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Oral Contraceptives and Venous Thromboembolism

A Systematic Review and Meta-Analysis

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Abstract

Background: An association between oral contraceptive (OC) use and venous thromboembolism (VTE) has long been recognized. However, no summary estimates of the increase in VTE risk associated with OC use have been available since 1995, and no meta-analyses have evaluated the VTE risk of new preparations containing drospirenone.

Objective: The aim of the study was to carry out a meta-analysis to summarize existing evidence on the association between venous VTE and OC use, and to investigate how such an association may vary according to the type of OC, OC user characteristics, study characteristics and biases.

Methods: Relevant cohort or case-control studies were searched in MEDLINE and other electronic databases up to May 2010, with no language restriction. Data were combined using a generic inverse-variance approach. Meta-regression in addition to stratification was used to explore potential predictors of the summary estimate of risk.

Results: Sixteen cohort and 39 case-control studies were included in at least one comparison. Overall, the odds ratio (OR) of OC users versus non-users was 3.41 (95% CI 2.98, 3.92). This estimate was based upon nine cohort studies evaluating approximately 12 000 000 person-years, and 23 case-control studies including approximately 45 000 women. VTE risk for OC users was significantly lower in studies evaluating 'all VTE cases' than in those evaluating 'idiopathic VTE only' (OR 3.09 and 4.94, respectively). Among the carriers of genetic mutations G20210A and Factor V Leiden (FVL), OC users showed a significantly increased VTE risk compared with non-users (OR 1.63; 95% CI 1.01, 2.65, and OR 1.80; 95% CI 1.20, 2.71, respectively). When the newest OCs containing drospirenone were compared with non-drospirenone-containing OCs (except those containing levonorgestrel only), VTE risk did not significantly increase (OR 1.13; 95% CI 0.94, 1.35).

Conclusions: This meta-analysis confirms that OC use significantly increases VTE risk. The strength of this association, however, varies according to the generation of OC, type of outcome and presence of a genetic mutation, with ORs ranging from 3 to 5.

1. Background

Oral contraceptives (OCs) are currently used by approximately 11 million women in the US,[1] and more than 100 million women worldwide.[2]

An association between OC use and venous thromboembolism (VTE) has long been recognized[3] and has been confirmed in a number of observational studies.[4-9] The magnitude of the association, however, varied widely across studies and within the same study according to several variables, including type of OC, oestrogen dose, women's age, presence of some genetic mutations, duration of OC use, study design, study setting and, more recently, outcome definition (i.e. idiopathic VTE only vs all VTE cases).[6,10-13]

No summary estimates of the increase in VTE risk associated with OC use have been available since 1995, when the last meta-analysis was published.[14] Moreover, no meta-analyses have evaluated the VTE risk of the newest preparations containing drospirenone, which are among the most commonly prescribed OCs in Western countries.[15] We carried out a meta-analysis to summarize the existing evidence on the association between VTE and OC use, as well as to investigate how any association may vary according to the type of OC, characteristics of users and study characteristics. Because meta-analysis of observational studies may be strongly affected by single-study biases and heterogeneity, we also focused on the potential impact of confounders using stratification and meta-regression.

2. Materials and Methods

2.1 Bibliographic Search and Data Extraction

Studies evaluating the risk of thromboembolism in users of OCs versus non-users (or users of a different OC preparation) were initially searched in MEDLINE (to May 2010) using the following search strategy: (thrombosis OR thromboembolism* OR pulmonary embolism* OR thrombophlebitis) AND (contraceptive* OR estrogen* OR oestrogen* OR ethinyl estradiol OR levonorgestrel OR norgestrel OR norgestimate OR gestodene OR desogestrel OR drospirenone OR cyproterone OR norethisterone OR lynesterol) as words in the title/abstract. Additional searches in EMBASE and Healthstar were carried out using the above terms; experts were consulted and bibliographies of relevant articles, including reviews and meta-analyses, were systematically reviewed. No language restriction was applied. Inclusion criteria were (i) cohort or case-control design; (ii) enough data were provided to compare the risk of thromboembolism (venous thrombosis and/or pulmonary embolism) between users of OCs and non-users; and (iii) OCs were administered with the main aim of preventing pregnancy, and the sample was therefore composed of women aged 16 years or older without diseases precluding delivery (e.g. polycystic ovarian syndrome).

Several papers reported different analyses of databases from some large longitudinal studies. To avoid duplication of data from the same subjects, information was selected using the following criteria, in order of priority: availability of data, higher level of statistical adjustment (the multivariate model including the highest number of potential confounders), larger sample size and longer follow-up. Despite some of the included studies using the same databases, they were included in different comparisons and an effort was made to avoid duplication of data.

Each included article was independently evaluated by two reviewers (LM, CDV), who extracted main study characteristics and relevant relative risks (in terms of odds ratio [OR] or hazard ratio [HR]), and 95% confidence intervals (CI), standard errors (SEs) or p-values (or all data useful to derive such estimates). In case of ambiguous information of discrepancies in the data extracted by the two reviewers, a third author was contacted (PV) and consensus achieved through discussion.

