interpretation: EC exposure increased acrolein metabolites in urine and thus increases risk of CV dysfunction.	Sex: Male mice (n=28)	Same as study findings of entire population.	
Shi et al., 2022a;[64] US	Independent funding organization; no COI	Acute (4hrs)	N=80; 5 months old Sprague-Dawley rats; 40% male, 50% female.	Control: (n=16) exposed to pure air, EC conditions (N=64): 50:50 PG:VG, classic tobacco flavour; randomized to either stainless steel (SS) n=16 or nickel-chromium (NC) n=16	Cardiac inflammation (Not measured)	NS histologic changes in cardiac tissue. EC vapor generated using burnt coils caused myocarditis. Interpretation: EC apparently does not	N/A	N/A	

				heating element, each of which again were divided into high power (70 W) n=16 or low power (45 W) n=16 settings.		cause cardiac inflammation, except aerosol generated by burnt coil.			
Chhor et al., 2023;[74] Australia	Independent funding organizations; no COI	Acute (24 hrs)	N=28; 7-week-old Balb/c female mice	Control: exposed to air. PG/VG: Exposed to non-flavored EC aerosol condensate containing 80%/20% PG/VG. Non-nic EC: Exposed to tobacco flavored non-nicotine EC aerosol condensate containing 80%/20% PG/VG. Nic EC: Exposed to tobacco flavored EC aerosol condensate containing 80%/20% PG/VG and 18 mg/ml nicotine.	Endothelial dysfunction (Not measured)	Biomarker protein expression: mRNA expression for ICAM-1 (endothelial cell adhesion molecule) significantly increased following Nic EC exposure compared to control ($p < 0.05$). mRNA expression for FKBPL (anti-angiogenic marker) significantly increased following Non-nic EC exposure compared to control ($p < 0.05$). Interpretation: EC exposure, both nicotine and non-nicotine, induced significant endothelial dysfunction.	Sex: Female mice (n=28)	Same as study findings of entire population.	
Dai et al., 2023;[75] US	Independent funding organizations; no COI	Short to medium term (8 weeks)	N=120; 6 weeks old Sprague Dawley rats; both male and female rats	Control (n=32): exposed to filtered air, EC with nicotine (n=26): exposed to EC vapor with 15 mg/ml nicotine, EC without nicotine (n=26): exposed to only EC vapor, Standard Cig smoke (n=31): exposed to 1R6F reference Cig. Exposure was given as	MI, cardiac function (irreversible)	Ishchaemic risk area (%), infarct size, no reflow zone: NS difference was seen between groups. LV wall thickness: was significantly higher among EC with nicotine group than others ($p<0.001$). Cardiac output, LV positive and negative dp/dt: Significant reduction ($p<0.01$ and $p<0.05$	N/A	N/A	

				5 hours/day, 4 days/week for 8 weeks followed by 30 mins of LCA occlusion and 3 hours of reperfusion thereafter.		respectively) was seen among EC with nicotine compared to standard Cig group. SVR: Significant increase ($p<0.05$) was seen in EC with Nicotine group compared to cigarette group. Interpretation: Exposure to EC did not worsen MI, but impacted cardiac function more than smoking cigarette.			
Han et al., 2023;[79] US	Independent funding organizations; no COI	Acute (5 min); short-to-medium (2 weeks)	N=32; 10-week-old Sprague-Dawley rats; 50% male and 50% female	Acute exposure: Single session of 10 cycles of pulsatile 5s exposure over 5 minutes in 4 groups: Air (n=8): Exposed to air and DMSO (vasodilator/vehicle) or RAGEi (inhibitor of RAGE- hypothesized mediator of endothelial dysfunction in EC) PG/VG (n=8): Exposed to flavorless PG/VG and either DMSO or RAGEi Nic-EC (n=8): Exposed to PG/VG with 12 mg/ml freebase nicotine containing EC aerosol and either DMSO or RAGEi Cig (n=8): Exposed to Marlboro Red Cig and either DMSO or RAGEi.	Endothelial/vascular dysfunction (Not measured)	FMD: Significantly reduced following both acute and short-to-medium term exposure of Nic-EC + DMSO ($p<0.01$ for both) compared to pre-exposure value, which was recovered by introduction of RAGEi. Significantly reduced following acute exposure of PG/VG + DMSO ($p<0.01$) compared to pre-exposure value, which was recovered by introduction of RAGEi. Interpretation: Acute exposure to EC, both nicotine and non-nicotine and Short-to medium term exposure to nicotine EC significantly impaired vascular relaxation,	N/A	N/A	

				Short-to-medium term exposure: Single session of 120 cycles of pulsatile 5s exposure over 1 hour/day for 2 weeks in 2 groups: Air: Exposed to air and either DMSO or RAGEi Nic-EC: Exposed to PG/VG with 12 mg/ml freebase nicotine containing EC aerosol and either DMSO or RAGEi		which was mediated by RAGE.			
Whitehead et al, 2024;[76] US	Independent funding organizations; no COI	Short to medium term (10-12 weeks)	N= 80-96; 6-7 weeks old male and female C57BL/6N mice	Mice were randomly assigned to one of four groups: Air+ RD: received regular diet (22 kcal% fat) and exposed to air, Air + HFD: received high fat diet (60 kcal% fat) and exposed to air, Nic + RD: received regular diet (22 kcal% fat) and exposed to Nicotine vapor, Nic + HFD: received high fat diet (60 kcal% fat) and exposed to nicotine vapor. The nicotine exposure was carried out on a 12-h on/12-h off schedule for 10-12 weeks	HR, BP, endothelial/vascular dysfunction, Cardiac dysfunction and remodelling	HR: Significantly decreased ($p<0.05$) in both Nic + RD and Nic + HFD male mice compared to Air + RD and Air + HFD male mice respectively. BP: NS difference was seen between male mice groups. LV posterior wall thickness, LV end diastolic pressure: Significantly increased ($p<0.05$ at least) in Nic + HFD male mice compared to either Air + RD, or Nic + RD male mice. Similar increase in LV end diastolic pressure was also seen in Nic + HFD female mice LV internal diameter:	Sex: Male mice (n=56); Female mice (n=40)	Same as study findings of entire population.	

