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Review article

Hormonal contraception among electronic cigarette users and cardiovascular risk: a systematic review^{☆,☆☆,★}

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Abstract

Background: Women who use combined hormonal contraceptives and cigarettes have an increased risk for cardiovascular (CV) events. We reviewed the literature to determine whether women who use hormonal contraceptives (HC) and electronic cigarettes (e-cigarettes) also have an increased risk.

Study Design: Systematic review.

Methods: We searched for articles reporting myocardial infarction (MI), stroke, venous thromboembolism, peripheral arterial disease or changes to CV markers in women using e-cigarettes and HC. We also searched for indirect evidence, such as CV outcomes among e-cigarette users in the general population and among HC users exposed to nicotine, propylene glycol or glycerol.

Results: No articles reported on outcomes among e-cigarette users using HC. Among the general population, 13 articles reported on heart rate or blood pressure after e-cigarette use. These markers generally remained normal, even when significant changes were observed. In three studies, changes were less pronounced after e-cigarette use than cigarette use. One MI was reported among 1012 people exposed to e-cigarettes in these studies. One article on nicotine and HC exposure found both exposures to be significantly associated with acute changes to heart rate, though mean heart rate remained normal. No articles on propylene glycol or glycerol and HC exposure were identified.

Conclusion: We identified no evidence on CV outcomes among e-cigarette users using HC. Limited data reporting mostly acute outcomes suggested that CV events are rare among e-cigarette users in the general population and that e-cigarettes may affect heart rate and blood pressure less than conventional cigarettes. There is a need for research assessing joint HC and e-cigarette exposure on clinical CV outcomes. © 2016 Elsevier Inc. All rights reserved.

Keywords: Electronic cigarettes; Hormonal contraceptives; Nicotine; Propylene glycol; Glycerol; Cardiovascular disease

1. Introduction

Use of electronic nicotine delivery systems, especially electronic cigarettes or e-cigarettes (ECs), is increasing in the United States [1–3]. Among 2012–2013 National Adult Tobacco Survey respondents, 14.1% reported ever use of

ECs, and 4.2% reported using ECs every day, some days or rarely. Among female respondents, 3.6% reported use every day, some days or rarely [1]. ECs were also the most commonly used tobacco product reported in a 2011–2014 nationally representative survey of US high school students, with 13.4% reporting use in the past 30 days [4]. At the same time, rates of current conventional cigarette use appear to be decreasing among women of reproductive age (WRA). In a 2013 national survey, 15.4% of women aged 18–24 and 17.1% of women aged 25–44 years reported regular cigarette use, down from 18.3% and 22.6%, respectively, in 2005 [5]. However, among EC users, simultaneous use of cigarettes appears to be common [6]. Although ECs are often promoted as safer alternatives to cigarettes, data on health effects associated with their use are limited [7–9].

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ECs generally consist of a sensor, a microprocessor that is activated when air is inhaled, a battery, a heating device or aerosol generator and a storage unit containing e-liquid. Several generations of EC devices exist, and products may be rechargeable, reusable and modifiable by users [10]. During use (often referred to as *vaping*), users activate devices' heating components to create an inhaled aerosol [11,12]. Contents of the e-liquid differ by brand and type but generally include nicotine, glycerol and/or propylene glycol, flavoring and other additives. One study analyzed EC aerosol for carcinogens and toxicants and detected formaldehyde, acetaldehyde, acrolein, volatile organic compounds, tobacco-specific nitrosamines and metals (cadmium, nickel and lead). The presence of these toxicants was found to be lower in ECs than in conventional cigarettes but higher compared with nicotine inhaler mist [10,13]. E-liquid nicotine levels also varied by brand and type, with many containing 6–24-mg nicotine/mL e-liquid [14]. In some cases, true nicotine content differed significantly from concentrations indicated on product labels [15–17]. By comparison, conventional cigarettes contain about 10–15-mg nicotine/cigarette and deliver about 1-mg nicotine for each cigarette smoked [14]. Evidence is mixed on whether ECs deliver nicotine at rates comparable to conventional cigarettes, but several studies have found ECs to increase users' blood and saliva nicotine and cotinine levels [10].

For more than 50 years, evidence has accumulated on the causal link between conventional cigarette smoking and cardiovascular disease (CVD) through various mechanisms, including atherogenesis, changes in endothelial function and prothrombotic effects [18]. Women who smoke and use combined hormonal contraceptives (CHC) are at an even higher risk of CVD compared with women having only one of these risk factors. CHCs contain both estrogen and a progestin and include combined oral contraceptives (COCs), the combined contraceptive vaginal ring and the combined transdermal contraceptive patch. Observational studies and meta-analyses have reported elevated risks of coronary heart disease, myocardial infarction (MI), stroke, venous thromboembolism (VTE) and peripheral arterial disease (PAD) among women who smoke and use CHCs [18–29]. The mechanisms underlying increased CVD risk in female smokers who use CHCs are poorly understood but could include effects of products of combustion, nicotine exposure or both.

Women who are exposed to nicotine through cigarette smoking, EC use, nicotine replacement therapy (NRT) or other sources and who become pregnant are at increased risk for poor pregnancy outcomes [30–40]. Therefore, preventing unintended pregnancy in these women and delaying pregnancy until cessation of tobacco to prevent nicotine exposure is a key strategy for improving pregnancy and perinatal outcomes. National evidence-based recommendations for contraceptive use generally recommend that smokers should not use CHCs because of increased risk for CVD [41,42], but no guidelines for EC use exist. Although ECs do not produce the products of combustion found in conventional cigarettes, there is concern among

family planning providers as to whether EC users may be at increased risk of CVD if they use CHCs.

The safety of hormonal contraceptive (HC) use among women who use ECs is an important clinical question. In a 2012 survey of members of the American College of Obstetricians and Gynecologists ($n=252$), 13.5% of respondents reported that they believed ECs had no health effects, and 36.5% of respondents ($n=92$) reported that they did not know the health effects of EC use [43]. Given the increase in EC use in the United States and the popularity of HC, especially CHCs, family planning providers may increasingly see EC users who wish to initiate or continue CHCs. The objective of this review is to evaluate data regarding cardiovascular risks among EC users who are exposed to HC.

2. Materials and methods

We conducted this systematic review according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines [44]. We searched for studies that addressed one of four research questions.

Research question #1 (our primary research question) was, “Are female e-cigarette users who use HC at heightened risk for adverse cardiovascular outcomes compared with female e-cigarette users who do not use HC?” While CHCs specifically have been associated with increased risk for cardiovascular events among women who smoke, to be comprehensive, we included all HC methods in our search.

Because we anticipated that we would identify little evidence for this question, we developed three additional research questions to search for indirect evidence that could help assess the risk for cardiovascular events among HC users who use ECs.

Research question #2: Among the general population (men and women), are EC users at increased risk of adverse cardiovascular outcomes (clinical events or changes to intermediary markers) compared with people who do not use ECs (regardless of HC use status)?

Research question #3: Among women exposed to nicotine (a common component of ECs) from any source other than cigarettes including smokeless tobacco products and NRT, are those who use HC at increased risk of adverse cardiovascular outcomes (clinical events or changes to intermediary markers) compared with women who do not use HC?

Research question #4: Among women exposed to inhaled propylene glycol or glycerol (additional common components of ECs), are those who use HC at increased risk of adverse cardiovascular outcomes (clinical events or changes to intermediary markers) compared with women who do not use HC?

We searched the PubMed and Cochrane Library databases from database inception through June 2015 for articles

in any language that addressed our research questions. Search strategies can be found in [Appendix A](#). We did not include case studies, case reports or conference proceedings. For research question #2, we included studies of both women and men, because evidence on EC use is limited and because existing studies generally do not report results by sex. For EC exposure, we included studies in which participants primarily used nicotine-containing ECs. For contraceptives, we included any HC method, including COCs, the combined transdermal contraceptive patch, the combined hormonal vaginal ring, combined injectable contraceptives, progestin-only pills, progestin-only implants, progestin-only injectables and levonorgestrel-releasing intrauterine devices. We were primarily interested in the clinical outcomes of MI, stroke, VTE and PAD but included studies that reported on intermediary outcomes that might serve as proxy measures for risk. For intermediary outcomes, we included changes in blood pressure (BP), lipid levels [cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL) and triglycerides] and C-reactive protein levels, all measures of cardiovascular risk [45,46], in addition to changes in heart rate, as that is a widely reported cardiovascular marker.

Two authors (HR and KC) reviewed titles, abstracts or full articles to identify studies that met inclusion criteria. Evidence was summarized and assessed using standard data abstraction forms [47]. We considered multiple methodological factors that could introduce bias, including whether a standardized exposure was used in intervention trials, whether an appropriate comparison group (a non-EC comparison, single-group before-and-after comparison only or no comparison group) was used, whether the study measured outcomes over an acute or longer duration, whether the outcome was validated biochemically or by self-report only, whether there was adequate adjustment for confounders and whether sample size, power and follow-up rates were adequate. The quality of each individual study was assessed using the United States Preventive Services Task Force grading system [48]. Because of heterogeneity in study design and measurement of outcomes, we did not compute summary measures of association across studies.

3. Results

3.1. Research question #1

Our search for evidence on risk for CVD among women using HC and ECs yielded no articles.

3.2. Research question #2

Our search for evidence on EC use and risk for adverse cardiovascular events among men and women yielded 535 articles. Of these, 13 articles met inclusion criteria for this review [49–61]. One article reported on the clinical outcomes of interest (two cases of MI) [49]. Eleven articles measured heart rate and BP after EC exposure [50–60]. In 5

of these articles, investigators followed participants for at least 1 week [49,57–60], but in 7 articles, authors only reported acute outcomes (changes over <5 h of exposure) [50–56]. One article reported on a cross-sectional survey in which EC users reported on perceived changes to health after switching from cigarettes to ECs [61]. Twelve articles included data on both men and women together, with one reporting on women alone [56].

