Oral Contraceptive Pill Use and the Risk of Stroke
-A Meta-Analysis of Observational Studies

By

WEE-SHIAN CHAN

A Thesis submitted in conformity with the requirements for the degree of Masters of Science
Graduate Department of Community Health
University of Toronto
2000

©Copyright by Wee-Shian Chan, 2000.
The author has granted a non-exclusive licence allowing the National Library of Canada to reproduce, loan, distribute or sell copies of this thesis in microform, paper or electronic formats.

L’auteur a accordé une licence non exclusive permettant à la Bibliothèque nationale du Canada de reproduire, prêter, distribuer ou vendre des copies de cette thèse sous la forme de microfiche/film, de reproduction sur papier ou sur format électronique.

The author retains ownership of the copyright in this thesis. Neither the thesis nor substantial extracts from it may be printed or otherwise reproduced without the author’s permission.

L’auteur conserve la propriété du droit d’auteur qui protège cette thèse. Ni la thèse ni des extraits substantiels de celle-ci ne doivent être imprimés ou autrement reproduits sans son autorisation.
Abstract


Wee-Shian Chan
Masters of Science, 2000
Graduate Department of Community Health
University of Toronto

The oral contraceptive pill (OCP) is common and effective form of birth control for women worldwide. Ever since its introduction in the 1960s, use of OCP was reported to be associated with increased stroke risk. However, with formulation changes in OCP over the last four decades the association with stroke risk required evaluation.

In this thesis, a meta-analysis was conducted to investigate if current use of low-dose OCP was associated with increased stroke risk. After pooling all available observational studies, the risk of stroke was found to be increased with current use of low-dose OCP. In particular, this risk increase was significant for thrombotic strokes, but not for hemorrhagic strokes or stroke deaths. There were however aspects of study design and study quality that might influence the pooled effect estimate, like the use of hospital- versus community-based controls, use of various comparison groups (never versus past users).

When one is counseling women with regards to OCP use, the potential small increase in absolute risk of stroke should be weighed against the tremendous benefit of the pill.
Acknowledgement

To Members of My Thesis Committee:

Dr Mary Hannah, Dr Paul Corey, Dr Laura Magee and

Dr Jeffrey S. Ginsberg

Sincere Thanks for seeing me to the end.
I. Introduction

II. Background
   A. Oral Contraceptive Pills
   B. Meta-analysis of Observational Studies
   C. Previous Systematic Reviews of OCP and Stroke
   D. Proposed Approach to the Assessment of Quality in Studies
      Investigating OCP and Stroke Risk

III. Research Question

IV. Objectives

V. Method
   A. Article Selection
   B. Data Abstraction
   C. Study Variable Definitions
   D. Statistical Model
      (i) Pooling Studies
      (ii) Comparisons Among Subgroups
   E. Publication Bias

VI. Results
   A. Retrieval of Studies
   B. Study Patient Demographics
   C. Study Quality
      (i) Design
      (ii) Definition and Verification of Stroke Outcomes
      (iii) Verification and Type of Exposure
      (iv) Comparison Groups for OCP use
      (v) Confounders
   D. Analysis
      (i) Pooling Adjusted ORs
      (ii) By Stroke Type
LIST OF FIGURES

Figure 1. Retrieval of Eligible Studies 42

LIST OF TABLES

Table 1. Characteristics of Patients in Final List of Articles for Data Abstraction 44
Table 2. Assessment of Study Quality-Design, Exposure, Outcomes and Blinding 46
Table 3. Study Handling of Confounders 48
Table 4. Articles used in the Calculation of Odds Ratios for Various Subgroups 49
Table 5. Pooled Odds Ratio From Various Studies by Exposure Type, Stroke Outcomes and Risk Factors 50

LIST OF GRAPHS

Graph 1. Plot of Reported Odds Ratio versus Year in which Study Commenced 43
Graph 2. Pooled Odds Ratios Of studies investigating all strokes and Oral Contraceptive Pill use 52
Graph 3. Pooled Odds Ratios of studies investigating thrombotic stroke and Oral Contraceptive Pill use 53
Graph 4. Pooled Odds Ratios of studies investigating hemorrhagic stroke and Oral Contraceptive Pill use 54
Graph 5. Pooled OR of studies investigating stroke deaths and Oral Contraceptive Pill use 55
Graph 6. Funnel Plot Exploring Publication Bias: Graph of Sample Size Versus Natural Logarithm of Odds Ratio 56

LIST OF APPENDICES

Appendix 1. Data Collection 57
I. Introduction

The oral contraceptive pill (OCP) is an important form of birth control for women worldwide. The use of OCP was reported to be associated with an increased risk of stroke in the literature. Since its introduction four decades ago, the OCP has undergone important formulation and dose changes and larger studies using better methodologies have been published; whether the association with stroke is still present is unknown.

The overall purpose of this thesis was to investigate, using meta-analysis, if an association exists between stroke and the OCP. As well, we investigated the impact of several aspects of study methodology on the reported effect size.

II. Background

A. Oral Contraceptive Pills

Subsequent to the introduction of the OCP in the early 1960s, a case report of stroke associated with OCP use was published [1]. Following this case report, several larger case-control studies supported the association [2-4]. Stroke is rare in young women, but the effects can be devastating. The OCP is an important form of birth control for millions of Canadians with a third of Canadian women between the ages of 15-44 years (who practise birth-control) choosing the OCP [5,6]. With the high prevalence of OCP use and the potential clinical impact of even a small increase in the risk of stroke, the examination of whether an association exists between currently used OCPs and stroke is important; and if an association exists, the magnitude of that increase.
Over the last three to four decades, the OCP has undergone two important formulation changes. Formulations now contain lower doses of estrogens, and the types of progestins have also changed [5,6].

Oral contraceptives inhibit ovulation. Other mechanisms of action include interference with egg transport, endometrial development, and cervical mucous production to inhibit movement of sperm [6]. Two forms of estrogens are used in OCP: ethinyl estradiol and mestranol. Mestranol is a "prodrug" that is converted in vivo to ethinyl estradiol [8,9]. In terms of pharmacokinetics, 35 ug of ethinyl estradiol is bioequivalent to 50 ug of mestranol. Estrogens affect lipid profiles and carbohydrate metabolism [10]. The lipid effects include an increase in LDL-cholesterol and triglycerides, and decrease of HDL. Estrogens may also alter the body's handling of glucose, potentially creating a 'diabetogenic' state. These two metabolic effects form a plausible mechanism for an alleged increased risk of stroke with long term OCP use by creating a state of "accelerated atherosclerosis".

Newer progestins [11] developed in the last decade (desogestimate, gestodene, norgestimate) have less androgenic activity and are more specific for the progesterone receptors than their earlier predecessors. Both desogestrel- and gestodene-containing OCP's are often referred to as "third generation" OCP's [11]. These progestins have the potential to cause fewer metabolic changes that would favor the development of arteriosclerotic disease with long term use, and therefore, have the potential to reduce the risk of stroke and myocardial infarction (MI) with long term use. Short-term studies (up to two years in duration) of the lipid profiles in patients taking third generation OCP's [12-15] lend support to this hypothesis; however, epidemiological data exploring an association between OCP and arterial thrombosis (stroke and MI) are inconclusive.
Over the last four decades, significant changes have also occurred to the estrogenic component of OCP [7]. In 1964, the average ethinyl estradiol dose in prescriptions was 50ug and the mean mestranol dose was 91 ug; these decreased to 35 ug and 57 ug respectively. By 1988, the relative proportion of prescriptions containing ethinyl estradiol also significantly exceeded those containing mestranol preparations by about 9 fold. Further reductions in the estrogenic component of OCP in the last 10 years to less than 35ug of ethinyl estradiol, became possible after the introduction of newer, more selective progestins [6].

As summarized in the next section, most studies showed that older first generation OCPs containing more than or equal to 50ug estrogen and early second generation OCPs containing less than 50ug estrogen combined with progestins other than the non-androgenic formulations listed above were associated with an increased risk of stroke. However, these changes in the doses of estrogen as well as the changes in progestin types, necessitate a re-evaluation of the studies linking OCP and stroke risks to explore if such an association exists with currently used OCPs.

B. Meta-analysis of Observational Studies

Meta-analysis is best described as the statistical analysis that combines or integrates the results of several independent studies considered by the analyst to be 'combinable' [24]. The advocates of meta-analysis believe that by pooling smaller studies, a more 'accurate' conclusion is drawn from the resultant larger numbers. While most meta-analyses have been performed with randomized controlled trial (RCTs), many have also been performed with observational studies [25,26]. Some experts contend that meta-analytic techniques should not be applied to observational studies [27] because the meta-analysis of RCTs is based on the assumption that each individual trial provides an unbiased estimate of a treatment effect,
with the variability among studies due to random variation [27, 30]. The variability among observational studies may not be random variation alone, but instead, a result of inherent biases or confounders. Therefore they argue that meta-analysis of observational studies is liable to produce "spurious precision" [30].

On the other hand, other experts [28,29] argue that systematic reviews of observational studies are still important, as a return to non-systematic "summaries" of studies in the literature are more likely to lead to biased conclusions. They argue that instead of only aiming to arrive at one summary statistic, attempts should be made to examine individual studies, decide if heterogeneity exists among studies, explain the areas of heterogeneity, and then "combine" the data from different studies only if it is appropriate to do so [28-30].

As part of any meta-analysis, assessment of study quality is deemed essential [31, 32]. Study quality is best defined as a construct reflected by "biases" in study methodology, so that the presence of bias or biases lowers the "quality" of the study [31]. The eventual effect of biases may produce a significant impact on the validity of the conclusions. The approach to determining "quality" of a study therefore, lies in determining the presence or absence of biases within the study. Much of the literature on quality assessment of studies was however published on assessing RCTs.