						NS difference between male mice groups. eNOS function and endothelium dependent vasodilatation: Significantly impaired ($p<0.05$ at least) in Nic + HFD male mice compared to male mice of other 3 groups. Interpretation: Exposure to EC with high fat diet did not increase HR and BP, but impaired cardiac and cardiovascular functions.			
Roxlau et al., 2023;[77] Germany	Independent funding organization(s); no COI	Short to medium term (8 months)	Wild-type C57BL/6 J mice	Control: Exposed to filtered air, EC: exposed to nicotine free EC vapour prepared from 60%/30% PG/VG containing e-liquid. EC+ Nic: exposed to EC vapour prepared from 60%/30% PG/VG and 18mg/mL nicotine containing e-liquid. EC vapor was given as 6 hr/day, 5 days/week for 8 months.	PAH, cardiac dysfunction; not measured	RV systolic pressure, Fulton index, cardiac index, RV wall thickness: NS difference was seen between groups. Interpretation: EC exposure did not affect cardiac function and pulmonary vasculature.	N/A	N/A	

Abbreviation: Abbreviations: AA, African American; AAA, abdominal aortic aneurysm; ABI, ankle brachial index; ACh, Acetylcholine; AqE, aqueous aerosol extract; BP, blood pressure; CAC, circulatory angiogenic cells; CHD, coronary heart disease; Cig, cigarette; CI, confidence interval ; COI, conflict of interest; CV, cardiovascular; CVC, cutaneous vascular conductance; CVD, cardiovascular disease; DBP, diastolic blood pressure; DMSO, Dimethyl sulfoxide; EC, e-cigarette; EHR, electronic health record; ENDS, electronic nicotine delivery system; eNOS, endothelial nitric oxide synthase; FAO, Fatty acid oxidation; FBS, Fetal bovine serum; FMD, flow mediated dilatation; HDL, high density lipoprotein; HFD, High fat diet; HR, heart rate; hsCRP, High sensitivity C-reactive protein; HTN, hypertension; HUVEC, human umbilical vein endothelial cells; H_2O_2, hydrogen peroxide; LDH, lactate dehydrogenase; LV, left ventricle; MAP, mean arterial pressure; MCA, middle cerebral artery; MI, myocardial infarction, MPO, Myeloperoxidase; NRT, nicotine replacement therapy; N/A, not applicable; NO, nitric oxide; NH, Non-Hispanic; NS, not significant; NT, nitrotyrosine; OR, odds ratio; PAH, Pulmonary arterial hypertension; PG, propylene glycol; PWV, Pulse wave velocity; RAGE, Receptor for Advanced Glycation Endproducts; RD, Regular diet; RHI, Reactive hyperemia index; ROS, reactive oxygen species; RPP, rate pressure product; RV, right ventricle; SBP, systolic blood pressure; sd, standard deviation; SNP, sodium nitroprusside; SVR, systemic vascular

resistance; TC, total cholesterol; US, The United States; UK; The United Kingdom; VEGF, vascular endothelial growth factor; VG, vegetable glycerin; 3HPMA, 3-hydroxypropylmercapturic acid; 23HPMA, 2,3-dihydroxypropylmercapturic acid.

Supplementary File 3. Summary of studies retrieved from the 2022 McNeill et al. review for subgroup analysis (n=7).

Author and year; countries	Funding source	Type of exposure (exposure length/follow-up duration)	Total Participants. characteristics	Intervention/ grouping(s)	Health condition/ Outcome (reversibility of health condition)	Study findings	Subgroup characteristics	Subgroup findings
Sex-based analysis: Humans								
George et. al, 2019;[80] UK	Independent funding organization	Short-to-medium term (1 month)	N=114	Participants were randomised into: EC Nicotine Group (n=37): containing 16 mg nicotine EC Nicotine Free Group (n=37), TC Nicotine Group (n=40)	Endothelial function following transition from smoking to vaping. (Not measured)	FMD: Those with the lowest tertile of CO (best compliance with EC and least dual use) had the greatest gain in FMD improvement.	EC Nicotine Group (n=37): Male n= 14, female n= 23 EC Nicotine Free Group (n=37): Male n=12, female n= 25, TC Nicotine Group (n=40): Male n=13, female n=27	FMD: Significantly greater improvement in vascular function was seen in females ($p<0.05$) who switched from TC to EC. Interpretation: Switching from smoking to vaping improved vascular function more in females than males.
Haptonstall, 2020;[86] US	Independent funding organization	Acute (30 min)	N=136	Chronic (>12 months) EC vapers who did not smoke TCs (no dual users): n=49, Chronic (>12 months) TC smokers: n=40, Nonsmokers: n=47, Chronic EC vapers participated in 4 acute exposure sessions in random order separated by 4 wk; 1. sham vaping,	Endothelial dysfunction (Not measured)	Baseline FMD: NS change in EC nicotine or EC nicotine free groups.	Sex: Nonsmokers: 22 Male, 25 Female E-Cig: 36 Male, 13 Female TC: 26 Male, 14 Female	Baseline FMD - no interaction effect for group and sex in percent change, absolute change, or normalized shear stress. Interpretation: No sex-based differences seen for endothelial dysfunction

				a control session consisting of puffing on an empty EC; 2) EC with nicotine; 3) EC without nicotine; and 4) nicotine inhaler				seen between male and female.
Sex Studies: Animals								
Li et al., 2021; [81] US	Independent funding organizations	Short to medium term (16 week)	ApoE−/− Female and Male (8-week-old mice) n = 5-10 per group	Mice received exposure to e-cig aerosol (classic tobacco flavor containing 2.4% nicotine) or filtered air. Mice received whole body exposure for 2 h per day for 5 successive days per week, over a 16-week period	Atherosclerosis (Not measured)	See subgroup findings	ApoE−/− Female and Male (8-week-old mice)	EC exposure significantly upregulated atherosclerotic lesion size and TLR9 expression in lesions of both male and female mice. Females had significantly increased expression of inflammatory markers-TLR9, VCAM-1, Mac-2 in the lesions; and increased plasma levels of RANTES, 8-OHdG, mtDNA/nDNA. Interpretation: EC exposure promotes atherosclerosis; the effects was higher in female than male mice.