3.2.1. Longitudinal studies

In the five articles that reported on cardiovascular outcomes among EC users followed longitudinally [49,57–60] (Table 1), follow-up periods ranged from 7 days to 1 year. One double-blind randomized controlled trial (RCT) of fair quality assigned 300 smokers (110 women) to one of three arms [58]. Investigators provided all users with the same EC model, but each arm received cartridges with different nicotine content (a 12-week supply of 7.2-mg nicotine/mL, a 6-week supply of 7.2-mg nicotine/mL and a 6-week supply of 5.4-mg nicotine/mL or a 12-week supply of 0.0-mg nicotine/mL). Participants used ECs as they wished for up to 12 weeks, with study visits every 2 weeks and additional visits at weeks 24 and 52 weeks. The investigators made no restrictions on conventional cigarette use. At each study visit, investigators measured heart rate and BP and collected data on adverse events. No serious adverse events were reported. The authors reported no statistically significant changes in resting heart rate or BP from baseline to the end of the study or between groups throughout the study but reported no values for these outcomes.

Two poor quality case series (uncontrolled longitudinal studies) and one fair quality randomized crossover study provided current smokers with ECs and followed them for 7–14 days [57,59,60]. In the first report, investigators provided 15 smokers (5 women) with ECs containing 0.0144-mg nicotine/0.8-mL e-liquid [57]. Participants were instructed to use ECs rather than cigarettes for 2 weeks. Investigators measured BP and heart rate at baseline and day 14 and reported no statistically significant changes to either parameter, but no values were reported. The second case series provided 29 smokers (10 women) with an EC containing a 26-mg nicotine/mL e-liquid cartridge [59]. Participants used ECs for 20 min at the study site then used them as they wished for 7–10 days with no restrictions on conventional cigarette use. Participants returned after 7–10 days and used the ECs under observation (for two 10-puff bouts). No serious adverse events were reported. During the second observation session (after 7–10 days of exposure), heart rate increased statistically significantly from a baseline mean of 68 beats per minute (bpm) to 73.3 bpm at 10 min after the first 10-puff bout and to 72.8 bpm at 10 min after the second 10-puff bout. Even with these statistically significant increases, mean heart rate remained well within normal range for resting heart rate (60–100 bpm for adults) [62].

In the crossover study, 20 participants (9 women) were randomized to receive ECs containing 18-mg nicotine/mL e-liquid in either menthol or nonmenthol tobacco flavor.

Table 1
Longitudinal studies of EC use.

Author, year, location, sources of support	Study design	Population (including WRA)	Exposure(s)	Cardiovascular outcome(s)	Results	Strengths	Weaknesses	Grading of quality*
Caponnetto, 2013 [58], Italy. Lega Italiana AntiFumo/University of Catania, Italy	Double-blind RCT (3 arms)	300 smokers (110 women) who had smoked ≥ 10 cigarettes/day for ≥ 5 years. Average age = 44 years (SD ± 12.5 years). Excluded: symptomatic CVD, respiratory disease, psychotropic drug use, current or past alcohol abuse, use of smokeless tobacco, or NRT, pregnancy/lactation.	Three products, participants randomized to exposure condition. Products: All participants used the same EC model, with different cartridges provided. 1) 7.2-mg nicotine/mL cartridges (12-week supply). 2) 7.2-mg nicotine/mL cartridges (6-week supply) + 5.4-mg nicotine cartridges (6-week supply). 3) 0-mg nicotine/mL cartridge (12-week supply). Product administration: Participants used ECs provided <i>ad lib</i> . Participants could return to study site every 2 weeks for 12 weeks (seven study visits) for additional study supplies.	Resting heart rate, measured at each study visit (baseline, weeks 2, 4, 6, 8, 10, 12, 24, 52). BP, measured at each study visit (baseline, weeks 2, 4, 6, 8, 10, 12, 24, 52). Adverse events reported.	No statistically significant changes in mean resting heart rate or systolic/diastolic BP from baseline to end of the study observed overall. No statistically significant differences in heart rate or systolic/diastolic BP reported between 3 study groups throughout study. No point estimates reported. No serious adverse events reported.	Randomization and blinding procedures described. Controlled for effects of smoking by enrolling only smokers. Two different nicotine content ECs compared with nonnicotine exposed control group. Long-term follow-up (1 year). Excluded symptomatic CVD (unclear whether hypertensive individuals were excluded)	No point estimates reported for changes in resting heart rate or BP. Study powered on quit rate, not on changes in BP or heart rate. High loss to follow-up (35%–45% over 52 weeks) and differential by groups (0-mg nicotine group lost more than either nicotine group). Results not reported by sex. No standardized study exposure (participants used ECs <i>ad lib</i> ; participants were allowed to use cigarettes throughout the study).	I; Fair
van Staden, 2013 [57], South Africa. ECs used in study provided by Twisp EC Company	Case series	15 smokers (5 women) who had smoked 10–30 cigarettes/day; had been smoking for a median of 17 years. Age range: 23–46 years (median, 38 years). Excluded: individuals with known history of heart disease.	Product: EC containing 0.0144-mg nicotine/0.8-mL e-liquid. Product administration: Participants used EC instead of cigarettes (as they would use cigarettes) for 2 weeks.	BP and heart rate, at baseline and at 2 weeks.	No statistically significant changes in BP or heart rate from baseline to day 14.	Controlled for effects of smoking by enrolling only smokers. Participants used ECs in “real life” setting. ~87% of participants followed for 2 weeks.	No nonuser comparison group. Small sample size. No standardized dose (<i>ad lib</i> EC use). No clear description of sample frame/recruitment strategy. Authors were unable to determine participants’ cigarette exposure status. Results not reported by sex. No exclusions for chronic health conditions other than chronic lung disease. Powered on changes in arterial COHb	II-3; Poor

Table 1 (continued)

Author, year, location, sources of support	Study design	Population (including WRA)	Exposure(s)	Cardiovascular outcome(s)	Results	Strengths	Weaknesses	Grading of quality*
Nides, 2014 [59], US. NJOY, Inc. (EC company)	Case series	29 smokers (10 women) who had smoked ≤ 10 cigarettes/day for past year. Age range: 18–63 years (mean, 43 years). 45% of participants had never used an EC, 48% had used < 10 ECs in lifetime, 7% had used > 10 ECs. Excluded: pregnant or breastfeeding women, individuals reporting current drug abuse, use of prescription psychiatric or opioid medications, use of EC within 14 days prior to study; use of nicotine replacement products within 30 days prior to study; consumption of alcohol within 24 h prior to Session 3.	Product: EC with 26-mg nicotine/mL e-liquid cartridge. Product administration: 1) Participants used ECs <i>ad lib</i> for 20 min in clinic. 2) Participants were given ECs and instructed to use them as often as they liked for 7–10 days, maintaining EC use diary. 3. Participants used ECs for 2 series of 10-puff bouts with 30 s interpuff interval.	Heart rate measured at 20-s intervals beginning 5 min before the first puff of each visit and continuing until 35 min after each set of puffs.	During Session 3, heart rate increased statistically significantly from a baseline mean of 68 bpm to 73.3 bpm at 10 min after first 10-puff bout and to 72.8 bpm at 10 min after second 10-puff bout ($p < 0.004$).	Controlled for effects of smoking by enrolling only smokers. Participants used ECs in “real life” setting. ~88% follow up over 3 weeks.	levels (not BP or heart rate). No nonuser control group. Nonstandardized EC dose. Participants were allowed to use cigarettes throughout the study. Authors only measured acute outcomes after brief exposure; no long-term follow-up. Results not reported by sex. No sample size or power calculations provided. Participants were in “general good health”; unclear if this included those with high BP or other risk factors for CVD.	II-3, Poor
Oncken, 2015 [60], US. Funded by internal funding from University of Connecticut Health Center.	Randomized crossover study	20 smokers (9 women) who smoked ≥ 10 cigarettes/day and agreed to switch to ECs for 2 weeks. Excluded: pregnant women, individuals with history of MI or stroke, uncontrolled hypertension, insulin dependent diabetes, COPD, current asthma, or allergy to propylene glycol.	Products: 18-mg/mL nicotine e-liquid cartridge flavored with a) menthol-tobacco flavoring and menthol, b) tobacco flavoring only. Product Administration: Participants used each EC for 7–10 days and then were monitored using EC in laboratory for 5 min <i>ad lib</i> (heart rate and BP measured during laboratory session). Participants then repeated procedures with alternative flavor.	Heart rate and BP measured 5 min before and 5, 10, 15, 29 and 30 min after 5 min of <i>ad lib</i> EC use.	No significant increases in systolic or diastolic BP or heart rate were observed during laboratory sessions. No main effects for sex were observed for these parameters. Mean heart rate (collapsed over sessions) changed from ~67.5 bpm at baseline to 68.5 bpm after 5 min of EC use, then remained between 66 and 68 bpm for remainder of the sessions. Systolic blood pressure remained between	Analyzed heart rate and BP by sex. Standardized exposure during laboratory session.	Nonstandardized exposure during 7–10 days of use. No non-EC comparison group. Small sample size. Randomization procedures not described. Study powered on changes to nicotine levels, not on changes in BP or heart rate. 66% follow-up rate.	I, Fair

