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Cardiovascular autonomic effects of electronic cigarette use: A systematic review

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Abstract

**Background.** Electronic cigarettes (ECs) are the fastest rising tobacco product in the United States, and ECs, like tobacco cigarettes (TCs) have cardiovascular autonomic effects, with clinical implications.

**Purpose.** The purpose of this review is to collect and synthesize available studies investigating the autonomic cardiovascular effects of EC use in humans. Special attention will be paid to the acute and chronic effects of ECs, the relative contributions of the nicotine vs non-nicotine constituents in emissions from ECs, and their relative effects compared to TCs.

**Methods.** Using the methodology described in the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement, a literature search using Ovid PubMed and Embase databases was conducted December 6, 2019 using keywords in titles and abstracts of published literature. Acute (minutes to hours) and chronic (days or longer) changes in heart rate variability (HRV), heart rate (HR), and blood pressure (BP) were used as estimates of cardiovascular autonomic effects.

**Results.** Nineteen studies were included in this systematic review, all of which used earlier-generation EC devices. Acute EC vaping increased HR and BP less than acute TC smoking. Nicotine, not non-nicotine, constituents in EC aerosol were responsible for the sympathoexcitatory effects. Chronic EC vaping studies were consistent with a chronic sympathoexcitatory effect as
estimated by HRV, but this did not translate into chronic increases in HR or BP.

**Conclusions.** ECs are sympathoexcitatory. Vaping the earlier generation ECs has less cardiac sympathoexcitatory effects than TC smoking. Additional studies of the latest pod-like EC devices, which deliver nicotine similarly to a TC, are necessary.

Key words: Electronic cigarettes, vaping, nicotine, smoking, autonomic nervous system, sympathetic nervous system
Electronic cigarettes (ECs), introduced in the United States in 2007, are currently used by over 10 million adults and almost 5 million youths, making them the fastest rising tobacco product available today [10, 50]. Despite the ready availability and widespread use of ECs, little is known about their short and long-term cardiovascular health effects [30]. In contrast, it is well known that tobacco cigarette (TC) smoking is the most important modifiable risk factor for cardiovascular disease in the United States. Approximately 480,000 Americans die from TC-related diseases each year, of which cardiovascular disease is the most prevalent. As part of a harm reduction strategy, TC smokers have been encouraged to switch to ECs, although it remains unproven and unknown whether adverse cardiovascular effects of ECs are less than those of TCs. Further, the short and especially long-term health effects of the epidemic of EC vaping in our youth [17], most of whom have never smoked TCs, is of concern and remains unknown.

TC smoking promotes cardiovascular disease through increases in oxidative stress and inflammation, leading to endothelial dysfunction and platelet activation [1]. Additionally, TCs have adverse effects on the autonomic nervous system. Specifically, several robust investigative techniques, including microneurography to record direct post-ganglionic sympathetic nerve activity, norepinephrine spillover to determine systemic and/or organ-specific sympathetic activation, and heart rate variability (HRV) to determine cardiac sympathetic to parasympathetic balance, have been
used to show that TC smoking increases sympathetic nerve activity in humans [13, 33, 37]. Sympathetic activation increases heart rate (HR) and blood pressure (BP), potentially triggering ischemia and arrhythmias [4, 33], and may also promote atherosclerosis [29].

Although most toxicants from smoking are orders of magnitude lower - if present at all - in EC vapers compared to TC smokers, one toxicant is not - nicotine [19, 20, 31]. Plasma nicotine levels in EC vapers are similar to those in TC smokers [42, 49], and nicotine is a sympathomimetic agent. Several recent studies have reported that ECs, too, increase sympathetic nerve activity, as estimated by acute and chronic changes in HR, BP and HRV [2, 5, 8, 15, 16, 26, 34, 35, 44, 47, 52].

It is clear that the autonomic effects of ECs have clinical importance. The publication of these recent reports, coupled with the widespread and increasing use of ECs, mandate review and synthesis of the available data relevant to the autonomic cardiovascular effects of acute and chronic EC use in humans. Thus, the autonomic effects of ECs in humans as estimated by HR, BP and HRV have been systematically reviewed based on the methodology described in the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement [36]. Special attention was paid to the acute (minutes to hours) and chronic (days or longer) effects of ECs, the relative contributions of the nicotine vs non-nicotine constituents in emissions from ECs, and their relative effects compared to TCs.

**METHODS**
PRISMA guidelines were followed during the creation of this systematic review in order to ensure transparency and completeness of the review process.

**Search Criteria**

A literature search using Ovid PubMed and Embase databases was conducted December 6, 2019 using keywords in titles and abstracts of published literature. A librarian from the UCLA Biomedical Library was consulted for recommendations regarding appropriate search keywords and search strategies. The specific search key words used were:

"Autonomic nervous system" OR "Blood pressure" OR "Heart rate" OR "Sympathetic nerve OR "sympathetic nervous" OR vagal OR vagus OR sympathetic OR parasympathetic OR "Blood Pressure" OR "Heart Rate" OR "Autonomic Nervous System" AND “Electronic Nicotine Delivery Systems" OR "Electronic cigarettes" OR "e-cigarettes" OR “vape” OR “vaping.” References from articles and related reviews were perused for additional articles. An additional search of the Ovid Pubmed database using key words “microneurography AND electronic cigarettes” and “norepinephrine spillover AND electronic cigarettes” was conducted and yielded no articles.

**Inclusion, exclusion, and study eligibility criteria.**

Inclusion criteria included publications written or translated to the English language published in any journal. Given the recent invention and introduction of ECs into global markets, the search for publications included in this systematic review was not limited to a specific time frame since all EC
studies have been conducted within the last 10 years. All study designs were included in the search and no limitations were based on country of publication. Exclusion criteria for published literature included absence of autonomic outcomes such as HR, BP and HRV. Research studies that only studied cannabidiol (CBD) or tetrahydrocannabinol (THC), active ingredients in cannabis, and/or cannabis liquid in ECs were also excluded. Experimental studies which only involved animals were excluded since the focus of this review was the autonomic effects ECs in humans.

Data extraction and organization
Excel was used for further qualitative synthesis of included articles and for the extraction and organization of data. Excel tables were generated in which the following data were extracted: Participants, interventions, outcomes, and limitations. The approach to the analysis was organized into two comparisons: 1) TC vs ECs, 2) ECs with nicotine(ECN) vs ECs without nicotine (EC0), and further divided by acute (minutes to hours) versus chronic (days or longer) effects. Data from studies were included in more than one analysis if relevant to both; for example, a study involving three exposures, e.g. ECN, EC0 and TC would be included in the TC vs EC analysis and the ECN vs EC0 analysis.

