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Review article

Combined oral contraceptive use among women with hypertension: a systematic review

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Abstract

Women with hypertension are at increased risk for cardiovascular events. Combined oral contraceptive (COC) use, even among low-dose users, has been associated with a small excess risk for cardiovascular events among healthy women. In this systematic review, we examined cardiovascular risks among COC users with hypertension. After searching MEDLINE for all articles published from 1966 through February 2005 relevant to COC use, hypertension and cardiovascular disease, we identified 25 articles for this review. Overall, these studies showed that hypertensive COC users were at higher risk for stroke and acute myocardial infarction (AMI) than hypertensive non-COC users, but that they were not at higher risk for venous thromboembolism (VTE). Women who did not have their blood pressure measured before initiating COC use were at higher risk for ischemic stroke and AMI, but not for hemorrhagic stroke or VTE, than COC users who did not have their blood pressure measured.

Keywords: Combined oral contraceptives; Hypertension; Stroke; Myocardial infarction; Venous thromboembolism; Systematic review

1. Introduction

Hypertension is a primary risk factor for stroke and other cardiovascular events. While rates of cardiovascular events among healthy women of reproductive age are very low, hypertension increases that risk substantially. It is estimated that approximately 1.7 cases of myocardial infarction and 34.1 strokes occur each year per 1 million normotensive women aged 30–34 years, and that the rates of these events among hypertensive women of the same age rise to 10.2 for myocardial infarction and 185.3 for stroke [1]. Combined oral contraceptive (COC) use, even among low-dose users, has been associated with a small excess risk for cardiovascular events among healthy women. To help determine the effects of COC use on risk for cardiovascular events among women with hypertension, we conducted a systematic review of studies that have examined cardiovascular risks among women with hypertension who use COCs, specifically the effects of COC use on blood pressure and development of peripheral arterial disease (PAD), acute myocardial infarctions (AMI), ischemic and hemorrhagic stroke, and venous thromboembolism (VTE).

We conducted this systematic review in preparation for an Expert Working Group of international family planning experts convened by the World Health Organization (WHO) in October 2003 to develop and revise medical eligibility criteria for contraceptive use. In this report, we provide the evidence obtained through our systematic review regarding COC use among women with hypertension, as well as the WHO recommendations that were derived in part from this evidence. This review also includes evidence identified since the 2003 meeting through February 2005.

2. Materials and methods

We searched MEDLINE for all relevant articles published from 1966 through February 2005 using the following search strategy: [(exp Contraceptives, Oral/ or oral contracept:) and (hypertension or blood pressure)] and (stroke. or exp Cerebrovascular Accident/ or exp Myocardial Infarction/ or pulmonary embolism/ or exp thromboembolism/ or exp venous thrombosis/ or thromboembolism or exp Peripheral

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Table 1
Studies of oral contraceptive use, hypertension and cardiovascular events