Manzoli [49], 2015, Italy. No source of funding reported.	Prospective cohort study	12-month follow-up data provided for: - 236 EC users (88 women): had used any type of EC ≥ 50 puffs/week for ≥ 6 months prior to baseline. - 491 conventional cigarettes smokers (252 women): smoked ≥ 1 cigarette/day for ≥ 6 months prior to baseline. - 232 dual users (83 women): had used both conventional cigarettes and ECs in the same week for the past 6 months Excluded: age <30 or >75 years, pregnancy/lactation, illicit drug use, major depression, severe allergies, angina and past major smoking-related disease.	Products: Participants provided their own ECs and conventional cigarettes. Reported nicotine content of ECs used: EC group: No nicotine, 12.8% 3–8 mg: 23.5% 9 mg: 40.7% 10–24 mg: 23.0%. Dual users: No nicotine, 5.6% 3–8 mg: 19.1% 9 mg: 34% 10–24 mg: 41.4%. >90% of all EC users reporting use of nicotine-containing ECs. Product administration: Participants used products on their own for 12 months and recorded smoking behavior through questionnaire.	Possibly related serious adverse events reported at 12 months.	120–125 mmHg from baseline through 30 min after 5 min of use. Diastolic BP remained between 70 and 80 mmHg from baseline through 30 min after 5 min of use. One acute MI reported in group of dual users who quit tobacco cigarettes and continued with ECs only at 12 months ($n=24$). One acute MI reported in group of smokers who continued with tobacco cigarettes only at 12 months ($n=381$). Age, sex and level of nicotine intake not reported for either individual experiencing MI.	Included non-EC comparison group 12-month follow-up. Clear description of sample frame/recruitment strategies.	Nonstandardized exposure (participants used cigarettes or ECs under “real life” conditions) and self-reported use. Nonstandardize product: individuals could use their own ECs. Nonvalidated outcomes (25% of participants reporting tobacco cigarette abstinence tested for CO levels; results nonvalidated for others). Results not reported by sex. No power calculations reported. ~30% of sample lost to follow up between baseline and 12 months (no significant differences in loss to follow up between groups).	II-2, Poor
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COHb: Carboxyhemoglobin; COPD, chronic obstructive pulmonary disease; SD, standard deviation; WRA, women of reproductive age.

* US Preventive Services Task Force (USPSTF) grading criteria used to assess study quality [48].

Participants used ECs for 7–10 days in lieu of conventional cigarettes, returned to the laboratory for a monitoring session (5 min of EC use with heart rate and BP recorded) and then repeated the procedure with the alternative flavor [60]. No significant increases to heart rate or BP were recorded in the 30 min of observation following either laboratory session, with mean heart rate ranging from ~66 to 69 bpm, mean systolic BP ranging from 120 to 125 mmHg and mean diastolic BP remaining ~75 mmHg throughout the observation periods.

One prospective cohort study (poor quality) recruited 1355 Italian adults who reported either conventional cigarette use (at least one cigarette per day for 6 months prior to recruitment, $n=693$), EC use (at least 50 puffs per week for 6 months prior to recruitment, $n=343$) or dual use (use of both products within the same week for 6 months prior to recruitment, $n=319$) [49]. Investigators planned to follow participants for 60 months but reported preliminary results at 12 months for 491 conventional cigarette users (252 women), 236 EC users (88 women) and 232 dual users (83 women). Participants provided their own cigarettes and ECs, with e-liquid nicotine levels ranging from 0- to 24-mg nicotine/mL (with >90% of all EC users reporting use of nicotine-containing ECs). Two acute MIs reported in year 1 of the study were classified as adverse events possibly related to the study exposure. One occurred among the group of dual users who had switched to EC use only ($n=24$), and the other was reported among the group of conventional cigarette smokers who continued with cigarette use only ($n=381$). Authors did not report age, sex or level of EC or cigarette use for individuals experiencing MIs.

3.2.2. Studies of acute exposures

We identified seven studies in which investigators observed individuals using ECs in laboratory settings for short time periods (≤ 5 h of observation per session) [50–56] (Table 2). Participants attended one [50,54] to six [53] sessions. Each of these studies reported only acute results (e.g., changes to heart rate or BP after short periods of EC use). None reported on clinical cardiovascular outcomes of interest.

One fair quality nonrandomized trial compared 40 current EC users (all former smokers) with 36 current smokers (6 women total) [50]. There were no statistically significant differences in baseline diastolic or systolic BP, heart rate, total cholesterol, LDL cholesterol, HDL cholesterol or triglycerides between current smokers and current EC users. Participants in the EC group used an EC containing 11-mg nicotine/mL e-liquid for 7 min *ad lib*, while participants in the smoker group smoked one cigarette under observation. In the EC group, no statistically significant changes to mean heart rate (from 67.1 ± 10.3 to 67.5 ± 10.6 bpm) or systolic BP (from 123.9 ± 8.6 to 124.6 ± 9.9 mmHg) were observed between baseline and after exposure, but a statistically significant change in mean diastolic BP was observed after EC use (from 75.6 ± 6.2 to 78.5 ± 5.9 mmHg, $p<0.001$). In the smoker group, investigators reported statistically significant increases for each of these

parameters after cigarette exposure. Mean heart rate increased from 67.5 ± 10.3 to 73.5 ± 6.8 bpm ($p<0.001$), mean systolic BP increased from 123 ± 8.6 to 129.6 mmHg ($p<0.001$) and mean diastolic BP increased from 75.8 ± 5.6 to 80.2 ± 5.8 mmHg ($p<0.001$). Between-group changes were significantly different for mean heart rate and systolic BP ($p<0.001$ for both parameters). In both groups, diastolic BP and heart rate remained within normal ranges [63]. Mean systolic BP was in the prehypertensive range [63] at baseline and remained in this range.

Two randomized crossover studies exposed individuals to four [52] or six products [53], with participants randomized to exposure order. In the first study (poor quality), 32 smokers (13 women) used four products (an EC with a cartridge containing 18-mg nicotine/mL e-liquid, an EC with a cartridge containing 16-mg nicotine/mL e-liquid, chosen brand of conventional cigarette and an unlit cigarette) for 10 puffs, then repeated the procedure after an hour with the same product, with heart rate measured every 20 s [52]. Four sessions were completed (one session per product) with a ≥ 48 -h washout period between sessions. The authors reported no statistically significant changes in heart rate after exposure to either EC or the unlit cigarette. Mean heart rate increased significantly between baseline and 5 min after exposure to conventional cigarettes (from 65.7 bpm to 80.3 bpm) compared with the unlit cigarette or either EC (no p -value reported). In the second crossover study (fair quality), 23 smokers (12 women) took 50 puffs of six products (five ECs containing from 1.6% to 2.4% nicotine and varying levels of propylene glycol and glycerin and a conventional cigarette), then used each product *ad lib* for 1 h. Participants completed six sessions (one per product) with a ≥ 24 -h washout period between sessions [53]. The authors observed statistically significant increases to mean diastolic BP after use of all products compared with baseline (with baseline means ranging from 70 ± 8.9 to 73 ± 8.6 mmHg over the six sessions and postexposure means ranging from 76 ± 9.3 to 78 ± 10.1 mmHg) and observed a statistically significant increase to mean systolic BP after use of the EC containing 1.6% nicotine and ~75% glycerin (from 118 mmHg to 124 mmHg, $p=0.02$) and the conventional cigarette (from 120 mmHg to 126 mmHg, $p=0.04$). For all other products, authors observed nonstatistically significant (NS) increases to systolic BP. The authors noted statistically significant increases to mean heart rate after use of an EC containing 2.4% nicotine, ~50% glycerin and ~20% propylene glycol (from 71 to 75 bpm, $p=0.008$), an EC containing 2.4% nicotine and ~75% glycerin (from 70 to 74 bpm, $p=0.002$) and the conventional cigarette (from 70 to 74 bpm, $p=0.001$).

We identified two fair quality nonrandomized crossover studies in which investigators examined cardiovascular markers after conventional cigarette versus EC exposure. In the first study, 42 individuals (21 women) participated in two sessions separated by a 7-day washout period [55]. In the first session, individuals smoked a conventional cigarette for

Table 2
Acute studies of EC use.

Author, year, location, sources of support	Study design	Population (including WRA)	Exposure(s)	Cardiovascular outcome(s)	Results	Strengths	Weaknesses	Grading of quality*
Farsalinos, 2014a [50], Greece. No specific grant funding listed. Authors have performed other studies funded by EC companies.	Nonrandomized trial; 2 arms	76 participants: - 36 smokers (3 women), smoking for \geq 15 cigarettes/day for \geq 5 years - 40 current EC users, all former smokers (3 women) using ECs for \geq 1 month, using 9–12 mg/mL nicotine e-liquid Mean age: 36 years. Excluded individuals with major risk factors for CVD, including hypertension and with abnormal echocardiograph results.	Products: 1) EC containing 11-mg nicotine/mL e-liquid (former smoker exposure). 2) Conventional cigarette (smoker exposure). Product Administration: 1) Participants in EC group used EC <i>ad lib</i> for 7 min). 2) Participants in smoking group smoked one cigarette.	Heart rate and BP at baseline and after exposure.	EC: No statistically significant changes to mean heart rate (from 67.1 \pm 10.3 to 67.5 \pm 10.6 bpm) after EC administration compared with baseline. No statistically significant changes to mean systolic BP (from 123.0 \pm 8.6 to 124.6 \pm 9.9 mmHg) after EC administration compared with baseline. Statistically significant increase in diastolic BP after EC administration (from 75.6 \pm 6.2 to 78.5 \pm 5.9 mmHg, p <0.001) compared with baseline. Cigarette: Statistically significant increases in heart rate (67.5 \pm 7.9 to 73.5 \pm 6.8 bpm, p <0.001), systolic BP (123 \pm 9.8 to 129.6 \pm 9.2 mmHg, p <0.001), and diastolic BP (from 75.8 \pm 5.6 to 80.2 \pm 5.8 mmHg, p <0.001) after cigarette exposure, compared with baseline. Changes to heart rate and systolic BP were significantly different between groups (p <0.001), but not for diastolic BP (p =0.079).	Standardized dose. Included non-EC comparison group. Excluded those with risk factors for CVD and family history of CAD and with abnormal results on echocardiograph studies.	>90% of the study population was male. Results not reported by sex. Only short-term, acute effects measured. Small sample size. No sample size or power calculations provided.	II-1, Fair
Vansickel, 2010 [52], US. NIH (NCI)	Randomized crossover study	32 smokers (13 women) who smoked \geq 15 cigarettes/day	Four sessions with >48-h washout period between sessions.	Heart rate, measured every 20 s during the study sessions,	EC (18-mg and 16-mg nicotine) and unlit cigarette groups:	All participants were new EC users. Controlled for	Authors only measured acute outcomes after	I, Poor