Conflict of interest and sources of bias
Analysis of potential sources of bias included ties to, or funding from, the TC or EC industry. The potential for reporting bias was addressed by using the PRISMA guidelines to write a protocol before beginning the review process
and not deviating from this protocol throughout all steps of the systematic review.

**Statistical Analysis**

Within each comparison (TC vs EC and ECN vs EC0), using the extracted data, the summary mean difference and its confidence bounds for a given outcome was computed and combined using the random effects model of Viechtbauer under the R software system [46]. This model assumes heterogeneity. The forest plot entry for each study is the mean difference with the corresponding lower and upper 95% confidence bounds.

**RESULTS**

**Study Selection (Figure 1)**

Two researchers (PDG, HRM) conducted the search and screening of articles. The electronic search yielded 224 studies. A screening of titles and abstracts for inclusion or exclusion was then done. During this first step, 53 studies were removed because they were found to be duplicates and 115 studies were excluded because they did not meet inclusion criteria, or a full text was not available for review (n=17). Then a full text review was performed on the remaining 39 studies, which led to the exclusion of 21 studies because 1 study was an editorial, and 20 studies had no relevant outcome measures. One additional study [18], published after the literature search, was included while the paper was under review. In total, 19 studies were included in this systematic review.
Acute autonomic cardiovascular effects of TC smoking vs EC vaping (Figure 2, Supplemental Table 1)

Eight studies included in this systematic review investigated the acute effects of TC vs EC with nicotine, and/or ECs without nicotine on autonomic cardiovascular activity as estimated by HR, SBP and DBP, summarized in Figure 2, and Supplementary Table 1. The difference in the acute effect of the TC compared to the EC on each variable (SBP, DBP, and HR) in each study is depicted in Figure 2. The vertical line is no effect, and those to the right of the vertical line indicate TC effect is greater than the EC effect. Most [5, 15, 26, 44, 52], but not all [16, 25, 47] studies are consistent with the concept that acute cardiovascular autonomic effects of TC smoking are greater than EC vaping. The overall mean differences between TC and EC across all studies for SBP was 1.58 mmHg (95% confidence interval [CI] 0.20 to 2.97, p=0.025), DBP was 1.57 mmHg (95% CI 0.37 to 2.78, p=0.01), and HR was 3.06 bpm (95% CI 2.01 to 4.10, p=0.00001). Unfortunately, most studies did not confirm comparable TC and EC exposures as estimated by acute increases in plasma nicotine levels. No studies used the latest generation pod-like EC device (e.g. Juul). Two studies reported potential biases (received or were planning to receive funding from the EC industry [15, 52]. When these studies were removed, the results of the analysis remained essentially unchanged: Overall mean differences between TC and EC across all studies for SBP was 1.64 mmHg (95% CI 0.09 to 3.20, p=0.033), DBP was 2.09 mmHg (95% CI 0.74 to 3.44, p=0.002), and HR was 1.86 bpm (95% CI 0.98 to 2.74, p=0.00001).
Ikonomidis et al [25] was the only study that had two phases: an acute phase discussed here, and a chronic phase, discussed below. In the acute crossover study [25], 35 chronic TC smokers, first vaped an EC with nicotine (eGo, 1.2% nicotine) for 7 minutes, and then after a 60 minute washout period, smoked a TC; 35 different chronic TC smokers first vaped an EC without nicotine for 7 minutes, and then after a 60 minute washout period, smoked a TC. HR, and brachial SBP and DBP were unchanged after acutely using the TC or EC, with and without nicotine, compared to baseline [25]. Plasma nicotine levels following smoking the TC or vaping the EC were not measured.

Biondi-Zoccai et al [5] studied ECs vs TCs in a randomized cross-over trial in 20 chronic TC smokers. These investigators also studied the heat-not-burn-cigarette, but this intervention is beyond the scope, and thus not included in this qualitative systematic review. This study found that the increase in SBP and DBP was significantly greater after acutely smoking 1 commercially available TC compared to 9 puffs of EC vaping (Blu Pro, tobacco flavored, nicotine 16 mg) [5]. Increases in plasma cotinine but not nicotine levels were compared after smoking/vaping, and were found to increase similarly after acute TC smoking and EC vaping.

In a controlled trial [15], 36 heavy TC smokers smoked a commercially available TC and 40 chronic EC users vaped an EC with nicotine (11 mg/ml), and the cardiovascular effects of smoking were compared. SBP and HR, but not DBP, were significantly greater after TC smokers smoked a TC compared
to after EC users vaped the EC with nicotine. The increase in plasma nicotine levels were not compared after smoking/vaping [15]. The investigators reported a potential source of bias; they declared that after this study was completed, they received funding the EC industry. When this study was excluded from the analysis, results were not significantly changed (see above).

Vansickel et al [44] measured the HR in a randomized crossover trial in which 32 TC smokers underwent 4 different exposures in random order: 1) own brand TC, 2) EC with 18 mg nicotine cartridge, 3) EC with 16 mg nicotine cartridge, or 4) sham control (unlit cigarette). HR increased only after acute TC smoking, not after EC vaping (16 or 18 mg cartridge), or the sham-control group. Plasma nicotine only increased after TC smoking, not after EC vaping[44].

Franzen et al [16] performed a randomized crossover trial in which 15 chronic TC smokers smoked a TC, an EC with nicotine (24 mg/ml), and an EC without nicotine, in random order. SBP, DBP and HR increased similarly after the TC and the EC with nicotine, but not after the EC without nicotine. Changes in plasma nicotine/cotinine were not measured.

Vlachopoulos et al [47] measured SBP, DBP and HR after 24 TC smokers used either a TC or an EC with an unspecified amount of nicotine for 5 minutes and 30 minutes in a randomized crossover trial. HR, SBP, and DBP increased similarly after smoking the TC and vaping the EC for 30 minutes,
but not 5 minutes [47]. Acute changes in plasma nicotine levels were not measured.

Yan et al [52] conducted a randomized crossover trial with 23 chronic TC smokers who were clinically confined for the 11-day study and used 5 different ECs (2 commercially available ECs, and 3 non-commercially available ECs) and 1 commercially available TC, in random order, each session separated by a 36 hour washout period. Increases in HR, SBP, and DBP were significantly greater after smoking the TC compared to vaping the EC [52]. Plasma nicotine after TC smoking had a steeper slope of increase and remained higher than the plasma nicotine after acute EC vaping [52]. The investigators reported a potential source of bias; they declared that they received funding the EC industry. When this study was excluded from the analysis, results were not significantly changed (see above).