Author, year	Study setting	No. of cases/controls (control type)	Results	Adjustments	Weaknesses	Quality
Hypertensive disorders						
Narkiewicz et al., 1995 [4]	Europe	Cross-sectional study 94 women with mild hypertension	Daytime and nighttime systolic blood pressure was significantly higher in COC users (mean difference of 8.3 and 6.1 mm Hg, respectively); differences in diastolic pressure were not significant	Age, body mass index, duration of COC use, smoking	Cross-sectional design	Very low
Lubianca et al., 2003 [5]	Brazil, 1989–1997	Cross-sectional study 171 hypertensive women using COCs, other method users, non-method users	COC users had significantly higher diastolic blood pressure than the other two groups (100.3 vs. 93.0 and 93.5 mm Hg, respectively), had higher % of women with uncontrolled hypertension (83.3% vs. 65.4% and 68.4%, respectively), and had a higher % classified at stage 2 and 3 hypertension (21.2% vs. 19.2% and 12.7%, respectively)	Age, body mass index, use of antihypertensive drugs	Cross-sectional design	Very low
Van Den Bosch et al. 2003 [6]	Netherlands, RATIO Study, 1990–1995	152/925 (P)	ORs for PAD No HTN/no OC 1.0 (referent) No HTN/OC use 4.7 (2.8–7.8) HTN/no OC use 4.9 (2.5–9.5) HTN/OC use 8.8 (3.9–19.8)	Age, residence, calendar year	Selection bias — OC users more likely to be diagnosed with PAD	Low
Myocardial infarction						
Croft and Hannaford, 1989 [7]	United Kingdom, Royal College of General Practitioners Study, nested case-control 1968–1987	158/158 (population controls)	No HTN/no OC 1.0 (referent) No HTN/OC use 2.0 (1.1–3.9) HTN/no OC use 5.4 (2.6–11.2) HTN/OC use 7.7 (1.2–49.2)	Age	Unclear if authors adjusted for other potential confounders No specified diagnostic criteria	Intermediate
D'Avanzo et al., 1994 [8]	Italy, 1983–1992	251/475 (hospital controls)	OR 28.4 (6.7–120.1) for OC use/hypertension compared to never use/normotensive	Not stated	Unclear if authors adjusted for potential confounders Validation of cases not described	Low
WHO, 1997 [9]	Developing countries, 1989–1995	170/461 (hospital controls)	No HTN/no OC 1.0 (referent) No HTN/OC use 3.66 (1.81–7.39) HTN/no OC use 9.52 (4.90–18.5) HTN/OC use 15.3 (3.27–71.6) Blood pressure check 3.48 (1.39–8.70) No blood pressure check 6.04 (2.77–13.2)	Abnormal blood lipids, diabetes, history of hypertension in pregnancy, smoking	Self-reported hypertension Possible recall bias (OC use)	Intermediate
WHO, 1997 [9]	European countries, 1989–1995	205/472 (hospital controls)	No HTN/no OC 1.0 (referent) No HTN/OC use 3.85 (1.88–7.89) HTN/no OC use 5.43 (2.39–12.4) HTN/OC use 68.1 (6.18–751) Blood pressure check 2.60 (1.15–5.89) No blood pressure check 9.47 (3.72–24.1)	Abnormal blood lipids, BMI, diabetes, history of hypertension in pregnancy, smoking	Self-reported hypertension Possible recall bias (OC use)	Intermediate

Lewis et al., 1997 [10]	Europe, Transnational Study, 1993–1996	182/635 (hospital and population controls)	OR for OC use OR for HTN No interaction Blood pressure check No blood pressure check	2.26 (1.32–3.86) 3.31 (1.74–6.31) 1.07 (0.66–1.74) 2.76 (1.36–5.61)	Age, study center, parity, smoking, hypercholesterol, diabetes, body mass index, family history of AMI, study year	Self-reported hypertension Possible recall bias (COC use)	Intermediate
Dunn et al., 1999 [11]	UK, MICA Study, 1993–1995	448/1728 (clinic controls)	OR for OC use OR for HTN Blood pressure check	1.40 (0.78–2.52) 4.23 (3.03–5.89) 2.07 (0.81–5.30)	Smoking, diabetes, family history, drugs taken in past year, body mass index, history of hypertension, history of angina, whether blood pressure taken	Self-reported hypertension Possible recall bias (OC use)	Intermediate
Tanis et al., 2001 [12]	Netherlands, RATIO Study, 1990–1995	248/925 (population controls)	No HTN/no OC No HTN/OC use HTN/no OC use HTN/OC use	1.0 (referent) 2.1 (1.5–3.1) 5.1 (2.9–8.8) 6.1 (3.1–12.1)	Age, area of residence, calendar year	Self-reported hypertension Possible recall bias (OC use)	Intermediate
Hemorrhagic stroke							
Collaborative Group, 1975 [13]	US	185/342 (hospital controls)	No HTN/no OC No HTN/OC use HTN/no OC use HTN/OC use	1.0 (referent) 1.8 (0.8–4.4) Borderline HTN 2.2 (1.1–4.3) Moderate HTN 5.0 (2.5–9.9) Severe HTN 21.6 (11.1–42.3) Borderline HTN 2.8 (1.0–7.9) Moderate HTN 8.4 (3.0–23.1) Severe HTN 25.7 (9.4–70.7)	Age, race	Did not assess confounding of factors other than age and race Hospital controls	Low
WHO, 1996 [14]	Developing countries, 1989–1993	815/2265 (hospital controls)	No HTN/no OC No HTN/OC use HTN/no OC use HTN/OC use	1.0 (referent) 1.43 (1.06–1.93) 9.41 (7.08–12.5) 14.3 (6.72–30.4) ORs not affected by whether OC users had a blood pressure check or not	Age, smoking	Self-reported hypertension Possible recall bias (OC use)	Intermediate
WHO, 1996 [14]	European countries, 1989–1993	246/643 (hospital controls)	No HTN/no OC No HTN/OC use HTN/no OC use HTN/OC use	1.0 (referent) 1.05 (0.61–1.80) 4.94 (2.98–8.19) 10.3 (3.27–32.3) ORs not affected by whether OC users had a blood pressure check or not	Age, smoking	Self-reported hypertension Possible recall bias (OC use)	Intermediate
Ischemic or thrombotic stroke and cerebrothromboembolic attack							
Collaborative Group, 1975 [13]	US	135/342 (hospital controls)	No HTN/no OC No HTN/OC use HTN/no OC use	1.0 (referent) 3.1 (1.5–7.2) Borderline HTN 1.3 (0.6–2.6) Moderate HTN 3.6 (1.7–7.5) Severe HTN 6.9 (3.3–14.5)	Age, race	Did not assess confounding of factors other than age and race Hospital controls	Low