(continued on next page)

Table 2 (continued)

Author, year, location, sources of support	Study design	Population (including WRA)	Exposure(s)	Cardiovascular outcome(s)	Results	Strengths	Weaknesses	Grading of quality*
		Age range: 18–55 years (mean: 33.6 years) Excluded individuals with self-report of chronic health condition, including high BP; excluded pregnant or breastfeeding women and those who reported previous EC use.	Products: 1) Chosen brand cigarette. 2) Unlit own brand cigarette. 3) EC with 18-mg nicotine/mL e-liquid cartridge. 4) EC with 16-mg nicotine/mL e-liquid cartridge. Product administration: Participants took 10 puffs w/30-s interpuff interval with each product. Product readministered after 60 min.	averaged over 5 min before and after product exposure.	No statistically significant changes in heart rate observed for either 18-mg nicotine/mL EC, 16-mg nicotine/mL EC or sham after exposure compared with baseline (mean heart rate between 60 and 70 bpm at all time points). Cigarette: Statistically significant increase in mean heart rate from mean 65.7 bpm at baseline to peak of 80.3 bpm 5 min after cigarette exposure. Increase after smoking conventional cigarette was statistically significantly higher than both sham and both EC doses ($p > 0.001$).	effects of smoking by only recruiting smokers. Standardized EC exposure. Non-EC comparison conditions. Authors compared two ECs with different nicotine contents. Excluded participants with health conditions.	brief exposure; no long-term follow-up. Did not report results for subset of women No sample size or power calculations provided. No clear description of sample frame/recruitment strategy.	
Yan, 2014 [53], US. Blu ECs (LOEC, Inc)	Randomized, partially single-blinded crossover study (6 sessions)	23 smokers (≥ 10 cigarettes/day for at least 1 year); 12 women. Age range: 23–58 years (mean: 39 years). Excluded those with chronic mental or physical health condition; pregnancy or breastfeeding; elevated systolic or diastolic BP or heart rate; use of other tobacco or nicotine-containing products and certain medications (including prescription smoking cessation drugs).	Six exposures sessions with ≥ 24 h between sessions. Products: 1) 2.4% nicotine, ~75% glycerin EC. 2) 2.4% nicotine, ~50% glycerin, ~20% propylene glycol EC. 3) 2.4% nicotine, ~75% glycerin menthol EC. 4) 1.6% nicotine, ~75% glycerin EC. 5) 1.6% nicotine, ~50% glycerin, ~20% propylene glycol EC. 6) Cigarette. Product administration: EC sessions: 50 puffs (5-s long puffs with 30-s interpuff intervals); 30 min later, participants	Systolic BP, diastolic BP and heart rate measured 30 min before exposure and 20 min after each exposure session.	Heart rate: Statistically significant increase in heart rate compared with baseline for Products 2, 3 and 6. Product 2: 71 ± 8.95 to 75 ± 8.63 bpm, $p = 0.008$ Product 3: 70 ± 7 to 74 ± 7 bpm, $p = 0.002$ Product 6: 70 ± 5.9 to 74 ± 8.6 bpm, $p = 0.001$. No statistically significant differences in change to heart rate between products. Authors observed correlation between users' nicotine plasma level and increased heart rate. BP: Statistically significant increase in diastolic BP after use of all products	Standardized dose. Controlled for effects of smoking by only recruiting smokers. Non-EC comparison condition; authors compared ECs with different nicotine contents. Excluded participants with health conditions (including elevated BP or heart rate).	Short-term, acute effects only. No sample size or power calculations provided. No clear description of sample frame/recruitment strategy. Results not reported by sex.	1; Fair

			used EC <i>ad lib</i> for 1 h. Cigarette session: Smoked one cigarette (normal puffs with 30-s interpuff intervals); 30 min later, participants smoked cigarettes as desired for 1 h.		compared with baseline. Product 1: 71±9.5 to 78±10 mmHg, p=6.77 E-05. Product 2: 70±10 to 77±9.8 mmHg, p=4.83 E-05. Product 3: 73±8.6 to 76.1 mmHg, p=0.048. Product 4: 70±9 to 77±8 mmHg, p=0.19 E-08. Product 5: 72±7 to 76±9 mmHg, p=0.00017. Product 6: 71±9.5 to 78±9.5 mmHg, p=0.00014. Conventional cigarette (Product 6) resulted in significantly higher change to diastolic BP than product 3. No other statistically significant changes in diastolic BP between products. Statistically significant increase in systolic BP after use of Products 4 and 6 compared with baseline. Product 4: 118±10 to 124±12.5 mmHg, p=0.02. Product 6: 120±12.6 to 123±12.96 mmHg, p=0.04. No statistically significant differences in change to systolic BP between products.				
Czogala, 2012 [55], Poland. Ministry of Science and Higher Education of Poland.	Nonrandomized crossover study	42 smokers (21 women) who smoked ≥ 5 cigarettes/day, had been smokers for ≥ 1 year and had not used ECs before study initiation. Each participant participated in 2 sessions with a 7-day washout period between sessions. Age range: 18–62 years (mean age: 24.88 years old) Excluded individuals with allergies, respiratory	Two products; each participant was exposed to each product. Participants participated in two sessions with 1 week washout period between sessions. Products: 1) EC containing 14 mg/mL nicotine. 2) Conventional cigarette. Product administration: Participants used each product for 5 min (smoked one cigarette	Heart rate, measured at baseline and 5 min after exposure. Systolic and diastolic BP, measured at baseline and 5 min after exposure.	EC: No statistically significant changes in heart rate, systolic BP or diastolic BP after using an EC compared with baseline. No statistically significant changes found when results stratified by sex (for systolic BP). Cigarette: Statistically significant increase in heart rate (from 78.50±11.96 to 90.90±15.40 mmHg,	Results (changes to systolic BP) reported by sex. Non-EC comparison condition. Recruited only smokers. Excluded those with chronic medical conditions.	Authors only measured acute outcomes; no long-term follow-up. No sample size or power calculations provided. No clear description of sample frame/ recruitment strategy. Authors did	II-1; Fair	

Table 2 (continued)

Author, year, location, sources of support	Study design	Population (including WRA)	Exposure(s)	Cardiovascular outcome(s)	Results	Strengths	Weaknesses	Grading of quality*
		and cardiovascular conditions, arterial hypertension, cancer and pregnant women. Excluded people who had used ECs before study.	and used one EC).		p=0.000) after smoking cigarette compared with baseline. No statistically significant increase to systolic BP after smoking cigarette compared with baseline. Statistically significant increases to diastolic BP (from 78.79±11.00 to 84.14±10.44 mmHg, p=0.02) after smoking cigarette compared with baseline.		not specify whether EC exposure was consistent among participants (e.g., all participants took the same number of puffs).	
Szoltyssek-Boldys [56], 2014, Poland. Funded by Chic Group LTD (manufacturer of ECs in Poland) and internal funding from the Institute of Occupational and Environmental Health, Poland and Medical University of Silesia, Poland.	Nonrandomized within subject crossover study (2 sessions)	15 healthy female smokers (smoking ≥ 5 cigarettes/day for ≥ 2 years) aged 19–25 years who also reported using ECs ≥ 10 times. Excluded: Individuals aged < 18 years; individuals with hypertension, other circulatory system diseases, cancer, hypercholesterolemia, diabetes or pregnancy/lactation, use of estrogen, progestin or other hormones, heart medications, NRT or general health programs, (e.g., chronic bronchitis and asthma).	Exposure: Session 1: Participants smoked one conventional cigarette (10–12 puffs) using filtered, slim cigarette with nicotine content: 0.7 mg. Session 2: Participants took 15 puffs with same model EC containing 24-mg nicotine/mL e-liquid.	Changes to BP and heart rate, measured before and 10 min after exposure.	No statistically significant changes to heart rate or BP were recorded after conventional cigarette or EC exposure. Heart rate: Increased from ~78 bpm to ~80 bpm after EC exposure (NS). Increased from ~78 bpm to ~86 bpm after conventional cigarette exposure (NS). Systolic BP: Increased from ~120 mmHg to ~122 mmHg after e- cigarette exposure (NS). Increased from ~116 mmHg to ~118 mmHg after conventional cigarette exposure (NS). Diastolic BP: Remained at ~73 mmHg from baseline to after EC exposure (NS). Increased from ~74 mmHg to ~76 mmHg after EC exposure (NS).	Standardized exposure. Controlled for sex and age by only including WRA. Controlled for smoking status by recruiting only smokers with some EC experience.	Authors only measured acute outcomes; no long-term follow-up. Small sample size. No sample size or power calculations provided. No nonuser comparison group.	II–I, Fair
Vansickel, 2012 [51], US. NIH (NCI/NIDA).	Interrupted time series (same exposure repeated 5 times)	20 smokers (9 women) who smoked ≥ 15 cigarettes/Day. Age range: 18–55 years	Product: EC containing 18-mg nicotine/mL e-liquid. Product administration:	Heart rate, measured every 20 s, averaged over 5 min. BP, measured	Heart rate: Statistically significant increase in mean heart rate from preadministration	Standardized EC exposure. Controlled for effects of	No nonuser comparison group or condition. Authors only	II-3, Fair

