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Combined oral contraceptives: the risk of myocardial infarction and ischemic stroke (Review)

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Combined oral contraceptives: the risk of myocardial infarction and ischemic stroke.
Cochrane Database of Systematic Reviews 2015, Issue 8. Art. No.: CD011054.
DOI: 10.1002/14651858.CD011054.pub2.

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[Intervention Review]

Combined oral contraceptives: the risk of myocardial infarction and ischemic stroke

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Editorial group: Cochrane Fertility Regulation Group.
Publication status and date: Edited (no change to conclusions), comment added to review, published in Issue 3, 2018.

Citation: Roach RE, Helmerhorst FM, Lijfering WM, Stijnen T, Algra A, Dekkers OM. Combined oral contraceptives: the risk of myocardial infarction and ischemic stroke. *Cochrane Database of Systematic Reviews* 2015, Issue 8. Art. No.: CD011054. DOI: 10.1002/14651858.CD011054.pub2.

ABSTRACT

Background

Combined oral contraceptives (COCs) have been associated with an increased risk of arterial thrombosis, i.e. myocardial infarction or ischemic stroke. However, as these diseases are rare in young women and as many types of combined oral contraception exist, the magnitude of the risk and the effect of different hormonal contents of COC preparations remain unclear.

Objectives

To estimate the risk of myocardial infarction or ischemic stroke in users compared with non-users of different types, doses and generations of combined oral contraception.

Search methods

We searched electronic databases (MEDLINE (1966 to July 08, 2015), EMBASE (1980 to July 08, 2015), Popline (1970 to July 08, 2015) and LILACS (1985 to July 08, 2015) for eligible studies, without language restrictions.

Selection criteria

We included observational studies that recruited women in the reproductive age group (18 to 50 years) and compared the risk of myocardial infarction or ischemic stroke between users and non-users of COCs.

Data collection and analysis

Two review authors independently selected relevant studies and extracted data. We pooled relative risks ()(combined odds ratios and one incidence rate ratio) and 95% confidence intervals (CIs) for myocardial infarction or ischemic stroke in users versus non-users of COCs. We combined the outcomes of myocardial infarction and ischemic stroke and also analysed these outcomes separately. Analyses were stratified according to estrogen dose and progestagen type.

Main results

In total, we identified 1298 publications through the search strategy. We included 28 publications reporting on 24 studies. COC users were at increased risk of myocardial infarction or ischemic stroke compared with non-users: relative risk (RR) 1.6 (95% CI 1.3-1.9).These RRs were similar for myocardial infarction (1.6, 95% CI 1.2 to 2.1) and ischemic stroke (1.7, 95% CI 1.5 to 1.9). The risks did not vary clearly according

to the generation of progestagen or according to progestagen type. When we stratified preparations according to estrogen dose, the risk of myocardial infarction or ischemic stroke seemed to increase with higher doses of estrogen.

Authors' conclusions

This meta-analysis showed that the risk of myocardial infarction or ischemic stroke was 1.6-fold increased in women using COCs . The risk was highest for pills with > 50 microgram estrogen. When combined with the results of studies on the risk of venous thrombosis in COC users, it seems that the COC pill containing levonorgestrel and 30 µg of estrogen is the safest oral form of combined oral hormonal contraception.

PLAIN LANGUAGE SUMMARY

The risk of heart attack and stroke in women using birth control pills

Background

Since their introduction, combined oral contraceptive pills have become one of the most popular birth control methods. These pills contain two types of female hormones, estrogen and progestagen. When used correctly, the failure rate (i.e. the occurrence of unwanted pregnancy) is less than one per 100 women per year. Despite their reliability, oral contraceptive pills have been found to increase the risk of a blood clot forming in an artery, i.e. arterial thrombosis (heart attack or stroke). As arterial thrombosis is rare in young women, and as many types of oral contraceptive pills exist, the size of the risk is unclear. Furthermore, the effect of different types of progestagens or different doses of estrogen on the risk of arterial thrombosis is unknown.

Review question

In this Cochrane Review we aimed to assess the risk of arterial thrombosis in different types of oral contraceptive pills. To do this, we searched the literature on July 8, 2015 for all studies that assessed the risk of arterial thrombosis associated with oral contraceptive pills in women under the age of 50 years.

Study characteristics

In total, 28 articles on 24 unique studies met the inclusion criteria.

Key results

Our results showed that the overall risk of arterial thrombosis was was 1.6-fold increased in women using oral contraceptive pills compared with women who did not use oral contraceptive pills. The risk did not vary clearly according to progestagen type. However, we found that the risk of arterial thrombosis seemed to be twice as high in women taking pills with higher doses of estrogen. Also, the risk of other side effects of oral contraceptive pills (such as a blood clot in a vein-venous thrombosis) should be considered before any type of oral contraceptive pill is prescribed. It is likely that the COC pill containing levonorgestrel and 30 µg of estrogen is the safest oral form of combined oral hormonal contraception.

Quality of the evidence

The overall quality of evidence in this review was moderate. Most studies (22 out of 28) correctly confirmed that patients had been diagnosed with arterial thrombosis. However, only four studies also checked that the type of pill a patient had been using was reported correctly. In addition, only half of the studies ensured that the correct comparisons were made between patients with and patients without arterial thrombosis. Also of importance is the fact that the analysis on progestagen type was based on few studies only.

BACKGROUND

Description of the condition

Worldwide, myocardial infarction and ischemic stroke are two of the most important causes of morbidity and mortality (WHO 2013). It is estimated that over 17 million people die from cardiovascular diseases annually, with over 80% of deaths occurring in low- and middle-income countries (Nabel 2012). Myocardial infarction most often occurs when an atherosclerotic plaque (a collection of fatty acids, fibrous tissue and leukocytes) ruptures in the wall of a coronary artery. The plaque contents obstruct the artery and deprive the downstream part of the heart muscle of oxygen (Nabel 2012). This can cause permanent cell damage or necrosis and leads to heart failure, stroke or death in up to 10% of cases (Brieger 2009; Roe 2010).

Ischemic stroke is characterized by brain ischemia due to the obstruction of a cerebral artery (Caplan 2009). As in myocardial infarction, a cerebral artery can be obstructed due to the rupture of an atherosclerotic plaque. Alternatively, a thrombus can embolize from elsewhere in the body and become lodged in the cerebral vasculature (Caplan 2009). The affected part of the brain rapidly loses function, leading to both transient and permanent disabilities such as loss of speech and movement (Di Carlo 2003).

The most important risk factors for myocardial infarction and ischemic stroke are hyper cholesterolemia, hypertension, diabetes and smoking (Wilson 1998). These risk factors generally accumulate over time, explaining why most patients with a cardiovascular event are aged 50 years or older (Berry 2012). Nevertheless, there are also risk factors that can contribute to myocardial infarction or ischemic stroke in younger (female) individuals. Studies in young women have shown an association between combined oral contraception use and an increased risk of myocardial infarction and ischemic stroke (Zakharova 2011). However, as these diseases are rare in young women and as many types of combined oral contraception exist, the magnitude of the risk and the effect of different hormonal contents of combined oral contraceptive (COC) preparations remain unclear.

Description of the intervention

COCs are the most commonly used reversible form of contraception in developed countries (United Nations 2011). They contain an estrogen and a progestagen that are usually taken together in one pill for the first 21 days of every menstrual cycle, followed by a pill-free week (Speroff 2011). COCs prevent ovulation, mainly by suppressing the surge in luteinizing hormone (due to the progestagen content) (Speroff 2011). With full compliance, the failure rate (i.e. the occurrence of unwanted pregnancy) is less than one per 100 women per year (Trussell 2011).

How the intervention might work

COCs are associated with an increase in many coagulation factors (e.g. factor VII, VIII, X), increased activity of the fibrinolytic inhibitors Plasminogen Activator Inhibitor (PAI)-1 and PAI-2 and a reduced anticoagulant response (activated protein C resistance) (Tchaikovski 2010). Research has recently found hypercoagulability to be an important determinant of atherogenesis and atherosclerosis (Borissoff 2011), which in turn precedes myocardial infarction and ischemic stroke. In addition, COCs have been associated with increases in triglycerides, Low Density Lipoprotein cholesterol and insulin levels, and a reduced glucose tolerance (Godsland 1990), which are all well known risk factors for arterial cardiovascular disease (Wilson 1998).

Why it is important to do this review

In order to reduce the harmful thrombotic side-effects, the dose of estrogen in COCs has been gradually reduced from 150 µg in the first preparations to ≤ 30 µg today (Speroff 2011). In addition to preparations with so-called 'first generation' progestagens lynestrenol and norethisterone, preparations containing second (levonorgestrel and norgestrel) or third generation progestagens (desogestrel and gestodene) and preparations containing drospirenone were developed in an attempt to improve the cardio-metabolic profile of COCs (Godsland 1990; Bringer 1992; Badimon 1999; Krattenmacher 2000). Still, results of studies on the risk of myocardial infarction and ischemic stroke associated with various types of COCs are conflicting. As over 100 million women use COCs worldwide (WHO 2004) and all combined preparations are equally effective for the prevention of unwanted pregnancies (Lawrie 2011), the issue of safety is paramount. Therefore, it is important to obtain a systematic overview of all available evidence on this topic in order to advise women as to the safest choice of combined oral contraception with regards to the risk of myocardial infarction and ischemic stroke.

OBJECTIVES

1. To estimate the risk of myocardial infarction and ischemic stroke in combined oral contraception users compared with non-users.
2. To compare the risk of myocardial infarction and ischemic stroke associated with the three generations of COCs, as well as with preparations containing drospirenone or cyproterone acetate.
3. To compare the effect of varying doses of estrogen and types of progestagen in COCs on the risk of myocardial infarction and ischemic stroke.

METHODS

Criteria for considering studies for this review

Types of studies

Myocardial infarction and ischemic stroke are potential side effects of COC use. Previous research has suggested that results of observational studies are credible when studying side effects of medication(Vandenbroucke 2004). This was supported by a meta-analysis that showed no difference between the risk of side-effects assessed in meta-analyses of experimental data and the risk of side-effects assessed in meta-analyses of observational data(Golder 2011). Therefore in this Cochrane Review we included observational studies with a cohort, case-control or nested case-control design and, if available, data from randomised controlled trials (RCTs).

Types of participants

The participants were women in the reproductive age group (18 to 50 years) who either used or did not use COCs. We excluded studies on women using postmenopausal hormone therapy, non-oral contraceptives or progestagen-only contraceptives.

Types of interventions

We compared the risk of myocardial infarction and ischemic stroke between combined oral contraception users and non-users. Both previous combined oral contraception users and never users were considered to be non-users. The risk of myocardial infarction and ischemic stroke was assessed for different types of COC preparations. We categorized COCs according to their generation (progestagens). We classified preparations containing lynestrenol or norethindrone as first generation preparations, levonorgestrel and norethisterone acetate as second generation progestagens, and desogestrel and gestodene as third generation preparations. In addition, we categorized COCs separately according to the dose of estrogen and the type of progestagen used.

Types of outcome measures

The outcome measures of interest were objectively diagnosed fatal or non-fatal first myocardial infarction or ischemic stroke. We classified a myocardial infarction as objectively confirmed if diagnosed based on a medical examination and pain assessment combined with an electrocardiogram (ECG), serum cardiac biomarkers or other specified strict diagnostic criteria of myocardial infarction, or by autopsy examination. Ischemic stroke was classified as objectively confirmed if a sudden onset focal neurological deficit was diagnosed on the basis of a medical history and neurological examination combined with brain imaging, or by autopsy examination.

We quantified the risk of developing either myocardial infarction or ischemic stroke in COC users compared with non-users by obtaining crude numbers of users and non-users of combined oral contraception, and crude numbers of women with and women without an arterial thrombotic event. We combined these numbers to compute an overall relative risk of myocardial infarction or ischemic stroke in COC users.

Primary outcomes

- Fatal or non-fatal arterial thrombosis (i.e. myocardial infarction or ischemic stroke).

Secondary outcomes

- Fatal or non-fatal myocardial infarction.
- Fatal or non-fatal ischemic stroke.

Search methods for identification of studies

We created the search in association with an expert librarian (C. Manion, Cochrane).

Electronic searches

We searched the following databases: MEDLINE (1966 to July 08, 2015), EMBASE (1980 to July 08, 2015), Popline (1970 to July 08, 2015) and LILACS (1985 to July 08, 2015). The study search was performed without language restrictions.

Searching other resources

The references of the selected studies and of reviews were additionally checked in case we did not capture any relevant studies through our search strategy.

Data collection and analysis

We used the study results to compare the relative risk of myocardial infarction and ischemic stroke between users and non-users of COCs, and between women using different types and doses of COCs. Most studies included women without oral contraception or women who use preparations containing levonorgestrel with 30 µg of ethinylestradiol as a reference group. Standard meta-analytic techniques were used, a random effect model being set as default.