Chalmers and co-workers [32] proposed a Likert-type scale, for which different aspects of study design such as authors' background, protocol, analysis and presentation of results are assessed and given a "score" for each item. The scores from each of these sections are summed and then assigned a weight depending on their perceived importance for the contribution to the final score. The advantages to this way of measuring quality is the assessment of as many aspects of a study as possible, and listing of items as objectively as possible so that reader subjectivity is reduced. The disadvantages include the fact that such
scales may be ‘insensitive’ to differences among articles. When these authors applied this technique to 107 primary studies as part of seven meta-analyses [33], they found that there was no relationship between treatment effects and quality scores, either within each meta-analysis or overall. The authors believed that the study showed that quality scores should not be used for technical adjustment of an estimated treatment difference. In addition, they suspected that methodologically inferior trials produced biases in both directions, therefore, negating the effect of any one bias. Indeed, later authors [34] showed that for RCTs, an association did exist between effect size and either poor concealment of allocation schedule or failure to double-blind. Odds ratios were exaggerated by 41% for inadequately concealed trials, and by 17% in studies that were not double-blind. This study also lends support to the importance of quality assessment of studies in meta-analyses of RCTs as failure to address the presence of specific biases can influence the estimate of treatment effect.

Quality assessment for meta-analysis of epidemiological studies is less well defined. Some authors generate [35, 36] an a priori list in which studies with bias deemed crucial to the study topic are excluded from the primary analysis. Other authors use a modified version of the scoring system proposed by Chalmers et al for RCTs [37], adding questions about unique aspects of observational study designs that do not exist for RCTs and may be particularly important in determining the direction of effect, such as reliability of outcome or exposure verification, control of important confounders, adequate matching, and selection of appropriate control subjects. The weight that each of these biases should carry in determining the overall “score” of the Chalmers scale has to be determined for each question of interest.

Quality assessment of epidemiologic studies can thus be incorporated into a systematic review in the following ways: a) develop inclusion criteria to include only articles meeting a “pre-determined standard” of study design, b) “score” individual studies
based on a Likert-type scale of various aspects of the study and report the overall score of the articles, c) segregate articles with or without specific design “flaws” and calculate the corresponding risk estimates from these groups of studies, thereby reducing a potential source of heterogeneity. Each of these methods carries inherent weaknesses, and none of these methods has been demonstrated to be superior for epidemiologic studies.

C. Previous Systematic Reviews of OCP and Stroke

Investigation of the relationship between OCP and stroke in a randomized clinical trial is not feasible because stroke is rare in young women, and given the proven efficacy of the pill in preventing pregnancy, it would be difficult to justify on ethical grounds [16]. Evidence for the association between OCP and stroke is thus limited to case-control and cohort studies.

Several systematic reviews (defined as a methodological search of the literature with predetermined inclusion criteria) of the association between OCP and the risk of stroke have been published since 1985 [17-23].

The specific question of whether OCP exposure is associated with the risk of subarachnoid hemorrhage (SAH) was addressed [17] in a meta-analysis, following an earlier review [18]. Johnston and co-workers [17] identified 11 studies published from 1966 to Dec 1997 as eligible for the meta-analysis based on pre-defined “quality criteria” including study design (case-control or cohort), method of SAH diagnosis, and control for important variables such as age. Summary relative risk estimates of these studies were stratified by confounding factors (smoking and hypertension), estrogen dose (high or low), study design, outcome measure and exposure classification (current-users, ever-users, past-users). When they combined the relative risks by taking into account only within study variability, they reported that the relative risk of SAH associated with OCP exposure was 1.42 (95%
Confidence Interval, CI, 1.12 to 1.80). When adjusted for smoking, no apparent differences in the risk of SAH were found between “high” (>50 ug) and “low” (≤ 50 ug) dose estrogen containing OCP. It is unclear from this meta-analysis if other methodologic issues such as the source of controls (hospital versus community), the exposure status of controls (that is, never or past user) and cases (that is current ever or past users), or the blinding of investigators to exposure and case verification were examined. In this thesis, we will examine if these methodologic issues influence the reported effect size, and determine if a similar association exists between OCP use and stroke.

The prevalence of bias in these observational studies examining the association between OCP use and stroke was specifically demonstrated in two earlier systematic reviews. In these reviews, the authors [20, 21] examined epidemiological studies (published from 1960 to 1987) investigating the association between OCP and cardiovascular events, for presence of biases in observational studies [16]. The authors found that in all studies, methodological flaws existed. In the specific area of stroke, the authors concluded [21] that most of these observational studies failed to investigate equally aggressively strokes in women who were using OCP and controls; there were few studies that fulfilled the standards for unbiased data collection; and finally, the criteria for equal clinical susceptibility to stroke for both cases and controls were not always met. The authors went on to show in a separate univariate analysis [21] that at least for stroke, avoidance of Berkson’s Bias (the use of hospital- versus community-based subjects) was inversely related to the risk of stroke. That is, if community-based controls were used, there was a weaker association between OCP use and stroke.

There are other descriptive systematic reviews of studies assessing the association of low-dose OCP with stroke [19, 22, 23] but an overall estimate of risk was not calculated.
D. Proposed Approach to the Assessment of Quality in Studies Investigating OCP and the Risk of Stroke

Selection of any of these methods listed in Section II.B, to assess the quality of studies investigating the risk of stroke in OCP users for this thesis will be depend on whether the intent is to be “as inclusive” as possible by selecting many of the articles evaluating the association between OCP and stroke, thereby increasing the sample size upon which an estimate is made, or to evaluate only evidence from “best designed” studies (defined by an empiric list of study methodologies) thereby excluding more studies in arriving at an effect size estimate.

Until the best method of obtaining reliable estimates from observational studies is determined, for the purpose of the thesis, we opted to include as many studies as possible in our analysis of effect size, but recognize that studies of different “quality” may create heterogeneity in our results, and the biases present in various studies of different quality, will more often than not, result in an association between stroke and OCP use.

All studies would be assessed for “quality” from a pre-defined list of important biases to allow the reader to ascertain the validity of the overall conclusion. In this thesis, we selected a priori, five specific aspects of study quality to be examined closely, and when adequate sample sizes made it possible, we investigated the impact these aspects of study quality had on effect size. These included:

a) Type of study design (case-control versus cohort)

b) Method of verification of exposure (OCP users) and outcomes (stroke)

c) Whether investigators were blinded to use of OCP when assessing stroke (in both cohort and case-control studies) or to the presence or absence of stroke when assessing for OCP use in case-control studies.

d) Source of control (hospitalised versus community-based control)
e) Definition of OCP use status in the comparative groups (current versus non-current users, ever users versus never users).
III. Research Question

Is current use of low-dose (≤ 50ug estradiol or mestranol equivalent) OCP associated with an increased risk of stroke?

IV. Objectives

The primary objective is to perform a systematic review and conduct a meta-analysis of the published studies evaluating low dose OCP and the risk of stroke.

The secondary objective is to investigate the degree to which study design, and the definition of exposure and outcome variables, influence any association between OCP and stroke reported from these studies.
V. Method

A. Article Selection

A systematic search of MEDLINE (studies published between 1970 and May 1999), EMBASE (1980-May 1999), and Science Citation (1993 to May 1999) was conducted by two reviewers (WSC and JR), independently. Potential articles were identified from MEDLINE using MeSH headings [cerebrovascular disease] or [cerebrovascular accident], or [stroke] or [cerebral infarction] and [oral contraceptive pill] or [birth control pill] or [oral contraceptives]. Search terms used for EMBASE and Science Citation were [stroke] or [cerebrovascular disease] and [birth control pills] or [oral contraceptives].

For the purpose of this thesis, we included only articles that were published in English, and reported use of estrogen-based OCP use in women, and stroke outcomes of vascular origin. We included only studies that were published after 1970 because these studies were more likely conducted in women using low-dose OCP. We excluded articles if no control groups were given. Therefore, cohort, case-control and cross-sectional studies fulfilling the inclusion criteria were considered for data retrieval and uncontrolled case-series were excluded.

The retrieved articles were then reviewed independently by the same two investigators (W.S. Chan and J. Ray) to ensure that where multiple publications existed of the same population, only data from the most recent publication were abstracted or that publication with the most relevant information was used for data abstraction.
B. Data Abstraction

Data from these final articles were then abstracted by two other readers with knowledge of study methodology (S. Ginsberg and E Wai), for study design quality, patient variables, exposures and outcome definitions. The readers were blinded to the authors of the paper, institution, journal of publication, and funding source. Data abstracted from these papers included (Appendix 1):

1) Patient demographic variables such as age, country of study, period of study,
2) Type (and generation) of estrogen-based oral contraceptives,
3) Type of stroke outcomes,
4) Potential confounders-- smoking, hypertension, co-existing diabetes mellitus, body-mass index, migraine, and duration of OCP use.
5) Quality of individual study methodology as defined by five components:
   a) Study design (case-control versus cohort)
   b) Method of verification of exposure (OCP users) and outcomes (stroke)
   c) Whether investigators were blinded to use of OCP when assessing stroke (in both cohort and case-control studies) or to the presence or absence of stroke when assessing for OCP use in case-control studies.
   d) Source of controls (hospitalized versus community-based control)
   e) Definition of OCP use status in the comparative groups (current versus non-current users, ever users versus never users).

When we found differing answers to the items listed above, an initial check was made by W.S Chan to ensure that these differences were not simply a result of individual oversight. If further disagreements persist (e.g. for answers pertaining to quality issues), a consensus was then sought from an independent review by W. S. Chan and J. Ray.
C. Study Variable Definitions

For the purpose of this study, the following definitions were used:

Stroke Outcomes:

1. "Ischemic stroke" was the term used to define thromboembolic and thrombotic strokes.
2. "Hemorrhagic strokes" included subarachnoid, intracranial and intraparenchymal hemorrhage.
3. Stroke death was defined as death resulting from any stroke (defined by the respective authors in each paper), and could include death from ischemic or hemorrhagic strokes.