Shi et. al, 2019;[83] US	Independent funding organizations	Short to medium (14 days)	Male and Female mice (n ~24)	Exposure to e-cigarette vapor (24 mg/ml nicotine) in mice vs. exposure of air. Whole body exposure to e-cig for 3 hours per day for 14 consecutive days.	Cardiac angiogenesis/function (Not measured)	Heart weight: NS change was seen in e-cig exposure.	See group characteristics	Collagen 1 protein: increased slightly, NS difference between males and females. CD31, CD 34 expression: increased in cardiac tissue compared to control for both male and female (p=0.02, p=0.04). VEGF expression in cardiac tissue: NS changes in both sexes. Interpretation: No sex-based differences seen in cardiac angiogenesis.
Jin et al., 2021;[85] US	Independent funding organization	Not reported	5-18 mice per group Male and Female (C57BL/6J mice)	Mice were exposed to: 1) air 2) formaldehyde (FA) aerosol - 5 ppm 3) acetylaldehyde (AA) aerosol - 5 ppm 4) propylene glycol and vegetable glycerin (PG-VG) aerosol - 30:70	Endothelial dysfunction	See subgroup findings	Male and female mice	Female mice had a decrease in ACh-dependent relaxation or phenylephrine-induced contraction. NS change was

								seen in male mice. Interpretation: Only female mice showed signs of endothelial dysfunction.
Single-Sex Studies: Animal								
Olfert et al., 2018;[82] US	Independent funding organizations	Short to medium (8 months)	N=45,15 10-wk-old female C57BL/6J mice	E-cig vapor (cappuccino-flavored, 18 mg/ml nicotine), 3R4F reference cigarette smoke, Filtered air (control) Whole body exposure was given for 4 hours a day in a 6h window for 5 days a week for 8 months	Cardiovascular function (Not measured)	See subgroup analysis	10-wk-old female C57BL/6J mice	Aortic arterial Stiffness: A nearly threefold greater increase in E-cig was seen compared to air-exposed mice ($p < 0.05$) EF%: Significantly lower ($p < 0.10$) in E-cig-exposed mice, compared to air-exposed mice. Interpretation: EC exposure increases arterial stiffness and lower EF.
Szostak et al., 2020;[84] Switzerland	Independent funding organization	Short-to-medium term (6 months)	N=35 Female ApoE-mice (12-14 wk old)	Sham (exposed to fresh air, 3R4F reference cigarette (3R4F),	Vascular inflammation and atherosclerosis (Not measured)	See subgroup findings	N=35 Female ApoE-mice (12-14 wk old	Vascular inflammation: NS changes in urinary 2,3-d-TXB2, 11-dh-

				PG/VG (carrier), PG/VG/nicotine: (base) (4% nicotine) PG/VG/nicotine/flavoring (test) (4% nicotine) Exposed to TC or E-vapor aerosols for 3 h/day, 5 days/wk in whole body				TXB2, and HETE levels were observed. Atherosclerotic Plaque Surface and Volume: decreased in mice exposed to the carrier, base, and test aerosols showed smaller plaque areas compared to 3R4F mice, , at 3 and 6 months of exposure. Pulse Wave Velocity (PWV): the base and test groups showed a significant increase ($p < 0.05$) in PWV compared to sham group and decrease in PWV compared to 3R4F CS group ($p < 0.05$). Interpretation: EC exposure caused no vascular inflammation

								and less atherosclerotic change than TC.

Abbreviations: EC, e-cigarette; ECV, e-cigarette vapor; OR, odds ratio; CI, confidence interval; NS, not significant; N/A, not applicable; PG, propylene glycol; VG, vegetable glycerin; US, the United States; UK, the United Kingdom.

Supplementary File 4. Sources and risk of bias of studies included in the meta-analysis (n=12).

Author and year	Our analysis	2022 McNeill et al. review	Risk of bias
Benowitz et al., 2020[9]		✓	Some concerns
Kerr et al., 2019[10]		✓	Some concerns
Maloney et al., 2020[11]		✓	Some concerns
Dimitriadis et al., 2022[25]	✓		High
Majek et al., 2023[66]	✓		Low
Chaumont et al., 2018[12]		✓	Low
Chaumont et al., 2020[13]		✓	Some concerns
Boas et al., 2017[14]		✓	Moderate
Fetterman et al., 2020[15]		✓	Moderate
Mohammadi et al., 2022[39]	✓		Low
Boakye et al., 2023[70]	✓		Low
Biondi-Zoccai et al., 2019[16]		✓	Some concerns

Note: The details of the 2022 McNeill et al., review studies (i.e., study population, comparator groups, study findings, risk of bias assessments) can be found in their paper (McNeill A, Simonavičius E, Brose L, et al. Nicotine vaping in England: an evidence update including health risks and perceptions, 2022. A report commissioned by the Office for Health Improvement and Disparities. London: Office for Health Improvement and Disparities, 2022).

Supplementary File 5: Methodology of meta-analyses.

We conducted meta-analysis of human studies for any specific outcome if the studies met following eligibility criteria: 1) consistent comparison groups between studies; 2) clear definition of the exposure received and the comparison groups; 3) same study designs. We excluded studies that provided data in arithmetic mean and standard deviation (SD) in graphs, but no studies were excluded based on their quality.

Studies that assessed effects on heart rate (HR) and blood pressure (BP) only met the eligibility criteria for conducting mete-analyses. For this purpose, we added eligible studies from our review to the existing meta-analyses of the 2022 McNeill et al. review[1] and update the findings. As HR and BP measurement were provided as arithmetic mean and SD, we calculated the mean difference with 95% confidence interval (CI) and p-value. We considered statistically significant results when the p value was <0.05 or 95% CI did not cross the null value. Heterogeneity in the dataset was determined as low, moderate and high, when the I^2 statistics value was <25%, 25-50% and >50% respectively.[2] If the number of studies included in the meta-analysis was higher than 2, we used a random effect model, otherwise we used a fixed effect model.[3] Additionally, we conducted sensitivity analysis by removing one study at a time and observing the change in the effect estimates and heterogeneity.[4] As the number of studies included in each meta-analysis were less than 10, we avoided assessment of publication bias in the included stidies.[5] R statistics (version 4.3.0) was used for the meta-analyses.

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Supplementary File 6: Methodology of quality assessment.

We used different risk of bias assessment tools for different types of study designs. For randomized controlled trials (RCTs) and cross-over trials, we used the Cochrane risk of bias tool for randomized trials (Version 2) (RoB2).[1] For non-randomized experimental studies and longitudinal observational studies, we used the Risk of Bias in Non-randomized Studies of Interventions tool (ROBINS-I)[1] and Risk of Bias in Non-randomized Studies- of Exposure (ROBINS-E) tool respectively.[2] We used the BIOCROSS risk of bias tool[3] for cross-sectional studies when it involved assessment of the health effects by biomarkers, otherwise we used the Joanna Briggs Institute (JBI) critical appraisal tool for analytical cross-sectional studies.[4] For case reports and case series, we also used the JBI critical appraisal tools.[4] We did not assess quality of cell/*in vitro* studies and animal studies.