Selection of studies

Two review authors (REJR, FMH) independently evaluated the title and abstract of all studies retrieved from the search strategy. This was done using standard piloted forms and specific inclusion and exclusion criteria. We resolved any disagreements by consensus and consulted a third review author (OMD) if necessary.

Data extraction and management

Two review authors (REJR and FMH) independently extracted data using standard, piloted data extraction forms and entered data into Review Manager (RevMan). We resolved all disagreements by consensus.

Assessment of risk of bias in included studies

Our 'Risk of bias' assessment was equipped for observational studies and adapted from the Newcaste Ottowa scale. We examined the risk of bias in the included observational studies based on four aspects that may affect the association between the exposure (COCs) and the outcome (myocardial infarction and ischemic stroke).

Firstly, exposure to combined oral contraception had to be confirmed through a prescription database in order for the risk of bias to be classified as 'low'. We classified other, less objective, methods such as interviews and questionnaires as a 'high' risk of bias, as research has shown that women have difficulty accurately recalling the type of preparations they used (Nischan 1993; Norell 1998).

Secondly, the diagnosis of a myocardial infarction or ischemic stroke had to be ascertained by objective measures. We classified studies in which myocardial infarction had been diagnosed on the basis of an ECG, serum cardiac biomarkers or other specified strict diagnostic criteria of myocardial infarction, or by autopsy examination as having a low risk of bias. For ischemic stroke these criteria were a neurological examination combined with brain imaging or other specified strict diagnostic criteria of ischemic stroke, or autopsy examination.

In cohort studies, loss to follow-up can lead to biased risk estimates. We classified studies with < 10% loss to follow-up as having a low risk of bias.

Finally, in case-control selection, the selection of controls affects the validity of the results. We classified case-control studies including controls from the source population of the cases (i.e. controls from the same neighbourhood as the cases who would most likely have been admitted to the same hospital as the cases if they had developed myocardial infarction or ischemic stroke) as low risk of bias (Grimes 2005).

As myocardial infarction and ischemic stroke are side effects of using COCs, and it is unethical to perform a RCT for side effects alone, we did not anticipate finding any RCTs on this topic. However, if such studies were found, we would have assessed the risk of bias according to recommended principles (Higgins 2011). We did not use an aggregate 'Risk of bias' score as this is generally discouraged (Jüni 1999).

Two review authors (REJR, FMH) independently assessed the risk of bias using a standard piloted form. Both review authors are trained in Clinical Epidemiology and Study Methodology. We resolved any persistent disagreement by consensus or discussion with a third review author (OMD). We did not use the 'Risk of bias' assessment to accept or reject studies.

Measures of treatment effect

From each matched case-control study (matched on age and calendar time) included , we extracted the crude number of women who were exposed to combined oral contraception, the crude number of women not exposed to combined oral contraception, the crude number of women with myocardial infarction or ischemic stroke and the crude number of women without myocardial infarction or ischemic stroke event. In addition we extracted the crude numbers of women in separate subgroups (i.e. different doses of estrogen, different types of progestagen). We used these numbers to calculate odds ratios for COC users versus non-users at the study level . For one cohort study (Lidegaard 2012a) this matching assumption was not met, and we extracted adjusted estimates (incidence rate ratio).

Unit of analysis issues

Current use of COCs, stratified according to the dose of ethinylestradiol and the type of progestagen, was analysed in women without a history of myocardial infarction or ischemic stroke. Also we studied the effect of previous combined oral contraception use on the risk of cardiovascular disease if data were available.

Dealing with missing data

We only included participants with complete data on exposure to COCs and the outcomes myocardial infarction or ischemic stroke, or both.

Assessment of heterogeneity

For results from standard meta-analytic techniques, we presented statistical measures of heterogeneity (Chi^2 test and I^2 statistics).

Assessment of reporting biases

We made an overview of possible reporting biases for each included study. In addition, for the overall comparison of COC users with non-users, we performed sensitivity analyses according to the presence or absence of various types of bias.

Data synthesis

We combined data from studies with similar designs, interventions and outcome measures. For the analysis on use versus non-use and the analysis at the level of estrogen generations, we performed a random effects meta-analysis based on data that were adjusted for age and calendar time by design or by analysis. For one cohort study (Lidegaard 2012a) we first performed a fixed effect meta-analysis based on risk estimates for various contraceptives from that study. The pooled analysis was subsequently used in the random effects meta-analysis. For analyses with 5 or less studies, both fixed and random effect analyses are presented as, in this case, the between study variability cannot be estimated reliably.

The matched case-control studies provided odds ratios. As these studies were matched on calendar time the odds ratios are a valid estimate of the incidence rate ratio (Knol 2008, Vandenbroucke 2012). Moreover, as the outcome is very rare, relative risks, incidence rate ratios and odds ratios will be similar. We used the term relative risk to denote the pooled effect, even though formally speaking, this consisted of odds ratios and an incidence rate ratio.

We initially aimed to perform a formal network analysis. However, this requires the use of raw data in case of multiple arm studies. Raw data can only be used if unadjusted estimates provide meaningful effect estimates, which was not the case for the cohort study mentioned above Lidegaard 2012a. We therefore applied standard random effects meta-analysis techniques throughout the review.

Sensitivity analysis

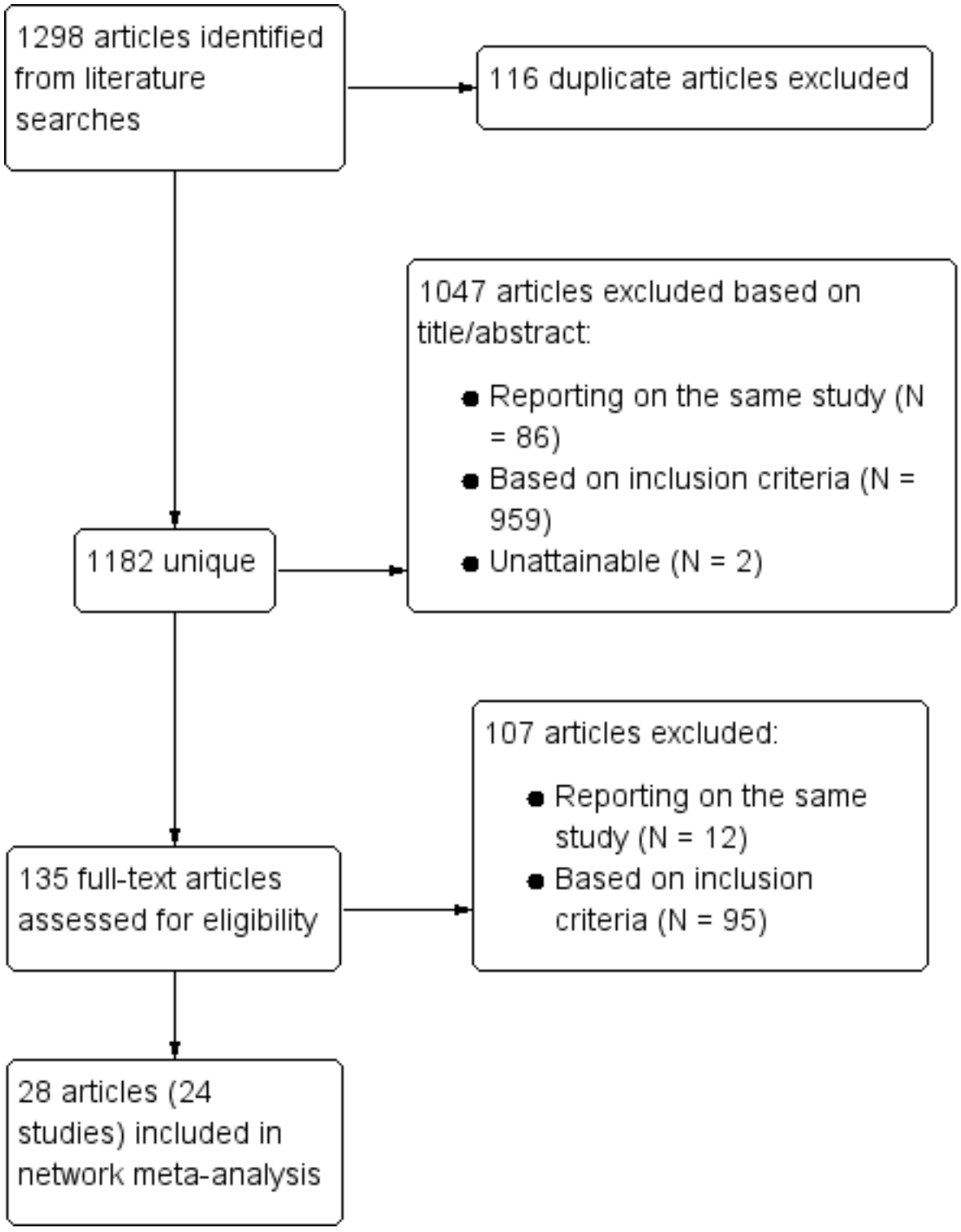
The outcomes myocardial infarction and ischemic stroke were pooled as well as analysed separately. To explore heterogeneity, we performed sensitivity analyses according to funding source and risk of bias. We defined funding as any financial support for the study from pharmaceutical companies.

RESULTS

Description of studies

In total, we identified 1182 unique publications by searching electronic databases and checking the reference lists of the selected articles. Of these, we excluded 1047 publications based on the title or abstract, or both, and excluded a further 107 articles after detailed assessment of the full text (Figure 1). Twenty-eight articles reporting on 24 separate studies met the inclusion criteria and were eligible for analysis. Heinemann 1998 and Lewis 1997 both presented results from the 'Transnational Study on Oral Contraceptives and the Health of Young Women' study, with Heinemann 1998 reporting on ischemic stroke and Lewis 1997 reporting on myocardial infarction. Similarly, van Kemmeren 2002 reported on ischemic stroke in the RATIO, whereas Tanis 2001 presented the data on myocardial infarction. Shapiro 1979 and Slone 1981 reported different analyses of the same study from the USA. The two articles by Mann 1975a and Mann 1975b reported on different data from a single British study. Finally, the article by Sidney 1998 on myocardial infarction described data from the Kaiser Permanente study and the University of Washington study, from which the risk of ischemic stroke is separately reported in Pettiti 1996 and Schwartz 1997. Thirteen studies were performed in Europe, eight in the USA and three studies in several countries around the world.

Figure 1. Study flow diagram.



The eligible publications included one cohort study (Lidegaard 2012a), 22 case-control studies and one nested case-control study. We did not find any RCTs on this topic. Sixteen of the 28 articles reported on the relationship between COCs and myocardial infarction. Eleven articles reported on ischemic stroke and one study assessed both the risk of myocardial infarction and the risk of ischemic stroke. All included articles were published between 1975 and 2010 and reported on data collected between 1968 and 2009. The pharmaceutical industry sponsored six of the 24 included studies.

Risk of bias in included studies

We have presented the risk of bias per publication in Figure 2. In total, only five studies confirmed the use of combined oral contraception through a prescription database and were classified as having a low risk of bias. All other papers assessed the exposure by questionnaire or interview only (high risk of bias).

Figure 2. Risk of bias in the 28 included articles (reporting on 24 included studies). Green: low risk; red: high risk; yellow: unclear risk. Regarding Lidegaard 2012a "Source population": not applicable as this was a population study.

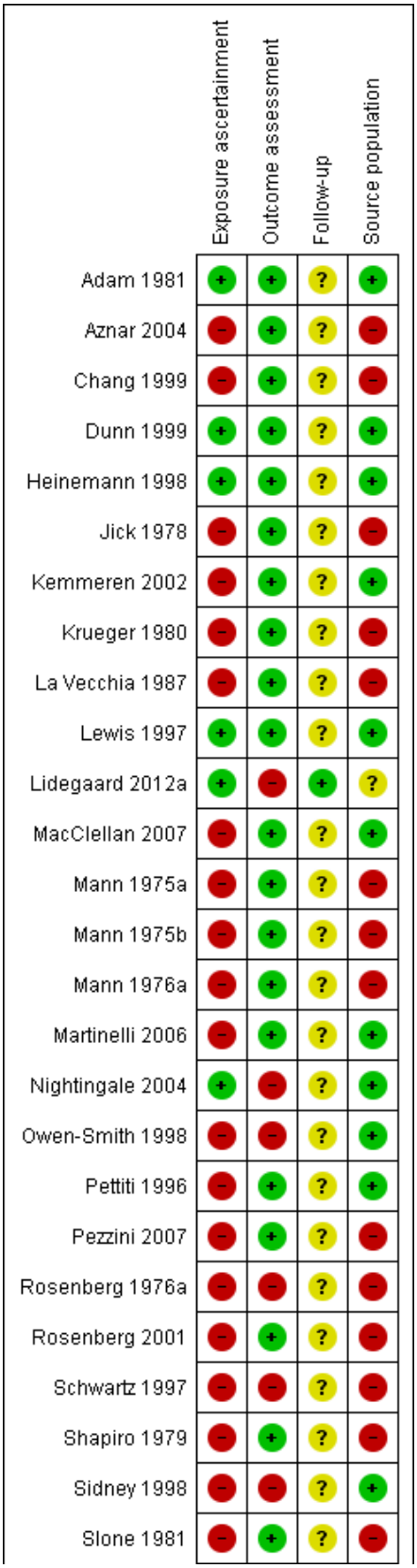
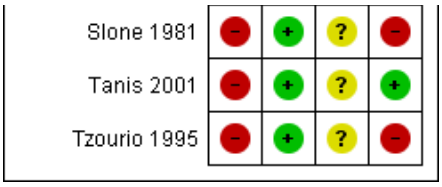


Figure 2. (Continued)



The outcomes myocardial infarction and ischemic stroke were ascertained by objective measures in 22 studies. Six studies had a high risk of bias as the diagnoses were not objectively confirmed.

