

Review article

# Hormonal contraception among electronic cigarette users and cardiovascular risk: a systematic review<sup>☆,☆☆,★</sup>

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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

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## 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

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