While the quality assessment in ROB2 and ROBINS-E tool is presented as 'low', 'some concerns', 'high'[1] and sometimes 'very high' risk of bias,[2] similarly the ratings in ROBINS-I are 'low', 'moderate', 'serious', or 'critical' risk of bias.[1] The BIOCROSS tools includes 10 items and for each item the score could be between 0 to 2.[3] Following the approach of Christou et al,[5] a study was considered to have a 'low', 'moderate' or 'high' risk of bias if the total score was 13-20, 7-12, and ≤6 respectively. The JBI critical appraisal tools for cross-sectional and case studies contain 8 item checklists, while the JBI tool for case series include 10 item checklist.[4] For each item appraised, we assigned a score of 1 if the criterion was met, and 0 if the criterion was not met or was unclear. We followed the approach applied by Goplen et al.[6] and considered a study to have a 'low', 'moderate' or 'high' risk of bias if the total score was ≥70%, 50-70%, <50% respectively.

Validation of the 2022 McNeill et al. review

As the 2022 McNeill et al. review[7] has already conducted their own quality assessment for their studies, we did not conduct any separate quality assessment for the studies retrieved from the 2022 McNeill et al. review for subgroup analysis. However, we aimed to replicate the study selection and data extraction process of their review. We repeated their search strategy in MEDLINE and used their search period between August 2017 to June 2021. We screened the first 1,000 search results based on our eligibility criteria and assessed whether the selected studies match with 2022 McNeilll et al. review.[7] For validating the data extraction process, we randomly selected 40 studies from the 427 original studies included in the 2022 McNeill et al. review[7] and conducted the full-data extraction on these 40 studies to assess whether our findings match their results. Our findings on the validation of the 2022 McNeill et al. review[8] found minor discrepancies, details will be provided upon further requests. Our findings on the validation of the 2022 McNeill et al. review[8] found minor discrepancies, details will be provided upon further requests.

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Supplementary File 7. Quality assessment findings (RoB tools)

Table 1. Risk of bias (RoB) assessment of randomized controlled trials and Cross-over trials with the Cochrane risk of bias tool for randomized trials (Version 2) (RoB2).

Author and year; countries	Domain 1: RoB arising from the randomization process	Domain 2: RoB due to deviations from the indented interventions	Domain 3: RoB due to missing outcome data	Domain 4: RoB in measurement of the outcome	Domain 5: RoB in selection of the reported result	Overall RoB
Klonizakis et al., 2022;[21] UK	Low	Low	Low	Low	Low	**Low**
Klonizakis et al., 2021;[22] UK	Low	Low	Low	Low	Low	**Low**
Maclean et al., 2021;[23] US	Low	Low	Low	Low	Low	**Low**
Gueorguieva et al., 2022;[24] US	Some concerns	Low	Low	Low	Low	**Some concerns**
Dimitriadis et al., 2022;[25] Greece	Low	High	Low	Low	Low	**High**
Belkin et al., 2023;[65] Switzerland	Low	Some concerns	Low	Low	Low	**Some concerns**

Table 2. Risk of bias(RoB) assessment of non-randomized experimental and longitudinal observational studies with the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) and Risk of Bias in Non-randomized Studies of-Exposure (ROBINS-E) tool respectively.

Non-randomized experimental studies									
Author and year; countries	**-**	**Domain 1: RoB due to confounding**	**Domain 2: RoB in selection of participants**	**Domain 3: RoB in classification of interventions**	**Domain 4: RoB due to deviations from intended interventions**	**Domain 5: RoB due to missing data**	**Domain 6: RoB in measurement of outcomes**	**Domain 7: RoB in selection of the reported results**	**Overall RoB**
Felicione et al., 2022;[26] US	-	Low	Low	Low	Low	Low	Moderate	Low	**Moderate**
Shahin et al., 2022;[27] Canada	-	Serious	Low	Low	Low	Low	Serious	Low	**Serious**
Majid et al., 2023;[28] US	-	Serious	Low	Low	Low	Low	Serious	Low	**Serious**
Lorkiewicz et al., 2022;[29] US	-	Serious	Low	Low	Low	Low	Low	Low	**Serious**
Mueller et al., 2021;[32] US	-	Critical	Low	Serious	Low	Low	Serious	Low	**Critical**
Majek et al., 2023;[66] UK	-	Moderate	Low	Low	Low	Low	Moderate	Low	**Low**
Longitudinal observational studies									
Author and year; countries	**Overall RoB: based on decision to proceed with a RoB assessment**	**Domain 1: RoB due to confounding**	**Domain 2: RoB in arising from measurement of the exposure**	**Domain 3: RoB in selection of participants**	**Domain 4: RoB due to post-exposure interventions**	**Domain 5: RoB due to missing data**	**Domain 6: RoB in measurement of outcomes**	**Domain 7: RoB in selection of the reported results**	**Overall RoB**
Mahoney et al., 2022;[30] US	Needs further assessment	Low	Low	Low	Low	Low	Low	Low	**Low**
Berlowitz et al., 2022;[31] US	Needs further assessment	Low	Low	Low	Low	Some concerns	Low	Low	**Some concerns**
Hirschtick et al., 2022;[17] US	Needs further assessment	Low	Low	Low	Low	Some concerns	Low	Low	**Some concerns**
Shi et al., 2022;[33] US	Needs further assessment	Low	Low	Low	Low	Low	Low	Low	**Low**
Goldberg Scott et al., 2023;[34] US	Needs further assessment	Low	Low	Low	Low	Low	Low	Low	**Low**
Cook et al., 2023;[20] UK	Needs further assessment	Low	Low	Low	Low	Some concerns	Low	Low	**Some concerns**

Table 3. Risk of bias (RoB) assessment of biomarker-based cross-sectional studies with the BIOCROSS tool.

Author and year; countries	Item 1: Hypothesis/ objective	Item 2: Study population selection	Item 3: Study population representativeness	Item 4: Study population characteristics	Item 5: Statistical analysis	Item 6: Interpretation and evaluation of results	Item 7: Study limitations	Item 8: Specimen characteristics and assay methods	Item 9: laboratory measurement	Item 10: Biomarker data modeling	Overall RoB
Okafor et al., 2022;[35] US	2	2	1	1	2	2	2	1	1	1	**Low (15/20)**
Mohammadi et al., 2022;[39] US	2	2	1	1	2	2	1	1	1	0	**Low (13/20)**
Metzen et al., 2021;[41] Germany	2	1	0	1	2	2	2	1	1	0	**Moderate (12/20)**
Podzolkov et al., 2021;[42] Russia	2	2	0	1	2	2	1	1	0	1	**Moderate (12/20)**
Amraotkar et al., 2023;[43] US	2	2	2	1	2	2	2	1	1	1	**Low (16/20)**
Halstead et al., 2023;[69] US	2	2	1	1	1	2	1	2	1	2	**Low (16/20)**
Boakye et al., 2023;[70] US	2	2	1	1	2	2	2	1	1	1	**Low (15/20)**
Kelesidis et al., 2023;[71] US	2	1	1	0	1	2	1	1	0	1	**Moderate (10/20)**
Shiffman et al., 2023;[72] UK	2	2	2	1	1	2	1	1	1	2	**Low (15/20)**

Abbreviation: NA= not applicable.