The only cohort study that was included in this Cochrane Review had almost complete follow-up and so was classified as having a low risk of bias. Follow-up was not applicable to the other included articles as they all reported on case-control studies.

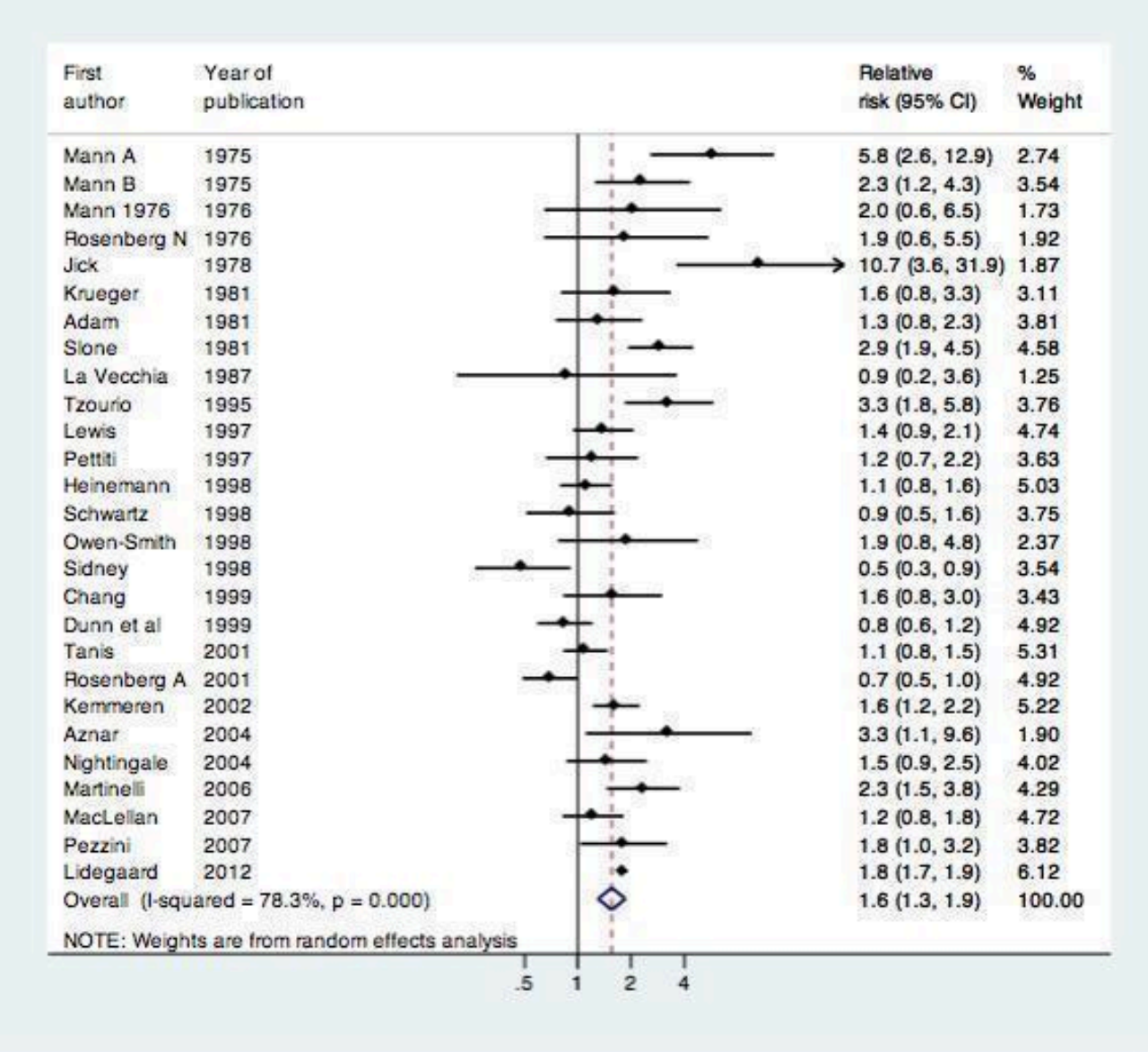
Thirteen studies had a low risk of bias as they included control subjects from the same source population as the cases. The 15 other studies included hospital controls as control subjects which is associated with a high risk of bias.

Effects of interventions

Current versus none use

All 24 included studies assessed the risk of myocardial infarction or ischemic stroke in current versus non-users of combined oral contraception (Table 1). We performed a standard random-effects meta-analysis to assess the risk of myocardial infarction or ischemic stroke in these groups. (Figure 3) COC users were at increased risk of myocardial infarction or ischemic stroke compared with non-users: relative risk 1.6 (95% CI 1.3-1.9).These RRs were similar for myocardial infarction (1.6, 95% CI 1.2 to 2.1) and ischemic stroke (1.7, 95% CI 1.5 to 1.9).

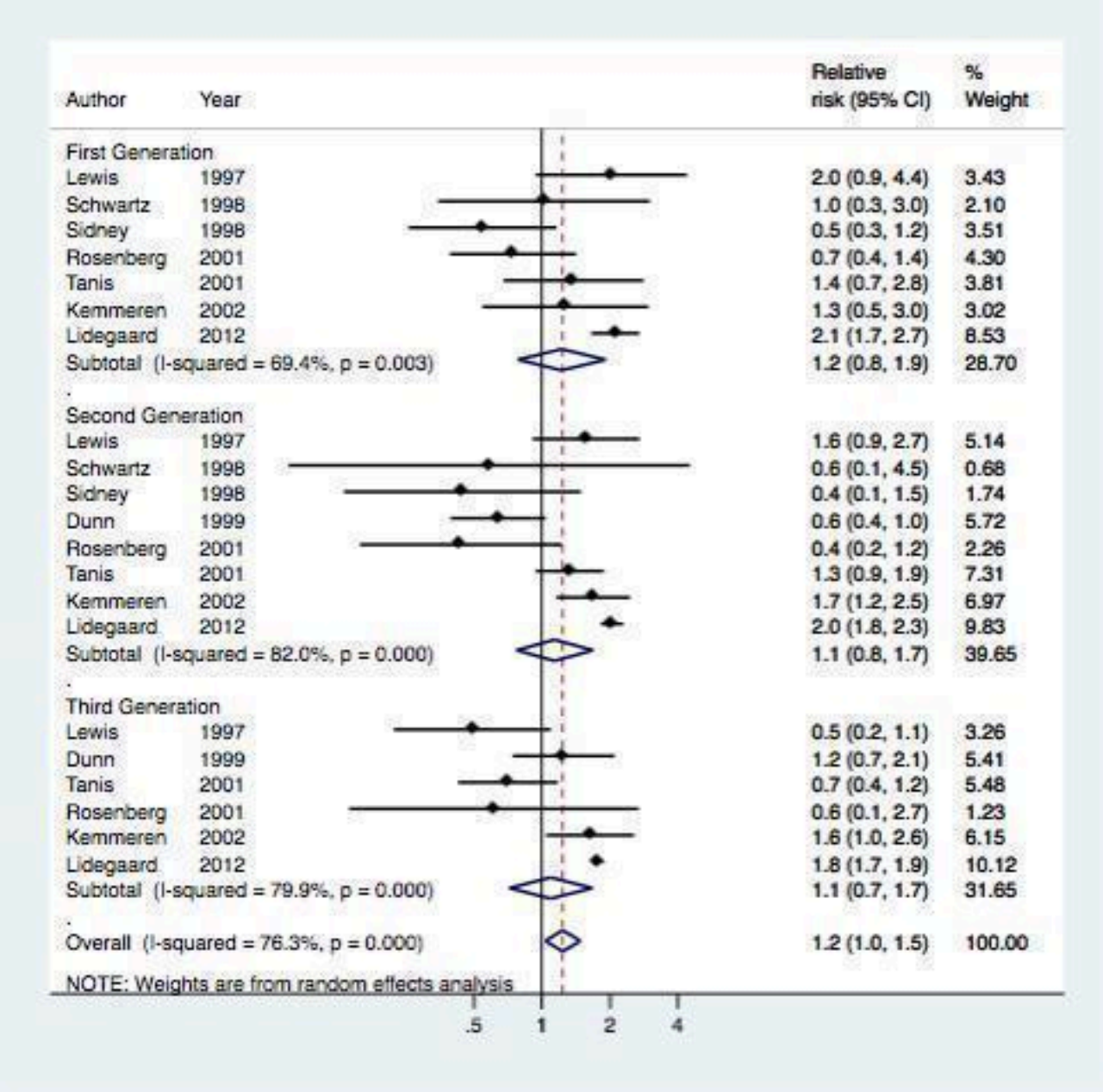
Figure 3. Effect of myocardial infarction and/or stroke in oral contraceptive users versus non-users.



Progestagen generation

Overall, eight studes assessed the risk of myocardial infarction or ischemic stroke for different generations of COC preparations (Table 2, Figure 4). The results of the meta-analysis showed that first generation preparations were not clearly associated with an increased risk of myocardial infarction or ischemic stroke: pooled RR 1.2 (95% CI 0.8 to 1.9) compared with non-use. The pooled relative risks for second generation versus non-use and third generation versus non-use were 1.1 (95% CI 0.8-1.7) and 1.1 (95% CI 0.7-1.7) respectively.

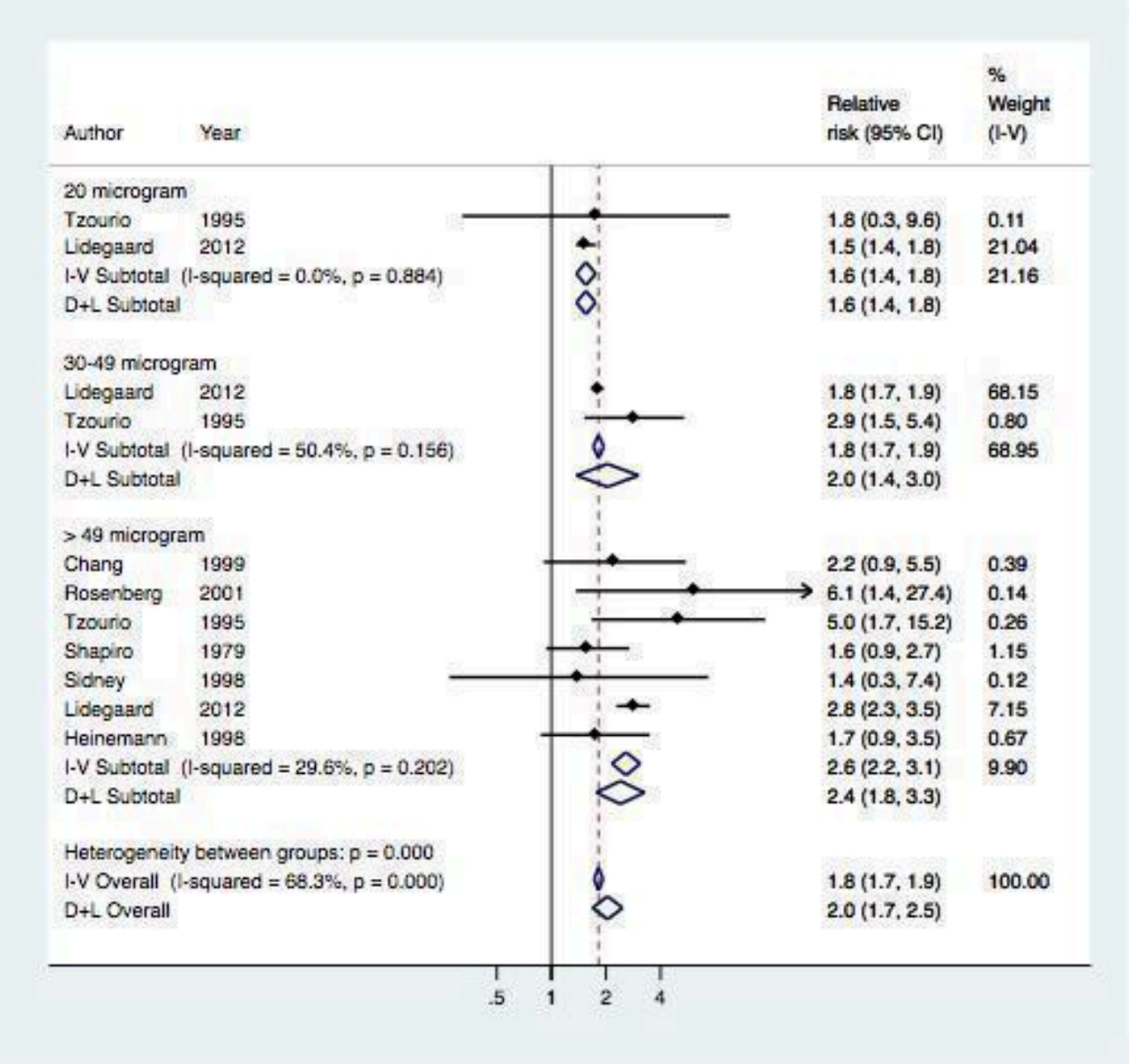
Figure 4. Effect of myocardial infarction and/or stroke in oral contraceptive users versus non-users stratified per generation