OCP Exposure:

1. Low-dose OCPs was defined as OCP containing ≤ 50ug of ethinyl estradiol. We accepted the author's statement of "low-dose" to mean less than or equal to 50ug, even if this dose was not explicitly stated.
2. Second generation OCPs were defined as pills containing less than or equal to 50 ug of ethinyl estradiol with norgestimate, norethisterone, levonorgesterel, or lynestrenol as the progestins [40, 43].
3. Third generation OCP were defined as pills containing less than or equal to 50 ug of ethinyl estradiol with either gestodene or desogestrel progestins [40,43].
D. Statistical Model

(i) Pooling Studies

Meta-analysis is a statistical method that can be used to combine summary statistics from many studies. The summary statistic taken from each study might be a mean, a proportion or a difference between means or proportions as would be the case in comparative trials. In this thesis the summary statistic for each study is the relative risks obtained from cohort or odds ratio (which approximates relative risks) from case-control studies of OCP and stroke.

Because the OR is a ratio of products of frequency counts, it has a positively skewed sampling distribution. For this reason, we used the natural logarithm (Ln) of the OR to combine across studies. The anti-logarithm of this summary estimate provides an overall estimate of risk (OR) for all of the studies combined.

One might consider the simple arithmetic mean of these Ln ORs as the summary measure for all of the studies. This approach gives “equal weighting” to each of the studies and would not take into account the differences in precision of the individual estimates due to the different sample sizes of the studies upon which they are based.

Another method that has been proposed is a weighted mean of the individual Ln OR ratios where the weights used are the reciprocals of the individual variances [77]. From the following 2 by 2 contingency table of counts obtained from the ith case control study:

<table>
<thead>
<tr>
<th>EXPOSURE</th>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>CASE</td>
<td>Ai</td>
<td>Bi</td>
</tr>
<tr>
<td>CONTROL</td>
<td>Ci</td>
<td>Di</td>
</tr>
</tbody>
</table>

the odds ratio, ORi is given by:
\[
OR_i = \frac{A_i \times D_i}{B_i \times C_i}
\]

The variance of the log odds ratio \( \log(OR_i) \) is well known to be approximately equal to [77]:

\[
V_i = \frac{1}{A} + \frac{1}{B} + \frac{1}{C} + \frac{1}{D} = W^{-1}
\]

Therefore the weighted mean \( \ln(OR_{\text{MEAN}}) \) is given by:

\[
\ln(OR)_{\text{MEAN}} = \frac{\sum_{i=1}^{N} W_i \times \ln(OR_i)}{\sum_{i=1}^{N} W_i}
\]

with variance given by:

\[
Var[\ln(OR_{\text{MEAN}})] = \frac{1}{\sum W_i}
\]

The formula for the variance of the \( \ln \) OR required in equation EQ3 and EQ4 can be derived by assuming that the frequency counts \( A, B, C \) and \( D \) from each study follows the Binomial or Poisson probability distribution. In either case it is assumed that the mean is constant across studies, that is, the same Binomial or Poisson probability distribution is used to describe the frequency counts within each study.

The variance in equation EQ1 takes into account only the variation within each study. The ORs may vary across studies due to differing characteristics of the populations from which the samples were taken. This extra Binomial (or Poisson) variation is tested using a chi-square test [77]. This test determines whether the variation among the study \( \ln \) ORs exceeds what would be expected if the true mean \( \ln \) ORs were constant across studies.
If such extra Binomial variation exists, then the formulae for the variance of the Ln OR given in equation EQ1 is incorrect. Denoting the variance of the Ln OR of the ith study by \( \text{Vi} \), the correct variance of the Ln OR is given by:

\[
\text{VAR}[\text{Ln(ORi)}] = \sigma^2_B + \text{Vi} \quad \text{EQ4}
\]

where \( \sigma^2_B \) is the pure variance of the Ln OR between studies. The between study variance \( \sigma^2_B \) can be estimated using analysis of variance techniques. The same formula EQ2 is used to estimate the overall Ln OR with the weights now being the reciprocal of the variances given in equation EQ4 rather than equation EQ1.

We have thus created this model for our thesis to ensure that our calculated confidence interval for stroke association and OCP is a conservative one, and would allow us to take into account the differences between studies. The large sample size of many of the studies will provide sufficiently large statistical power to the chi-square test of heterogeneity. Therefore even if significant heterogeneity is found, the actual size of the between study variance, \( \sigma^2_B \) may be small and the pooled Ln ORs produced using formulae EQ4 for the variance may not differ much from those in which formula EQ1 is used.

(ii) Comparisons Among Subgroups

We were interested in comparing the ORs between smokers and non-smokers, and between hypertensive and normotensive users of OCP. One could estimate using the above formulae the pooled log odds ratio for smokers and non-smokers separately and then compare them using the standard Gaussian Z-statistic. For example if the two estimated Ln odds ratios are \( \text{Ln(OR1)} \) and \( \text{Ln(OR2)} \) with variances \( \text{V1} \) and \( \text{V2} \) then the Z statistic is given by:
Such an analysis would not take advantage of the fact that in many of the studies, the pooled estimates of the odds ratios were reported separately for the smokers and non-smokers. Therefore each of these studies could provide a comparison of the log odds ratio across the two groups. Such a comparison would not suffer from the possible heterogeneity that might exist across the studies. Therefore, if the difference between the Ln OR between smokers and non-smokers in the ith study is denoted by $D_i$ then we have:

$$D_i = \ln(OR_{2i}) - \ln(OR_{1i})$$

EQ6

The corresponding variance of this difference is thus derived from:

$$VAR(D_i) = V_{1i} + V_{2i} = \frac{1}{W_{1i}} + \frac{1}{W_{2i}} = WS_i^{-1}$$

EQ7

where the $V_{1i}$ and the $V_{2i}$ are obtained using formula EQ1 for the smokers and non-smokers separately. The weighted estimate of the difference can be obtained using the formula:

$$\text{Ln}(D)_{mean} = \frac{\sum_{i=1}^{n} WS_i \times D_i}{\sum_{i=1}^{n} WS_i}$$

EQ8

The within study weights $WS$, because they are the reciprocals of within group variances $V_{1i}$ and $V_{2i}$, do not contain the between study component of variance $\sigma_B^2$ thereby providing a
more sensitive comparison than that derived by pooling log odds ratios across studies. M is the subset of studies that provides estimates of the log odds ratio for both the smokers and the non smokers. The variance of this pooled difference is given by:

\[ \text{VAR}[\ln(D)_{\text{Mean}}] = \frac{1}{\sum_{i=1}^{\infty} W_i S_i^{-1}} \]  

EQ9

The square root of this variance is the standard error of the pooled difference. The estimate of the pooled difference (EQ9) divided by the standard error results in the standard Gaussian Z-statistic which can be used to test the null hypothesis that the difference in the odds ratio between smokers and non smokers is zero as well as calculate the corresponding 95% confidence interval.

**E. Publication Bias**

We investigated for the presence of publication bias (for case-control studies) by plotting a funnel plot of the sample size (number of stroke cases in case control studies) against the natural logarithm of reported OR [78]. We also examined the influence that sample size (in case-control studies) had on the pooled ORs of stroke risk and OCP use. For that purpose, we examined the effect size reported in studies with greater than 250 cases of stroke and compared this to studies with less than 250 cases of stroke since it is unlikely that a study would not have been published if it had recruited at least that number of stroke cases.
VI Results

A. Retrieval of Studies

On initial search, a list of 779 potential articles from Medline was found. After screening of initial titles, a list of 37 [38-42, 45-76] articles from MEDLINE was derived [Figure 1]. We identified no further articles from Science Citation and EMBASE that were potentially eligible. No additional articles were found through review of bibliographies of retrieved papers. Four articles that fulfilled eligibility criteria were excluded for two main reasons: a) the exposure to OCP was not a primary analysis [73,74] so that no appropriate data were available for analysis, or b) the primary outcome was a composite of cardiovascular events that included stroke [75,76]. Thus, a final list of 33 articles [38-42, 45-72] representing 18 distinct study populations, listed in Table 1, was thus obtained. In addition, two publications [43, 44] detailing the methodology for three of these study populations [41, 42, 52] were also retrieved.

The initial inter-reader agreement (E. Wai and S.Ginsberg) for data abstraction for study design, exposure type, outcome definition and verification, blinding of investigators, handling of confounders was 68% (Sections 1-6, Data Collection Sheet). On reviewing the discrepant items by a third reader (WSC), 25% of discrepant items were found to be secondary to individual error. The remaining discrepant items were resolved through consensus.

B. Study Patient Demographics

These 18 studies were conducted over three decades. Eight studies [40, 43, 48, 52, 53, 57, 60, 67] were conducted after 1980, when the most common used OCP preparation
was “low-dose”. Of these eight studies, three [40, 48, 53] were conducted in the 1990’s, when exposure to third generation OCP was most likely to occur. Two of these studies spanned two decades [55, 65]. The graph of the best adjusted OR reported in each study versus the year in which the study commenced is shown in Graph 1. Visually, we observed that possibly a J-shaped curve best describes the relationship between time and year of study inception. The single outlier study, was that of a small case-control study [72], published in 1978, with 14 stroke cases and 56 controls.

Seven studies were performed in North America [38, 45, 48, 53, 60, 71, 72], four in the United Kingdom [55, 65, 67, 69], three studies were from single countries within Europe [57, 63, 70] and one study was from Asia [62] [Table 1]. Three studies involved participants from more than one distinct population [40, 43, 52].

The number of cases and controls from the 14 case-control studies are displayed in Table 1; there were a combined total of 8984 controls and 4038 cases. In the four cohort studies, there were 130 stroke outcomes from an overall pool of a million women.

C. Study Quality

(i) Design

There were 14 retrospective studies [Table 2]: 13 case-control studies [38, 40, 43, 48, 52, 53, 57, 62, 63, 67, 69, 71, 72] and one retrospective cohort study [70]. There were four prospective studies: one nested case-control [55], and three cohort studies [45, 60, 65] [Table 2]. There were no prospective randomized controlled trials.