	to single group)	(mean age: 33.2). Excluded individuals with self-report of chronic health condition, including high BP, women who were pregnant, breastfeeding, or in active menopause and current EC users.	Participants took 10 puffs with 30-s interpuff interval, repeated 5 times at 30-min intervals.	every 5 min.	average of 67.5 bpm to 75 bpm observed within 5 min of first 10-puff bout. Heart rate remained statistically significantly elevated compared with baseline for first two 10-puff bouts only. BP: No statistically significant changes in systolic or diastolic BP were observed after EC administration compared with baseline.	smoking by only recruiting smokers. Excluded those with chronic medical conditions.	measured acute outcomes; no long-term follow-up. Did not report results for subset of women. No sample size or power calculations provided. No clear description of sample frame/recruitment strategy. BP values not reported.	
Vansickel, 2013 [54], US. NIH (NCI/NIDA).	Case series	8 EC users (3 women) who had been using ECs ≥ 3 months, using ≥ 2–3 mL of nicotine solution or 2 cartridges/day; smoked ≤ 5 cigarettes/day. Age range: 18–55 years (mean age: 33.5 years). Excluded those with self-report of chronic health condition, including high BP.	Products: Participants provided their own ECs. One participant used 9-mg/mL nicotine solution; Six participants used 18-mg/mL nicotine solution; one participant used 24-mg/mL nicotine solution. Product administration: Participants took 10 puffs with a 30-s interpuff interval. Participants then used ECs for 60 min <i>ad lib</i> (number of puffs ranged from 4–76).	Heart rate, measured every 20 s.	Mean heart rate increased statistically significantly from 73.2 bpm at baseline to mean of 78 bpm within 5 min of first puff. Heart rate remained elevated during remainder of session.	All participants were experienced with EC use and used own, chosen devices (real-world exposure). Excluded current smokers. Excluded participants with health conditions.	Nonstandardized EC dose. No nonuse comparison group or condition. No clear description of sample frame/recruitment strategy. Authors only measured acute outcomes; no long-term follow-up. Did not report results for subset of women. No sample size or power calculations provided.	II-3; Poor
Farsalinos, 2014b [61], Greece. E-Cigarette Research Advocates Group (www.ecigarette-research.com), EC user group.	Cross-sectional Web-based survey	19,411 current, former or never smokers (4900 women) aged 31–47 years (mean: 39 years).	Exposure: Self-reported EC use. Participants reported on: duration of use; EC use patterns (daily, occasionally, not anymore); EC device type most often used; EC liquid use; EC daily	Self-reported changes to preexisting disease conditions (including hypertension and CAD) after initiating	Hypertension: 2365 participants (390 smokers, 1975 former smokers) reported hypertension prior to EC initiation. Of these, 19 (0.8%, 6 smokers and 13 former smokers)	Global sample. Large sample size. Multivariate analysis included adjustment for confounders, including demographics and amount of current smoking and/or EC use.	No information on sampling frame or how participants were recruited. Self-reported outcomes with no validation. Changes to	II-3; Poor

(continued on next page)

Table 2 (continued)

Author, year, location, sources of support	Study design	Population (including WRA)	Exposure(s)	Cardiovascular outcome(s)	Results	Strengths	Weaknesses	Grading of quality*
			consumptions; current nicotine levels in EC; nicotine levels used at initiation of EC use.	EC use.	reported condition worsening after EC initiation, 944 (39.9%, 194 smokers and 750 former smokers) reported that their condition remained stable, and 1149 (49.9%, 139 smokers and 1040 former smokers) reported improvement. CAD: 318 participants (68 smokers and 250 former smokers) reported CAD prior to EC initiation. Of these, 7 (4 smokers and 3 former smokers) reported condition worsening, 116 (30 smokers and 86 former smokers) reported that their condition remained stable, and 171 (24 smokers and 147 former smokers) reported improvement. In multivariate analysis, odds of reporting improvements were 1.96 times higher for former smokers than smokers ($p<0.001$). for hypertension, and 2.02 times higher for former smokers than smokers ($p=0.048$) for CAD. Among never smokers using ECs, 18% reported any condition (7 options), with 81.3% reporting that conditions remained stable.		disease conditions not reported by disease for never smokers. Results not reported by sex.	

NCI, National Cancer Institute; NIDA, National Institute on Drug Abuse; NIH, National Institutes of Health; WRA, women of reproductive age.

* USPSTF grading criteria used to assess study quality [48].

5 min, and in the second, the same individuals used one EC for 5 min. BP and heart rate were measured before and directly after each exposure. The authors reported results by sex for systolic BP only. No changes to systolic BP were observed among females after EC use (~119 mmHG at baseline with no increase after exposure), but they observed a NS increase in systolic BP among females after conventional cigarette exposure (from ~120 mmHG to ~125 mmHG, $p > 0.05$). Among men and women combined, mean diastolic BP increased statistically significantly after conventional cigarette use (from 78.79 mmHg to 84.14 mmHg, $p = 0.02$) but not after EC use (from 76.71 mmHg to 78.60 mmHg, no p -value reported). Heart rate increased statistically significantly after conventional cigarette use (from 78.5 bpm to 90.9 bpm, p -value reported as 0.000) and nonsignificantly after EC exposure (77.93 bpm to 79.36 bpm, no p -value reported). The change in heart rate after conventional cigarette use was significantly higher than the change after EC use. In the second nonrandomized crossover study, authors recruited healthy female smokers ($n = 15$) to participate in two sessions, separated by at least 11 days [56]. In the first session, individuals smoked one cigarette (10–12 puffs), and in the second, participants took 15 puffs with an EC containing 24-mg nicotine/mL e-liquid. Changes to heart rate and BP were measured before and 10 min after each exposure. No statistically significant changes to heart rate or BP were recorded after either exposure. All parameters remained within normal ranges, other than systolic BP after conventional cigarette exposure, which rose to the prehypertensive range (~122 mmHG). However, baseline systolic BP was borderline prehypertensive, and this change was not significant. This was the only study identified that controlled for sex by including only females in the study sample.

Two studies examined outcomes before and after acute EC exposure in single groups without comparison groups [51,54]. In the first (fair quality), 20 smokers (nine women) participated in one session [51]. Individuals took 10 puffs using ECs containing 18-mg nicotine/mL e-liquid. This procedure was repeated five times at 30-min intervals. Heart rate was measured every 20 s and averaged over 5 min. BP was measured every 5 min. Heart rate rose statistically significantly after the first two 10-puff bouts (from 67.5 bpm at baseline to 75 bpm after the first 10-puff bout and ~72 bpm after the second), then fell for the remainder of the session. No statistically significant changes to systolic or diastolic BP were observed. Point estimates were not reported. In the second study (poor quality), eight current EC users (three women) provided their own products, which ranged in nicotine content from 9 to 24-mg nicotine/mL e-liquid [54]. Individuals took 10 puffs under observation, then used ECs *ad lib* for 1 h, taking from 4 to 76 puffs. Mean heart rate increased statistically significantly from baseline within 5 min of participants' first puff (from 73.2 bpm to 78 bpm) and remained elevated throughout the session.

3.2.3. Cross-sectional survey

We identified one poor quality cross-sectional Web-based survey that recruited a global sample of EC users ($n = 19,411$,

4900 women) [61]. Investigators asked participants about past and present smoking and EC use, perceived health benefits, side effects, adverse events and changes to chronic health conditions that they believed were related to EC use. No users reported history of MI, stroke, VTE or PAD. Of those reporting hypertension prior to initiating EC use ($n = 2365$), 19 individuals (0.8%) reported that their condition had worsened, 944 (39.9%) reported that their condition had remained stable and 1149 (49.9%) reported that their condition improved. Of those reporting coronary artery disease (CAD) ($n = 318$), seven participants (2.2%) reported worsening of the condition, 116 (36.5%) reported that it remained stable and 171 (53.8%) reported improvement. No results were reported by sex.

3.3. Research question #3

Our search for evidence on adverse outcomes associated among women exposed to HC and nicotine from sources other than cigarettes yielded 111 articles, 1 of which met inclusion criteria [64] (Table 3). In this fair quality nonrandomized trial, investigators exposed 46 female smokers and nonsmokers (some taking COCs, some not) to a transdermal nicotine patch and a placebo patch for 2.5 h with a 48-h washout period between exposures. The authors divided participants into four groups: smoking COC users, smoking non-COC users, nonsmoking COC users and nonsmoking non-COC users. Smokers abstained from cigarette use for 6 h prior to testing. Heart rate and BP were measured after patch administration, and authors compared cardiovascular parameters using a 2 (smoker/nonsmoker) \times 2 (oral contraceptive [OC]/non-OC) \times 2 (nicotine/placebo) repeated measures analysis of variance. For all groups of women, nicotine administration statistically significantly increased resting heart rate by a mean of 5.1 bpm ($F [1.42] = 5.7$, $p < 0.05$). Authors observed statistically significant effects of nicotine administration ($p < 0.05$) and OC use (OC > non-OC, $p < 0.001$) on heart rate. Among smokers, COC users had a mean heart rate of 69.1 bpm using the placebo and 77.7 bpm after nicotine administration; among non-COC users, mean resting heart rate was 72.5 bpm using placebo and 78.5 bpm after nicotine administration. Among nonsmokers, COC users had a mean heart rate of 72.6 bpm using the placebo and 73.8 bpm after nicotine exposure, while non-COC users had a mean heart rate of 65.3 bpm using the placebo and 70 bpm after nicotine exposure. No similar relationships were observed for BP.