Table 4. Risk of bias assessment of non-biomarker based cross-sectional studies and case reports with the Joanna Briggs Institute (JBI) critical appraisal tools.

Cross-sectional studies									
Author and year; countries	**Item 1: Criteria for inclusion in the sample**	**Item 2: Study subjects and settings**	**Item 3: Measurement of exposure in a valid and reliable way**	**Item 4: Standard criteria used for measurement**	**Item 5: Identifying confounding factors**	**Item 6: Strategies to deal with confounding factors**	**Item 7: Measurement of outcome in a valid and reliable way**	**Item 8: Appropriate statistical analysis**	**Overall RoB**
Bricknell et al., 2021;[18] US	Y	Y	N	N	Y	Y	N	Y	**Moderate (5/8)**
Critcher and Siegel, 2021;[36] US	N	Y	N	Y	Y	Y	N	Y	**Moderate (5/8)**
Kim et al., 2022;[37] South Korea	Y	Y	N	Y	Y	Y	Y	Y	**Low (7/8)**
Liu et al., 2022;[38] US	Y	Y	N	Y	Y	Y	N	Y	**Low (6/8)**
Falk et al., 2022;[19] US	Y	Y	N	Y	Y	Y	Y	Y	**Low (7/8)**
Patel et al., 2022;[40] US	Y	Y	N	Y	Y	Y	N	Y	**Low (6/8)**
April-Sanders et al., 2023;[67] US	Y	Y	Y	Y	Y	Y	Y	N	**Low (7/8)**
Austin-Datta et al., 2023;[68] US	Y	Y	N	N	Y	Y	N	Y	**Moderate (5/8)**
Shi et al., 2023;[73] China	Y	Y	Y	Y	Y	Y	Y	Y	**Low (8/8)**
Case reports									
Author and year; countries	**Item 1: Patient's demographic characteristics**	**Item 2: Patient's history**	**Item 3: Current clinical condition**	**Item 4: diagnostic tests or assessment methods and the results**	**Item 5: Intervention(s) or treatment procedure(s)**	**Item 6: Post-intervention clinical condition**	**Item 7: Adverse events (harms) or unanticipated events**	**Item 8: Takeaway lessons**	**Overall RoB**
Glenski et al., 2021;[44] US	Y	N	Y	Y	Y	Y	Y	Y	**Low (7/8)**
Grech et al., 2022;[45] Australia	Y	Y	Y	Y	Y	Y	Y	Y	**Low (8/8)**

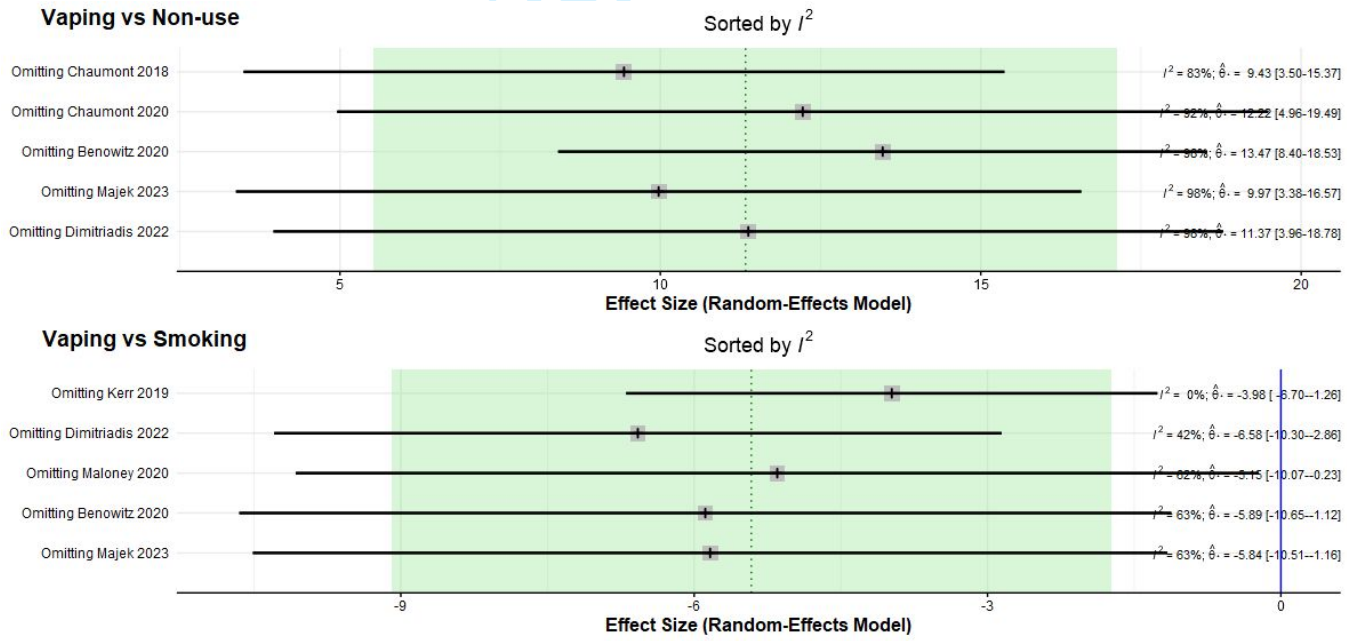
Abbreviation: Y= yes, N=No, UC= unclear, NA= not applicable.

Supplementary File 8. Sensitivity analyses of heart rate and blood pressure meta-analyses.