(ii) Definition and Verification of Stroke Outcomes

The stroke outcomes were largely reported as falling into one of three categories [Table 2]: thrombotic, hemorrhagic or stroke deaths. Nine studies [38, 45, 48, 53, 55, 60, 61,
65, 71, 72] included both thrombotic and hemorrhagic strokes, four studies [40, 43, 57, 63] evaluated only thrombotic strokes, and one study evaluated only hemorrhagic strokes [52]. Three studies only evaluated stroke deaths [67, 60, 70]. In most studies [38, 40, 43, 45, 48, 52, 53, 72], a combination of clinical and/or objective diagnostic testing was used to define stroke cases; in six studies [55, 57, 60, 62, 63, 65], the definition of stroke was not explicitly stated. The reviewer was blinded to the status of use of OCP when diagnosing strokes in only four studies [43, 45, 52, 67]. The stroke cases were independently verified in seven studies [38, 40, 43, 48, 52, 55, 62] either by an independent physician or a committee.

(iii) Verification and Type of Exposure

The most commonly reported estrogenic preparation used in the studies was ethinyl-estradiol [Table 2]. The estrogenic dose of OCP was specified, and the exposure of patients to low-dose OCP (i.e. ≤ 50ug) was explicitly stated in eight studies [40, 43, 48, 52, 53, 57, 60, 65]. In the remaining ten studies [38, 45, 55, 62, 63, 67, 69, 70, 71, 72], the dose of OCP used was not explicitly stated in the published study.

Information on exposure to OCP was obtained mostly through direct patient interview or questionnaire [38, 40, 43, 45, 48, 52, 53, 57, 62, 63, 65, 72], or via physicians’ records or prescriptions [55, 60, 67, 69, 70]. The investigators were blinded to the outcome status (i.e. whether stroke occurred) when assessing for OCP use in only two studies [45, 62].

(iv) Comparison Groups for OCP use

In 14 of these 18 studies [38, 40, 43, 48, 52, 53, 57, 60, 63, 65, 67, 69, 70, 72] the authors presented the risk of stroke in current users of OCP. These studies however, provided varying definition of “current” OCP use; one month or less [38, 53, 55, 67], three months or less [40, 43, 52, 69] and one year or less [60, 65]. Three studies presented data on
ever users [45, 55, 62] of OCP, one study [71] was did not state the status clearly, expressing exposure to OCP as “user”. In the former three studies, ever-users of OCP encompassed both current and non-current users of the pill.

The risk of stroke in these OCP-exposed participants was compared to non-current users of OCP in the majority of studies [38, 40, 43, 48, 52, 53, 60, 69, 70, 72], to never users in six studies [45, 55, 57, 62, 65, 67], not clearly stated in one study [67], and simply to “non-users” in one study [71].

(v) Confounders

In most studies [38, 40, 43, 45, 48, 52, 53, 55, 57, 60, 62, 63, 65, 67, 69, 71, 72], cases and controls were matched for age [Table 3]. In the cohort studies [45, 60, 63, 70], age-adjustments were made when calculating relative risks. Most studies also accounted for the presence of hypertension [38, 40, 43, 45, 48, 52, 53, 55, 57, 60, 63, 65, 67, 69, 71, 72] by adjusting or stratifying for hypertension in the analysis; five studies [57, 60, 65, 71, 72] excluded hypertensive patients. Similarly, in most studies smoking was either adjusted for [45, 48, 55, 63, 65], or stratified for in the analysis [38, 40, 43, 52, 53, 57, 67, 71].

The presence of concurrent diabetes, increased Body Mass Index (BMI), and migraine were not often addressed by these studies. None of the studies reported systematic investigation for the presence of an underlying thrombophilia.

D. Analysis

(i) Pooling Adjusted OR's

The 18 studies were pooled to yield 24 ORs, that were used to obtain an overall OR of the risk of stroke in OCP users compared to that of non-users. Six studies [38, 43, 48, 52, 57, 67] contributed two ORs from each study because of separate reporting of stroke risk
according to stroke type or exposure type [Table 4]. The OR$_y$ (not accounting for 'between-study' variability of stroke (any type) in women who used OCP (current or ever) compared to women who were non-users was 1.82 (95% CI 1.66-2.00) [Table 5]. There was significant heterogeneity among these studies, p<0.0001. After accounting for between-study variability, the OR$_z$ was 1.86 (95% CI 1.37-2.54), which still excluded the null hypothesis. The adjusted ORs from these 18 individual studies (providing 24 individual ORs), together with the pooled OR are displayed in Graph 2.

The pooled OR$_z$ of the 14 studies [38, 40, 43, 48, 52, 53, 57, 60, 63, 65, 67, 69, 70,72] that provided data on current users of OCP was 1.92 (95%CI 1.31-2.82), the corresponding OR$_z$ for studies describing risk of stroke in ever users was not significant at 1.21 (95%CI 0.86-1.71).

(ii) By Stroke Type

Heterogeneity among the pooled studies was reduced when the studies were pooled according to stroke type. Eight studies, [38, 40, 43, 48, 52, 53, 55, 65, 67] providing nine individual ORs [Table 4], were used to evaluate the risk of thrombotic stroke with OCP use (Graph 3). The combined OR$_y$ was 3.06 (95% CI 2.54-3.68); heterogeneity was borderline at p=0.0589. The corresponding OR$_z$ was 2.90 (95%CI 2.23-3.78).

Similarly, eight studies [38, 48, 52, 53, 55, 67, 69, 70], provided ten separate ORs [Table 4] for evaluating the risk of hemorrhagic stroke and OCP use. The pooled OR$_y$ was 1.45 (95% CI 1.23-1.71) [Table 5]. The p-value for heterogeneity testing was just significant at 0.0471. The 95% CI for the corresponding OR$_z$ (1.30), did however cross one (95% CI 0.99-1.71). These ORs are displayed in Graph 4.
Finally, the pooled OR of studies investigating stroke deaths as a result of OCP exposure was 0.99 (95% CI 0.70-1.38), with a similar non significant OR (0.94 95% CI 0.51 to 1.74)[Graph 5].

(iii) By OCP Type

When the eight studies [38, 40, 48, 52, 53, 57, 67, 70] that specified the use of \( \leq 50 \mu g \) of estradiol were pooled, the OR for any stroke was statistically significantly increased at 1.85 (95% CI 1.59-2.15); there was significant heterogeneity (p=0.0029). The corresponding OR was 1.75; the 95% CI remained statistically significant at 1.35 to 2.26.

Both second and third generation OCP were associated with an increased risk of stroke. There was no significant heterogeneity among studies investigating the risk of stroke in both 2\(^{nd}\) and 3\(^{rd}\) generation OCPs. The pooled OR from the six studies [40, 43, 48, 52, 53, 55] for patients exposed to 2\(^{nd}\) generation OCP was 2.35 (95% CI 1.81-3.05), and for 3\(^{rd}\) generation OCP was 2.87 (95% CI 1.84-4.48). There was no significant difference between these odds ratio (p=0.4472).

(iv) By Risk Factors

Eight studies [38, 40, 43, 48, 52, 53, 55, 57, 60, 65] provided twelve ORs for the risk of stroke in non-smoking users of OCP. The pooled OR was 1.92 (95%CI 1.58-2.34), and heterogeneity was significant at 0.0068. The calculated OR was still significantly greater than 1.0 (1.86, 95% CI 1.46-2.37). In smokers, the pooled OR was 2.76 (95% CI 2.30-3.32), the OR was 3.50 (95%CI 2.17-5.64). We compared the risk of stroke in non-smoking and smoking users of OCP using only the eight studies [38, 40, 43, 48, 52, 53, 55, 71] that provided ORs for both the respective groups of patients; the pooled OR among the non-smokers in the subset of studies that presented ORs for the presence and absence of smoking, was 1.92 (95%CI 1.58-2.34), compared to that among the smokers which was 4.00
The ratio of this difference in these two ORs, using EQ 8, was 47% (95% CI, 34% to 64%) for non-smokers compared to smoking users of OCP.

The ORz for stroke in normotensive patients using OCP was increased at 2.06 (95% CI 1.46-2.92). In patients who were hypertensive users of OCP, the pooled ORz was also increased at 9.82 (95% CI 6.97 to 13.84). For the five studies that reported on the risk of stroke in both normotensive and hypertensive users of OCP [38, 40, 43, 52, 55], the risk of stroke in the normotensive group [38, 40, 43, 52, 55] was 1.93 (95% CI 1.66-2.26), compared to that among hypertensive patients at 9.46 (95% CI 6.72-13.30); the ratio of this difference (EQ 8) was 20% (95% CI 14-30%) in normotensive compared to hypertensive users of OCP.

We do not have any information on the risk of stroke in women who are both smokers and hypertensive users of OCP. These patients, are likely to be uncommonly found in the general population.

(v) By Study Design

When data from the four cohort studies were pooled [45, 60, 65, 70], there was no increase in the risk of stroke with OCP use. Despite heterogeneity among the four studies, both ORy and ORz similarly crossed one. The pooled ORz of stroke, accounting for between study variability was 0.95 (95%CI 0.51-1.78). Pooling the 15 case-control studies, [38, 40, 43, 48, 52, 53, 55, 57, 62, 63, 67, 69, 71, 72] similarly resulted in a significant value for heterogeneity (p <0.0001). The ORz was however significantly greater than 1.0 {OR 2.08, 95%CI 1.52-2.85}. The pooled OR from the cohort studies was significantly different from that of the case-control studies (p=0.0286)
(vi) By Control Type and Status of OCP Use in Comparison Group

We examined possible differences in effect size by the source of controls in case-control studies. When ORs from studies using community controls were pooled [38, 40, 48, 53, 55, 57, 67, 69, 72], the OR₂ of stroke was significantly greater than 1.0 (1.70 (95% CI 1.35-2.13)); Using hospital controls only, the pooled OR₂ was similarly significant (OR 2.85, 95% CI 1.65-3.23). The pooled OR was however, not significantly different for studies using hospital versus community-based controls (p=0.0854).