Estrogen dose

Seven studies provided data on the risk of myocardial infarction or ischemic stroke according to the dose of estrogen (Table 3 , Figure 5). The risk of myocardial infarction or ischemic stroke increased with increasing doses of estrogen (RR 1.6, 95% CI 1.4 to 1.8) for preparations containing 20 µg of estrogen (RR 2.0, 95% CI 1.4 to 3.0) for 30 to 49 µg of estrogen and RR 2.4 (95% CI 1.8 to 3.3) for ≥ 50 µg of estrogen.

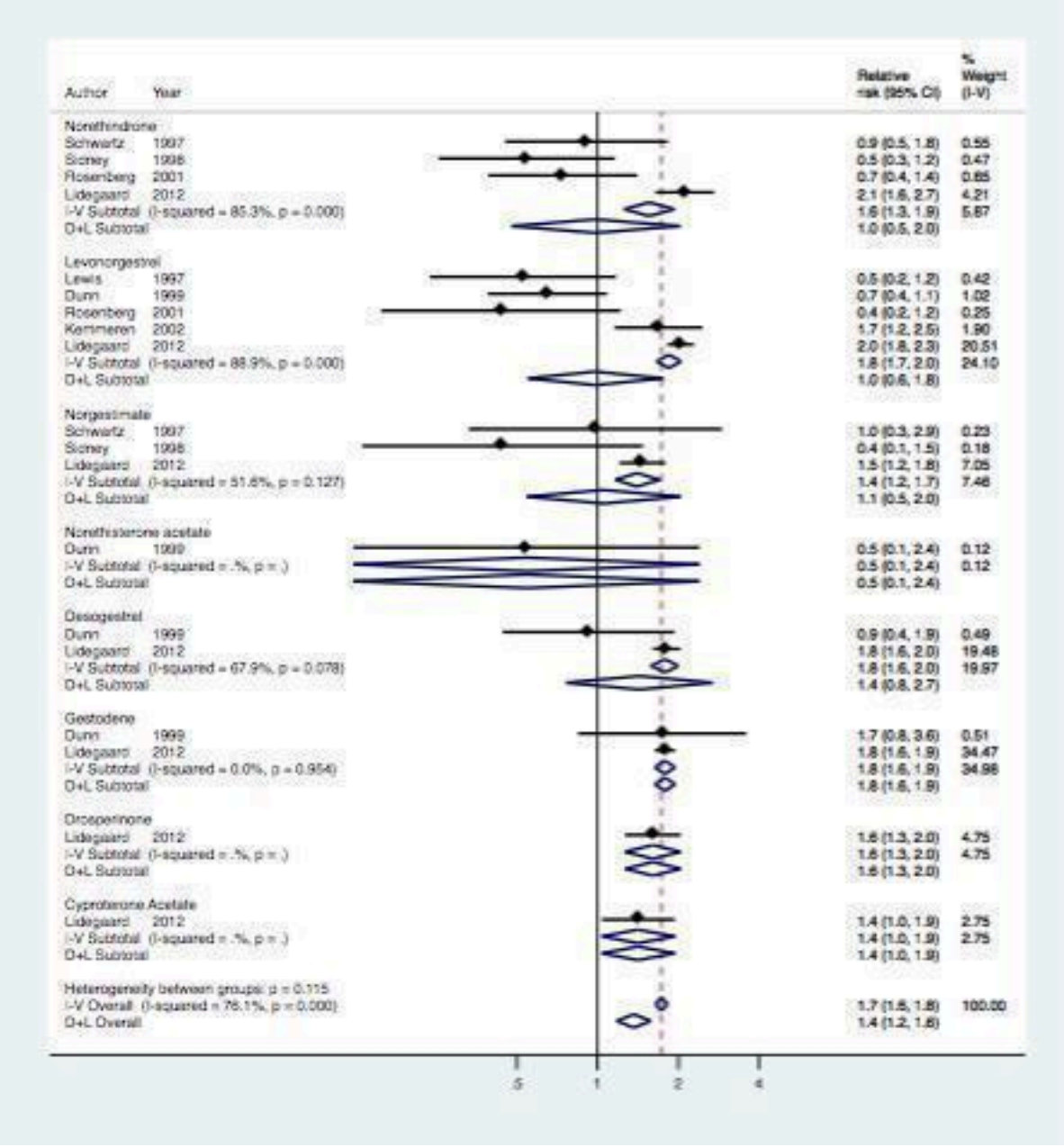
Figure 5. Effect of myocardial infarction and/or stroke in oral contraceptive users versus non-users stratified by estrogen dose



Progestagen type

Finally, seven studies assessed the risk of myocardial infarction or ischemic stroke for various types of progestagen (Table 4, Figure 6). Of note, only few studies contributed data per progestagen type (maximum 5 studies, minimum 1 study).

Figure 6. Effect of myocardial infarction and/or stroke in oral contraceptive users versus non-users stratified per prosgestagen type



Check for consistency

Most analyses showed evidence of considerable heterogeneity. The overall analyses for use versus non-use showed clear evidence of between study heterogeneity beyond chance (i^2 78%).

Sensitivity analysis

We performed sensitivity analyses for the risk of myocardial infarction or ischemic stroke in users compared with non-users of combined oral contraception according to funding source, and according to the risk of bias. Risk estimates were similar in studies sponsored by a pharmaceutical company: RR 1.6 (95% CI 0.9 to 2.4) versus non-industry studies RR 1.5 (95% CI 1.2 to 1.9). Also no clear difference was found between studies with and without a objective diagnostic measures (p=0.3 from meta-regression), or between studies with and without a biased selection of control subjects (p=0.2).

DISCUSSION

Summary of main results

In this Cochrane Review, we performed a meta-analysis of 28 publications to assess the risk of myocardial infarction or ischemic stroke in women using COCs. Overall, the risk of myocardial infarction or ischemic stroke was 1.6 fold increased in women that used COC compared with non-users. This risk did also not

vary according to the generation of progestagen or according to progestagen type. When we stratified preparations according to estrogen dose, the risk of myocardial infarction or ischemic stroke seemed to increase with higher doses of estrogen.

Overall completeness and applicability of the evidence

We have discussed this topic under the 'Potential biases in the review process' section.

Quality of the evidence

We have discussed this topic under the 'Potential biases in the review process' section and presented it in Figure 2.

Potential biases in the review process

We mostly included raw data for the analysis in our review. Therefore, we cannot rule out that our results may have been confounded by factors that influence both the type of COC preparation that is prescribed and the risk of myocardial infarction or ischemic stroke (e.g. age, body mass index, smoking and calendar time). However, all except one (Lidegaard 2012a) of the included studies were case-control studies, in which adjustment for age and calendar time is usually dealt with by design (matching). In addition, body mass index and smoking are only weakly associated with COC use and so we do not expect that the lack of adjustment for these variables will have introduced important bias. Indeed, in the six studies that presented both crude and (extensively) adjusted risk estimates for myocardial infarction or ischemic stroke, adjustment only affected the results in two instances (Table 5). Furthermore, if certain types of COCs had been preferentially prescribed to 'less healthy' women (e.g. obese women or smokers) who have a higher risk of myocardial infarction of ischemic stroke, the number of arterial thrombotic events associated with these preparations would have been overestimated. As our results showed no increased risk of myocardial infarction or ischemic stroke in women using COC preparations, any further reduction in this risk estimate due to elimination of confounding would not change the conclusion of our meta-analysis.

A second point that warrants comment, is the lack of a generally accepted way of classifying oral contraceptives. For instance, in some studies, norgestimate is classified as a third generation preparation, whereas most studies only consider desogestrel and gestodene to be third generation preparations. In this meta-analysis, we chose not to classify norgestimate as a third generation preparation, but only to include desogestrel and gestodene in this definition. However, as we did not find any large differences between the risk of myocardial infarction or ischemic stroke associated with desogestrel, gestodene and norgestimate in the analysis of each progestagen type separately , we do not expect that this choice has greatly influenced our results.

A third point is that some analyses (especially the analyses based on progestagen type) are based on very few studies only. It goes without saying that these results are therefore accompanied by much uncertainty.

Finally, in the analysis on estrogen dose, we did not take the type of progestagen into account. The reason for this was that most studies that provided data on the dose of estrogen did not specify the type of progestagen. However, we consider it unlikely that this classification greatly influenced our results, as preparations containing ≥ 50 µg of estrogen almost always contain levonorgestrel and we did not find this preparation to be associated with an increased risk of myocardial infarction or ischemic stroke in the analysis according to generation (second generation) or the analysis according to progestagen type. For the same reason, we could not take the estrogen dose into account in the analysis on progestagen type. However, as most preparations contained 30 to 49 µg of estrogen (Table 3) a large confounding effect of estrogen dose seems unlikely.

Agreements and disagreements with other studies or reviews

A previous systematic review on the relationship between COCs and myocardial infarction or ischemic stroke found the risk of myocardial infarction or ischemic stroke to be increased with COC use (Plu-Bureau 2013). However, the review only included studies that were set up after 1990 and only assessed preparations containing low doses of estrogen, third generation progestagens (in which norgestimate was included) or progestin-only contraceptives, making the two reviews incomparable. Four previous meta-analyses, two on the risk of myocardial infarction or ischemic stroke (Baillargeon 2005; Peragallo-Urrutia 2013), one on the risk of myocardial infarction alone (Khader 2003) and one on the risk of ischemic stroke alone (Gillum 2000), similarly found an increased risk in combined oral contraception users compared with non-users. However, the inclusion criteria for these studies were less strict than for our current meta-analysis, e.g. defining COC use within the past year as current use, including studies with non-incident arterial events, analyzing studies with women up to 60 years of age, and including studies that did not present crude numbers of exposed or diseased cases and controls. To our knowledge, our Cochrane Review is the first meta-analysis to assess the risk of incident myocardial infarction or ischemic stroke in women < 50 years of age who used COCs at or within one month before the date of inclusion.

AUTHORS' CONCLUSIONS

Implications for practice

As all oral contraceptive preparations are equally effective for preventing unwanted pregnancies (Hardman 2009; van Hylckama Vlieg 2009), it is important that only the safest preparations are prescribed. The results of our meta-analysis showed that the risk of myocardial infarction or ischemic stroke was 1.6-fold increased in women using COCs. The risk was highest for pills containing ≥ 50 µg of estrogen.The risk of myocardial infarction or ischemic stroke did not differ clearly between progestogen generation in combination with estrogens However, COCs are especially known to increase the risk of venous thrombosis, and this risk should be kept in mind when counselling women about their choice of contraception (de Bastos 2014).When combined with the results of studies on the risk of venous thrombosis in COC users, it is likely that the COC pill containing levonorgestrel and 30 µg of estrogen is the safest oral form of combined oral hormonal contraception.

Implications for research

The purpose of this meta-analysis was to assess the risk of myocardial infarction or ischemic stroke in women using oral forms of hormonal contraception. However, there are also a number of (newer) non-oral hormonal contraceptive preparations, such

as the levonorgestrel-releasing intrauterine device, transdermal contraceptive patches, subcutaneous hormonal implants and the vaginal ring. As yet, only a very small number of studies have assessed the risk of myocardial infarction or ischemic stroke in women using these preparations. In the coming years, information on (thrombotic) side-effects of these preparations should be collected and analysed, so that the associated risk of myocardial infarction or ischemic stroke, if any, can be quantified.