Kerr et al [26] performed a randomized crossover study in 20 chronic TC who smoked a TC and vaped an EC with 18mg/ml of nicotine in random order. The increase in HR and SBP, but not DBP, was significantly greater after smoking the TC compared to vaping the EC [26]. Plasma nicotine levels were not measured.

**Acute autonomic cardiovascular effects of ECN vs EC0 vaping (Table 2, Figure 3)**

There were 5 studies included in this systematic review that compared the autonomic effects of EC with and without nicotine, or the solvents alone, as summarized in Figure 3 and Supplemental Table 2. The difference in the acute effect of the EC with nicotine (ECN) compared to the EC without
nicotine (EC0) on each variable (SBP, DBP, and HR) in each study is depicted in Figure 3. The vertical line is no effect, and those to the right of the vertical line indicate ECN effect is greater than the EC0 effect. Most [8, 16, 34], but not all [2, 9] acute EC vaping studies were consistent with the notion that nicotine, not non-nicotine constituents in EC aerosol were responsible for the acute sympathomimetic effects of EC vaping. The overall mean differences between ECN and EC0 across all studies for SBP was 3.73 mmHg (95% CI 0.59 to 6.87, p=0.02), DBP was 3.25 mmHg (95% CI 1.21 to 5.30, p=0.0018), and HR was 6.44 bpm (95% CI 3.52 to 9.36, p<0.00001). No study declared any potential financial biases.

Only one study, Moheimani et al [34], measured HRV as an estimate of cardiac sympathetic activity. In this study, the effects of acute EC vaping with nicotine (1.2%) and EC vaping without nicotine(0%) on cardiac sympathetic to parasympathetic balance in 33 healthy nicotine-naive participants was measured. In this open label, randomized, crossover study, each participant vaped an EC with nicotine, EC without nicotine and sham control (empty EC) in random order. Only the EC with nicotine, but not the EC without nicotine or sham control, caused an acute sympathomimetic effect as estimated by HRV. HR, but not SBP or DBP also increased significantly only after vaping the EC with nicotine. Plasma nicotine levels were measured immediately after EC use in this study, and the increase in plasma nicotine levels were directly related to the increase in cardiac sympathetic activity, as well as to the increases in SBP and HR [34].
Chaumont et al [8] performed a randomized, single-blind crossover study in 25 young healthy TC smokers in which TC smokers vaped an EC with nicotine (3mg/ml), an EC without nicotine, and a sham-control in random order. SBP, DBP, and HR increased significantly only after using the EC with nicotine, not after the EC without nicotine, or the sham-control [8]. Plasma nicotine levels increased after vaping the EC with nicotine, but the increase did not correlate with changes in HR or BP.

Franzen et al [16] conducted a randomized crossover trial in 15 chronic TC smokers before and after vaping an EC with nicotine (24 mg/ml) and an EC without nicotine and found that peripheral SBP was significantly increased after vaping the EC with, but not without, nicotine [16]. Plasma nicotine levels were not measured.

In contrast to these 3 trials, Cossio et al [9] conducted a randomized single-blinded trial of 16 young healthy nicotine-naïve participants, and found no significant changes in HR, SBP, DBP after vaping an EC with nicotine (18 puffs in 6 minutes) or without nicotine [9]. An increase in plasma nicotine levels was not measured, or confirmed, in this trial in nicotine-naïve participants [9].

Surprisingly, and uniquely, a double-blinded cross-over study conducted in 17 healthy occasional TC smokers reported that SBP, DBP and HR increased after vaping an EC with nicotine (19 mg/ml), and SBP and DBP, but not HR, increased similarly after vaping an EC without nicotine [2]. This is the only trial comparing ECs with and without nicotine in which the EC
without nicotine significantly increased BP, although it remains uncertain that this pressor effect was mediated by an increase in sympathetic vasoconstriction.

**Chronic autonomic cardiovascular effects of ECs**

Robust techniques to measure chronic autonomic cardiovascular system activity include heart rate variability, direct sympathetic nerve activity directed to the muscle vasculature, using microneurography [37], and norepinephrine spillover - either systemic or directed to specific organs and tissues [13]. To date, no studies have measured muscle sympathetic nerve activity or norepinephrine spillover results in acute or chronic EC use. The use of HR and BP as surrogate endpoints for changes in autonomic cardiovascular effects is less secure in the chronic compared to the acute setting, due to many potential confounders.

Our search uncovered two studies [35, 38] conducted in chronic EC users who did not also smoke TCs (no dual users); HRV [35], and HR and BP [38] were the primary autonomic outcomes measured, respectively [35, 38]. In the first study which enrolled 23 chronic EC vapers and 19 non-vaper controls [35], HRV was used to determine the cardiac sympathetic to parasympathetic balance in EC vapers who refrained from vaping for 12-hours prior to the study, confirmed by non-detectable plasma nicotine levels at the time of the study. Chronic EC users exhibited sympathetic predominance compared to similarly-aged, non-vaper controls (Figure 4). There was no difference in resting HR or BP. In a second, 3.5 year
prospective study [38], HR and BP were periodically measured in nine chronic EC vapers who refrained from vaping for 60 minutes before HR and BP measurements. Twelve nicotine-naïve participants were enrolled as age- and sex-matched controls. No differences in HR or BP were found in EC vapers compared to baseline, or compared to nicotine-naïve controls, over time. In summary, these data support the concept that EC smokers have chronically elevated cardiac sympathetic activation compared to non-vapers as measured by HRV, but this cardiac sympathetic activation does not translate into clinically detectable greater heart rates or blood pressures.

**Chronic autonomic cardiovascular effects of switching from chronic TC smoking to EC vaping (Supplementary Table 3)**

Our search uncovered 6 TC to EC chronic switch studies which reported HR and BP outcomes, summarized below, and in Supplementary Table 3. In the only short term (5 day) switch study[11], in which participants were confined and smoking behavior monitored, 105 chronic TC smokers were randomized to 3 general groups: 1) TC to EC complete switch, TC to EC plus allowed to use TCs, and complete TC and nicotine cessation. The flavors in the ECs included cherry and tobacco. At 5 days, there were no significant overall changes in HR or BP reported.