(*continued on next page*)

Table 1 (*continued*)

Author, year	Study setting	No. of cases/controls (control type)	Results		Adjustments	Weaknesses	Quality
Ischemic or thrombotic stroke and cerebrothromboembolic attack							
Collaborative Group, 1975 [13]			HTN/OC use	Borderline HTN 5.2 (2.3–12.0) Moderate HTN 8.9 (3.5–22.8) Severe HTN 13.6 (4.8–38.6)			
Lidegaard et al. 1993, 1995, 1996 [15–17]	Denmark, 1985–1989	497/1370 (population)	OR for HTN OR for COC No interaction; estimate of OR for HTN and COC ~5.6	3.1 ($p<.001$) 1.8 (1.1–2.9)	Age, education, smoking	Self-reported hypertension Possible recall bias (COC use)	Low
WHO, 1996 [18]	Developing countries, 1989–1993	553/1577 (hospital)	No HTN/no OC No HTN/OC use HTN/no OC use HTN/OC use Blood pressure check No blood pressure check	1.0 (referent) 2.73 (1.97–3.77) 7.70 (5.36–11.0) 14.5 (5.36–39.0) 1.91 (1.19–3.06) 3.79 (2.56–5.59)	Age, rheumatic heart disease, smoking	Self-reported hypertension Possible recall bias (OC use)	Intermediate
WHO, 1996 [18]	European countries, 1989–1993	141/373 (hospital)	No HTN/no OC No HTN/OC use HTN/no OC use HTN/OC use Blood pressure check No blood pressure check	1.0 (referent) 2.71 (1.47–4.99) 4.59 (2.39–8.82) 10.7 (2.04–56.6) 2.26 (1.12–4.55) 3.90 (1.83–8.33)	Age, parity, smoking	Self-reported hypertension Possible recall bias (OC use)	Intermediate
Heinemann et al., 1998 [19]	Europe, Transnational Study, 1993–1996	220/775 (hospital and population controls)	No HTN/no OC No HTN/OC use HTN/no OC use HTN/OC use Blood pressure check No blood pressure check	1.0 (referent) 3.92 (2.24–6.97) 9.6 (3.25–30.57) 3.07 (0.85–11.05) 2nd generation 1.8 (1.0–3.0) 3rd generation 2.5 (1.4–4.4) 2nd generation 4.5 (2.1–9.6) 3rd generation 4.6 (2.0–10.9)	Abnormal blood lipids, age, body mass index, diabetes, hypertension in pregnancy, smoking	Self-report of hypertension Pooling of different control types in analysis Possible recall bias (OC use)	Intermediate
Lidegaard et al., 2002 [20]	Denmark, 1994–1998	626/4054 (population)	OR for 30–40 μg ethinyl estradiol COC use OR for HTN No interaction; estimated OR for HTN and COC ~8	1.6 (1.3–2.0) 5.0 (3.3–7.4)	Age, year, smoking, migraine, education	Self-reported hypertension Possible recall bias (OC use)	Low