For many women, such as the women included in the studies in our meta-analysis, it is too late to prevent a first episode of myocardial infarction or ischemic stroke. However, advising women with a first myocardial infarction or ischemic stroke to discontinue the use of hormonal preparations seems important to prevent a recurrent event. To our knowledge, no studies have specifically compared the risk of recurrent myocardial infarction or ischemic stroke in women who continued or discontinued the use of oral contraceptive preparations after a first arterial event. The two studies to answer this question for venous thrombosis found that all oral hormonal preparations were associated with an increased risk of recurrent venous thrombosis compared with no hormone use (Christiansen 2005; Christiansen 2010). The only preparation that was not associated with an increased risk was the levonorgestrel-releasing intrauterine device. It is possible that the levonorgestrel-releasing intrauterine device is also a safe option for women after a first arterial thrombotic event, as, from the small amount of available research, this preparation does not seem to increase the risk of a first myocardial infarction or ischemic stroke (Lidegaard 2012b). However, large studies on women using a levonorgestrel-releasing intrauterine device need to be performed before this preparation is recommended without reservation.

ACKNOWLEDGEMENTS

We thank Carol Manion, Reference Librarian at FHI360, Durham, USA, and Jan W. Schoones, Walaeus Library, LUMC, Leiden, NL for developing the search strategies.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Adam 1981

Methods	Case-control study
Participants	139 cases/276 controls Aged 15 to 44 years
Interventions	Combined oral contraception: current, past and none use
Outcomes	Fatal myocardial infarction Events: current use 24/38, past use 35/70, none use 99/207
Notes	UK

Risk of bias

Bias	Authors' judgement	Support for judgement
Exposure ascertainment	Low risk	Myocardial infarction objectively confirmed.
Outcome assessment	Low risk	COC use objectively confirmed.
Follow-up	Unclear risk	Not applicable as this was a case-control study.
Source population	Low risk	Controls from the same source population as the cases.

Aznar 2004

Methods	Case-control study
Participants	29 cases/66 controls

Aznar 2004 *(Continued)*

	Aged 18 to 50
Interventions	Combined oral contraception: current and none use
Outcomes	Ischemic stroke Events: current use 9/8, none use 20/58
Notes	Spain

Risk of bias

Bias	Authors' judgement	Support for judgement
Exposure ascertainment	High risk	Ischemic stroke not objectively confirmed.
Outcome assessment	Low risk	COC use objectively confirmed.
Follow-up	Unclear risk	Not applicable as this was a case-control study.
Source population	High risk	Controls from a different source population to the cases.

Chang 1999

Methods	Case-control study
Participants	291 cases/736 controls Aged 20 to 44 years
Interventions	Combined oral contraception: current and none use, < 50 µg of oestrogen and ≥ 50 µg of oestrogen
Outcomes	Ischemic stroke Events: current use 19/42, none use 41/146, <50 µg 10/28, ≥ 50 µg 9/14
Notes	UK, Germany, Hungary, Serbia and Slovenia

Risk of bias

Bias	Authors' judgement	Support for judgement
Exposure ascertainment	High risk	Ischemic stroke not objectively confirmed.
Outcome assessment	Low risk	COC use objectively confirmed.
Follow-up	Unclear risk	Not applicable as this was a case-control study.
Source population	High risk	Controls from a different source population to the cases.

Dunn 1999

Methods	Case-control study

Dunn 1999 *(Continued)*

Participants	448 cases/1728 controls Aged 16 to 44
Interventions	Combined oral contraception: current and none use, 2nd generation (norethisterone acetate or levonorgestrel), norethisteron acetate, levonorgestrel, 3rd generation (desogestrel or gestodene), desogestrel, gestodene
Outcomes	Myocardial infarction Events: current use 40/180, none use 386/1467, 2nd generation 20/119, levonorgestrel 18/105, norethisterone acetate 2/14, 3rd generation 20/61, desogestrel 9/37, gestodene 11/24
Notes	UK

Risk of bias

Bias	Authors' judgement	Support for judgement
Exposure ascertainment	Low risk	COC use objectively confirmed.
Outcome assessment	Low risk	COC use not objectively confirmed.
Follow-up	Unclear risk	Not applicable as this was a case-control study.
Source population	Low risk	Controls from the same source population as the cases.

Heinemann 1998

Methods	Case-control study
Participants	220 cases/775 controls Ages 16 to 44
Interventions	Combined oral contraception: current and none use, 1st generation, 2nd generation, 3rd generation
Outcomes	Ischemic stroke Events during: current use 124/182, none use 96/257, 1st generation 15/23, 2nd generation 58/97, 3rd generation 45/54
Notes	UK, Germany, France, Switzerland and Austria

Risk of bias

Bias	Authors' judgement	Support for judgement
Exposure ascertainment	Low risk	COC use objectively confirmed.
Outcome assessment	Low risk	Ischemic stroke objectively confirmed.
Follow-up	Unclear risk	Not applicable as this was a case-control study.
Source population	Low risk	Controls from the same source population as the cases.

Jick 1978

Methods	Case-control study
Participants	26 cases/59 controls Aged < 46 years
Interventions	Combined oral contraception: current, past and none use
Outcomes	Myocardial infarction Events: current use 20/14, past use 4/16, none use 6/45
Notes	USA

Risk of bias

Bias	Authors' judgement	Support for judgement
Exposure ascertainment	High risk	COC use not objectively confirmed.
Outcome assessment	Low risk	Myocardial infarction objectively confirmed.
Follow-up	Unclear risk	Not applicable as this was a case-control study.
Source population	High risk	Controls from a different source population to the cases.

Kemmeren 2002

Methods	Case-control study
Participants	203 cases/925 controls Aged 18 to 49 years
Interventions	Combined oral contraception: current use, none use, 1st generation, 2nd generation, 3rd generation
Outcomes	Ischemic stroke Events: current use 102/348, none use 101/568, 1st generation 7/31, 2nd generation 52/173, 3rd generation 32/110
Notes	The Netherlands

Risk of bias

Bias	Authors' judgement	Support for judgement
Exposure ascertainment	High risk	COC use not objectively confirmed
Outcome assessment	Low risk	Ischemic stroke objectively confirmed.
Follow-up	Unclear risk	Not applicable as this was a case-control study.

Kemmeren 2002 *(Continued)*

Source population	Low risk	Controls from the same source population as the cases.

Krueger 1980

Methods	Case-control study
Participants	75 cases/326 controls Aged 15 to 44 years
Interventions	Combined oral contraception: current and none use
Outcomes	Fatal myocardial infarction Events: current use 12/34, none use 63/292
Notes	USA

Risk of bias

Bias	Authors' judgement	Support for judgement
Exposure ascertainment	High risk	COC use not objectively confirmed
Outcome assessment	Low risk	Myocardial infarction objectively confirmed.
Follow-up	Unclear risk	Not applicable as this was a case-control study.
Source population	High risk	Controls from a different source population to the cases.

La Vecchia 1987

Methods	Case-control study
Participants	52 cases/91 controls Aged < 45 years
Interventions	Combined oral contraception: current, past and none use
Outcomes	Myocardial infarction Events: current use 3/6, past use 15/12, none use 49/85
Notes	Italy

Risk of bias

Bias	Authors' judgement	Support for judgement
Exposure ascertainment	High risk	COC use not objectively confirmed
Outcome assessment	Low risk	Myocardial infarction objectively confirmed.

La Vecchia 1987 *(Continued)*

Follow-up	Unclear risk	Not applicable as this was a case-control study.
Source population	High risk	Controls from a different source population to the cases.

Lewis 1997

Methods	case-control study
Participants	75 cases/326 controls Aged 16 to 44 years
Interventions	Combined oral contraception: current use, none use, 1st generation, 2nd generation, 3rd generation, levonorgestrel
Outcomes	Myocardial infarction Events: current use 57/89, none use 125/272, 1st generation 14/14, 2nd generation 27/35, 3rd generation 8/33, levonorgestrel 22/29
Notes	UK, Germany, France, Switzerland, Austria

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Exposure ascertainment	Low risk	COC use objectively confirmed,
Outcome assessment	Low risk	Myocardial infarction objectively confirmed.
Follow-up	Unclear risk	Not applicable as this was a case-control study.
Source population	Low risk	Controls from the same source population as the cases.

Lidegaard 2012a

Methods	Cohort study
Participants	5036 events/9,336,662 person years Aged 15 to 49 years
Interventions	Combined oral contraception: current use, none use, 1st generation, 2nd generation, 3rd generation, 20 µg oestrogen, 30 to 49 µg oestrogen, ≥ 50 µg oestrogen, levonorgestrel, norethindrone, norgestimate, desogestrel, gestodene, drospirenone, cyproterone acetate
Outcomes	Myocardial infarction and ischemic stroke Events: current use 1548/4,528,151, none use 3488/9,336,662, 1st generation 62/170,218, 2nd generation 303/515,033, 3rd generation 920/3,345,929, levonorgestrel 303/515,033, norethindrone 62/170,218, norgestimate 106/453,536, desogestrel 287/1,009,163, gestodene 527/1,883,230, drospirenone 70/286,770, cyproterone acetate 41/187,145.

Lidegaard 2012a *(Continued)*

Notes	Denmark

Risk of bias

Bias	Authors' judgement	Support for judgement
Exposure ascertainment	Low risk	COC use objectively confirmed.
Outcome assessment	High risk	Information on myocardial infarction and ischemic stroke obtained from a diagnostic registry
Follow-up	Low risk	No loss to follow up.
Source population	Unclear risk	Not applicable as this was a population study.

MacClellan 2007

Methods	Case-control study
Participants	386 cases/614 controls Aged 15 to 49 years
Interventions	Combined oral contraception: current use and none use
Outcomes	Ischemic stroke Events: current use 48/64, none use 338/550
Notes	USA

Risk of bias

Bias	Authors' judgement	Support for judgement
Exposure ascertainment	High risk	COC use not objectively confirmed.
Outcome assessment	Low risk	Ischemic stroke objectively confirmed.
Follow-up	Unclear risk	Not applicable as this was a case-control study.
Source population	Low risk	Controls from the same source population as the cases.

Mann 1975a

Methods	Case-control study
Participants	153 cases/196 controls Aged 15 to 49 years
Interventions	Combined oral contraception: current, past and none use

Mann 1975a *(Continued)*

Outcomes	Fatal myocardial infarction Events: current use 31/19, past use 10/20, none use 114/162
Notes	UK

Risk of bias

Bias	Authors' judgement	Support for judgement
Exposure ascertainment	High risk	COC use not objectively confirmed.
Outcome assessment	Low risk	Myocardial infarction objectively confirmed.
Follow-up	Unclear risk	Not applicable as this was a case-control study.
Source population	High risk	Controls from a different source population to the cases.

Mann 1975b

Methods	Case-control study
Participants	49 cases/166 controls Aged 15 to 49 years
Interventions	Combined oral contraception: current, past and none use
Outcomes	Non-fatal myocardial infarction Events: current use 20/16, past use 8/24, none use 52/174
Notes	UK

Risk of bias

Bias	Authors' judgement	Support for judgement
Exposure ascertainment	High risk	COC use not objectively confirmed.
Outcome assessment	Low risk	Myocardial infarction objectively confirmed.
Follow-up	Unclear risk	Not applicable as this was a case-control study.
Source population	High risk	Controls from a different source population to the cases.

Mann 1976a

Methods	Case-control study
Participants	54 cases/54 controls Aged 40 to 44 years

Mann 1976a *(Continued)*

Interventions	Combined oral contraception: current, past and none use
Outcomes	Fatal myocardial infarction Events: current use 10/5, past use 8/5, none use 44/45
Notes	UK

Risk of bias

Bias	Authors' judgement	Support for judgement
Exposure ascertainment	High risk	COC use not objectively confirmed.
Outcome assessment	Low risk	Myocardial infarction objectively confirmed.
Follow-up	Unclear risk	Not applicable as this was a case-control study.
Source population	High risk	Controls from a different source population to the cases.

Martinelli 2006

Methods	Case-control study
Participants	105 cases/293 controls Aged < 50 years
Interventions	Combined oral contraception: current and none use
Outcomes	Ischemic stroke Events: current use 43/67, none use 62/226
Notes	Italy

Risk of bias

Bias	Authors' judgement	Support for judgement
Exposure ascertainment	High risk	COC use not objectively confirmed.
Outcome assessment	Low risk	Ischemic stroke objectively confirmed.
Follow-up	Unclear risk	Not applicable as this was a case-control study.
Source population	Low risk	Controls from the same source population as the cases.