The status of use in the comparative reference group also significantly influenced the effect size estimate. When the comparison group used was non-current users of OCP (including ever and never users), the OR₂ was 1.91 (95% CI 1.21-3.02). However, when the comparative control group was only never users, the point estimate of the pooled OR₂ was lower at 1.55 (95% CI 1.06-2.27). The difference in OR between studies using different types of comparative groups was not significant (p=0.4902).

E. Publication Bias

We investigated the possibility of publication bias by plotting a graph [Graph 6] of number of stroke cases in each case-control study against the natural logarithm (Ln) of the OR of stroke risk. There are no study points in the lower left corner of the “inverted funnel plot” suggesting that publication bias exists against publication of “small” studies reporting no increased risk of stroke. In other words, studies that are “small” and report no association of stroke risk with OCP use might have been unpublished or not submitted for publication. When we performed further subgroup analysis of case-control studies with 250 or more cases compared to those with less than 250 cases, the OR₂ was similar at 1.86 (95%CI 1.39-2.50) and 2.50 (95%CI 1.45-4.32) respectively (p=0.3504).
V. Discussion

This systematic review of 18 observational studies demonstrated that the risk for any stroke in users of OCP is likely increased. Although the type of OCP exposure was not clearly stated in all studies, our conclusion likely applies to low-dose OCP (containing less than or equal to 50ug), as this was likely the most prevalent form of OCP in use during the study period. Furthermore, when we restricted our analysis to only those studies of current-users of OCP, increased stroke risk was still seen.

The risk with various stroke types however, differed; the pooled OR of thrombotic stroke associated with OCP use was 2.90 (95%CI 2.23-3.78), the risk for hemorrhagic stroke was 1.30 (95%CI 0.99-1.71) and that for stroke death was 0.99 (95%CI 0.58-1.69). In patients who smoked, or who were hypertensive, the pooled ORs for stroke were clearly increased when compared to non-users of OCP, at 3.50 (95%CI 2.17-5.64) and 9.82 (95%CI 6.97-13.84), respectively. Among patients who use OCP, smokers clearly demonstrated increased risk of stroke compared to non-smoking users of OCP. A similar pattern was seen among hypertensive and non-hypertensive users of OCP.

Our finding for a positive association for thrombotic stroke and OCP use was further supported by a recently published (July 2000) meta-analysis of ischemic stroke risk with OCP use [82] in which the authors, reported that the relative risk of ischemic stroke was 2.75 (95% 2.24-3.38) in current users of low-dose estrogen preparations.

Our conclusions for the risk of hemorrhagic stroke in OCP users differed somewhat from an earlier meta-analysis [17]. The most likely explanation for this is a difference in statistical pooling used to combine the data, as we utilized a more conservative approach for the calculation of the ORs and 95% CI that took into consideration, the variability between studies.
When we pooled data across different studies, heterogeneity was found in most cases. Sources of heterogeneity were likely derived from differences in study exposures and outcomes. As well, various study methodologic issues stated below were likely contributory. By using a statistical model to account for between study heterogeneity, a “wider” 95%CI was derived. From Table 5, it was apparent that these values (OR$_2$) did not differ from those ORs derived without accounting for between study variability (OR$_1$); the significance of the association of OCP and hemorrhagic stroke was however lost.

The magnitude of association between stroke and OCP in our meta-analysis, across these studies may be influenced by many methodologic issues. The first of which is study quality. When we examined all studies for certain pre-defined aspects of study “quality” in assessment of stroke and exposure determination, most studies did not adequately avoid biases. Among case-control studies, most studies [38, 48, 53, 55, 57, 63, 69, 71, 72] did not clearly state that study investigators were blinded to the patient’s exposure to OCP when diagnosing stroke cases or blinded to whether the patient had had a stroke when determining their use of OCP. In only four case-control studies [40, 52, 62, 67], was there some aspect of blinding of study investigators to either a subject’s exposure to OCP or to their stroke status. The importance of blinding to stroke status or OCP exposure should not be underestimated since it has been demonstrated in RCTs that unblinding has the potential to exaggerate effect size [32]; and we would expect that unblinding of investigators in these observational studies to have a similar effect. In this thesis, we were not able to estimate how much unblinding increased the effect size because of the small number of studies available for our analysis.

In addition, we cannot ascertain how the stroke diagnosis was made in all studies. The widely accepted WHO definition of stroke, stated in most studies, “rapidly developing clinical signs of focal (at times global) disturbance of cerebral function, lasting more than 24
hours or leading to death with no apparent cause other than that of ‘vascular origin’ is associated with various difficulties with implementation in studies [78]. This definition, as stated by Sudlow et al [78], would exclude subarachnoid hemorrhages which present with sudden-onset of headache and no focal or global disturbance of cerebral function, as well as transient ischemic attacks (TIA’s), which last less than 24 hours. Finally, the definition above implies that all other diagnoses should be excluded before a stroke diagnosis is made.

The extent to which each young woman presenting with neurological symptoms is investigated, imaged and diagnosed by “stroke experts” as having stroke can present a significant source of bias; diagnostic suspicion bias is increased especially if the clinician and investigator are not blinded to the status of the patient’s use of OCP. To reduce the risk of this bias, independent adjudication of suspected stroke by a blinded committee or expert verifying the diagnosis of stroke is important. In our meta-analysis, only six case-control studies [38, 43, 48, 52, 53, 62], incorporated such a process in their study design.

The magnitude of association between stroke and OCP in our meta-analysis, across these studies was also clearly influenced by source of the control group (community versus hospital), and definition of the comparative reference group (never users versus non-current users). In the former situation, when we compared the risk of stroke in studies using these two groups of controls (community versus hospital), the pooled OR reported for stroke in OCP users using community controls was 1.70 (95%CI 1.35-2.13) compared to 2.85 using hospitalized controls (95%CI 1.65-4.93). In the two studies [38, 40, 62] which provided separate analyses with community and hospital controls, only one study [40] showed a difference between the two groups in the risk of stroke. Our finding that the use of community controls could result in a weaker association of stroke in users of OCP is supported by the earlier analysis of epidemiological studies of OCP and cardiovascular disease by Katerndal et al [21]. In that article [21], an inverse relationship was found in the
magnitude of the reported ORs if Berkson’s Bias was avoided. That is, when observational studies investigating the risk of cardiovascular diseases (heart disease and strokes) used community-based controls, an association was less apparent. We hypothesize that this bias stems from the possibility that there may be less complete ascertainment of exposure in hospital-based controls compared to that of community-based controls. The use of community-based controls will thus better reflect the risk association between stroke and OCP use.

In addition, we found that the status of OCP use in the comparative reference group also influenced the magnitude of this risk. When this reference group was defined as “non-current” users (thereby including past or never users), the pooled OR of stroke was 1.91 (95%CI 1.21-3.02). This pooled OR was somewhat lowered when the corresponding reference group was never users, with OR at 1.55 (95% CI 1.06-2.27). Although the differences between these two ORs did not achieve statistical significance, the potential contribution of the choice of the comparative reference group to the overall association to determining stroke risk in such a meta-analysis may be clinically significant. By comparing stroke risk in users of OCP to never-users, we may be comparing users of OCP to women who do not use OCP or have not been prescribed OCP because of the presence of other risk factors like hypertension, smoking, diabetes mellitus, personal or family history of cardiovascular disease and thus have an inherent increased base-line risk of stroke. Similarly, when authors use non-current users as the comparative reference group, a cohort of women with an inherent lower baseline risk of stroke may have been selected. These women who are non-current users of the pill may have previously been “challenged” with higher dose OCP and remained stroke-free. Therefore, the resultant difference in stroke risk
in this group compared to users of OCP may appear inflated. To answer our specific question of whether current use of OCP results in an increase risk of stroke, the comparative group should likely be that of non-current users of OCP. Participants in the group should however have the same baseline risks (biological susceptibility) of stroke as users of the pill, and a minimal biologically plausible length of time must have lapsed since last use of the pill, minimum 6 months. Such a comparative group would however be difficult to achieve in the context of an observational study, and may always remain a limitation of these studies.

Perhaps the strongest argument that despite the statistical significance, we should not simply conclude that OCP is associated with stroke, stems from the differences in pooled ORs among case-control studies and cohort studies. Case-control studies are clearly subjected to greater sources of biases that could result in a positive association: publication bias, the use of hospital based controls, selection of controls that are non-current users, and possible diagnostic suspicion bias (from not blinding investigators to the participants' use of OCP). There are however certain difficulties with simply accepting the results of the four cohort studies. In these four studies, there were clearly methodologic issues that might influence the results. In one study [70], the stroke outcome was that of stroke death. From our pooled analysis, we found that death from stroke was not likely associated with OCP use. In the other large prospective cohort study [45], the status of OCP users included those of "past users" of OCP. Clearly, any association between OCP use and stroke will not be found if the time that has elapsed since OCP use was distant. In the remaining two cohort studies [60,65], the association between stroke and OCP use was significant in one [65] and not significant in the other [60]. Moreover, when we considered only the two large case-control studies [40, 43] performed by two groups of authors [Transnational Research Group
and World Health Organization], where stringent research protocols were published [42, 44], an association of thrombotic stroke and OCP was found.

We acknowledge that publication bias may be present against small studies that reported no stroke association with OCP use. When we performed subgroup analysis with studies with more than 250 cases of strokes, our pooled OR for stroke risk was still significant. Studies of this size, once completed, are unlikely to be rejected for publication. When we omitted the outlier in Graph 1, we observe that an approximate J-shaped graphical relationship was observed between the year at inception of study versus reported OR. Since the dose of estradiol in OCP preparation was lowered through the 1970s into the early 1980s, this observed drop in OR in this same time period is consistent with biological plausibility; few studies are thus likely to be missed in our selection of only published studies. The apparent increase in OR following the early 1980s provides grounds for speculation; this increase if correct, could be a result of the possible contribution of the progestinic component to increased risk of stroke. The plausibility of such a hypothesis should be further studied.