Kemmeren et al., 2002 [21]	Netherlands, RATIO Study, 1990–1995	203/925 (population)	No HTN/no OC No HTN/OC use HTN/no OC use HTN/OC use	1.0 (referent) 2.7 (1.8–4.0) 6.8 (3.7–12.2) 7.6 (3.5–26.3)	Age, area of residence, calendar year	Self-report of hypertension Possible recall bias (OC use)	Intermediate
Siritho et al., 2003 [22]	Australia, MERFS Study, 1984–1996	234/234 (population)	OR for OC use OR for HTN No interaction	1.76 (0.86–3.61) 2.18 (1.22–3.91)	Smoking, alcohol use, exercise, cholesterol, history of myocardial infarction, history of transient ischemic attack, diabetes	Self-report of hypertension Possible recall bias (OC use)	Intermediate
Nightingale and Farmer, 2004 [23]	United Kingdom, General Practice Research Database, 1992–1998	190/1129 (clinic controls), nested case-control study	OR for OC use OR for HTN No interaction	2.30 (1.15–4.59) 4.61 (2.71–7.84)	Adjusted, but variables included were not specified	Lack of reporting of potential confounders	Intermediate
All stroke							
Hannaford et al., 1994 [24]	United Kingdom, Royal College of General Practitioners Study, 1968–1990	253/759 (population controls), nested case-control study	No HTN/no OC No HTN/OC use HTN/no OC use HTN/OC use	1.0 (referent) 1.6 (1.1–2.2) 4.9 (2.4–9.9) 4.8 (2.4–9.4)	Smoking and social class		Intermediate
Venous thromboembolism							
WHO, 1997 [25]	17 countries, 1989–1995	1143/2998 (hospital controls)	No consistent or important effect of hypertension on OC-associated risk of VT History of HTN and VT Europe Developing countries OC use and venous thromboembolism Europe Developing countries	 0.95 (0.56–1.62) 1.82 (1.25–2.65) 4.15 (3.09–5.57) 3.25 (2.59–4.08)	None for hypertension; OC use adjusted for history of hypertension in pregnancy	Self-report of hypertension Possible recall bias OC use) No report of joint effects for hypertension and OC use	Intermediate

HTN indicates hypertension.

Vascular Diseases/). Articles in all languages were accepted. We also searched reference lists of identified articles and relevant review articles for additional citations of interest. We did not consider unpublished studies, abstracts of conference presentations or dissertations, nor did we contact the authors of individual articles.

2.1. Study selection

Our MEDLINE search identified 335 articles, from which we selected primary research articles that examined changes in blood pressure or development of PAD, or risk of AMI, ischemic or hemorrhagic stroke, or VTE among women with hypertension who also used COCs. We also selected articles that examined the association between having a blood pressure measurement prior to the initiation of COC use and risk for these outcomes. After excluding articles that did not examine simultaneously the effects of hypertension and COC use on women's risk for a cardiovascular event, we were left with 22 articles that described 13 studies, as well as 3 published meta-analyses. All studies described in the articles that we reviewed were observational; no randomized controlled trials were identified.

2.2. Study quality assessment and data synthesis

We summarized and systematically assessed the evidence through the use of standard abstract forms [2] and assessed the quality of each individual piece of evidence using a preliminary draft of a grading system developed by members of the Grades of Recommendation Assessment, Development, and Evaluation (GRADE) Working Group (Appendix A) [3].

A summary of all the studies reviewed is shown in Table 1. Some studies reported relative risks for cardiovascular events separately by hypertension and COC use and then commented on whether any interaction was observed between these two risk factors. Other studies reported directly on the joint effects of COC use and hypertension on the risk for cardiovascular events and gave odds ratios that compared risks among women in four groups: women with neither hypertension nor COC use, women with hypertension but no CDC use, women with COC use but no hypertension and women with both hypertension and COC use. In addition, some studies reported on the effects of blood pressure measurement prior to initiation of COC use.