Nightingale 2004

Methods	Case-control study
Participants	190 cases/1129 controls

Nightingale 2004 *(Continued)*

	Aged < 50 years
Interventions	Combined oral contraception: current and none use
Outcomes	Ischemic stroke Events: current use 19/80, none use 171/1049
Notes	UK

Risk of bias

Bias	Authors' judgement	Support for judgement
Exposure ascertainment	Low risk	COC use objectively confirmed.
Outcome assessment	High risk	Ischemic stroke not objectively confirmed.
Follow-up	Unclear risk	Not applicable as this was a case-control study.
Source population	Low risk	Controls from the same source population as the cases.

Owen-Smith 1998

Methods	Case-control study
Participants	103 cases/309 controls Average age 29 years
Interventions	Combined oral contraception: current, past and none use
Outcomes	Myocardial infarction Events: current use 8/13, past use 57/140, none use 95/296
Notes	UK

Risk of bias

Bias	Authors' judgement	Support for judgement
Exposure ascertainment	High risk	COC use not objectively confirmed.
Outcome assessment	High risk	Myocardial infarction not objectively confirmed.
Follow-up	Unclear risk	Not applicable as this was a case-control study.
Source population	Low risk	Controls from the same source population as the cases.

Pettiti 1996

Methods	Case-control study

Pettiti 1996 *(Continued)*

Participants	142 cases/378 controls Aged 15 to 44 years
Interventions	Combined oral contraception: current, past and none use
Outcomes	Ischemic stroke Events: current use 17/43, past use 82/271, none use 125/335
Notes	USA

Risk of bias

Bias	Authors' judgement	Support for judgement
Exposure ascertainment	High risk	COC use not objectively confirmed.
Outcome assessment	Low risk	Ischemic stroke objectively confirmed.
Follow-up	Unclear risk	Not applicable as this was a case-control study.
Source population	Low risk	Controls from the same source population as the cases.

Pezzini 2007

Methods	Case-control study
Participants	108 cases/216 controls Aged < 45 years
Interventions	Combined oral contraception: current and none use
Outcomes	Ischemic stroke Events: current use 43/31, none use 65/185
Notes	Italy

Risk of bias

Bias	Authors' judgement	Support for judgement
Exposure ascertainment	High risk	COC use not objectively confirmed.
Outcome assessment	Low risk	Ischemic stroke objectively confirmed.
Follow-up	Unclear risk	Not applicable as this was a case-control study.
Source population	High risk	Controls from a different source population to the cases.

Rosenberg 1976a

Methods	Case-control study
Participants	33 cases/1096 controls Aged 37 to 49 years
Interventions	Combined oral contraception: current and none use
Outcomes	Myocardial infarction Events: current use 4/75, none use 29/1021
Notes	USA, UK, New Zealand, Canada, Germany, Italy and Israel

Risk of bias

Bias	Authors' judgement	Support for judgement
Exposure ascertainment	High risk	COC use not objectively confirmed.
Outcome assessment	High risk	Myocardial infarction not objectively confirmed.
Follow-up	Unclear risk	Not applicable as this was a case-control study.
Source population	High risk	Controls from a different source population to the cases.

Rosenberg 2001

Methods	Case-control study
Participants	627 cases/2947 controls Aged < 45 years
Interventions	Combined oral contraception: current use, past use, none use, 30 to 49 µg oestrogen, ≥ 50 µg oestrogen, norethindrone, levonorgestrel, desogestrel/norgestimate
Outcomes	Myocardial infarction Events: current use 36/237, past use 412/1926, none use 591/2710, 30 to 49 µg oestrogen 13/108, ≥ 50 µg oestrogen 4/20, norethindrone 11/68, levonorgestrel 4/42, desogestrel/norgestimate 2/15
Notes	USA

Risk of bias

Bias	Authors' judgement	Support for judgement
Exposure ascertainment	High risk	COC use objectively confirmed.
Outcome assessment	Low risk	Myocardial infarction objectively confirmed.
Follow-up	Unclear risk	Not applicable as this was a case-control study.
Source population	High risk	Controls from a different source population to the cases.

Schwartz 1997

Methods	Case-control study
Participants	60 cases/485 controls Aged 18 to 44 years
Interventions	Combined oral contraception: current use, past use, none use, norethindrone, norgestrel
Outcomes	Ischemic stroke Events: current use 6/46, past use 39/363, none use 52/424, norethindrone 4/32, norgestrel 1/14
Notes	USA

Risk of bias

Bias	Authors' judgement	Support for judgement
Exposure ascertainment	High risk	COC use not objectively confirmed.
Outcome assessment	High risk	Ischemic stroke not objectively confirmed.
Follow-up	Unclear risk	Not applicable as this was a case-control study.
Source population	High risk	Controls from a different source population to the cases.

Shapiro 1979

Methods	Case-control study
Participants	234 cases/1742 controls Aged 25 to 49 years
Interventions	Combined oral contraception: < 50 µg oestrogen, 50 µg oestrogen, > 50 µg oestrogen
Outcomes	Myocardial infarction Events: < 50 µg oestrogen 8/39, 50 µg oestrogen 16/78, > 50 µg oestrogen 2/11
Notes	USA

Risk of bias

Bias	Authors' judgement	Support for judgement
Exposure ascertainment	High risk	COC use not objectively confirmed.
Outcome assessment	Low risk	Myocardial infarction objectively confirmed.
Follow-up	Unclear risk	Not applicable as this was a case-control study.
Source population	High risk	Controls from a different source population to the cases.

Sidney 1998

Methods	Case-control study
Participants	271 cases/993 controls Aged 18 to 44 years
Interventions	Combined oral contraception: current use, past use, none use, norethindrone, norgestrel, < 50 µg oestrogen, ≥ 50 µg oestrogen
Outcomes	Myocardial infarction Events: current use 12/87, past use 214/769, none use 41/135, norethindrone 8/52, norgestrel 3/24, < 50 µg oestrogen 9/78, > 50 µg oestrogen 2/5
Notes	USA

Risk of bias

Bias	Authors' judgement	Support for judgement
Exposure ascertainment	High risk	COC use not objectively confirmed.
Outcome assessment	High risk	Myocardial infarction not objectively confirmed.
Follow-up	Unclear risk	Not applicable as this was a case-control study.
Source population	Low risk	Controls from the same source population as the cases.

Slone 1981

Methods	Case-control study
Participants	234 cases/1742 controls Aged 25 to 49 years
Interventions	Combined oral contraception: current use, past use and none use
Outcomes	Myocardial infarction Events: current use 41/51, past use 206/762, none use 556/2036
Notes	USA

Risk of bias

Bias	Authors' judgement	Support for judgement
Exposure ascertainment	High risk	COC use not objectively confirmed
Outcome assessment	Low risk	Myocardial infarction objectively confirmed.
Follow-up	Unclear risk	Not applicable as this was a case-control study.

Slone 1981 *(Continued)*

Source population	High risk	Controls from a different source population to the cases.

Tanis 2001

Methods	Case-control study
Participants	249 cases/925 controls Aged 18 to 49 years
Interventions	Combined oral contraception: current use, none use, 1st generation, 2nd generation, 3rd generation
Outcomes	Myocardial infarction Events: current use 99/348, none use 146/568, 1st generation 11/31, 2nd generation 59/173, 3rd generation 20/110
Notes	The Netherlands

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Exposure ascertainment	High risk	COC use not objectively confirmed.
Outcome assessment	Low risk	Myocardial infarction objectively confirmed.
Follow-up	Unclear risk	Not applicable as this was a case-control study.
Source population	Low risk	Controls from the same source population as the cases.

Tzourio 1995

Methods	Case-control study
Participants	75 cases/173 controls Aged < 49 years
Interventions	Combined oral contraception: current use, past use, none use, 20 µg oestrogen, 30 to 49 µg oestrogen, 50 µg oestrogen
Outcomes	Ischemic stroke Events: current use 47/63, past use 19/85, none use 25/110, 20 µg oestrogen 2/5, 30 to 49 µg oestrogen 30/46, 50 µg oestrogen 8/7
Notes	France

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Tzourio 1995 *(Continued)*

Exposure ascertainment	High risk	COC use not objectively confirmed.
Outcome assessment	Low risk	Ischemic stroke objectively confirmed.
Follow-up	Unclear risk	Not applicable as this was a case-control study.
Source population	High risk	Controls from a different source population to the cases.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Adachi 2005	No extractable number of exposed and non-exposed cases/controls.
Ananijević-Pandey 1989	No extractable number of exposed and non-exposed cases/controls.
Andersson 2012	RATIO study, data included elswhere (Tanis 2001; Kemmeren 2002).
Arscott 2001	Same data as Dunn 1999.
Azarpazhooh 2008	No extractable number of exposed and non-exposed cases/controls.
Barinagarrementeria 1998	Arteritis included as ischemic stroke.
Beaumont 1986	No control group.
Berheci 1975	Review.
Bonnar 1986	Review.
Borovská 1981	Case series.
Burnhill 1999	Included progestagen-only contraceptives.
Chang 1986	Not possible to distinguish between current and ever users.
Chasan-Taber 2001	Editorial.
Chen 2001	Unattainable.
Colditz 1986	Not possible to distinguish between current and ever users.
Collaborative Group for the Study of Stroke 1973	Transient ischemic attack (TIA) included as ischemic stroke.
Corfman 1974	Editorial.
Croft 1989	Not possible to distinguish between current and ever users.
D'Avanzo 1994	Same data as La Vecchia 1987.
Dalen 1981	Review.

Study	Reason for exclusion
Elagib 2008	No extractable number of exposed and non-exposed cases/controls.
Farley 1998	Simulated data.
Fortney 1986	Review.
Gronich 2011	Study on risk of venous thrombosis.
Haapaniemi 1997	Women up to 60 years of age included.
Hannaford 1998	Same data as Owen-Smith 1998.
Heinemann 1997	Current COC use defined as within 3 months before inclusion.
Heinemann 1999	Same data as Heinemann 1998.
Heyman 1969	No extractable number of exposed and non-exposed cases/controls.
Heyman 1972	No control subjects included.
Huang 2014	No upper age limit: average age was 58 in both cases and controls.
Jain 1976	No extractable number of exposed and non-exposed cases/controls.
Jain 1977	Meta-analysis.
Jensen 1991	No extractable number of exposed and non-exposed cases/controls.
Jick 1978b	No control subjects included.
Jick 1996	No extractable number of exposed and non-exposed cases/controls.
Jick 2007	Same data as Jick 1978.
Jugdutt 1983	Case series.
Kisjanto 2005	No extractable number of exposed and non-exposed cases/controls.
Lewis 1996	Study on postmenopausal hormone therapy.
Lewis 1997b	Same data as Lewis 1997.
Li 2002	Intrauterine device as reference group.
Li 2006	Risk of hemorrhagic stroke.
Li 2010	Intrauterine device as reference group.
Lidegaard 1986	TIA and cerebral apoplexy included as ischemic stroke.
Lidegaard 1998a	TIA and cerebral apoplexy included as ischemic stroke.
Lidegaard 1998b	TIA and cerebral apoplexy included as ischemic stroke.
Lidegaard 1999	No extractable number of exposed and non-exposed cases/controls.

Study	Reason for exclusion
Lidegaard 2001	Review.
Lui 2003	Data included elsewhere (Shapiro 1979).
Maguire 1979	Thrombosis defined as arterial or venous thrombosis.
Mann 1975c	Same data as Mann 1975b.
Mann 1976b	Review.
Mant 1987	Progestagen-only preparations included as COC.
Mant 1998	Current use defined as use within past 12 months.
Margolis 2007	Current use defined as use within past 12 months.
Matias-Guiu 1990	Unclear stroke definition.
Matthews 1989	Review.
Meinel 1988	Thrombosis defined as arterial or venous thrombosis.
Parazzini 1991	Women up to 55 years of age included.
Porter 1982	Ischemic stroke and hemorrhagic stroke combined.
Porter 1985	Ischemic stroke and hemorrhagic stroke combined.
Poulter 1996	Methodological study.
Poulter 1999	Current use defined as within previous 3 months.
Presl 1976	Translated summary of Mann 1975a.
Pruissen 2008	RATIO study, data included elsewhere (Tanis 2001; Kemmeren 2002).
Psaty 1994	Study on postmenopausal hormone therapy.
Riedel 1993	Commentary.
Rosenberg 1976b	Same data as Rosenberg 1976a.
Rosenberg 1980	Women up to age 64 included.
Rosenberg 1990	Same data as Rosenberg 1976a and Rosenberg 2001.
Royal College of General Practitioners 1983	No extractable number of exposed and non-exposed women.
Salobir 2003	Follow-up study of patients with arterial thrombosis.
Salobir 2004	No risk of arterial thrombosis calculated for oral contraception users.
Salonen 1982	No extractable number of exposed and non-exposed cases.