There were 5 long term switch studies. Farsalinos [14] et al followed 300 TC smokers enrolled in a prospective 1-year randomized switch study comparing ECs with 2.4% nicotine, low (1.8%) nicotine and no (0%) nicotine. Most participants continued to use TCs during the study. Of the 183 participants who completed the study, a slight but significant decrease in
SBP and DBP but not HR was reported. Unfortunately, there was no time control, so whether this reduction in BP was attributable to switching from TCs to ECs, or to becoming more comfortable with the study procedures, is not known. In a retrospective analysis of medical records of 43 hypertensive TC smokers who reduced TC smoking and/or switched to ECs in order to quit smoking, Polosa [39] et al found that significant reduction in SBP and DBP. There was no change in BP the chronic TC control group. Ikonomidis [25] et al enrolled 70 TC smokers in an EC switch study, and TC cessation was confirmed by periodic exhaled CO monitoring. Twenty age-matched TC smokers served as a time control. At 1 year, SBP, but not DBP or HR, was significantly lower in the compliant and partially compliant participants compared to baseline values. BP and HR did not change in TC smoking controls. George et al [18] conducted a randomized controlled trial of TC smokers randomized to ECN or EC0 for 1 month. Approximately 50% of those who switched to ECs, either with or without nicotine, continued to smoke TCs as estimated by elevated exhaled carbon monoxide levels at follow up. Another cohort of TC smokers who did not want to quit were followed in a parallel preference cohort. When adjusted for baseline variables, there was no difference in BP or HR in either of the EC arms compared to the TC arm. Finally, Veldheer et al [45] enrolled 263 chronic TC smokers into a switch study, switching to ECs or a non-EC substitute. Although the majority of participants had reduced the number of TCs smoked each day, almost all were still smoking TCs at 3 months. At 3 months, similar to the George [18]
switch study, there was no decrease in HR or BP. In summary, most [14, 25, 39], but not all [18, 45] chronic TC to EC switch studies tended to show a small decrease in BP, but not HR, over time.

**Discussion**

In this systematic review of 19 studies which used the earlier generation EC devices, findings support the notion that acute EC vaping has acute autonomic cardiovascular effects, specifically, sympathetic excitation as estimated by acute increases in HRV, HR and BP. Further, acute sympathoexcitatory effects of ECs are largely attributable to nicotine, not the non-nicotine constituents in EC emissions [2, 8, 16, 34]. Additionally, sympathoexcitatory effects of acute EC vaping are less than those of acute TC smoking as estimated by HR and BP [5, 15, 16, 25, 26, 44, 47, 52]. Finally, limited data suggest that chronic EC use is associated with sympathetic activation [35], even in the absence of acute nicotine inhalation, although more data are needed to confirm this.

**Acute EC vaping increases sympathetic nerve activity: A nicotine effect**

Several studies of acute vaping compared the autonomic cardiovascular effects of ECs with and without nicotine [2, 8, 9, 16, 34]. All but two of these studies showed that acute increases in HRV, HR and/or BP, surrogates for sympathetic nerve activity, were significantly greater after using the ECs with nicotine compared to ECs without nicotine. Increases in plasma nicotine levels after vaping the EC with nicotine were not confirmed in either of the
two negative studies [2, 9]. In fact, in one of these two studies, the participants were non-smokers, and had never used an EC prior to the study[9]. Ineffective nicotine delivery has been reported in inexperienced EC vapers using ECs for the first time - especially early generation devices [7]. It is conceivable that the participants in this study were not exposed to significant EC aerosol. In another study, the acute effects of vaping the solvents propylene glycol and vegetable glycerol alone, without nicotine or flavorings, were studied [6]. Vaping the solvents alone did not increase the HR and BP, consistent with the previous data that it is the nicotine, not non-nicotine, constituents in EC aerosol that acutely increase SNA.

**Mechanisms of acute sympathetic excitation with ECNs**

The mechanisms underlying the acute sympathomimetic effects of inhaled nicotine are complex. Nicotine has direct, pharmacological effects on peripheral post-ganglionic nerve endings, increasing exocytotic norepinephrine release [22]. Norepinephrine release in cardiac tissue interacts with β-adrenergic receptors to increase heart rate and contractility; exocytotic norepinephrine release in vascular tissue binds to α-adrenergic receptors, causing vasoconstriction [22]

Nicotine may also acutely increase post-ganglionic sympathetic nerve firing, which can be directly recorded using the technique of peroneal microneurography [37]. However, this peripheral sympathetic nerve excitation may be suppressed in young people, in whom the pressor effect, mediated by exocytotic norepinephrine release, activates inhibitory
baroreflexes in a negative feedback loop. The baroreflexes exert an acute sympathoinhibitory effect, thereby restoring blood pressure towards normal [33]. Studies in TC smokers have confirmed that baroreflex activation by the pressor responses masks the increase in post-ganglionic sympathetic nerve traffic following acute TC smoking [21, 37]. Pharmacological strategies to prevent the pressor response have been utilized to unmask increased post-ganglionic sympathetic nerve activity recorded with microneurography following TC smoking[37]. In older smokers in whom the baroreflexes may be attenuated, TC smoking is accompanied by increased sympathetic traffic [23, 24]. Thus, although the sympathoexcitatory effects of smoking may be reflexively suppressed in healthy young people in whom baroreflexes are intact, sympathoexcitation may be exaggerated - and thus potentially more lethal - in older smokers in whom baroreflex function is attenuated.

**Cardiovascular sequelae of acute increases in sympathetic nerve activity during smoking**

The clinical importance of acute increases in sympathetic nerve activity associated with EC vaping may be extrapolated from TC smoking studies. Periodic, recurrent increases in sympathetic nerve activity, may be accompanied by abrupt increases in HR and BP, which occur throughout the day. Recurrent bouts of hypertension may contribute to endothelial injury [3]. Additionally, increases in HR and BP increase myocardial oxygen demand [4]. This augmented demand may further be exacerbated by decreased nutrient supply, since TC smoking also causes sympathetically-
mediated coronary vasoconstriction and vasospasm [51]. Finally, acute sympathetic activation may trigger atrial and ventricular arrhythmias in TC smokers [27, 41].