3. Results

3.1. Hypertensive disorders

Two cross-sectional studies compared blood pressure levels among hypertensive women who were COC users with levels among hypertensive nonusers. In one study of 94 Italian women with mild hypertension (defined as supine diastolic blood pressure from 90 to 99 mm Hg), COC users (mean duration of use 3.0 years) were found to have significantly higher mean daytime and nighttime ambulatory systolic blood pressure values (mean 8.3 mm Hg higher for daytime and mean 6.1 mm Hg higher for nighttime) than nonusers, though the mean diastolic blood pressure values of the two groups did not differ significantly [4]. In the second study, 171 hypertensive women from a hypertension outpatient clinic in Brazil were divided into three groups: those using COCs, those using other contraceptive methods and those using no method [5]. COC users had significantly higher mean diastolic blood pressure than the other two groups (100.3 vs. 93.0 and 93.5 mm Hg, respectively), a higher prevalence of uncontrolled hypertension (83.3% vs. 65.4% and 68.4%, respectively) and a higher prevalence of severe hypertension, defined as systolic blood pressure of $\geq$160 mm Hg or diastolic blood pressure $\geq$100 mm Hg (21.2% vs. 19.2% and 12.7%, respectively). An additional study found that among 152 women aged 18–49 years with angiographically confirmed PAD and 925 population-based controls, the risk for PAD was increased nearly four times among COC users than nonusers (OR 3.8; 95% CI 2.4–5.8) [6]. The odds ratio for PAD both among normotensive COC users and among hypertensive non-COC users was approximately 5, and the odds ratio among hypertensive COC users was 8.8 (95% CI 3.9–19.8), compared with normotensive non-COC users. Though the authors did not estimate absolute risks for PAD, they stated that PAD is rare in young women.

3.2. Acute myocardial infarction

We identified four case-control studies that reported on the risk for AMI associated with COC use and hypertension [7–9,12]. All of these studies reported statistically significantly higher risks for AMI among hypertensive COC users than among normotensive nonusers, with odds ratios ranging from 6 to 68 [7–9,12]. Two of these four studies reported little difference in risk for AMI between hypertensive women who used COCs and hypertensive women who did not use COCs (ORs approximately 1.2–1.6) [7,12]. The WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception showed that European COC users with a history of hypertension were 68.1 times more likely to have an AMI than were nonusers with no history of hypertension (95% CI 6.18–751), whereas non-COC users with a history of hypertension were only 5.43 times as likely to have an AMI as nonusers with no history of hypertension (95% CI 2.39–12.4) [9]. When examining the relative risk among women with hypertension, COC users with hypertension had approximately 12 times the risk of AMI as nonusers with hypertension. Among developing country participants in the WHO study, women with both COC use and hypertension had 15.3 times the risk of those with neither factor (95% CI 3.27–71.6), representing a 1.6-fold risk for COC users with hypertension compared with nonusers with hypertension.

Three studies examined the association between AMI risk and having a blood pressure measurement prior to initiating COC use. The odds ratios for COC use and AMI were

generally higher among COC users who had not had their blood pressure checked (OR range 2.76–9.47; 95% CI range 1.36–24.1) than among COC users who had (OR range 1.07–3.48; 95% CI range 0.66–8.70) [9–11].

A meta-analysis of the relationship between COC use and risk for AMI [26] used data from four of the studies described above [7–9,12] and estimated that AMI risk among hypertensive COC users was 9.30 times (95% CI 1.83–53.53) that among nonusers without hypertension.

3.3. Ischemic and hemorrhagic stroke

We reviewed eight studies that examined the risk for ischemic stroke associated with COC use and hypertension [13,15–23]. Results showed that odds ratios for ischemic stroke among hypertensive COC users ranged from 3.1 to 14.5 compared with nonusers without hypertension. Most of the studies also found that hypertensive COC users had between 1.5 and 2 times the risk for stroke as hypertensive non-COC users [13,15–18,20–23]. However, the Transnational Study reported a higher risk of ischemic stroke for non-COC users with hypertension (OR 9.6, 95% CI 3.25–30.57) than for COC users with hypertension (OR 3.07 95% CI 0.85–11.05), when compared with nonusers without hypertension [19]. None of these studies reported a statistically significant interaction between COC use and hypertension upon the risk for ischemic stroke, nor did the reported odds ratios suggest such an effect.