Study	Reason for exclusion
Salvesen 2000	Review.
Schoenberg 1970	No extractable number of exposed and non-exposed cases.
Schwartz 1998	Same data as Schwartz 1997.
Sidney 1996	Same data as Sidney 1998.
Siegerink 2010	RATIO Study (Tanis 2001; Kemmeren 2002).
Siegerink 2011a	RATIO Study (Tanis 2001; Kemmeren 2002).
Siegerink 2011b	RATIO Study (Tanis 2001; Kemmeren 2002).
Siritho 2003	Women up to age 55 included.
Slone 1978	Same data as Slone 1981.
Slooter 2005	RATIO Study (Tanis 2001; Kemmeren 2002).
Stiefelhagen 2003	Medical quiz.
Stolley 1982	Thrombosis defined as arterial or venous thrombosis.
Sun 2004	Data on hemorrhagic stroke.
Sørensen 2002	Review.
Tanis 2003a	Review.
Tanis 2003b	RATIO Study (Tanis 2001; Kemmeren 2002).
Tanis 2004	RATIO Study (Tanis 2001; Kemmeren 2002).
Thompson 1989	No extractable number of exposed and non-exposed women.
Thorogood 1991	Non-incident myocardial infarction included.
Urbanus 2009	RATIO Study (Tanis 2001; Kemmeren 2002).
Vessey 1969	No extractable number of exposed and non-exposed women.
Wang 2012	Same data as Li 2006.
WHO 1995	Description of background, pilot study, methods and the analyses carried out to validate the methods used in the study.
WHO 1996a	Current use defined as within previous 3 months.
WHO 1996b	Study on hemorrhagic stroke.
WHO 1997	Current use defined as within previous 3 months.
WHO 1998	Progestagen-only preparations and combined injectable contraceptives included.

Study	Reason for exclusion
Yang 2009	Current use defined as within previous 12 months.
Zamorski 1996	Summary of Pettiti 1996.

ADDITIONAL TABLES

Table 1. Type of outcome in included studies

Study	Publication year	Study design	Outcome[a]
Adam 1981.	1981	Case control	Myocardial infarction
Aznar 2004	2004	Case control	Ischemic stroke
Chang 1999	1999	Case control	Ischemic stroke
Dunn 1999	1999	Case control	Myocardial infarction
Heinemann 1998/Lewis 1997.	1998/1997	Case control	Both
Jick 1978	1978	Case control	Myocardial infarction
Kemmeren 2002/Tanis 2001	2002/2001	Case control	Both
Krueger 1980	1981	Case control	Myocardial infarction
La Vecchia 1987	1987	Case control	Myocardial infarction
Lidegaard 2012a	2012	Cohort	Both
MacClellan 2007.	2007	Case control	Ischemic stroke
Mann 1975a/Mann 1975b	1975/1976	Case control	Myocardial infarction
Mann 1975b	1975	Case control	Myocardial infarction
Martinelli 2006	2006	Case control	Ischemic stroke
Nightingale 2004	2004	Nested case control	Ischemic stroke
Owen-Smith 1998	1998	Case control	Ischemic stroke
Pettiti 1996	1997	Case control	Ischemic stroke
Pezzini 2007	2007	Case control	Ischemic stroke
Rosenberg 1976a	1976	Case control	Myocardial infarction
Rosenberg 2001	2001	Case control	Myocardial infarction

Table 1. Type of outcome in included studies *(Continued)*

Schwartz 1997	1998	Case control	Ischemic stroke
Sidney 1998	1998	Case control	Myocardial infarction
Shapiro 1979/Slone 1981	1981/1981	Case control	Myocardial infarction
Tzourio 1995	1995	Case control	Ischemic stroke

[a]Denotes both myocardial infarction and ischemic stroke.

Table 2. Included studies with data on COC generation

Study	Design	Outcome	Non-use Event (n)/ Total (n)	1st generation Event (n)/ Total (n)	2nd generation Event (n)/ Total (n)	3rd generation Event (n)/ Total (n)
Dunn 1999	Case-control	Myocardial infarction	386/1853	—	20/139	20/81
Kemmeren 2002	Case-control	Ischemic stroke	101/669	7/38	52/225	32/142
Lewis 1997	Case-control	Ischemic stroke	125/397	14/28	27/62	8/41
Lidegaard 2012a	Cohort	Both	*	*	*	*
Rosenberg 2001	Case-control	Myocardial infarction	591/3301	11/79	4/46	2/17
Schwartz 1998	Case-control	Ischemic stroke	52/476	4/36	1/15	—
Sidney 1998	Case-control	Myocardial infarction	255/1159	8/60	3/27	—
Tanis 2001	Case-control	Myocardial infarction	146/714	11/42	59/232	20/130

Abbreviations: COC: combined oral contraceptives; n: number.
1st generation: preparations containing lynestrenol or norethisterone acetate.
2nd generation: preparations containing levonorgestrel.
3rd generation: preparations containing desogestrel or gestodene.
* Adjusted effect estimates extracted

Table 3. Included studies with data on oestrogen dose

Study	Design	Outcome	Non-use Event (n)/Total (n)	20 µg E2 Event (n)/ Total (n)	30 to 49 µg E2 Event (n)/ Total (n)	≥ 50 µg E2 Event (n)/ Total (n)
Chang 1999	Case-control	Ischemic stroke	42/188	—	—	9/23
Heinemann 1998	Case-control	Ischemic stroke	96/353	—	—	15/38
Lidegaard 2012a	Cohort	Both	*	*	*	*
Rosenberg 2001	Case-control	Myocardial infarction	591/3301	—	—	4/7

Table 3. Included studies with data on oestrogen dose *(Continued)*

Shapiro 1979	Case-control	Myocardial infarction	205/1812	—	—	18/107
Sidney 1998	Case-control	Myocardial infarction	255/1159	—	—	2/7
Tzourio 1995	Case-control	Ischemic stroke	25/135	2/7	30/76	8/15

Abbreviations: µg: micrograms; E2: ethinylestradiol; n: number.
* Adjusted effect estimates extracted

Table 4. Studies including data on progestagen type

Study	Design	Outcome	Event (n)/Total (n)								
			Non-use	Norethindron	Levonorgestrel	Norethisterone acetate	Desogestrel	Gestodene	Norgestimate	Drospirenone	Cyproterone acetate
Dunn 1999	Case-control	Myocardial infarction	386/1853	—	18/123	2/16	9/46	11/35	—	—	—
Kemmeren 2002	Case-control	Ischemic stroke	101/669	—	52/225	—	—		—	—	—
Lewis 1997	Case-control	Myocardial infarction	125/397	—	8/41	—	—	—	—	—	—
Lidegaard 2012a	Cohort	Both	*	*	*	—	*	*	*	*	*
Rosenberg 2001	Case-control	Myocardial infarction	591/ 3301	11/79	4/46	—	—	—	—	—	—
Schwartz 1997	Case-control	Ischemic stroke	156/ 921	10/64	—	—	—	—	4/24	—	—
Sidney 1998	Case-control	Myocardial infarction	255/ 1159	8/60	—	—	—	—	3/27	—	—

Abbreviations: n: number.
* Adjusted effect estimates extracted

Table 5. Adjusted risk of myocardial infarction or ischemic stroke in COC users versus non-users per study

Study	Crude OR (95% CI)	Adjusted OR (95% CI)	Adjustment variables per study
Heinemann 1998	1.8 (1.3 to 2.5)	2.8 (1.8 to 4.5)	Age, hypertension, body mass index, lipid levels, diabetes, smoking, alcohol, family history of stroke, duration of COC use, study centre
La Vecchia 1987	2.1 (0.7 to 7.1)	1.8 (0.3 to 11.5)	Age, geographic area, marital status, education, social class, smoking, alcohol and coffee consumption, parity, age at menopause, diabetes, hypertension, obesity, hyperlipidemia, family history of ischemic heart disease
Martinelli 2006	2.3 (1.5 to 3.8)	2.3 (1.4 to 3.8)	Age, educational level, hypertension, hypercholesterolemia, obesity, smoking
Nightingale 2004	1.6 (0.9 to 2.9)	2.3 (1.2 to 4.6)	Heart disease, diabetes, hypertension, previous venous thrombosis, migraine, alcohol, smoking
Owen-Smith 1998	2.9 (1.0 to 8.7)	2.9 (0.9 to 9.6)	Social class, smoking status, history of hypertension
Pettiti 1996	1.0 (0.5 to 1.9)	1.2 (0.5 to 2.6)	Hypertension, diabetes, smoking, race, body mass index

Abbreviations: OR: odds ratio; COC: combined oral contraception.
For all other studies, the crude OR or the adjusted OR, or both, were not presented in the manuscript.

APPENDICES

Appendix 1. Search strategy

PubMed (http://www.ncbi.nlm.nih.gov/entrez/)

("Contraceptives, Oral"[mesh] OR "oral contraceptives" OR "oral contraceptive" OR "combined oral contraceptives" OR "combined oral contraceptive" OR ((norethisteron* OR norethindron* OR "ethynodiol diacetate" OR lynestrenol* OR norethynodrel* OR dienogest* OR levonorgestrel* OR norgestrel* OR dl-norgestrel* OR desogestrel* OR norgestimat* OR gestoden* OR "medroxyprogesterone acetate" OR "chlormadinone acetate" OR nomegestrol* OR nestoron* OR "Cyproterone acetate" OR Drospirenon* OR oestrogen*[ti] OR estrogen[ti]) AND ("Ethinyl Estradiol" OR ethinylestradiol* OR Mestranol* OR "estradiol valerate" OR progestogen*[ti]))) AND (risk* OR risk factor*) AND ("Intracranial Arterial Diseases/chemically induced"[Mesh] OR "Intracranial Arterial Diseases/epidemiology"[Mesh] OR “intracranial arterial disease”[tiab] OR "Cerebral Infarction/chemically induced"[Mesh] OR "Cerebral Infarction/epidemiology"[Mesh] OR “cerebrovascular accident”[tiab] OR “cerebral infarction”[tiab] OR "Brain Ischemia/chemically induced"[Mesh] OR "Brain Ischemia/epidemiology"[Mesh] OR “brain ischemia”[tiab] OR “brain ischaemia”[tiab] OR "Stroke/chemically induced"[Mesh] OR "Stroke/epidemiology"[Mesh] OR “acute ischemic stroke”[tiab] OR “acute ischaemic stroke”[tiab] OR “ischemic stroke”[tiab] OR “ischaemic stroke”[tiab] OR "Myocardial Infarction/chemically induced"[Mesh] OR "Myocardial Infarction/epidemiology"[Mesh] OR “myocardial infarction”[tiab])

Popline (http://www.popline.org)

(stroke OR "cerebrovascular effects" OR ischemia OR "myocardio infarction") AND ("oral contraceptive" OR "oral contraceptives") AND (clinical research OR random* OR trial*)

EMBASE (http://gateway.ovid.com/ovidweb.cgi?T=JS&MODE=ovid&NEWS=N&PAGE=main&D=emez)

("contraceptives, oral" OR "ontraceptives, oral" OR "oral contraceptives" OR "oral contraceptive" OR "combined oral contraceptives" OR "combined oral contraceptive" OR ((norethisterone OR norethisteron* OR norethindron* OR "ethynodiol diacetate" OR lynestrenol* OR norethynodrel* OR dienogest* OR levonorgestrel* OR norgestrel OR norgestrel* OR "dl-norgestrel" OR desogestrel OR desogestrel* OR norgestimate OR norgestimat* OR gestodene OR gestoden* OR "medroxyprogesterone acetate" OR "chlormadinone acetate" OR nomegestrol OR nomegestrol* OR nestorone OR nestoron* OR "cyproterone acetate" OR Drospirenone OR Drospirenon* OR oestrogen* OR estrogen) AND ("Ethinyl Estradiol" OR "Ethinyl Estradiol" OR ethinylestradiol OR ethinylestradiol* OR Mestranol OR Mestranol* OR "estradiol valerate" OR "estradiol valerate" OR progestogen*))) AND (risk OR risks OR risk factor OR risk factors) AND (“intracranial arterial disease” OR "intracranial aneurysm" OR "cerebral infarction" OR “cerebrovascular accident” OR “cerebral infarction” OR “brain ischaemia” OR stroke OR “acute ischemic stroke” OR “acute ischaemic stroke” OR “ischemic stroke” OR “ischaemic stroke” OR “myocardial infarction”)

LILACs (https://mail.lumc.nl/owa/)

(contraceptives, oral OR anticonceptivos orales OR anticoncepcionais orais) AND (intracranial arterial diseases OR Enfermedades Arteriales Intracraneales OR Doenças Arteriais Intracranianas OR cerebral infarction OR infarto cerebral OR brain ischemia OR brain ischaemia OR isquemia encefalica OR stroke OR accidente cerebrovascular OR acidente vascular cerebral OR agudo isquemia accidente cerebrovascular OR agudo isquemia acidente vascular cerebral OR myocardial infarction OR infarto miocardio OR infarto do micardio)

F E E D B A C K

Professor Øjvind Lidegaard's comment, 5 October 2015

Summary

The risk of arterial thrombosis with use of combined oral contraceptives is increased.