Heart rate (HR):

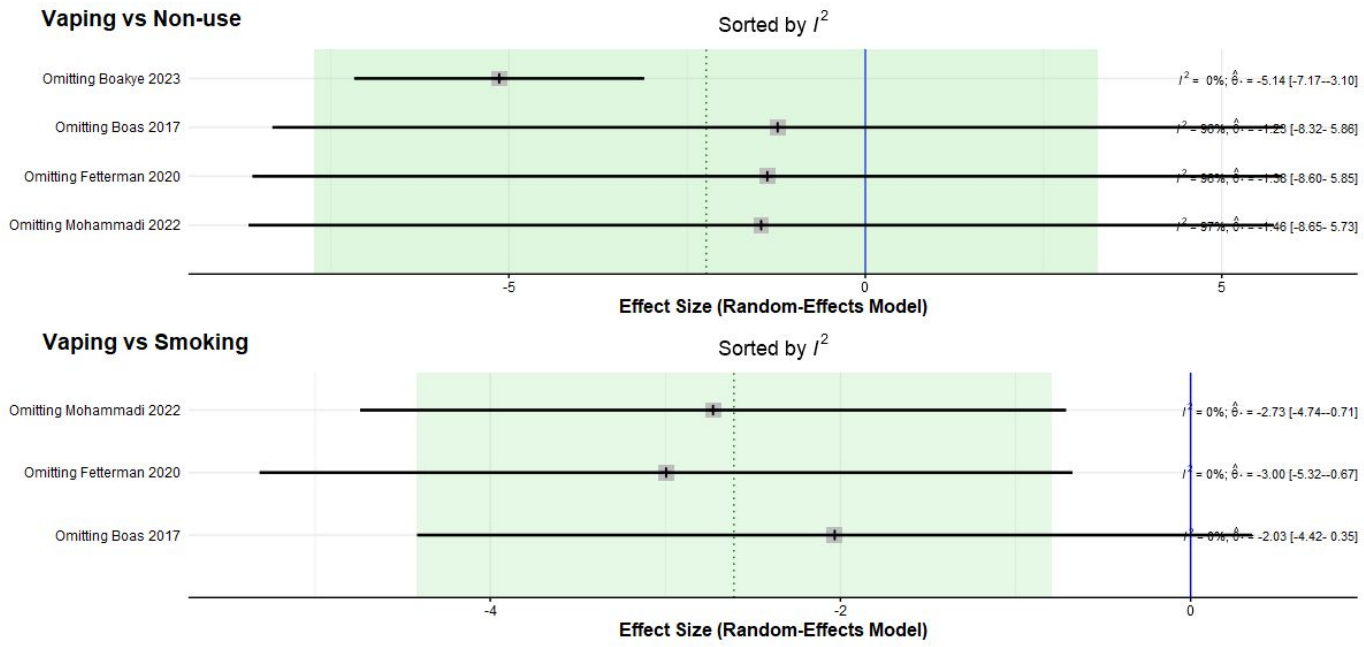
Removing studies in sensitivity analysis resulted in consistent associations with mean differences (MDs) ranging from 9.43 to 13.47 for e-cigarette vs non-use and -3.98 to -6.58 for e-cigarette vs cigarettes. While excluding Kerr et al., 2019 from e-cigarette vs cigarette comparison resulted in homogeneity (I^2 0%), no other study showed any significant impact.

Figure 1. Sensitivity analysis findings of impact of individual studies on acute exposure effects on heart rate comparisons: e-cigarettes vs non-use[1–5] (upper graph) and e-cigarettes vs cigarettes[1,4–7] (bottom graph).



In case of comparison between non-smoker current vapers vs non-users, removing Boakye et al., 2023[8] resulted in homogeneity and a statistically significant lower HR among non-smoker current vapers compared to non-users (MD -5.14; 95% CI -7.17, -3.10; I^2 0%), whereas excluding Boas et al., 2017[9] showed a statistically non-significant difference between non-smoker current vapers and non-vaper current smokers (MD -2.03; 95% CI -4.42, 0.35; I^2 0%), making them outliers.

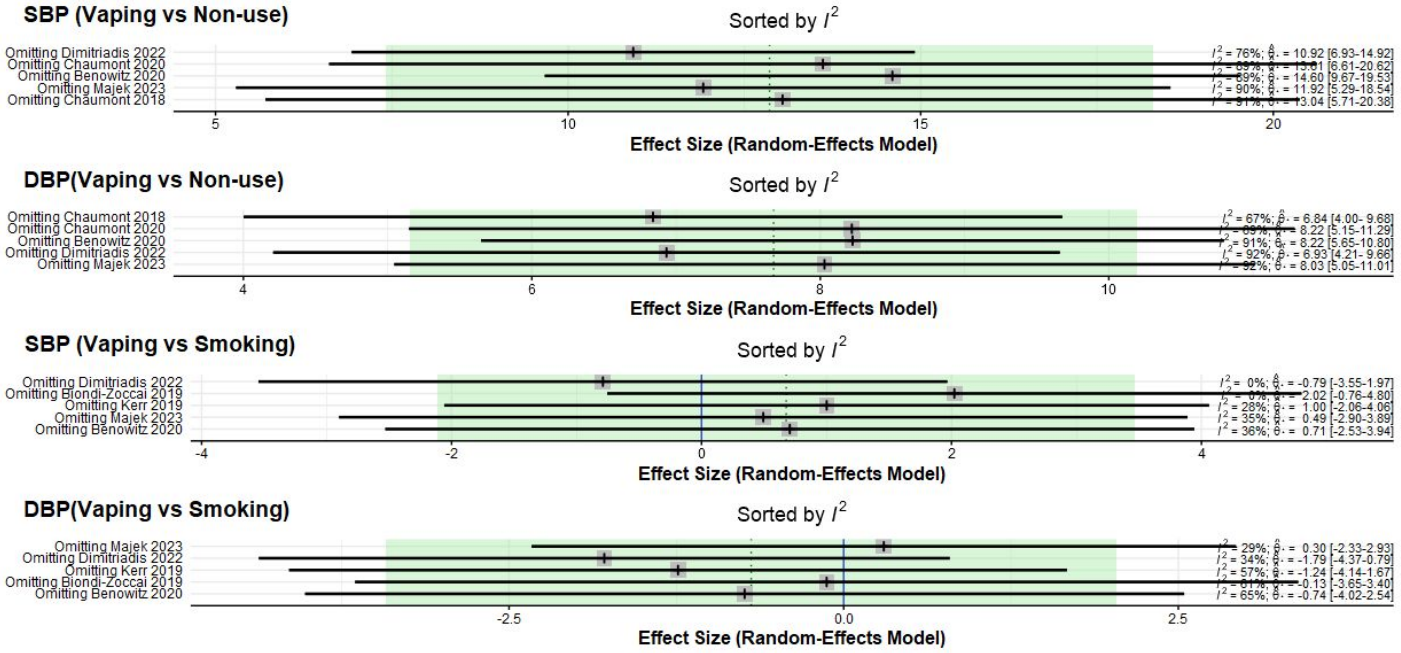
Figure 2. Sensitivity analysis findings of impact of individual studies on resting heart rate comparisons: non-smoker current vapers vs non-users[8–11] (upper graph) non-smoker current vapers vs non-vaper current smokers[9–11] (bottom graph).