Two studies examined COC use, hypertension and risk for hemorrhagic stroke [13,14]. Results from one study showed that non-COC users with severe hypertension had 21.6 times (95% CI 11.1–42.3) the risk for hemorrhagic stroke as normotensive nonusers, but that the addition of COC use only slightly increased the odds ratio (OR 25.6, 95% CI 9.4–70.7 for severe hypertension and COC use compared with no hypertension and no COC use) [13]. Results of the WHO study showed relatively large increases in risk for hemorrhagic stroke among COC users with hypertension than among nonusers without hypertension (OR 10.3, 95% CI 3.27–32.3 in Europe and OR 14.3, 95% CI 6.72–30.4 in developing countries) [14]. COC users with hypertension had about 2.1 times the risk of hemorrhagic stroke as non-COC users with hypertension for European participants, and 1.5 times the risk for participants in developing countries.

Results from the Royal College of General Practitioner's Study, which examined all stroke combined, showed no difference in risk for stroke between women with hypertension who used COCs and women with hypertension who did not, with the odd ratios for stroke in both groups five times that of nonusers without hypertension [24].

In two studies that examined the association between blood pressure screening and stroke risk among COC users, women who did not have their blood pressure checked prior to initiating COC use had about a 1.7- to 2.5-fold risk for ischemic stroke than women who did [18,19]. However, the odds ratios for hemorrhagic stroke among COC users were similar for those with and without a blood pressure measurement [14].

We also evaluated two published meta-analyses of the association between COC use and stroke risk [27,28]. The first focused on ischemic stroke and used data from 16 studies, three of which included information on hypertension. A pooled odds ratio derived from these three studies showed the overall risk for ischemic stroke among women with hypertension to be 1.73 times as high among COC users than among nonusers (95% CI 0.83–3.60). Analysis of data from five studies in the same meta-analysis showed that among women without hypertension, COC users had 2.47 times the risk for ischemic stroke of nonusers (95% CI 1.80–3.38). These findings are consistent with those of the individual studies described above, which generally do not suggest that COC use and hypertension act synergistically to increase risk of ischemic stroke. The second meta-analysis used data from 36 studies of COC use and all stroke, 12 of which included information on COC use among normotensive women and 5 of which included information on COC use among hypertensive women. Among hypertensive women, the pooled odds ratio for all stroke, comparing COC users with nonusers, was 9.82 (95% CI 6.97–13.84); for normotensive women, the corresponding pooled odds ratio was 2.06 (95% 1.46–2.92). These findings differ from those of the first meta-analysis, as well as from those of many of the individual studies, which do not suggest an interaction between hypertension and COC use on stroke risk.

3.4. Venous thromboembolism

While COC use by itself is a risk factor for VTE, results from the WHO Collaborative Study showed no effect of history of high blood pressure on the risk of VTE with COC use [25].

4. Discussion

In this review, we assessed 22 individual articles that described 13 studies of COC use and risk for cardiovascular events, as well as 3 meta-analyses. Evidence from two cross-sectional studies suggested that women with hypertension who use COCs may experience further increases in blood pressure; however, given the cross-sectional nature and the relatively small sample sizes involved, these studies were of "very low quality." Overall, the studies we examined showed that hypertensive COC users were at higher risk for AMI and stroke than hypertensive non-COC users, but not at higher risk for VTE. They also showed that women who did not have their blood pressure measured before initiating COCs were at higher risk for ischemic stroke and AMI than women who had a blood pressure measurement, but they were not at higher risk for hemorrhagic stroke or VTE. Most of these studies were well-conducted case-control studies of "intermediate quality" — most had adequate sample sizes, included validation of the

cardiovascular event and controlled for appropriate confounders. However, most of them used study participants' self-reports of "history of hypertension" as the exposure measure, which may have led to some misclassification of exposure status. For the WHO study, history of hypertension was defined as ever having had high blood pressure, other than in pregnancy [18]. However, women meeting this criterion may have included those with past high blood pressure but currently normal levels and those with treated/controlled hypertension (normal blood pressure), as well as those whose blood pressure was actually high at the time of study. In addition, history of hypertension most likely means different things in the various countries and settings where these studies took place. Similarly, a "blood pressure check" before the current episode of COC use does not necessarily mean that the woman had normal blood pressure. However, in the WHO study, blood pressure measurements correlated well with source of COC supply in developing countries (i.e., women who received COCs from a clinical source were more likely to have had their blood pressure measured than women who received COCs from a nonclinical source) [18]. The source of women's COC supply was also correlated with their risk of experiencing a cardiovascular event [e.g., the odds ratios for AMI was 2.34 (95% CI 0.94–5.83) for women obtaining COCs from a clinical source and 7.90 (95% CI 3.58–17.4) from a nonclinical source] [9].