**Acute sympathoexcitatory effects are less following acute EC vaping compared to acute TC smoking**

Several studies included in the review compared the acute autonomic cardiovascular effects of TCs and ECs, and found that the acute effects of ECs, including acute increases HR and BP, were significantly less than the acute effects of TC smoking. However, there are several limitations in these studies that must be acknowledged. First of all, HR and BP, outcomes indicative of sympathetic excitation, were not the pre-specified primary outcomes in most of these studies (Supplemental Table 1). Secondly, although the studies sought to compare TCs to ECs, it remains uncertain if the exposures to these tobacco products were, in fact, comparable, as estimated by increases in plasma nicotine. Plasma nicotine levels were not measured in many of the studies to confirm similar exposures. Additionally, investigations of ECs used a wide variety of EC devices, reflecting the rapidly evolving innovations in EC technology. Whereas early studies used devices that deliver nicotine with inferior pharmacokinetics compared to TCs, studies using the pod devices would be expected to deliver greater quantities of nicotine at a faster rate, resembling the pharmacokinetics of nicotine delivery by a TC. Additional studies comparing TC smoking to the pod EC (Juul) with measurement of pre/post nicotine levels are necessary.
The protocols in these laboratory investigations, by necessity, utilized a relatively short, intense vaping period, such as 60 puffs of an EC in 30 minutes. However, these protocols may not replicate how individuals consume their tobacco product outside the lab – especially their ECs. TC smokers typically smoke one TC in several rapid puffs over 7-10 minutes, since the TC is burning. But ECs, which do not burn, may be used in a much less concentrated fashion – with single, individual puffs taken randomly throughout the day, interspersed by large intervals. In fact, there is no standard or “normal” vaping topography. It does seem to be true that people use their tobacco device to achieve and maintain a certain satisfying level of nicotine [42], but the profile of vaping behavior to achieve that nicotine level may be quite variable.

Finally, participants in these studies varied from nicotine-naïve never smokers, to chronic EC vapers, or chronic TC smokers, and this heterogeneity in experience with ECs could be expected to impact both the efficiency of aerosol delivery during EC use, as well as the physiologic effect of the aerosol on hemodynamics. The length and strength of the inhalation effort required to use an EC is quite different from that required to smoke a TC, and thus those inexperienced with an EC device tend to receive a lower aerosol exposure [7]. Furthermore, chronic TC smoking leads to stiffening of the vasculature [48]; it is conceivable that the effects of comparable vaping sessions may have different hemodynamic effects in a chronic TC smoker, in whom arteries are less compliant, compared with a non-TC smoker. In
summary, there are several limitations inherent in the available data, and thus in the strength of its interpretation.

Based on the much lower levels, or even complete absence, of carcinogens and toxicants in EC aerosol compared with TC smoke, ECs have been promoted as a harm reduction strategy in TC smokers. However, it remains uncertain that the cardiovascular effects of EC use, especially the newer, pod-like devices which deliver nicotine with similar pharmacokinetics as TCs, will lead to significant harm reduction in cardiovascular disease.

**Chronic sympathoexcitation in chronic EC vapers**

In addition to these acute increases in sympathetic nerve activity, at least one small study was consistent with the concept that chronic EC vaping is associated with chronically elevated cardiac sympathetic activity, as estimated by HRV [35]. HR and BP were not different. Unfortunately, in this small study, there was no chronic TC smoking group, so it remains unknown whether cardiac sympathetic nerve activation was similar in chronic EC users and chronic TC smokers. There are no studies utilizing the powerful and specific techniques of microneurography or norepinephrine spillover technique to assess chronic autonomic effects of ECs [13, 37].

**Mechanisms of chronic sympathoexcitation in smokers**

TC smoking is associated with a hyperadrenergic state, and potential mechanisms have been proposed [33]. In addition to the intermittent sympathetic excitation associated with increases in nicotine throughout the day, sympathetic nerve activity may be elevated even in the absence of
acute exposure. The amygdala, a brain region in which nicotine receptors are present and that integrates autonomic responses to stress and addiction, has been found to be abnormal in TC smokers [40, 53]. Amygdalar dysregulation, may further contribute to the sympathomimetic effects of smoking, and, importantly, amygdalar dysregulation has been associated with increased cardiovascular risk [43].

**Cardiovascular sequelae of chronic sympathoexcitation**

The chronic hyperadrenergic state in EC users may contribute to the development of inflammatory atherosclerosis, as part of an integrated network called the “Splenocardiac Axis.” Evidence supports the concept that the brain (amygdala) [43], autonomic nervous system, and hematopoietic tissues (bone marrow and spleen) are linked in the development of atherosclerosis and myocardial infarction. In this model, norepinephrine released from sympathetic nerves binds to β-3 adrenergic receptors on mesenchymal stem cells [32] to mobilize hematopoietic progenitor cells, which migrate from the bone marrow to the spleen [28], where they multiply in response to growth factors. Augmented numbers of pro-inflammatory monocytes enter the circulation and reach the arterial wall, where increased monocyte recruitment coupled with pro-oxidative and pro-thrombotic factors promote atherosclerosis [12, 29].

**Limitations**

The focus of this review was the autonomic cardiovascular effects of ECs, but our literature search revealed almost no studies of direct autonomic
cardiovascular effects. Accordingly, we used surrogates HR and BP. With these terms, our search yielded 224 articles. Nonetheless, additional relevant articles may have been missed. Many of the included studies were of acute EC use. Acute EC use, which increases sympathetic nerve activity acutely, thereby potentially triggering arrhythmias and ischemia, may have only limited value in telling us about longer term autonomic effects. Finally, although we have discussed the potential atherogenic effect of chronic EC use, attributable to its sympathomimetic and inflammatory effects (splenocardiac axis), long term use of the smokeless tobacco (e.g. snus or chewing tobacco) has not been shown to cause early atherosclerosis. However, smokeless tobacco may have only limited relevance to the potential for inhaled nicotine to cause atherogenic effects. Due to differing pharmacokinetics and sites of delivery, ECs may have greater sympathoexcitatory effects, thereby potentially impacting pro-inflammatory effects, and effects on early atherosclerosis remain to be determined.