Blood Pressure (BP):

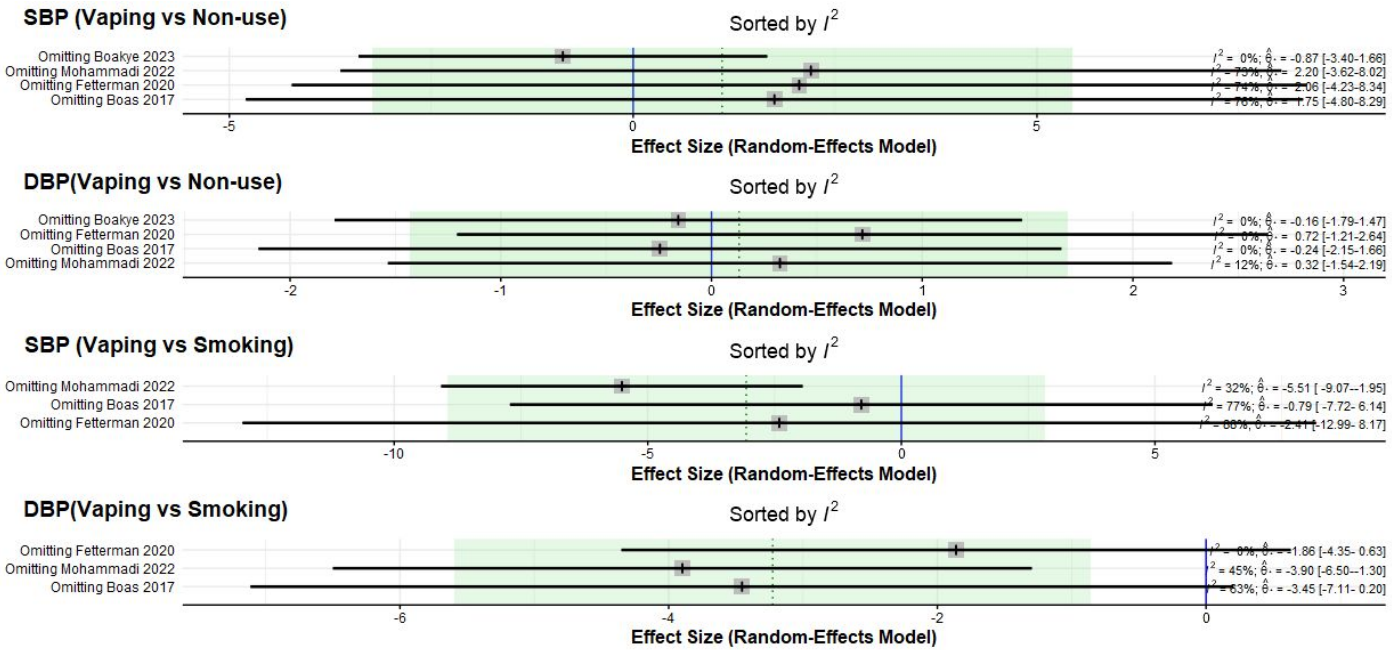
In sensitivity analysis, removing studies from e-cigarette vs non-use comparison did not affect study heterogeneity and direction of association with resultant MDs ranging 10.9-14.6 for systolic BP and 6.84-8.22 for diastolic BP. In case of comparing e-cigarettes vs cigarettes, we consistently found statistically non-significant association, but removing Dimitriadis et al., 2022 and Biondi-Zoccai et al., 2019[4,12] in systolic BP analysis resulted in homogeneity, while Dimitriadis et al., 2022 and Majek et al., 2023[4,5] examining effect on diastolic BP yielded low heterogeneity in the dataset.

Figure 3. Sensitivity analysis findings of impact of individual studies comparing systolic (SBP) and diastolic blood pressure (DBP) following acute exposure to e-cigarettes vs non-use[1–5] (upper 2 graphs) and e-cigarettes vs cigarettes[1,4–6,12] (bottom 2 graphs).



Furthermore, sensitivity analysis reaffirmed the statistically non-significant difference in resting BP between non-smoker current vapers and non-users, although removing Boakye et al., 2023[8] examining systolic BP resulted in homogeneity (I^2 0%). However, when compared to non-vaper current smokers, removing Mohammadi et al., 2022[10] resulted in a statistically significant effect in systolic BP (MD -5.51; 95% CI -9.07, -1.95; I^2 32%) and diastolic BP (MD -3.90; 95% CI -6.50, -1.30; I^2 45%) in non-smoker current vapers, making it an outlier.

Figure 4. Sensitivity analysis findings of impact of individual studies comparing resting systolic (SBP) and resting diastolic blood pressure (DBP) among non-smoker current vapers vs non-users[8–11] (upper 2 graphs) and among non-smoker current vapers vs non-vaper current smokers[9–11] (bottom 2 graphs).



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Supplementary File 9. Narrative review findings

Cardiovascular diseases

None of the 23 studies[1–23] that investigated the association between e-cigarette exposure and different cardiovascular diseases (CVDs) found any significant risk among non-smoker current vapers. Of them, 2 longitudinal observational studies[2,3] and 3 cross-sectional studies[7,18,19] assessed the risk of non-specific CVDs. Here non-specific CVDs indicate assessment of different CVDs (i.e., heart failure, stroke, myocardial infarction (MI), coronary heart disease, arrythmia, HTN, deep venous thrombosis or other heart conditions) under one broad term. While dual users were found to have significantly higher incident risk (hazard ratio (HR) 2.08, 95% CI 1.40-3.09) by one study,[3] and higher risk of prevalence (odds ratio (OR) 1.79, 95% CI 1.79-2.34) by one study,[7] no statistically significant incident risk was found by another study compared to non-users.[2] Additionally, 2 studies reported significantly higher prevalence of non-specific CVDs among ever vapers compared to never smokers (OR 2.33, 95% CI 1.52-3.56; and OR 1.1, 95% CI 1.0-1.3).[18,19] Additionally, dual users were reported to have higher odds of prevalence (OR 2.40, 95% CI 2.10-2.86; and OR 2.34, p<0.0001) of stroke,[8,21] MI (OR 3.84, 95% CI 3.23-4.56 ; and OR 1.94, 95% CI 1.07-3.50),[6,8] altered lipid profile (OR 1.64, 95% CI 1.01-2.70),[5] and diabetes mellitus (OR 1.22, 95% CI 1.11-1.34)[8] compared to non-users by separate studies. However, one study found no increased risk of incidence of stroke among them compared to non-users.[1] One RCT reported significant reduction in %Q-Risk scale (MD 1.8, p<0.001) and total cholesterol/HDL ratio (MD 0.23, p=0.009) following switching from cigarettes to e-cigarettes on a short-to-medium term,[24] while 2 cross-sectional studies did not find any significant cardiometabolic risk in current vapers.[18,20] Findings on other cardiovascular conditions (i.e., pulmonary arterial hypertension, abdominal aortic aneurysm, arrythmia) were scarce and inconclusive.[10–13,16,17,23] No meta-analysis could be conducted due to high heterogeneity and low number of studies detected for any individual CVD condition.