3.4. Research question #4

Our searches for studies on adverse outcomes associated with HC use among women also exposed to inhaled propylene glycol or glycerin yielded 81 articles. None met inclusion criteria for this review.

4. Discussion

We found no direct evidence related to health effects of EC use among HC users. Among studies of EC users in the general

population, serious adverse cardiovascular events were rare. Only one serious cardiovascular event (a case of MI) was reported among a group of dual EC and cigarette users who reported switching to ECs only during 12 months of observation, with no further details about this case provided. No instances of stroke, VTE or PAD were reported.

Eleven articles measured changes to heart rate after EC use. Of these, seven found no significant increases to heart rate after EC use compared with baseline, and four reported significant changes; however, mean heart rate remained within the normal range after EC exposures. In three articles, authors compared changes to heart rate after EC exposure with changes after conventional cigarette exposures; in two articles, the increase was significantly greater with conventional cigarette exposure [50,54]. Of seven articles that recorded changes to BP after EC exposure, two noted statistically significant increases to diastolic BP, with postexposure diastolic BP remaining in the normal range in both studies [50,53]; one article noted a statistically significant increase to systolic BP after use of one of four EC products, with mean systolic BP reaching the prehypertensive range [53]. In two articles, authors tested for differences in changes to BP after conventional cigarette versus EC exposure, with one study finding a significantly greater increased difference in change to diastolic BP after conventional cigarette use compared with one EC model tested (but not others), and no differences between groups in changes to systolic BP; the other found a significant difference in changes to systolic (but not diastolic) BP after conventional cigarette use compared with EC use [50,53].

One study found that acute exposure to both COC and nicotine patch was associated with increases in heart rate, though nicotine administration did not raise heart rate out of normal ranges for either COC users or non-COC users. We found no studies of propylene glycol or glycerin exposure among HC users. While propylene glycol exposure has been associated with eye and respiratory irritation, no evidence links exposure with adverse cardiovascular outcomes [10,65], and ingestion is generally considered safe [66]. Glycerin ingestion is also generally recognized as safe [67], but heated glycerin can produce acrolein, which may be associated with adverse cardiovascular risk [13,68,69].

The findings of this review are generally consistent with a recent narrative review that examined the connection between EC use and cardiovascular risk [68] and included three of the studies in this review, as well as evidence on NRT and the effect of ECs on other biological markers (e.g., nicotine and cotinine levels and pulmonary function). The authors of that paper concluded that EC use was associated with a smaller risk of adverse cardiovascular events than conventional cigarettes but that users should nonetheless exercise caution because of the possibility of adverse health effects, especially users who are at heightened risk of CVD.

The mechanisms through which conventional cigarette smoking and CHC exposure lead to adverse cardiovascular events are not fully understood; thus, it is difficult to determine whether ECs are likely to lead to increased risk through the same mechanisms. In the absence of direct evidence, it may be helpful to consider the mechanisms through which cigarettes may lead

to cardiovascular harm and whether ECs are similar to conventional cigarettes in these ways. Nicotine delivery may be the most important similarity between the two products. Nicotine is associated with adverse reproductive and cardiovascular outcomes [39,70]. However, nicotine does not appear to be the component of cigarettes most strongly linked with major adverse cardiovascular outcomes. Studies on the cardiovascular risk associated with NRT products (e.g., nicotine patches, nasal sprays and lozenges) and smokeless tobacco indicate that these products do not appear to be associated with major cardiovascular events [71,72]. Exposure to products of combustion (e.g., carbon monoxide and oxidant gas) likely plays a larger role, especially as a risk factor for thrombotic events [70,73].

The main limitation of this review is the lack of direct evidence for our research question, with no studies identified that examined EC use among women using HC. Thus, we examined indirect evidence only, making it difficult to draw conclusions about our primary research question.

There are shortcomings to the studies included in this review as indirect evidence. The vast majority of this evidence represents short-term findings related to cardiovascular markers (i.e., heart rate, BP and cholesterol levels), with only two studies following EC users for longer than 2 weeks [49,58] and only one study reporting on clinical cardiovascular events [49]. The relationship between changes to the intermediary markers reported in these studies and risk of developing clinical CVD is unclear. Thus, it is difficult to determine the clinical meaning of this evidence or the effects of long-term EC use on cardiovascular health.

Funding for the studies included in this review was provided by industry, government and academia. Three studies were sponsored by EC companies directly [53,56,59]. In a fourth, the EC test products were provided by an EC company [57], and in a fifth, authors reported having received previous funding from EC companies [50]. One study was sponsored by an EC user advocate group [61] and another by the Italian antismoking league [58]. The remaining six studies were government or university sponsored [51,52,54,55,60] or did not report funding [49].

Study quality ranged from fair to poor, with no good quality studies. Only two of the studies on EC safety reported results by sex [55,56], so we were not able to determine whether EC exposure affected males and females differently. In six of the studies, authors did not standardize EC dosage across the study sample [49,54,57–60]; in three, no comparison group was included [51,54,57]; and in one, neither exposures nor outcomes were validated [61].

ECs were introduced into the United States recently (in 2009), which partially explains the paucity of safety data. In order to answer our primary research question, additional research is needed to examine incidence of adverse cardiovascular events associated with both EC and HC use. Given the rarity of MI, stroke, VTE and PAD, especially among WRA, case-control study design could be considered. Additional prospective cohort studies should include a range of intermediary risk factors that are strongly associated with clinical cardiovascular outcomes and be adequately powered to detect

Table 3
Nicotine and HCs.

Author year, location, sources of support	Study design	Population (including WRA)	Exposure(s)	Cardiovascular outcome(s)	Results	Strengths	Weaknesses	Grading of quality*
Girdler, 1997 [64], US, University of California Tobacco-Related Disease Research Program; NIH	Nonrandomized trial	76 individuals ($n=46$ women). Women separated into four groups: - Smoker/COC users ($n=12$). - Smoker/non-COC users ($n=11$). - Nonsmoker/COC users ($n=12$). - Nonsmoker/non-COC users ($n=11$). All OC users were using COCs and had been using COCs for ≥ 2 years. Nonusers had not taken COCs for ≥ 2 years.	Nicotine condition: Nicotine patch applied for 2.5 h. Placebo condition: Placebo patch applied for 2.5 h 48-h washout period between sessions.	BP heart rate	For all groups of women, significant effects of nicotine administration ($p<0.05$) and COC use ($p\leq 0.001$) were observed for heart rate. Mean heart rate: Smokers/OC users- After placebo, 69 bpm After nicotine, 77.7 bpm Smokers/non-COC users: After placebo, 72.5 bpm After nicotine, 78.5 bpm Nonsmoker/OC users: After placebo, 72.6 bpm After nicotine, 73.8 bpm. Nonsmoker/non-COC users: After placebo, 65.3 bpm After nicotine, 70 bpm. No significant effects of OC status or nicotine exposure observed for systolic or diastolic BP.	Authors attempted to standardize COC exposure: All OC users using COCs for ≥ 2 years, and 75% of COC users using low dose estrogen/low dose androgenic progesterone COCs. Nicotine exposure standardized (measures taken 2.5 h after patch administration). Comparison condition (self-comparisons under placebo patch condition). Authors reported results by sex, smoking status and COC status. Groups of women (by smoking and COC status) did not differ in weight, height, family history of hypertension.	Authors reported acute effects only. COC users were significantly younger than nonusers. Authors relied on self-report to exclude individuals with health problems.	II-2; Fair

WRA, women of reproductive age.

* USPSTF grading criteria used to assess study quality [48].

changes in these markers. At least one clinical trial underway in the United States aims to determine cardiovascular risk associated with EC use and the relative contributions of nicotine and other components of EC aerosol to this risk [74]. Finally, to determine whether risk is further heightened among HC users, investigators should include WRA, collect data on contraceptive use and analyze outcomes by HC status.

Appendix A. Search strategies

Research question #1

((“Electronic cigarette” OR “E-cigarette” OR (Electronic nicotine delivery system) OR “electronic nicotine delivery device” OR (electrically heated cigarette) OR (electrically heated smoking system))) AND (“Contraceptives, Oral, Combined”[Mesh] OR “Contraceptives, Oral”[Mesh] OR “Contraceptives, Oral, hormonal”[Mesh] OR “Contraceptives, Oral, Combined”[Pharmacological Action] OR (contracept* AND (oral OR pill OR tablet)) OR ((combined hormonal) OR (combined oral) AND contracept*) OR (contracept* AND (ring OR patch)) OR “ortho evra” OR NuvaRing) OR (progestin* OR progestins[MeSH] OR Progesterone[MeSH] OR progesterone OR progestogen* OR progestagen* OR “Levonorgestrel”[Mesh] OR Levonorgestrel OR “Norgestrel”[Mesh] OR norgestrel OR etonogestrel AND contracept*) OR dmpa OR “depot medroxyprogesterone” OR “depo medroxyprogesterone” OR “depo provera” OR “net en” OR “norethisterone enanthate” OR “norethindrone enanthate” OR (contracept* AND (inject* OR implant)) OR ((levonorgestrel OR etonogestrel) AND implant) OR implanon OR nexplanon OR jadelle OR norplant OR uniplant OR sino-implant OR (levonorgestrel-releasing two-rod implant) OR (“Intrauterine Devices, Medicated”[Mesh] OR ((intrauterine OR intra-uterine) AND (device OR system OR contracept*)) OR IUD OR IUCD OR IUS OR mirena OR Skyla).