**Conclusions**

The articles included in this systematic review support the notion that ECs have acute sympathoexcitatory effects, which are attributable to the nicotine, not non-nicotine, constituents in EC aerosol. Further, these sympathoexcitatory effects appear to be less than those associated with TC smoking. However, due to the rapidly evolving EC technology and changing pharmacokinetics of nicotine delivery, one must be cautious in concluding that sympathoexcitatory effects of ECs are less than TCs. Additional, rigorous
studies comparing indices of autonomic cardiovascular effects of TC smoking with the latest-generation pod-like ECs (Juul), accompanied by measurements of plasma nicotine levels, are necessary.
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Conflicts of Interest

The authors declare that they have no conflicts of interest.
References

1. Ambrose JA, Barua RS (2004) The pathophysiology of cigarette smoking and cardiovascular disease: an update. J Am Coll Cardiol 43:1731-1737
2. Antoniewicz L, Brynedal A, Hedman L, Lundback M, Bosson JA (2019) Acute Effects of Electronic Cigarette Inhalation on the Vasculature and the Conducting Airways. Cardiovasc Toxicol 19:441-450
3. Benowitz NL (1991) Nicotine and coronary heart disease. Trends Cardiovasc Med 1:315-321
4. Benowitz NL (2003) Cigarette smoking and cardiovascular disease: pathophysiology and implications for treatment. Prog Cardiovasc Dis 46:91-111
5. Biondi-Zoccai G, Sciarretta S, Bullen C, Nocella C, Violi F, Loffredo L, Pignatelli P, Perri L, Peruzzi M, Marullo AGM, De Falco E, Chimenti I, Cammisotto V, Valenti V, Coluzzi F, Cavarretta E, Carrizzo A, Prati F, Carnevale R, Frati G (2019) Acute Effects of Heat-Not-Burn, Electronic Vaping, and Traditional Tobacco Combustion Cigarettes: The Sapienza University of Rome-Vascular Assessment of Proatherosclerotic Effects of Smoking (SUR-VAPES) 2 Randomized Trial. J Am Heart Assoc 8:e010455
6. Boulay ME, Henry C, Bosse Y, Boulet LP, Morissette MC (2017) Acute effects of nicotine-free and flavour-free electronic cigarette use on lung functions in healthy and asthmatic individuals. Respir Res 18:33
7. Bullen C, McRobbie H, Thornley S, Glover M, Lin R, Laugesen M (2010) Effect of an electronic nicotine delivery device (e cigarette) on desire to smoke and withdrawal, user preferences and nicotine delivery: randomised cross-over trial. Tob Control 19:98-103
8. Chaumont M, de Becker B, Zaher W, Culie A, Deprez G, Melot C, Reye F, Van Antwerpen P, Delporte C, Debbas N, Boudjeltia KZ, van de Borne P (2018) Differential Effects of E-Cigarette on Microvascular Endothelial Function, Arterial Stiffness and Oxidative Stress: A Randomized Crossover Trial. Sci Rep 8:10378
9. Cossio R, Cerra ZA, Tanaka H (2020) Vascular effects of a single bout of electronic cigarette use. Clin Exp Pharmacol Physiol 47:3-6
10. Cullen KA, Ambrose BK, Gentzke AS, Apelberg BJ, Jamal A, King BA (2018) Notes from the Field: Use of Electronic Cigarettes and Any Tobacco Product Among Middle and High School Students - United States, 2011-2018. MMWR Morb Mortal Wkly Rep 67:1276-1277
11. D'Ruiz CD, O'Connell G, Graff DW, Yan XS (2017) Measurement of cardiovascular and pulmonary function endpoints and other physiological effects following partial or complete substitution of cigarettes with electronic cigarettes in adult smokers. Regul Toxicol Pharmacol 87:36-53
12. Dutta P, Courties G, Wei Y, Leuschner F, Gorbatov R, Robbins CS, Iwamoto Y, Thompson B, Carlson AL, Heidt T, Majmudar MD, Lasitschka F, Etzrodt M, Waterman P, Waring MT, Chicoine AT, van der Laan AM, Niessen HW, Piek JJ, Rubin BB, Butany J, Stone JR, Katus HA, Murphy SA, Morrow DA, Sabatine MS, Vinegoni C, Moskowitz MA, Pittet MJ, Libby P, Lin CP, Swirski FK, Weissleder R, Nahrendorf M (2012) Myocardial infarction accelerates atherosclerosis. Nature 487:325-329

13. Esler M (1993) Clinical application of noradrenaline spillover methodology: delineation of regional human sympathetic nervous responses. Pharmacol Toxicol 73:243-253

14. Farsalinos K, Cibella F, Caponnetto P, Campagna D, Morjaria JB, Battaglia E, Caruso M, Russo C, Polosa R (2016) Effect of continuous smoking reduction and abstinence on blood pressure and heart rate in smokers switching to electronic cigarettes. Intern Emerg Med 11:85-94

15. Farsalinos KE, Tsiapras D, Kyrzopoulou S, Savvopoulou M, Voudris V (2014) Acute effects of using an electronic nicotine-delivery device (electronic cigarette) on myocardial function: comparison with the effects of regular cigarettes. BMC Cardiovasc Disord 14:78

16. Franzen KF, Willig J, Cayo Talavera S, Meusel M, Sayk F, Reppel M, Dalhoff K, Mortensen K, Droemann D (2018) E-cigarettes and cigarettes worsen peripheral and central hemodynamics as well as arterial stiffness: A randomized, double-blinded pilot study. Vasc Med 23:419-425

17. General. OotS (2018) Surgeon General's Advisory on E-Cigarette Use Among Youth. Available from: e-cigarettes.surgeongeneral.gov/documents/surgeon-generals-advisory-on-e-cigarette-use-among-youth-2018.pdf. Accessed June 13, 2019

18. George J, Hussain M, Vadiveloo T, Ireland S, Hopkinson P, Struthers AD, Donnan PT, Khan F, Lang CC (2019) Cardiovascular Effects of Switching From Tobacco Cigarettes to Electronic Cigarettes. J Am Coll Cardiol 74:3112-3120

19. Goniewicz ML, Gawron M, Smith DM, Peng M, Jacob P, 3rd, Benowitz NL (2016) Exposure to Nicotine and Selected Toxicants in Cigarette Smokers Who Switched to Electronic Cigarettes: A Longitudinal Within-Subjects Observational Study. Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco

20. Goniewicz ML, Knysak J, Gawron M, Kosmider L, Sobczak A, Kurek J, Prokopowicz A, Jablonska-Czapla M, Rosik-Dulewska C, Havel C, Jacob P, 3rd, Benowitz N (2014) Levels of selected carcinogens and toxicants in vapour from electronic cigarettes. Tobacco control 23:133-139

21. Grassi G, Seravalle G, Calhoun DA, Bolla GB, Giannattasio C, Marabini M, Del Bo A, Mancia G (1994) Mechanisms responsible for sympathetic activation by cigarette smoking in humans. Circulation 90:248-253