Further support for rejecting the null hypothesis comes from the fact that a differential risk of different stroke types was found. Based on biological plausibility, the likely mechanism by which OCP increases the risk of stroke would be through the acceleration of the atherosclerotic process: increased lipids, increase diabetogenic tendencies and altering hemostasis to favour thrombosis. Hence, finding a strong association with thrombotic, but not with hemorrhagic stroke (which usually results from chronic hypertension, aneurysms etc) supports that our finding may be valid. The absence of association with stroke death may be a result of a lack of power, or that case-fatality from thrombotic stroke in young women is low compared to that of hemorrhagic stroke.
With the extensive use of OCP by millions of women world-wide, the public health implications from a potential doubling or tripling of baseline stroke risk (albeit still low) in OCP users may be important. When counseling a woman regarding the potential risk of stroke and OCP use, the baseline risk of ischemic stroke in young women under age 35, estimated at between 6 to 20 per 100 000 [79] should be clearly stated. A two- to threefold increase in OR for current users of OCP could represent up to an additional 6-40 per 100 000 women who may suffer from ischemic stroke when using low-dose OCP. The significance of this increased risk should also take into consideration that a stroke in a previously healthy woman could be a devastating and disabling illness, and that the case-fatality for all strokes (thrombotic and hemorrhagic) is likely less than 30% in this young population [80]. On the other hand, published maternal mortality rate (USA) in the last two decades was 9 per 100 000 livebirths—a risk of pregnancy that is not insignificant [82].

The risk of stroke associated with OCP use is clearly increased in the presence of concurrent hypertension and smoking. Controlling and treating high blood pressure in these patients could be expected to decrease the risk of stroke but evidence for this was not provided for in these studies. OCP-users who smoke also have an increased risk of stroke. Prescribing OCPs to women who smoke or who are hypertensive should currently be done after careful counseling. The enormous benefits of OCP in prevent pregnancies (and complications of pregnancies) and regulating and treating disorders of the menstrual cycles however should not be overlooked as these benefits may exceed, by many fold, the risks of stroke associated with OCP use.
VI. Conclusion

Based on our meta-analysis of observational studies, there is probably an association between current users of low-dose OCP and stroke. This association was significant between low-dose OCP and thrombotic strokes, but not with hemorrhagic strokes and stroke deaths. The risk of stroke was increased with concurrent hypertension and smoking in OCP users.

There were however many aspects of study methodology and quality that may influence the effect size. In particular, the source of controls (community versus hospital) and status of comparative controls (non-current or never users) may influence the magnitude of the association.

Until more evidence is available to the contrary, counseling of women using OCP regarding stroke risk should be done within the context of its over-riding benefit.
VII. References


Figure 1. Retrieval of Eligible Studies

MEDLINE, EMBASE, Science Citation
779 Articles on Initial Search

37 potentially eligible articles

Exposure to oral contraceptive pill not stated
analysis (2)
Stroke outcome not primary analysis (2)

33 articles for data abstraction

18 distinct study populations
Graph 1. Plot of Reported Odds Ratio (OR) versus Year in which Study Commenced.

Trendline omits the use of the outlier point *
<table>
<thead>
<tr>
<th>Study Set</th>
<th>Group/Author (Year of Publication) [reference]</th>
<th>Year(s) study conducted</th>
<th>Country(ies) of Study</th>
<th>#Reported Odds Ratio/ Relative risks and 95% CI Stroke Type</th>
<th>OR/RR 95%CI</th>
<th>Study Size (Case-control)</th>
<th>STUDY SIZE (Cohort)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>CGS (75)[38]*,(73)[39]. 1969-1971</td>
<td>North America</td>
<td>Throm Hemor</td>
<td>4.4 2.0</td>
<td>2.8-6.9 1.3-3.2</td>
<td>H:429 C:451</td>
<td>430</td>
</tr>
<tr>
<td>II</td>
<td>TRG (98)[40]*, (97)[41], (96)[42] 1993-1996</td>
<td>Europe</td>
<td>Throm</td>
<td>2.86 2.02-4.04</td>
<td>2.02-4.04</td>
<td>H:336 C:439</td>
<td>220</td>
</tr>
<tr>
<td>IV</td>
<td>NHS (88)[45]*, 90[46], 94[47] 1976-1984</td>
<td>North America</td>
<td>All strokes</td>
<td>0.96 0.74-1.25</td>
<td></td>
<td></td>
<td>93</td>
</tr>
<tr>
<td>V</td>
<td>CKP (96)[48]*, (97)[49], WCCS (79)[50], (78)[51] 1991-1994</td>
<td>North America</td>
<td>Throm Hemor</td>
<td>1.18 1.14</td>
<td>0.54-2.59 0.60-2.16</td>
<td>774</td>
<td>290</td>
</tr>
<tr>
<td>VI</td>
<td>WHO-2 (96)[52]*, (95)[44] 1989-1993</td>
<td>Africa, Asia, Europe, Latin America</td>
<td>Hemor Hemor</td>
<td>1.38 1.76</td>
<td>0.84-2.25 1.34-2.30</td>
<td>2910</td>
<td>1068</td>
</tr>
<tr>
<td>VII</td>
<td>Schwartz (97)[53]*, Longstreth (94)[54] 1991-1995</td>
<td>North America</td>
<td>All strokes</td>
<td>1.33 0.71-2.49</td>
<td></td>
<td></td>
<td>470</td>
</tr>
<tr>
<td>VIII</td>
<td>RCGP (94)[55]*, (83) [56] 1968-1990</td>
<td>UK</td>
<td>All strokes</td>
<td>1.5 1.1-2.0</td>
<td></td>
<td></td>
<td>759</td>
</tr>
<tr>
<td>IX</td>
<td>Lidegaard (93)[57]*, (95)[58],(95) [59] 1985-1989</td>
<td>Denmark</td>
<td>All strokes (stratified dose)</td>
<td>1.8 2.9</td>
<td>1.1-2.9 1.6-5.4</td>
<td>329</td>
<td>178</td>
</tr>
<tr>
<td>X</td>
<td>GHCPS (85) [60]*, (82)[61] 1980-1982</td>
<td>North America</td>
<td>All strokes</td>
<td>0.9 0.1-6.4</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>XI</td>
<td>Chang (86)[62] 1978-1980</td>
<td>Taiwan</td>
<td>All strokes</td>
<td>1.04 0.66-1.67</td>
<td></td>
<td>H:250 C:646</td>
<td>323</td>
</tr>
<tr>
<td></td>
<td>Study Details</td>
<td>Year Range</td>
<td>Location</td>
<td>Type</td>
<td>Odds Ratio (95% CI)</td>
<td>Controls</td>
<td>1</td>
</tr>
<tr>
<td>---</td>
<td>---------------</td>
<td>------------</td>
<td>----------</td>
<td>------</td>
<td>---------------------</td>
<td>----------</td>
<td>---</td>
</tr>
<tr>
<td>X</td>
<td>GHCPM (85)[60]*, (82)[61]</td>
<td>1980-1982</td>
<td>North America</td>
<td>All strokes</td>
<td>0.9</td>
<td>0.1-6.4</td>
<td></td>
</tr>
<tr>
<td>XI</td>
<td>Chang (86)[62]</td>
<td>1978-1980</td>
<td>Taiwan</td>
<td>All strokes</td>
<td>1.04</td>
<td>0.66-1.67</td>
<td>H:250</td>
</tr>
<tr>
<td>XII</td>
<td>Haapaniemi (97)[63]*, Hillbom (95)[64]</td>
<td>Not stated</td>
<td>Finland</td>
<td>All strokes</td>
<td>4.19</td>
<td>1.74-10.11</td>
<td>126</td>
</tr>
<tr>
<td>XIII</td>
<td>OFPAS (98)[65]*, (84)[66]</td>
<td>1968-1994</td>
<td>UK</td>
<td>Throm</td>
<td>2.4</td>
<td>1.1-5.1</td>
<td></td>
</tr>
<tr>
<td>XIV</td>
<td>Thorogood (92)[67]*, (81)[68]</td>
<td>1986-1988</td>
<td>UK</td>
<td>Hemor Throm</td>
<td>1.1</td>
<td>0.6-1.9</td>
<td>0.8-24.4</td>
</tr>
<tr>
<td>XV</td>
<td>IMAN (79)[69]</td>
<td>1976</td>
<td>UK</td>
<td>Hemor</td>
<td>1.36</td>
<td>0.64-2.92</td>
<td>109</td>
</tr>
<tr>
<td>XVI</td>
<td>Hirvonen (90)[70]</td>
<td>1975-1984</td>
<td>Finland</td>
<td>Hemor</td>
<td>0.36</td>
<td>0.18-0.9</td>
<td></td>
</tr>
<tr>
<td>XVII</td>
<td>Oleckno(88)[71]</td>
<td>1975-1983</td>
<td>North America</td>
<td>All strokes</td>
<td>2.51</td>
<td>^0.73-8.61</td>
<td>349</td>
</tr>
<tr>
<td>XVIII</td>
<td>Jick(78)[72]</td>
<td>1972</td>
<td>North America</td>
<td>All strokes</td>
<td>25.7</td>
<td>^5.7-115.3</td>
<td>56</td>
</tr>
</tbody>
</table>

*Main article used for data abstraction
# These values were plotted in Graph 2.
^ The 95% CI was calculated from these studies using Wolff's method.