Research question #2

“Electronic cigarette” OR “E-cigarette” OR (Electronic nicotine delivery system) OR “electronic nicotine delivery device” OR (electrically heated cigarette) OR (electrically heated smoking system).

Research question #3

(“Nicotine”[Mesh] OR “Tobacco Use Disorder”[Mesh] OR nicotine OR “Cotinine”[Mesh] OR “cotinine-N-oxide” [Supplementary Concept] OR “cotinine receptor” [Supplementary Concept] OR “cotinine N-glucuronide” [Supplementary Concept] OR cotinine) OR “Tobacco, Smokeless”[Mesh] OR “smokeless tobacco” OR “Tobacco Use Cessation Products”[Mesh] OR (nicotine replacement therapy) OR NRT OR (Nicotine AND (patch OR inhaler OR gum) AND (“Contraceptive agents, female”[MeSH] OR “Contraceptives, Oral, Combined”[Mesh] OR “Contraceptives, Oral”[Mesh] OR “Contraceptives, Oral, hormonal”[Mesh] OR “Contraceptives, Oral, Combined”[Pharmacological Action]) OR (contracept*

AND (oral OR pill OR tablet)) OR ((combined hormonal) OR (combined oral) AND contracept*) OR (contracept* AND (ring OR patch)) OR “ortho evra” OR NuvaRing) NOT (“Animals”[Mesh] NOT “Humans”[Mesh]) OR ((progestin* OR progestins[MeSH] OR Progesterone[MeSH] OR progesterone OR progestogen* OR progestagen* OR “Levonorgestrel”[Mesh] OR Levonorgestrel OR “Norgestrel”[Mesh] OR norgestrel OR etonogestrel) AND contracept*) OR ((depo* AND medroxyprogesterone) OR dmpa OR (net en) OR (norethisterone enant*) AND (contracept* OR inject* OR depo*)) OR (implant AND contracept*) OR ((levonorgestrel OR etonogestrel) AND implant) OR implanon OR nexplanon OR jadelle OR norplant OR uniplant OR sino-implant OR (levonorgestrel-releasing two-rod implant) OR (“Intrauterine Devices”[Mesh] OR “Intrauterine Devices, Medicated”[Mesh] OR ((intrauterine OR intra-uterine) AND (device OR system OR contracept*)) OR IUD OR IUC OR IUCD OR IUS OR mirena OR Skyla).

Research question #4

((“Propylene Glycol”[Mesh] OR “propylene glycol”) OR (“Glycerol”[Mesh] OR glycerol OR glycerin OR glycerine OR “glycerol-containing”)) AND (((“Contraceptives, Oral, Combined”[Mesh] OR “Contraceptives, Oral”[Mesh] OR “Contraceptives, Oral, hormonal”[Mesh] OR “Contraceptives, Oral, Combined”[Pharmacological Action]) OR (contracept* AND (oral OR pill OR tablet)) OR ((combined hormonal) OR (combined oral) AND contracept*) OR (contracept* AND (ring OR patch)) OR “ortho evra” OR NuvaRing) OR (progestin* OR progestins[MeSH] OR Progesterone[MeSH] OR progesterone OR progestogen* OR progestagen* OR “Levonorgestrel”[Mesh] OR Levonorgestrel OR “Norgestrel”[Mesh] OR norgestrel OR etonogestrel AND contracept*) OR dmpa OR “depo medroxyprogesterone” OR “depo provera” OR “net en” OR “norethisterone enanthate” OR “norethindrone enanthate” OR (contracept* AND (inject* OR implant)) OR ((levonorgestrel OR etonogestrel) AND implant) OR implanon OR nexplanon OR jadelle OR norplant OR uniplant OR sino-implant OR (levonorgestrel-releasing two-rod implant) OR (“Intrauterine Devices, Medicated”[Mesh] OR ((intrauterine OR intra-uterine) AND (device OR system OR contracept*)) OR IUD OR IUCD OR IUS OR mirena OR Skyla).

References

- [1] Agaku IT, King BA, Husten CG, Bunnell R, Ambrose BK, Hu SS, et al. Tobacco product use among adults - United States, 2012–2013. *MMWR Morb Mortal Wkly Rep* 2014;63:542–7.
- [2] US Centers for Disease Control and Prevention. Tobacco product use among middle and high school students—United States, 2011 and 2012. *MMWR Morb Mortal Wkly Rep* 2013;62:893–7.
- [3] King BA, Alam S, Promoff G, Arrazola R, Dube SR. Awareness and ever-use of electronic cigarettes among US adults, 2010–2011. *Nicotine Tob Res* 2013;15:1623–7.
- [4] Arrazola RA, Singh T, Corey CG, Husten CG, Neff LJ, Apelberg BJ, et al. Tobacco use among middle and high school students — United States, 2011–2014. *MMWR Morb Mortal Wkly Rep* 2015;381–5.

- [5] Jamal A, Agaku IT, O'Connor E, King BA, Kenemer JB, Neff L. Current cigarette smoking among adults - United States, 2005–2013. *MMWR Morb Mortal Wkly Rep* 2014;63:1108–12.
- [6] Pepper JK, Brewer NT. Electronic nicotine delivery system (electronic cigarette) awareness, use, reactions and beliefs: a systematic review. *Tob Control* 2014;23:375–84.
- [7] Bertholon JF, Becquemain MH, Annesi-Maesano I, Dautzenberg B. Electronic cigarettes: a short review. *Respiration* 2013;86:433–8.
- [8] Al-hamdani M. A short note on e-cigarette issues: harm reduction, re-normalization, and big tobacco. *J Public Health Policy* 2014;35:132–4.
- [9] Callahan-Lyon P. Electronic cigarettes: human health effects. *Tob Control* 2014;23(Suppl 2):ii36–40.
- [10] Grana R, Benowitz N, Glantz SA. E-cigarettes: a scientific review. *Circulation* 2014;129:1972–86.
- [11] Brown CJ, Cheng JM. Electronic cigarettes: product characterisation and design considerations. *Tob Control* 2014;23(Suppl 2):ii4–i10.
- [12] Caponnetto P, Polosa R, Russo C, Leotta C, Campagna D. Successful smoking cessation with electronic cigarettes in smokers with a documented history of recurring relapses: a case series. *J Med Case Rep* 2011;5:585.
- [13] Goniewicz ML, Knysak J, Gawron M, Kosmider L, Sobczak A, Kurek J, et al. Levels of selected carcinogens and toxicants in vapour from electronic cigarettes. *Tob Control* 2014;23:133–9.
- [14] Bhatnagar A, Whitsel LP, Ribisl KM, Bullen C, Chaloupka F, Piano MR, et al. Electronic cigarettes: a policy statement from the American Heart Association. *Circulation* 2014;130:1418–36.
- [15] Cheng T. Chemical evaluation of electronic cigarettes. *Tob Control* 2014;23(Suppl 2):ii11–7.
- [16] Goniewicz ML, Kuma T, Gawron M, Knysak J, Kosmider L. Nicotine levels in electronic cigarettes. *Nicotine Tob Res* 2013;15:158–66.
- [17] Pisinger C, Dossing M. A systematic review of health effects of electronic cigarettes. *Prev Med* 2014;69C:248–60.
- [18] Johnson M, Pennington N. Adolescent use of electronic cigarettes: an emergent health concern for pediatric nurses. *J Pediatr Nurs* 2014;6:11–5.
- [19] US Centers for Disease Control and Prevention, Office on Smoking and Health. Women and smoking: a report of the Surgeon General. Atlanta, GA: Centers for Disease Control and Prevention (US); 2001.
- [20] WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. Venous thromboembolic disease and combined oral contraceptives: results of international multicentre case-control study. *Lancet* 1995;346:1575–82.
- [21] Gillum LA, Mamidipudi SK, Johnston SC. Ischemic stroke risk with oral contraceptives: a meta-analysis. *JAMA* 2000;284:72–8.
- [22] Jick SS, Walker AM, Stergachis A, Jick H. Oral contraceptives and breast cancer. *Br J Cancer* 1989;59:618–21.
- [23] Khader YS, Rice J, John L, Abueita O. Oral contraceptives use and the risk of myocardial infarction: a meta-analysis. *Contraception* 2003;68:11–7.
- [24] Lawson DH, Davidson JF, Jick H. Oral contraceptive use and venous thromboembolism: absence of an effect of smoking. *BMJ* 1977;2:729–30.
- [25] Lidegaard O, Edstrom B, Kreiner S. Oral contraceptives and venous thromboembolism. A case-control study. *Contraception* 1998;57:291–301.
- [26] Nightingale AL, Lawrenson RA, Simpson EL, Williams TJ, MacRae KD, Farmer RD. The effects of age, body mass index, smoking and general health on the risk of venous thromboembolism in users of combined oral contraceptives. *Eur J Contracept Reprod Health Care* 2000;5:265–74.
- [27] Petitti DB, Wingerd J, Pellegrin F, Ramcharan S. Risk of vascular disease in women. Smoking, oral contraceptives, noncontraceptive estrogens, and other factors. *JAMA* 1979;242:1150–4.
- [28] Rosenberg L, Palmer JR, Rao RS, Shapiro S. Low-dose oral contraceptive use and the risk of myocardial infarction. *Arch Intern Med* 2001;161:1065–70.
- [29] Van Den Bosch MA, Kemmeren JM, Tanis BC, Mali WP, Helmerhorst FM, Rosendaal FR, et al. The RATIO study: oral contraceptives and the risk of peripheral arterial disease in young women. *J Thromb Haemost* 2003;1:439–44.
- [30] England LJ, Levine RJ, Mills JL, Klebanoff MA, Yu KF, Cnattingius S. Adverse pregnancy outcomes in snuff users. *Am J Obstet Gynecol* 2003;189:939–43.
- [31] Baba S, Wikstrom AK, Stephansson O, Cnattingius S. Changes in snuff and smoking habits in Swedish pregnant women and risk for small for gestational age births. *BJOG* 2013;120:456–62.
- [32] England LJ, Kim SY, Shapiro-Mendoza CK, Wilson HG, Kendrick JS, Satten GA, et al. Effects of maternal smokeless tobacco use on selected pregnancy outcomes in Alaska Native women: a case-control study. *Acta Obstet Gynecol Scand* 2013;92:648–55.
- [33] Wickstrom R. Effects of nicotine during pregnancy: human and experimental evidence. *Curr Neuropharmacol* 2007;5:213–22.
- [34] Baba S, Wikstrom AK, Stephansson O, Cnattingius S. Influence of smoking and snuff cessation on risk of preterm birth. *Eur J Epidemiol* 2012;27:297–304.
- [35] Baba S, Wikstrom AK, Stephansson O, Cnattingius S. Influence of snuff and smoking habits in early pregnancy on risks for stillbirth and early neonatal mortality. *Nicotine Tob Res* 2014;16:78–83.
- [36] England LJ, Kim SY, Shapiro-Mendoza CK, Wilson HG, Kendrick JS, Satten GA, et al. Maternal smokeless tobacco use in Alaska Native women and singleton infant birth size. *Acta Obstet Gynecol Scand* 2012;91:93–03.
- [37] Wikstrom AK, Cnattingius S, Stephansson O. Maternal use of Swedish snuff (snus) and risk of stillbirth. *Epidemiology* 2010;21:772–8.
- [38] Gunnerbeck A, Wikstrom AK, Bonamy AK, Wickstrom R, Cnattingius S. Relationship of maternal snuff use and cigarette smoking with neonatal apnea. *Pediatrics* 2011;128:503–9.
- [39] National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health. Reports of the Surgeon General. The Health Consequences of Smoking-50 Years of Progress: A Report of the Surgeon General. Atlanta (GA): US Centers for Disease Control and Prevention; 2014.
- [40] Wikstrom AK, Stephansson O, Cnattingius S. Tobacco use during pregnancy and preeclampsia risk: effects of cigarette smoking and snuff. *Hypertension* 2010;55:1254–9.
- [41] Centers for Disease Control and Prevention. US Medical Eligibility Criteria for Contraceptive Use. *MMWR Recomm Rep* 2010;59:1–6.
- [42] American College of Obstetrics and Gynecology. Use of hormonal contraception in women with coexisting medical conditions. *ACOG Practice Bulletin No. 73, 107; 2006, pp. 1453–72.*
- [43] England LJ, Anderson BL, Tong VT, Mahoney J, Coleman-Cowger VH, Melstrom P, et al. Screening practices and attitudes of obstetricians-gynecologists toward new and emerging tobacco products. *Am J Obstet Gynecol* 2014;211:695.e1–7.
- [44] Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 2009;339:b2535.
- [45] Greenland P, Alpert JS, Beller GA, Benjamin EJ, Budoff MJ, Fayad ZA, et al. 2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2010;56:e50–103.
- [46] Goff Jr DC, Lloyd-Jones DM, Bennett G, Coady S, D'Agostino Sr RB, Gibbons R, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2014;63:2935–59.
- [47] Mohllajee AP, Curtis KM, Flanagan RG, Rinehart W, Gaffield ML, Peterson HB. Keeping up with evidence a new system for WHO's evidence-based family planning guidance. *Am J Prev Med* 2005;28:483–90.
- [48] Harris RP, Helfand M, Woolf SH, Lohr KN, Mulrow CD, Teutsch SM, et al. Current methods of the US Preventive Services Task Force: a review of the process. *Am J Prev Med* 2001;20:21–35.
- [49] Manzoli L, Flacco ME, Fiore M, et al. Electronic cigarettes efficacy and safety at 12 months: cohort study. *PLoS One* 2015;10:e0129443.
- [50] Farsalinos KE, Tsiapras D, Kyrzopoulos S, Savvopoulou M, Voudris V. Acute effects of using an electronic nicotine-delivery device (electronic cigarette) on myocardial function: comparison with the effects of regular cigarettes. *BMC Cardiovasc Disord* 2014;14:78.