22. Haass M, Kubler W (1997) Nicotine and sympathetic neurotransmission. Cardiovasc Drugs Ther 10:657-665
23. Hering D, Kucharska W, Kara T, Somers VK, Narkiewicz K (2010) Smoking is associated with chronic sympathetic activation in hypertension. Blood Press 19:152-155
24. Hering D, Somers VK, Kara T, Kucharska W, Jurak P, Bieniaszewski L, Narkiewicz K (2006) Sympathetic neural responses to smoking are age dependent. J Hypertens 24:691-695
25. Ikonomidis I, Vlastos D, Kourea K, Kostelli G, Varoudi M, Pavlidis G, Efentakis P, Triantafyllidi H, Parissis J, Andreadou I, Lliodromitis E, Lekakis J (2018) Electronic Cigarette Smoking Increases Arterial Stiffness and Oxidative Stress to a Lesser Extent Than a Single Conventional Cigarette: An Acute and Chronic Study. Circulation 137:303-306
26. Kerr DMI, Brooksbank KJM, Taylor RG, Pinel K, Rios FJ, Touyz RM, Delles C (2019) Acute effects of electronic and tobacco cigarettes on vascular and respiratory function in healthy volunteers: a cross-over study. J Hypertens 37:154-166
27. Kinoshita M, Herges RM, Hodge DO, Friedman L, Ammash NM, Bruce CJ, Somers V, Malouf JF, Askelin J, Gilles JA, Gersh BJ, Friedman PA (2009) Role of smoking in the recurrence of atrial arrhythmias after cardioversion. Am J Cardiol 104:678-682
28. Leuschner F, Rauch PJ, Ueno T, Gorbatov R, Marinelli B, Lee WW, Dutta P, Wei Y, Robbins C, Iwamoto Y, Sena B, Chudnovskiy A, Panizzi P, Keliher E, Higgins JM, Libby P, Moskowitz MA, Pittet MJ, Swirski FK, Weissleder R, Nahrendorf M (2012) Rapid monocyte kinetics in acute myocardial infarction are sustained by extramedullary monocytopoiesis. J Exp Med 209:123-137
29. Libby P, Nahrendorf M, Swirski FK (2016) Leukocytes Link Local and Systemic Inflammation in Ischemic Cardiovascular Disease: An Expanded "Cardiovascular Continuum". J Am Coll Cardiol 67:1091-1103
30. MacDonald A, Middlekauff HR (2019) Electronic cigarettes and cardiovascular health: what do we know so far? Vasc Health Risk Manag 15:159-174
31. Margham J, McAdam K, Forster M, Liu C, Wright C, Mariner D, Proctor C (2016) Chemical Composition of Aerosol from an E-Cigarette: A Quantitative Comparison with Cigarette Smoke. Chem Res Toxicol 29:1662-1678
32. Mendez-Ferrer S, Michurina TV, Ferraro F, Mazloom AR, Macarthur BD, Lira SA, Scadden DT, Ma'ayan A, Enikolopov GN, Frenette PS (2010) Mesenchymal and haematopoietic stem cells form a unique bone marrow niche. Nature 466:829-834
33. Middlekauff HR, Park J, Moheimani RS (2014) Adverse effects of cigarette and noncigarette smoke exposure on the autonomic nervous system: mechanisms and implications for cardiovascular risk. J Am Coll Cardiol 64:1740-1750
34. Moheimani RS, Bhatraratana M, Peters KM, Yang BK, Yin F, Gornbein J, Araujo JA, Middlekauff HR (2017) Sympathomimetic Effects of Acute E-
Cigarette Use: Role of Nicotine and Non-Nicotine Constituents. J Am Heart Assoc 6

35. Moheimani RS, Bhetraratana M, Yin F, Peters KM, Gornbein J, Araujo JA, Middlekauff HR (2017) Increased Cardiac Sympathetic Activity and Oxidative Stress in Habitual Electronic Cigarette Users: Implications for Cardiovascular Risk. JAMA Cardiol 2:278-284

36. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med 151:264-269, W264

37. Narkiewicz K, van de Borne PJ, Hausberg M, Cooley RL, Winniford MD, Davison DE, Somers VK (1998) Cigarette smoking increases sympathetic outflow in humans. Circulation 98:528-534

38. Polosa R, Cibella F, Caponnetto P, Maglia M, Prosperini U, Russo C, Tashkin D (2017) Health impact of E-cigarettes: a prospective 3.5-year study of regular daily users who have never smoked. Sci Rep 7:13825

39. Polosa R, Morjaria JB, Caponnetto P, Battaglia E, Russo C, Ciampi C, Adams G, Bruno CM (2016) Blood Pressure Control in Smokers with Arterial Hypertension Who Switched to Electronic Cigarettes. Int J Environ Res Public Health 13

40. Rose JE, Behm FM, Westman EC, Mathew RJ, London ED, Hawk TC, Turkington TG, Coleman RE (2003) PET studies of the influences of nicotine on neural systems in cigarette smokers. Am J Psychiatry 160:323-333

41. Sandhu RK, Jimenez MC, Chiuve SE, Fitzgerald KC, Kenfield SA, Tedrow UB, Albert CM (2012) Smoking, smoking cessation, and risk of sudden cardiac death in women. Circ Arrhythm Electrophysiol 5:1091-1097

42. Shahab L, Goniewicz ML, Blount BC, Brown J, McNeill A, Alwis KU, Feng J, Wang L, West R (2017) Nicotine, Carcinogen, and Toxin Exposure in Long-Term E-Cigarette and Nicotine Replacement Therapy Users: A Cross-sectional Study. Ann Intern Med 166:390-400

43. Tawakol A, Ishai A, Takx RA, Figueroa AL, Ali A, Kaiser Y, Truong QA, Solomon CJ, Calcagno C, Mani V, Tang CY, Mulder WJ, Murrough JW, Hoffmann U, Nahrendorf M, Shin LM, Fayad ZA, Pitman RK (2017) Relation between resting amygdalar activity and cardiovascular events: a longitudinal and cohort study. Lancet 389:834-845

44. Vansickel AR, Cobb CO, Weaver MF, Eissenberg TE (2010) A clinical laboratory model for evaluating the acute effects of electronic "cigarettes": nicotine delivery profile and cardiovascular and subjective effects. Cancer Epidemiol Biomarkers Prev 19:1945-1953