Roach RE, Helmerhorst FM, Lijfering WM, Stijnen T, Algra A, Dekkers OM. Combined oral contraceptives: the risk of myocardial infarction and ischemic stroke. Cochrane Database Syst Rev. 2015 Aug 27;8:CD011054.

Context

While the risk venous thrombosis with use of combined oral contraceptives (COC) is now convincingly quantified to be three to six fold increased depending mainly on the type of progestogen, studies on the risk of arterial end points are fewer and less consistent. Therefore, a meta-analysis on available evidence might be relevant.

Methods

This Cochrane review includes data from 24 studies assessing the risk of thrombotic stroke and/or myocardial infarction in women of reproductive age using COC as compared with non-users. Criteria for including and excluding studies were specified, as was information on categorising the studies’ risk of bias in ascertainment of exposure and assessment of end points.

Findings

The analysis included 23 case-control studies with together 4,631 or 48% of included events and one cohort study with 5,036 (52%) events. The meta-analysis concludes that low dose (<50 µg estrogen) COC do not confer an increased risk of neither thrombotic stroke nor myocardial infarction, that different progestogens don not confer a differential risk, but that high estrogen dose COC (50 µg estrogen) may double the risk of arterial thrombosis; RR = 2.0 (1.3-2.9).

Commentary

In a field of 24 studies with a single study accounting for more than half of the included events, it is relevant to ask, what a meta-analysis adds as compared to the one big study. First the one large cohort study assessed exposures daily through a 15-year period (1), whereas 22 of the 23 others were case-control studies assessing the exposure retrospectively (one was a nested case-control study). Next, young women suspected for thrombotic stroke or myocardial infarction are generally extensively examined, with relatively clear criteria for judging whether the event is real. Therefore, the outcome diagnoses in this age group are generally fairly valid.

The results of the cohort study nevertheless differed from the conclusion of the meta-analysis by concluding that COC conferred a significantly increased relative risk of ischemic stroke increasing from 1.6 (1.4-1.9) for COC with 20 µg estrogen over 1.8 (1.6-1.9) with 30-40 µg estrogen to 2.0 (1.5-2.7) with COC with 50 µg estrogen, the latter estimate in accordance with the meta-analysis.

Therefore, a substantial part of the 23 case-control studies must have found a protecting influence from COC on the risk of thrombotic stroke and myocardial infarction to achieve an overall relative risk of about unity. The problem is that all of the studies included in the meta-analysis have found odds ratios of thrombotic stroke with COC substantially above one, typically between two and four. Therefore the overall estimate of the risk of thrombotic stroke with use of COC in the meta-analysis is incompatible with the results of the included studies.

There are also some inconsistencies with the bias-table. According to the method section, *"Firstly, exposure to combined oral contraception had to be confirmed through a prescription database in order for the risk of bias to be classified as 'low'"* (page 4, paragraph 4). Nevertheless, the Danish cohort study with such an ascertainment was classified as a study with "high risk" of bias. The same study was classified as having a high risk of bias in the outcome assessment, despite all women in Denmark suspected for thrombotic stroke go through CT and/or MR examinations.

Implications for practice

The influence from COC on the risk of thrombotic stroke is significant and in the order of 50-100% increased for low-dose COC. There are no consistent differences according to the progestogen type. Therefore the total thrombotic risk with use of COC is mainly a result of the substantially increased risk of venous thromboembolism. Therefore women generally are advised to use COC with 1st or 2nd generation progestogens, that is with norethisterone, levonorgestrel, or norgestimate, with the lowest possible dose of estrogen.

Reference

Lidegaard Ø, Løkkegaard E, Jensen A, Skovlund CW,Keiding N. Thrombotic stroke and myocardial infarction with hormonal contraception. *New England Journal of Medicine* 2012;**366**(24):2257–66.

Commentator details

Name: Øjvind Lidegaard, clinical Professor in Obstetrics & Gynaecology

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Reply

Fra: F.M.Helmerhorst@lumc.nl [mailto:F.M.Helmerhorst@lumc.nl]
Sendt: 5. Oktober 2015 19:39
Til: Øjvind Lidegaard
Cc: R.E.J.Roach@lumc.nl; W.M.Lijfering@lumc.nl; A.Algra@umcutrecht.nl; O.M.Dekkers@lumc.nl
Emne: BMJ

Dear Dr Lidegaard, dear Øjvind

Many thanks again for your renewed interest in our paper. We agree that your NEJM paper indeed is crucial in our review.

Our network meta-analysis was based on raw data, and there were two reasons for this. The first reason was the theoretical consideration that confounding is generally not an issue when studying side-effects (Golder Plos Med 2011). The second reason for including only raw data is technical, i.e. due to the nature of a network analysis.

For these two reasons, we extracted the unadjusted rates from your article and included them in our analyses. The main difference with other studies is that your paper did not adjust for age by design (matching). Interestingly, the unadjusted rate ratios in your paper are often below 1.0, in contrast to the adjusted ratios. Your results bear a considerable weight in the meta-analyses which shifts the results towards the 1.0. So, the crucial issue is about confounding. It would be very helpful to this discussion if you could share data only adjusted for age. In our opinion, this is the only relevant confounding factor. If the age adjusted risk estimates are close to your overall adjusted estimates, we may have to reconsider some of the analyses presented.

On behalf of the team,

Frans M. Helmerhorst

Dept Clinical Epidemiology, Leiden University Medical Center

From: Øjvind Lidegaard [mailto:lidegaard@dadlnet.dk]
Sent: 05 October 2015 23:25
To: Helmerhorst, F.M. (EPI)
Cc: Roach, R.E.J. (COASS); Lijfering, W.M. (EPI); A.Algra@umcutrecht.nl; Dekkers, O.M. (EPI)
Subject: SV: BMJ

Dear Frans, dear all.

Thanks for your rapid response.

Our analysis includes all Danish women in the relevant age group. Use of hormonal

contraception is high in young ages, whereas thrombotic events, especially arterial thrombosis increases exponentially with increasing age. An analysis not adjusting for age will - therefore - certainly bring heavily age-confounded results, and therefore also - in my opinion - meaningless results. Of course an analysis not adjusted for age will bring about severely underestimated results due to the very screwed opposite development in use of contraception and incidence rate of thrombosis with increasing age.

So any analysis on this issue should always be adjusted for age, unless you match for age in the design, which we did not, and which many of the included case-control studies did neither.

Best regards

Øjvind

Øjvind Lidegaard

Professor, DMSc

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Emne: RE: BMJ

Dear Øjvind

After your critical comment for which we thank you very much indeed, we have to work.

Based on your comment we plan the following:

1. Redo the overall analysis ‘use vs non-use’ based on adjusted effect estimates

2. Redo the analyses per generation based on standard meta-analytic techniques using adjusted estimates

3. Rethink whether and how to adapt the network meta-analysis on pill type. Here the network approach is preferred, and confounding might not be a huge issue when comparing pill types.

Plan 1 and 2 can be implemented soon, and will hopefully lead to a revised Cochrane manuscript in 2-3 weeks.

From: Øjvind Lidegaard [mailto:lidegaard@dadlnet.dk]
Sent: 13 October 2015 15:14
To: Helmerhorst, F.M. (EPI)
Cc: Dekkers, O.M. (EPI); Roach, R.E.J. (COASS); Lijfering, W.M. (EPI); A.Algra@umcutrecht.nl
Subject: SV: BMJ

Dear Frans (dear all).

I think 1. and 2. are straight forward.

About 3: As long as case-control studies take cases and controls from about the same time period, and as long as they age match, it will probably be feasible to conduct a network analyses as you describe.

But if cases and controls are not matched on age, and if cases and controls are from different times, it will be crucial to adjust for both age and calendar year.

As you can find product specific adjusted estimates in the Danish NEJM publication, my suggestion is to apply these adjusted estimates also in the network model. This is because the different products were on the market at different times during a long study period, and because the age distribution of users of different product types are actually rather different. THerefore crude figures for also comparison between different product groups will be substantially confounded by age but also by year.

Best regards

Øjvind

Øjvind Lidegaard

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Contributors

dr O. Lidegaard, dr A.Algra, dr O.M. Dekkers, dr F.M.Helmerhorst, dr W.M. Lijfering, dr R.E.J. Roach.

Feedback via Wiley, 31 January 2018

Summary

On January 31, 2018 the review group received comments from Wiley. The review group worked with authors to resolve the comment and update the review.

Original comment from Wiley:

The original comment from Wiley was: “I believe that the concluding phrase in your review of the risk of MI and Stroke in patients on COCs is open to misinterpretation. 'This meta-analysis showed that the risk of myocardial infarction or ischemic stroke was 1.6-fold increase in women using COCs. The risk was highest for pills with > 50 microgram estrogen. When combined with the results of studies on the risk of venous thrombosis in COC users, it seems that the COC pill containing levonorgestrel and 30 µg of estrogen is the safest oral form of hormonal contraception' The concluding phrase could be interpreted as meaning that the COC is safer than a POP.”

Reply

Review group worked with review authors to address the comment changing the sentence to: COC pill containing levonorgestrel and 30 µg of estrogen is the safest oral form of *combined oral* hormonal contraception?

Contributors

Jeanne-Marie Guise, MD, MPH helped the review authors to address the comment

WHAT'S NEW

Date	Event	Description
28 February 2018	Feedback has been incorporated	Feedback received from Wiley prompted the authors and review group to edit the following sentence throughout the review: COC pill containing levonorgestrel and 30 µg of estrogen is the safest oral form of *combined oral* hormonal contraception?

HISTORY

Protocol first published: Issue 3, 2014
Review first published: Issue 8, 2015

Date	Event	Description
14 February 2016	Amended	typo's changed, final check up.
15 November 2015	Feedback has been incorporated	See Feedback 1 1. Redo the overall analysis ‘use vs non-use’ based on adjusted effect estimates. 2. Redo the analyses per generation based on standard meta-analytic techniques using adjusted estimates.

Date	Event	Description
		We abandoned therefore the network meta-analysis as presented in the first version of this review. Conclusion adapted accordingly.

CONTRIBUTIONS OF AUTHORS

REJR, OMD and FMH developed the study design. TS provided statistical expertise. AA and WML provided clinical expertise. REJR drafted the protocol. OMD and FMH edited the protocol. REJR and FMH independently selected the publications and extracted the data. REJR interpreted the data and drafted the manuscript. FMH, OMD, TS, AA and WML critically reviewed drafts of the manuscript.

DECLARATIONS OF INTEREST

REJR declares no conflict of interest.

FMH declares no conflict of interest.

WML declares no conflict of interest.

TS declares no conflict of interest.

AA declares no conflict of interest.

OMD declares no conflict of interest.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Netherlands Heart Foundation, Netherlands.

  Dr Willem Lijfering is a postdoctoral researcher for the Netherlands Heart Foundation (2011T012). This organization did not play a role in the design and conduct of this study; collection, management, analysis, and interpretation of the data; or preparation, review, or approval of the manuscript.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

During data extraction we noticed that the age cut-off for women included in the analyses differed per study. Some studies had an upper age limit of 45 years, whereas other studies had an upper limit of 60 or no upper age limit at all. In this review, we chose to include (mostly) pre-menopausal women, and so chose an age cut-off of 50 years. We did this by including studies that included women up to 50 years of age, and, where possible, also by extracting data on women < 50 years from studies that included older women.

In the protocol, Roach 2014, we stated that we would assess the risk of myocardial infarction or ischemic stroke for first, second and third generation contraceptive preparations in our analysis on COC generation, and also for preparations containing drospirenone. In the review we have now added cyproterone acetate to this sentence, as this is also a commonly used type of progestagen that cannot be assigned to a generation.

Information on how each generation of COC pill was classified was not present in the protocol 'Methods' section. This information is important as oral contraceptive generations can be classified in more than one way. We have added the definitions to the Types of interventions section.

We aimed to investigate the risk of reporting bias in a funnel plot. However, as our review included various different types of analysis (overall risk, and risk according to generation, estrogen dose and progestagen type), and four different types of bias were assessed along with confounding, making a funnel plot was not feasible. Instead, we presented the risk of bias in the review text, a 'Risk of bias' table and a 'Risk of bias' summary figure.

INDEX TERMS

Medical Subject Headings (MeSH)

Case-Control Studies; Cohort Studies; Contraceptives, Oral, Combined [*adverse effects]; Estrogens [administration & dosage] [*adverse effects]; Myocardial Infarction [*chemically induced]; Observational Studies as Topic; Progestins [administration & dosage] [*adverse effects]; Risk Assessment; Stroke [*chemically induced]

MeSH check words

Female; Humans