**Abbreviations**

CGS: Collaborative Group for the Study of Stroke in young women
TRG: Transnational Research Group on oral contraceptives and the health of young women
WHO-1: WHO collaborative Study of cardiovascular disease and steroid hormone contraception (ischemic stroke)
NHS: Nurses' Health Study
CKP: California Kaiser Permanente
WCCS: Walnut Creek Contraceptive Study
WHO-2: WHO collaborative Study of cardiovascular disease and steroid hormone contraception (hemorrhagic stroke)
RCGP: Royal College General Practitioners' oral contraceptive study
GHCPM: Group Health Cooperative of Puget Sound
OFPA: Oxford Family Planning Association Study
UK: United Kingdom
OCP: Oral Contraceptive Pill
H: Hospitalized controls
C: Community-based controls
Throm: thrombotic Hemor: Hemorrhagic OCP: oral contraceptives
<table>
<thead>
<tr>
<th>Study (Year) Type</th>
<th>STUDY TYPE</th>
<th>Stroke Type</th>
<th>STROKE OUTCOME Definition</th>
<th>Independent Verification</th>
<th>Blind to OCP use</th>
<th>Type</th>
<th>OCP EXPOSURE Verification</th>
<th>Blinding</th>
</tr>
</thead>
<tbody>
<tr>
<td>CGS (75) [38]</td>
<td>CC</td>
<td>Thrombotic Hemorrhagic Others</td>
<td>Clinical, imaging, spinal tap, arteriographic</td>
<td>One neurologist</td>
<td>ns</td>
<td>ns</td>
<td>Interviews with no recall aids, by proxy</td>
<td>ns</td>
</tr>
<tr>
<td>TRG (98) [40]</td>
<td>CC</td>
<td>Thrombotic</td>
<td>Clinical, imaging, spinal tap, arteriographic</td>
<td>Monitoring Committee</td>
<td>ns</td>
<td>≥50ug, &lt;50ug</td>
<td>Patient interview with use of recall aids</td>
<td>ns</td>
</tr>
<tr>
<td>WHO (96) [43]</td>
<td>CC</td>
<td>Thrombotic</td>
<td>Clinical, imaging, spinal tap, arteriographic</td>
<td>Monitoring Committee</td>
<td>yes</td>
<td>&lt;50, ≥50ug</td>
<td>Interview with recall aids, proxy</td>
<td>ns</td>
</tr>
<tr>
<td>NHS (88) [45]</td>
<td>Cohort</td>
<td>Thrombotic Hemorrhagic Deaths</td>
<td>Clinical, imaging, spinal tap, arteriographic</td>
<td>ns</td>
<td>yes</td>
<td>ns</td>
<td>Patient questionnaire every two years</td>
<td>yes</td>
</tr>
<tr>
<td>CKP (96) [48]</td>
<td>CC</td>
<td>Thrombotic Hemorrhagic Death</td>
<td>Clinical, imaging, spinal tap, arteriographic</td>
<td>Two physicians</td>
<td>ns</td>
<td>&lt;50ug</td>
<td>Interview with recall aids, proxy</td>
<td>ns</td>
</tr>
<tr>
<td>WHO (96) [52]</td>
<td>CC</td>
<td>Hemorrhagic</td>
<td>Clinical, imaging, spinal tap, arteriographic</td>
<td>Monitoring Committee</td>
<td>yes</td>
<td>&lt;50, ≥50ug</td>
<td>Interview with recall aids, proxy</td>
<td>ns</td>
</tr>
<tr>
<td>Schwartz (97) [53]</td>
<td>CC</td>
<td>Thrombotic Hemorrhagic Deaths</td>
<td>Clinical, imaging, spinal tap, arteriographic</td>
<td>One neurologist</td>
<td>ns</td>
<td>≤50ug</td>
<td>Interview with recall aid, proxy</td>
<td>ns</td>
</tr>
<tr>
<td>RCGP (94) [55]</td>
<td>Nested CC</td>
<td>Thrombotic Hemorrhagic Deaths</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>Reporting by physician</td>
<td>ns</td>
</tr>
<tr>
<td>Lidegaard (93) [57]</td>
<td>CC</td>
<td>Thrombotic</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>75% on ≤50ug, 2% on &gt;100ug</td>
<td>Questionnaire</td>
<td>ns</td>
</tr>
<tr>
<td>Author (Year)</td>
<td>DESIGN</td>
<td>Stroke Type</td>
<td>Definition</td>
<td>Independent Verification</td>
<td>Blind to OCP use</td>
<td>Type</td>
<td>OCP EXPOSURE Verification</td>
<td>Blind to stroke presence</td>
</tr>
<tr>
<td>--------------</td>
<td>--------</td>
<td>---------------------</td>
<td>----------------</td>
<td>--------------------------</td>
<td>------------------</td>
<td>------</td>
<td>----------------------------------</td>
<td>--------------------------</td>
</tr>
<tr>
<td>GHCP S (85)[60]</td>
<td>Cohort</td>
<td>Thrombotic Hemorrhagic</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>39% on &lt;50ug, 59% on 50-80ug</td>
<td>Prescription</td>
<td>ns</td>
</tr>
<tr>
<td>Chang (86)[62]</td>
<td>CC</td>
<td>Thrombotic Hemorrhagic</td>
<td>ns</td>
<td>Two neurologists</td>
<td>ns</td>
<td>ns</td>
<td>Interview with recall aids</td>
<td>yes</td>
</tr>
<tr>
<td>Haapan (97)[63]</td>
<td>CC</td>
<td>Thrombotic</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>Interview</td>
<td>ns</td>
</tr>
<tr>
<td>OFPA (98)[65]</td>
<td>Cohort</td>
<td>Thrombotic Hemorrhagic</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>68% on ≤ 50ug</td>
<td>Interview</td>
<td>ns</td>
</tr>
<tr>
<td>Thorogoo (92)[67]</td>
<td>CC</td>
<td>Death from Thrombotic Hemorrhagic</td>
<td>Death certificate and medical records</td>
<td>ns</td>
<td>yes</td>
<td>ns</td>
<td>Interview physicians</td>
<td>ns</td>
</tr>
<tr>
<td>Inman (79)[69]</td>
<td>CC</td>
<td>Death from Hemorrhagic</td>
<td>Death certificates</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>Interview FP, family</td>
<td>ns</td>
</tr>
<tr>
<td>Hirvonen (90)[70]</td>
<td>Cohort</td>
<td>Death from Hemorrhagic</td>
<td>Autopsy and medical records</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>FP records</td>
<td>ns</td>
</tr>
<tr>
<td>Oleckno (88)[71]</td>
<td>CC</td>
<td>Thrombotic Hemorrhagic</td>
<td>Medical records</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Jick (78)[72]</td>
<td>CC</td>
<td>Thrombotic Hemorrhagic</td>
<td>Clinical, “Diagnostic tests”</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>Interviews</td>
<td>ns</td>
</tr>
</tbody>
</table>

**Key**
- Blinding: refers to study investigator/interviewers
- ns: not stated
- CC: case-control study
- OCP: oral contraceptive pill
- FP: family physician
Table 2. Continued

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>DESIGN</th>
<th>Stroke Type</th>
<th>Definition</th>
<th>Independent Verification</th>
<th>Blind to OCP use</th>
<th>Type</th>
<th>Verification</th>
<th>Blind to stroke presence</th>
</tr>
</thead>
<tbody>
<tr>
<td>GHCP (85)[60]</td>
<td>Cohort</td>
<td>Thrombotic Hemorrhagic</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>39% on &lt;50ug 59% on 50-80ug</td>
<td>Prescription</td>
<td>ns</td>
</tr>
<tr>
<td>Chang (86)[62]</td>
<td>CC</td>
<td>Thrombotic Hemorrhagic</td>
<td>ns</td>
<td>Two neurologists</td>
<td>ns</td>
<td>ns</td>
<td>Interview with recall aids</td>
<td>yes</td>
</tr>
<tr>
<td>Haapan (97)[63]</td>
<td>CC</td>
<td>Thrombotic</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>Interview</td>
<td>ns</td>
</tr>
<tr>
<td>OFPA (98)[65]</td>
<td>Cohort</td>
<td>Thrombotic Hemorrhagic</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>68% on &lt; 50ug</td>
<td>Interview</td>
<td>ns</td>
</tr>
<tr>
<td>Thorogoo (92)[67]</td>
<td>CC</td>
<td>Death from Thrombotic Hemorrhagic</td>
<td>ns</td>
<td>Death certificate and medical records</td>
<td>ns</td>
<td>yes</td>
<td>Interview physicians</td>
<td>ns</td>
</tr>
<tr>
<td>Inman (79)[69]</td>
<td>CC</td>
<td>Death from Hemorrhagic</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>Interview FP, family</td>
<td>ns</td>
</tr>
<tr>
<td>Hirvonen (90)[70]</td>
<td>Cohort</td>
<td>Death from Hemorrhagic</td>
<td>ns</td>
<td>Autopsy and medical records</td>
<td>ns</td>
<td>ns</td>
<td>FP records</td>
<td>ns</td>
</tr>
<tr>
<td>Oleckno (88)[71]</td>
<td>CC</td>
<td>Thrombotic Hemorrhagic</td>
<td>ns</td>
<td>Medical records</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Jick (78) [72]</td>
<td>CC</td>
<td>Thrombotic Hemorrhagic</td>
<td>Clinical, &quot;Diagnostic tests&quot;</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>Interviews</td>
<td>ns</td>
</tr>
</tbody>
</table>

Key
Blinding: refers to study investigator/interviewers
ns: not stated
CC: case-control study
OCP: oral contraceptive pill
FP: family physician
<table>
<thead>
<tr>
<th>OR</th>
<th>95% CI</th>
<th>OR</th>
<th>95% CI</th>
<th>OR</th>
<th>95% CI</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.2</td>
<td>0.8, 1.7</td>
<td>1.0</td>
<td>0.8, 1.2</td>
<td>0.9</td>
<td>0.6, 1.2</td>
<td>0.7</td>
<td>0.4, 1.3</td>
</tr>
</tbody>
</table>

Table 4: Articles used in the calculation of odds ratios for various subgroups
Table 5. Pooled Odds Ratio From Various Studies by Exposure Type, Stroke Outcomes and Risk Factors