None of the studies examined risks for adverse events by blood pressure level. In general, however, the risk of stroke increases with increasing blood pressure. For example, the incidence of stroke has been shown to increase by 46% and the incidence of coronary heart disease by 29% for every 7.5-mm Hg increase in diastolic blood pressure [29]. A recent meta-analysis confirmed a direct and continuous relationship between blood pressure and the risk for death from cardiovascular-related causes at blood pressure levels down to at least 115/75 mm Hg [30]. Beginning at 115/75 mm Hg, cardiovascular disease risk doubles with every increase of 20/10 mm Hg. Because of this and similar reports, the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure in the United States recently revised it guidance for hypertension prevention and management [31], and now suggests that individuals with a systolic level of 120–139 mm Hg or a diastolic level of 80–89 mm Hg be considered "pre-hypertensive" and be encouraged to make lifestyle modifications to reduce their risk for cardiovascular disease.

While data from the studies that we examined show that women with hypertension and those who use COCs are at elevated risk for cardiovascular events, these findings must be put into the context of the low absolute risk for AMI, stroke and VTE among women of reproductive age. Farley et al. [1] have estimated that for women aged 20–24, the rate of cardiovascular events is 312 per million woman-years for women with hypertension who use low-dose COCs and 134 among women with hypertension and no COC use; at ages 40–44, the estimates increase to 1213 and 529, respectively. Deaths from cardiovascular events among women with hypertension increased with COC use from 29.8 to 63.4 per million woman-years at ages 20–24 and from 130 to 306 at ages 40–44 [1].

In 2003, a WHO Expert Working Group evaluated the evidence contained in this systematic review to assess medical eligibility criteria for contraceptive use [32], with the exception of the study by Nightingale et al. [23], which was published in 2004. This group recommended that for women with a history of hypertension whose current blood pressure cannot be evaluated, for women with adequately controlled hypertension and for women with elevated blood pressure (140–159 mm Hg systolic or 90–99 mm Hg diastolic), the use of COCs is not usually recommended unless other more appropriate methods are not available or not acceptable (WHO Category 3). Women with blood pressure levels of >160 mm Hg systolic or >100 mm Hg diastolic and women with hypertension with vascular disease should not use COCs (WHO Category 4). The WHO recommendations also note that blood pressure must be evaluated using properly taken measurements and that a single reading of blood pressure is not sufficient to identify hypertension.

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The findings and conclusions in this report are those of the author(s) and do not necessarily represent the views of the funding agencies.

Appendix A. Study quality assessment

A.1. Individual study

Each study was given a rating of very low, low, intermediate or high based on the interval validity of the study. If the study was indirect, the quality of the individual study was lowered by one level. If the study was direct, the quality of evidence was kept the same. Similarly, if there was sparseness of the data, the quality of the individual study was lowered by one level.

A.2. Body of evidence

The quality of the body of evidence was the highest rating given to an individual study. If the results were inconsistent, the quality of the body of the evidence was lowered by one level. If results were consistent, then the quality of the body of the evidence was left at the original level. Similarly, if there was reporting bias (publication

bias), then the quality of the body of evidence would be lowered by one level.

Quality of evidence across studies for each main outcome

RCT	Quality of the evidence	Observational studies
No serious flaws in study quality	High	Extremely strong association and no threats to validity
Serious flaws in design or execution or quasi-experimental design	Intermediate	Strong, consistent association and no plausible confounders
Very serious flaws in design or execution	Low	No serious flaws in study quality
Very serious flaws and at least one other serious threat to validity	Very low	Serious flaws in design and execution

Additional factors that lower study quality are as follows: important inconsistency of results; some uncertainty about directness; high probability of reporting bias; and sparseness of data. Major uncertainty about directness can lower the quality by two levels

Additional factors that may increase quality of observational studies are as follows: all plausible residual confounding, if present, would reduce the observed effect; and evidence of a dose–response gradient

Adapted from: Judging Confidence: Guidelines for Grading Evidence and Recommendations. Grades of Recommendation Assessment, Development, and Evaluation (GRADE) Working Group. Draft, January 2003.

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