- [51] Vansickel AR, Weaver MF, Eissenberg T. Clinical laboratory assessment of the abuse liability of an electronic cigarette. *Addiction* 2012;107:1493–500.
- [52] Vansickel AR, Cobb CO, Weaver MF, Eissenberg TE. A clinical laboratory model for evaluating the acute effects of electronic "cigarettes": nicotine delivery profile and cardiovascular and subjective effects. *Cancer Epidemiol Biomarkers Prev* 2010;19:1945–53.
- [53] Yan XS, D'Ruiz C. Effects of using electronic cigarettes on nicotine delivery and cardiovascular function in comparison with regular cigarettes. *Regul Toxicol Pharmacol* 2014;71:24–34.
- [54] Vansickel AR, Eissenberg T. Electronic cigarettes: effective nicotine delivery after acute administration. *Nicotine Tob Res* 2013;15:267–70.
- [55] Czogala J, Cholewinski M, Kutek A, Zielinska-Danch W. Evaluation of changes in hemodynamic parameters after the use of electronic nicotine delivery systems among regular cigarette smokers. *Przegl Lek* 2012;69:841–5.
- [56] Szoltysek-Boldys I, Sobczak A, Zielinska-Danch W, Barton A, Koszowski B, Kosmider L. Influence of inhaled nicotine source on arterial stiffness. *Przegl Lek* 2014;71:572–5.
- [57] van Staden SR, Groenewald M, Engelbrecht R, Becker PJ, Hazelhurst LT. Carboxyhaemoglobin levels, health and lifestyle perceptions in smokers converting from tobacco cigarettes to electronic cigarettes. *S Afr Med J* 2013;103:865–8.
- [58] Caponnetto P, Campagna D, Cibella F, Morjaria JB, Caruso M, Russo C, et al. Efficiency and Safety of an eElectronic cigAreTte (ECLAT) as tobacco cigarettes substitute: a prospective 12-month randomized control design study. *PLoS One* 2013;8:e66317.
- [59] Nides MA, Leischow SJ, Bhattar M, Simmons M. Nicotine blood levels and short-term smoking reduction with an electronic nicotine delivery system. *Am J Health Behav* 2014;38:265–74.
- [60] Oncken CA, Litt MD, McLaughlin LD, Burki NA. Nicotine concentrations with electronic cigarette use: effects of sex and flavor. *Nicotine Tob Res* 2015;17:473–8.
- [61] Farsalinos KE, Romagna G, Tsiapras D, Kyrzopoulos S, Voudris V. Characteristics, perceived side effects and benefits of electronic cigarette use: a worldwide survey of more than 19,000 consumers. *Int J Environ Res Public Health* 2014;11:4356–73.
- [62] US National Library of Medicine. Pulse. Medline Plus; 2013 [Accessed May 28, 2015, at <http://www.nlm.nih.gov/medlineplus/ency/article/003399.htm>].
- [63] Mayo Clinic. High blood pressure (hypertension); 2015 [Accessed May 28, 2015, at <http://www.mayoclinic.org/diseases-conditions/high-blood-pressure/in-depth/blood-pressure/art-20050982>].
- [64] Girdler SS, Jamner LD, Jarvik M, Soles JR, Shapiro D. Smoking status and nicotine administration differentially modify hemodynamic stress reactivity in men and women. *Psychosom Med* 1997;59:294–306.
- [65] Varughese S, Teschke K, Brauer M, Chow Y, van Netten C, Kennedy SM. Effects of theatrical smokes and fogs on respiratory health in the entertainment industry. *Am J Ind Med* 2005;47:411–8.
- [66] US Food and Drug Administration. Select Committee on GRAS Substances (SCOGS) opinion: propylene glycol. Springfield, VA: GRAS Substances (SCOGS) Database; 1973.
- [67] U.S. Food and Drug Administration. Select Committee on GRAS Substances (SCOGS) opinion: glycerin and glycerides. Springfield, VA: GRAS Substances (SCOGS) Database; 1975.
- [68] Lippi G, Favaloro EJ, Meschi T, Mattiuzzi C, Borghi L, Cervellini G. E-cigarettes and cardiovascular risk: beyond science and mysticism. *Semin Thromb Hemost* 2014;40:60–5.
- [69] Hajek P, Etter JF, Benowitz N, Eissenberg T, McRobbie H. Electronic cigarettes: review of use, content, safety, effects on smokers and potential for harm and benefit. *Addiction* 2014;109:1801–10.
- [70] Benowitz NL. The role of nicotine in smoking-related cardiovascular disease. *Prev Med* 1997;26:412–7.
- [71] Mills EJ, Wu P, Lockhart I, Thorlund K, Puhan M, Ebbert JO. Comparisons of high-dose and combination nicotine replacement therapy, varenicline, and bupropion for smoking cessation: a systematic review and multiple treatment meta-analysis. *Ann Med* 2012;44:588–97.
- [72] Benowitz NL, Hansson A, Jacob III P. Cardiovascular effects of nasal and transdermal nicotine and cigarette smoking. *Hypertension* 2002;39:1107–12.
- [73] Benowitz NL. Cigarette smoking and cardiovascular disease: pathophysiology and implications for treatment. *Prog Cardiovasc Dis* 2003;46:91–11.
- [74] University of California San Francisco. Cardiovascular assessment of the effects of tobacco and nicotine delivery products (ClinicalTrials.gov Identifier: NCT01964807). *ClinicalTrials.gov*: US National Institutes of Health; 2015.