Endothelial/vascular dysfunction

Two RCTs,[24,25] 1 cross-over trial,[26] 2 nonrandomized experimental studies,[27,28] 7 cross-sectional studies,[20,29–34] 7 cell/*in vitro* studies,[27,29,35–39] and 6 animal studies[38,40–44] looked into endothelial/vascular dysfunction from e-cigarette exposure. The RCTs evaluated impact of acute and short-to-medium term transitioning from cigarette to e-cigarette and found improvement of both flow mediated dilatation (FMD) (F=14.53, p<0.001 for acute; β=3.33, p=0.001 for short-to-medium term) and peak cutaneous vascular conductance responses (F=2.24, p<0.04 for acute; β=0.20, p=0.04 for short-to-medium term).[24,25] However, the cross-over trial[26] and five animal studies[40–44] found significant (p<0.05) impairment in FMD or vascular relaxation following e-cigarette exposure. Additionally, impairment of endothelial nitric oxide synthase function,[27,29,40,42,43] higher levels of acrolein metabolites in urine,[28] enhanced platelet reactivity and pro-atherogenic changes,[30,34] increased level of high sensitivity C-reactive protein, high albuminuria, and low ankle brachial index,[45] vascular injury, inflammation, or oxidative stress[20,27,31,35,37,38,40,42] following e-cigarette exposure were reported by several studies. The majority of the studies assessing oxidative stress[20,27,31,35,37,38,40,42] or endothelial nitric oxide synthase function[27,29,40,42,43] were cell/*in vitro* and animal studies. Since we limited our meta-analyses to human studies, no meta-analysis was conducted here.

Cardiac dysfunction and remodelling

We found only 10 animal studies[16,22,23,40,42,43,46–49] investigating cardiac dysfunction and remodelling. Two of these studies[22,40] found significantly (p<0.05) higher systolic vascular resistance, while one study reported reduced cardiac output[22] following e-cigarette exposure. Different degrees of ventricular remodelling were reported by five studies,[16,22,42,43,46] while oxidative stress in cardiomyocytes[48] and myocarditis[49] were reported by two

different studies. However, no significant changes in right ventricular systolic pressure,[23] cardiac output,[16] inflammatory markers and cardiac histology[47,49] were reported by several studies.

Subgroup findings

For the studies included in the subgroup analysis, no studies matched the criteria for meta-analysis. Hence, we used narrative synthesis approach and summarized the findings. Of 32 studies[5,7,9–12,14–16,24,28,29,32,38,40–43,45–47,50–60] included in the subgroups analyses, 94% (n=30) were in sex, 16% (n=5) were in age, 6% (n=2) were in race/ethnicity, 6% (n=2) were in income, 6% (n=2) in education and occupational categories, and 3% (n=1) were in embryonic exposure-based analysis. Overall, the studies were heterogenous, and often the findings were limited and inconclusive.

One RCT (β= -1.32 males vs females; p=0.005) and one cross-sectional study (β= 1.82 in females; p<0.0001) reported higher improvement in FMD in females than males following switching from cigarettes to e-cigarettes on a short-to-medium term.[24,54] The RCT also reported similar findings for improvement in BP in females (β= 4.33 males vs females; p=0.001) and younger age groups (β= 0.23 for males vs females; p= 0.001) following switching from cigarettes to e-cigarettes, but no age-based differences in FMD.[24] However, findings on sex-based differences in vascular damage were inconsistent between studies.[32,45,59,60]

One study found higher prevalence of HTN among male dual users (OR 1.24, 95% CI 1.11-1.39) and non-smoker current vapers (OR 1.22, 95% CI 1.02-1.48) compared to male non-users,[51] while another study found no statistically significant risk of developing HTN in both male and female non-smoker current vapers.[50] The previous study also reported higher prevalence of HTN among male non-smoker current vapers who were also older than 30 years (OR 1.36, 95% CI 1.01-1.83), had high income (OR 1.40, 95% CI 1.06-1.84), and had higher education (OR 1.32, 95% CI 1.05-1.65) compared to male non-users.[51] One study[9] found higher prevalence of stroke in female, non-Hispanic White, and very low income dual users compared to male, other race, and high income dual users respectively.[9] Another study found that up to age 30 years, non-smoker current vapers had significantly higher risk of reduced HDL-C (OR 2.14; 95% CI 1.01-4.41) compared to never users, while over 30 years, dual users had similar effect.[5]

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PRISMA Reporting Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2,3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5,6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5,6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplementary File 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5,6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6, Supplementary File 2-3
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7, Supplementary File 6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Supplementary File 5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6,7, Supplementary File 5

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Supplementary File 5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6,7, Supplementary File 5
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7,8, Fig 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Supplementary File 2-3, Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	9, Supplementary File 7
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Supplementary File 2-4, Fig 2-5
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	10-12
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	10-12, Supplementary File 8
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Supplementary File 8, 9
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	12-15
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	14, 15
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	15
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	16

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097.

doi:10.1371/journal.pmed1000097

Thank you for reviewing our paper. We appreciate the opportunity to improve the quality and content of our paper and have now completed revisions to our manuscript. Please find our responses below:

Word count not according the guidelines. It should not exceed a limit of 3000 words, eight figures and/or tables, and 30 references (up to 50 references are permitted for a meta-analysis).

We recommend that the results section is reduced is size and some of the material is moved to the supplement.

Response: We followed the guidelines and your suggestions. We cut down words mainly from the Results section and moved the sensitivity analysis findings of the meta-analyses as well as the narrative review findings (findings on cardiovascular diseases, Endothelial/vascular dysfunction, Cardiac dysfunction and remodelling, and subgroup findings) to Supplementary File 8 and 9 respectively. The current word count of the body of the manuscript is 3000, and no. of tables and/or figures are 6. We have total 96 references for this paper, of which 50 were included in the body of the manuscript and rest of them are added as Supplementary File 10.