45. Veldheer S, Yingst J, Midya V, Hummer B, Lester C, Krebs N, Hrabovsky S, Wilhelm A, Liao J, Yen MS, Cobb C, Eissenberg T, Fouls J (2019) Pulmonary and other health effects of electronic cigarette use among adult smokers participating in a randomized controlled smoking reduction trial. Addict Behav 91:95-101

46. Viechtbauer w (2010) Conducting meta-analyses in R with the metafor package. Journal of Statistical Software 36:1-48
47. Vlachopoulos C, Ioakeimidis N, Abdelrasoul M, Terentes-Printzios D, Georgakopoulos C, Pietri P, Stefanadis C, Tousoulis D (2016) Electronic Cigarette Smoking Increases Aortic Stiffness and Blood Pressure in Young Smokers. J Am Coll Cardiol 67:2802-2803

48. Vlachopoulos C, Kosmopoulou F, Panagiotakos D, Ioakeimidis N, Alexopoulos N, Pitsavos C, Stefanadis C (2004) Smoking and caffeine have a synergistic detrimental effect on aortic stiffness and wave reflections. J Am Coll Cardiol 44:1911-1917

49. Wagener TL, Floyd EL, Stepanov I, Driskill LM, Frank SG, Meier E, Leavens EL, Tackett AP, Molina N, Queimado L (2017) Have combustible cigarettes met their match? The nicotine delivery profiles and harmful constituent exposures of second-generation and third-generation electronic cigarette users. Tobacco control 26:e23-e28

50. Wang TW, Asman K, Gentzke AS, Cullen KA, Holder-Hayes E, Reyes-Guzman C, Jamal A, Neff L, King BA (2018) Tobacco Product Use Among Adults - United States, 2017. MMWR Morb Mortal Wkly Rep 67:1225-1232

51. Winniford MD, Wheelan KR, Kremers MS, Ugolini V, van den Berg E, Jr., Niggemann EH, Jansen DE, Hillis LD (1986) Smoking-induced coronary vasoconstriction in patients with atherosclerotic coronary artery disease: evidence for adrenergically mediated alterations in coronary artery tone. Circulation 73:662-667

52. Yan XS, D’Ruiz C (2015) Effects of using electronic cigarettes on nicotine delivery and cardiovascular function in comparison with regular cigarettes. Regul Toxicol Pharmacol 71:24-34

53. Zubieta JK, Heitzeg MM, Xu Y, Koepp RA, Ni L, Guthrie S, Domino EF (2005) Regional cerebral blood flow responses to smoking in tobacco smokers after overnight abstinence. Am J Psychiatry 162:567-577
Figure Legends

Figure 1. PRISMA study selection process. The electronic search yielded 224 studies. Fifty-three studies were removed because they were found to be duplicates and 115 studies were excluded because they did not meet inclusion criteria. Seventeen studies were excluded because a full-text was not available. Then a full text review was performed on the remaining 39 studies, which led to the exclusion of 21 studies because 1 study was an editorial, and 20 studies had no relevant outcome measures. One additional study[18], published after the literature search, was included while the paper was under review. In total, 19 studies were included in this systematic review.

Figure 2. Summary of acute hemodynamic effects of tobacco compared to electronic cigarettes. Data from 11 acute comparisons revealed that the effects of electronic cigarettes with nicotine compared to TCs on SBP (panel A), DBP (panel B) and HR (panel C) were significantly less. The forest plot entry for each study is the mean differences between TC and EC, with the corresponding lower and upper 95% confidence bounds. The plots to the right of the vertical line of no effect indicate that TC is worse than EC. DBP = diastolic blood pressure, ECN = electronic cigarette, HR = heart rate, SBP = systolic blood pressure, TC = tobacco cigarette.
Figure 3. Summary of acute hemodynamic effects of electronic cigarettes with nicotine compared to electronic cigarettes without nicotine. Data from 5 acute studies revealed that the effects of EC with nicotine compared to ECs without nicotine on SBP (panel A), DBP (panel B) and HR (panel C) were significantly less. The forest plot entry for each study is the mean differences between ECN and EC0, with the corresponding lower and upper 95% confidence bounds. The plots to the right of the vertical line of no effect indicate that ECN is worse than EC0. DBP = diastolic blood pressure, ECN = electronic cigarette with nicotine, EC0 = electronic cigarette without nicotine, HR = heart rate, SBP = systolic blood pressure, TC = tobacco cigarette.

Figure 4. Heart rate variability in chronic EC vapers compared to age-matched controls. The high-frequency (HF) component, an indicator of vagal activity, was significantly decreased in the EC vapers compared with nonuser control individuals (mean [SEM], 46.5 [3.7] nu vs 57.8 [3.6] nu, p = 0.04). B and C, The low-frequency (LF) component, an indicator largely of sympathetic activity, (mean [SEM], 52.7 [4.0] nu vs 39.9 [3.8] nu, p = 0.03), and the LF to HF ratio (1.37 [0.19] vs 0.85 [0.18], p = 0.05), were significantly increased in the EC users compared with nonuser controls, consistent with sympathetic predominance. These findings were present even in the absence of recent EC use, as verified by the absence of detectable nicotine in the plasma. Used with permission. HF= high frequency, LF= low frequency
Figure 1

PRISMA Study Selection Process

224 Studies Identified Through Database Search → 53 Duplicates Removed

171Studies Screened → 115 Studies Irrelevant 17 no full text available

39 Full-Text Studies Assessed For Eligibility → 21 Excluded Reasons:
(N = 1) Was an editorial
(N = 20) No Relevant Outcome Measure

1 Study published/added during the review process.

19 Studies Included In Qualitative Systematic Review
Figure 2

A.

B.

C.
Figure 3

A.  

B.  

C.  

\[ \Delta \text{Systolic BP (mmHg)} \]  

Franzen  

Cossio  

Chaumont  

Antoniewicz  

Moheimani  

Overall  

\[ \Delta \text{Diastolic BP (mmHg)} \]  

Franzen  

Chaumont  

Antoniewicz  

Moheimani  

Cossio  

Overall  

\[ \Delta \text{Heart rate (bpm)} \]  

Franzen  

Chaumont  

Antoniewicz  

Moheimani  

Overall  

\[ p=0.02 \]  

\[ p=0.0018 \]  

\[ p<0.00001 \]
Figure 4.

A | High-frequency component
---|---
E-Cigarette Users | Nonuser Control Participants

B | Low-frequency component
---|---
E-Cigarette Users | Nonuser Control Participants

C | Low frequency to high frequency ratio
---|---
E-Cigarette Users | Nonuser Control Participants

P = .04
P = .03
P = .05