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Studies Pooled [reference]</th>
<th>OR, (95% CI)</th>
<th>OR, (95% CI)</th>
<th>Heterogeneity p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Studies*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All users</td>
<td>[38,40,43,45,48, 52,53,55,57,60,62 63,65,67,69,70,71 72]</td>
<td>1.82 (1.66-2.00)</td>
<td>1.86 (1.37-2.54)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Current users</td>
<td>[38, 40, 43, 48, 52, 53, 57, 60, 63, 65, 67, 69, 70, 72]</td>
<td>2.07 (1.85-2.32)</td>
<td>3.92 (1.31-2.82)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Ever-users</td>
<td>[45, 55, 62, 71]</td>
<td>1.16 (0.97-1.39)</td>
<td>1.21 (0.86-1.71)</td>
<td>0.0874</td>
</tr>
<tr>
<td>By Stroke Types</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombotic</td>
<td>[38,40,43,48,53,55,65, 67]</td>
<td>3.06 (2.54-3.68)</td>
<td>2.90 (2.23-3.78)</td>
<td>0.0589</td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td>[38,48,52,53,55,67,69, 70]</td>
<td>1.45 (1.23-1.71)</td>
<td>1.30 (0.99-1.71)</td>
<td>0.0471</td>
</tr>
<tr>
<td>Death</td>
<td>[67,69,70]</td>
<td>0.99 (0.70-1.38)</td>
<td>0.94 (0.51-1.74)</td>
<td>0.0557</td>
</tr>
<tr>
<td>Type of OCP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Specified _≤50ug</td>
<td>[38,40,48,52,53,57,67, 70]</td>
<td>1.85 (1.59-2.15)</td>
<td>1.75 (1.35-2.26)</td>
<td>0.0029</td>
</tr>
<tr>
<td>2&lt;sup&gt;rd&lt;/sup&gt; Generation</td>
<td>[40,43,48,52,53,55]</td>
<td>2.43 (1.92-3.09)</td>
<td>2.35 (1.81-3.05)</td>
<td>0.1863</td>
</tr>
<tr>
<td>3&lt;sup&gt;rd&lt;/sup&gt; Generation</td>
<td>[40,43]</td>
<td>2.87 (1.84-4.48)</td>
<td>2.87 (1.84-4.48)</td>
<td>0.6055</td>
</tr>
<tr>
<td>Risk Factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-smokers</td>
<td>[38,40,43,48,52,53,55, 71]</td>
<td>1.92 (1.58-2.34)</td>
<td>1.86 (1.46-2.37)</td>
<td>0.0068</td>
</tr>
<tr>
<td>Smokers</td>
<td>[38,40,43,48,52,53,55,57 65,72]</td>
<td>2.76 (2.30-3.32)</td>
<td>3.50 (2.17-5.64)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Normotensive</td>
<td>[38,40,43,48,52,53,55,57 60,65,69,72]</td>
<td>1.93 (1.69-2.20)</td>
<td>2.06 (1.46-2.92)</td>
<td>0.0006</td>
</tr>
<tr>
<td>Hypertensive</td>
<td>[38,40,43,52,55]</td>
<td>9.69 (7.14-13.17)</td>
<td>9.82 (6.97-13.84)</td>
<td>0.1654</td>
</tr>
<tr>
<td>Criteria</td>
<td>Studies Pooled</td>
<td>OR, (95% CI)</td>
<td>OR, (95% CI)</td>
<td>Heterogeneity p-value</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>----------------</td>
<td>--------------</td>
<td>--------------</td>
<td>-----------------------</td>
</tr>
<tr>
<td>Study Design</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cohort studies</td>
<td>[45, 60, 65, 70]</td>
<td>0.96 (0.76-1.22)</td>
<td>0.95 (0.51-1.78)</td>
<td>0.0107</td>
</tr>
<tr>
<td>Case-control studies</td>
<td>[38, 40, 43, 48, 52]</td>
<td>1.99 (1.79-2.22)</td>
<td>2.08 (1.52-2.85)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Type of Controls</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Community</td>
<td>[38, 40, 48, 53, 55, 57, 62]</td>
<td>1.66 (1.45-1.90)</td>
<td>1.70 (1.35-2.13)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Hospital</td>
<td>[38, 40, 43, 52, 57, 63, 72]</td>
<td>2.36 (2.06-2.71)</td>
<td>2.85 (1.65-4.93)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Status of OCP use in comparison group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-current users</td>
<td>[38, 40, 43, 48, 52, 53, 60, 69, 70, 71, 72]</td>
<td>2.08 (1.83-2.37)</td>
<td>1.91 (1.21-3.02)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Never users</td>
<td>[45, 55, 57, 62, 65, 67]</td>
<td>1.27 (1.09-1.49)</td>
<td>1.55 (1.06-2.27)</td>
<td>0.9006</td>
</tr>
</tbody>
</table>

*Using Hospital controls, and comparing to non-users of OCP

Abbreviation

OR: Calculated OR accounting for within study variability only

OR: Calculated OR accounting for the presence of between and within study variability.
Graph 2. Pooled Odds Ratio of Studies
Investigating the Risk of All Strokes and Oral Contraceptive Pill Use

Reference

[38]
[38]
[40]
[43]
[43]
[45]
[48]
[48]
[52]
[52]
[53]
[55]
[57]
[57]
[60]
[62]
[63]
[65]
[67]
[67]
[69]
[70]
[71]
[72]

Pooled OR
Graph 3. Pooled Odds Ratio of Studies Investigating the Risk of Thrombotic Strokes and Oral Contraceptive Pill Use
Graph 4. Pooled Odds Ratio of Studies Investigating Hemorrhagic Stroke and Oral Contraceptive Pill Use
Graph 5. Pooled Odds Ratio of Studies Investigating Stroke Deaths and Oral Contraceptive Pill Use
Graph 6. Funnel Plot Exploring Publication Bias: Graph of Sample Size Versus Natural Logarithm of Odds Ratio
Appendix 1. Data Collection

Reader:  

Background
1. Study Type:
   a. Cohort-retrospective
   b. Cohort-prospective
   c. Case-control
   d. Cross-sectional
   e. Other: ________________________________
   f. Cannot Determine

Section 1a: Study population – Case-control/ Cross-sectional

1. Country(ies) of Study:

2. Age of population at risk:

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Cases (circle)</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Range
Mean
Standard deviation

3. Source of cases:
   a. Hospital/ Medical records
   b. Registry/Data base
   c. Self reporting
   d. Other: ________________________________
   e. Unspecified

4. Source of controls:
   a. Community/Ambulatory
   b. Hospital-based
   c. Other: ________________________________
   d. Unspecified
Section 1b: Study population -Cohort

1. Year of inception of cohort:

2. Years of follow-up:
   Range: ____________________________
   Mean: ____________________________ SD: ____________________________

3. Age of cohort:
   Range: ____________________________
   Mean: ____________________________ SD: ____________________________

4. Source of cohort:
   a. Hospital/Medical records
   b. Registry/Data base
   c. Self reporting
   d. Other: ____________________________
   e. Unspecified

Section 2. Exposure

1. Verification of exposure (circle all methods):
   a. Patient interview with no recall aids
   b. Patient interview with use of recall aids
   c. Prescription
   d. By proxy
   e. Cannot determine

2. Exposure Type:
   a. Ethinyl estradiol
   b. mestranol
   c. Other: ____________________________
   d. Not Specified
3a. Estradiol dose (in ≥75% of population)
   a. 35-50 ug
   b. 30-35 ug
   c. <30 ug
   d. Not specified

3b. Mestranol dose (in ≥75% of population)
   a. ≤ 75 mg
   b. Not specified

3. Progestin type (circle all appropriate):
   a. Norgestimate
   b. Desogestrel
   c. Gestodene
   d. Levonorgesterol
   e. Other: _______________________________
   f. Not specified

Section 3. Stroke Outcome

1. Outcome: stroke type
   a. hemorrhagic
   b. ischemic
   c. Both
   d. Stroke Deaths
   e. Unspecified
   f. Other: _______________________________

2. Verification of Outcome:
   a. Imaging Studies
   b. History only
      ➔Criteria used: _______________________________
   c. Cannot determine
   d. Other: _______________________________

3. Definition of Stroke (please state):
**Section 4: Blinding**

1. Blinding of Investigators to patients’ exposure when diagnosing stroke outcome (cohort):
   - a. Yes
   - b. No
   - c. Cannot Determine

2. Blinding of Investigators to patients’ outcomes when determining exposure (case-control):
   - a. Yes
   - b. No
   - c. Cannot Determine

**Section 5. Confounders Matched or Considered in the Study:**

1. Confounders:
   - a. Hypertension → Yes No
   - b. Smoking → Yes No
   - c. Age → Yes No
   - d. Geographical location → Yes No
   - e. Previous strokes → Yes No
   - f. Migraine → Yes No
   - g. Diabetes → Yes No
   - h. Family history of stroke → Yes No
   - i. Body mass index → Yes No
   - j. Alcohol → Yes No
   - k. Status of OCP use (e.g. current vs previous, etc) → Yes No
   - l. Any thrombophilia → Yes No
      → specify type
   - m. Others:
      (List below)

If Yes, state matched or No
**Section 6. Analysis**

1. Raw data (all strokes):

<table>
<thead>
<tr>
<th></th>
<th>OCP</th>
<th>No OCP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cases (stroke type)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Control (source)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
2. Adjusted odds ratio/ relative risks (please circle)
For *what stroke outcomes* :
(Use a different table for different stroke outcomes-thanks)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Cases (n)</th>
<th>Controls (n)</th>
<th>OR/RR</th>
<th>95% CI</th>
<th>Factors adjusted/matched for:</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>b.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>c.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>b.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>c.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>b.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>c.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Variable</td>
<td>Cases (nos)</td>
<td>Controls (nos)</td>
<td>OR/RR</td>
<td>95% CI</td>
<td>Factors adjusted/matched for:</td>
<td>Comments</td>
</tr>
<tr>
<td>----------</td>
<td>-------------</td>
<td>----------------</td>
<td>-------</td>
<td>-------</td>
<td>-------------------------------</td>
<td>----------</td>
</tr>
<tr>
<td>4.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>b.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>c.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>b.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>c.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>