We decided *a priori* not to use a formal quality scoring, but rather to examine the potential influence on overall estimates of single-study characteristics, including design, level of statistical adjustment, type of setting, sample size and outcome definition.

2.2 Data Analysis

Data have been combined using a generic inverse-variance approach[16] and, in order to account for between-study variance, the random-effect method

was adopted.[17] This approach enables the inclusion of diverse estimates of relative risk (i.e. OR and HR) into the same meta-analysis. Notably, the absolute risk of thromboembolism for OC users is small, therefore the ORs accurately estimate relative risks.

The generic inverse-variance model requires an estimate of the SE, but most papers did not report such information. In these cases, SEs were computed from 95% CI following a standard methodology.[16] When both SE and 95% CI were not presented, but the exact p-value was reported, the SE was estimated using the 'p2ci' tool of Stata software (StataCorp LP, College Station, TX, USA).[18]

If a paper reported the results of different multivariate models, the best adjusted, most comprehensive estimates were extracted. In the few cases of data not fully reported (i.e. HR/OR 0.75 and p-value between 0.001 and 0.01), a deductive process was used; in the above example, a p-value of 0.0099 was assigned.

Between-study heterogeneity was quantified using the I^2 statistic.[19] Potential publication bias was assessed graphically, using funnel plots (displaying the ORs of individual comparisons vs the logarithm of their SE);[20] and formally, using Egger's regression asymmetry test.[21] Finally, the impact of potential publication bias was evaluated by excluding 'smaller' studies (arbitrarily defined as those smaller than the median: $n < 700$ for case-control studies; <50 000 person-years for cohort studies), which are less likely to be published than larger ones in case of non-significant results.[19] In case it was not possible to derive the sample size, a study was assigned to the 'smaller' group.

The units of the meta-analysis were single comparisons of OC users versus non-users, with or without past users,[5,13,14,22,23] or between users of different OCs in predicting thromboembolism during the scheduled follow-up. Accordingly, when a study only reported relative risks, or reported separate relative risks for different OC preparations or characteristics (i.e. age classes), the overall estimate of risk for users was calculated from the separate HR/OR available using the fixed-effect model for generic inverse-variance outcomes.[24]

Several stratified meta-analyses were made to explore the patterns of risk in subgroups of users that may be less or more susceptible to bias, as well as to explore the potential difference in the risk associated with the various OC preparations. In particular, stratification factors were study design (cohort or case-control), setting (hospital- or population-based), outcome (only idiopathic VTE considered, with all cases of women who were at risk of VTE being excluded, or all VTE considered), multivariate analysis (adjusted or unadjusted estimates, which also included those adjusted for age only), funding source (non-profit, not reported, funded by one or more pharmaceutical companies), age (≥25 years or <25 years), smoking (current or non-smoking) and presence of one of the three most commonly evaluated genetic polymorphisms:[11,25] heterozygosity or homozygosity for polymorphism G20210A (prothrombin gene); heterozygosity or homozygosity for polymorphism G1691A (Factor V Leiden mutation [FVL]); and homozygosity for polymorphism C677T (methylenetetrahydrofolate reductase [MTHFR]). Finally, stratified meta-analyses were made according to duration of OC use (<1 year or ≥1 year), oestrogen dose (<50 μg or ≥50 μg), OC generation (second, including levonorgestrel, norgestrel and norgestimate;[26-28] third, including desogestrel and gestodene;[29] or fourth, including drospirenone) and most commonly used OC drug (levonorgestrel, desogestrel, gestodene and drospirenone).

In those meta-analyses where data from more than 20 studies were available, the independent association between variables related to study or sample characteristics and biases with estimates of VTE risk was also examined by means of meta-regression analyses with multiple co-variates.[30] In order to reduce potential overfitting and false positive results, the number of variables included in both final and intermediate models (during modelling) was limited to three.[31]

All meta-analyses were performed using RevMan software, version 5.0 (Cochrane Collaboration, Oxford, UK, 2007). STATA, version 10.1 (2007) was used to estimate SE from 95% CI, perform meta-regression and test for publication bias.

3. Results

Of the 2806 papers initially retrieved (figure 1), 55 studies met inclusion criteria and were included in at least one stratified meta-analysis: 16 were cohort studies,[8,32-46] and 39 were case-control studies.[4-7,9,10,22,27,47-77] The main characteristics of these studies are available in table S1 (see Supplemental Digital Content [SDC], http://links.adisonline.com/DSZ/A62).

3.1 Overall Meta-Analysis: All Oral Contraceptive (OC) Users vs Non-Users

Thirty-two studies (9 cohort[8,32-36,38,40,43] and 23 case-control studies[4,6,25,27,47-49,51-57,61,62,65,67,70,71,73,75,77]) were included in the overall meta-analysis comparing VTE risk in all OC users versus non-users regardless of OC type, dosage or any other stratification. These studies were published from 1967 to 2009, and most were performed in Western countries (nine in the US; six in the UK; three in Denmark, Germany and the Netherlands; five in other European countries; and three in countries outside Europe and North America). The nine cohort studies totalled more than 11 939 260 person-years (although the sample size could not be extracted from one study), while the 23 case-control studies included more than 44 932 women overall (again, sample size was unavailable in one study).

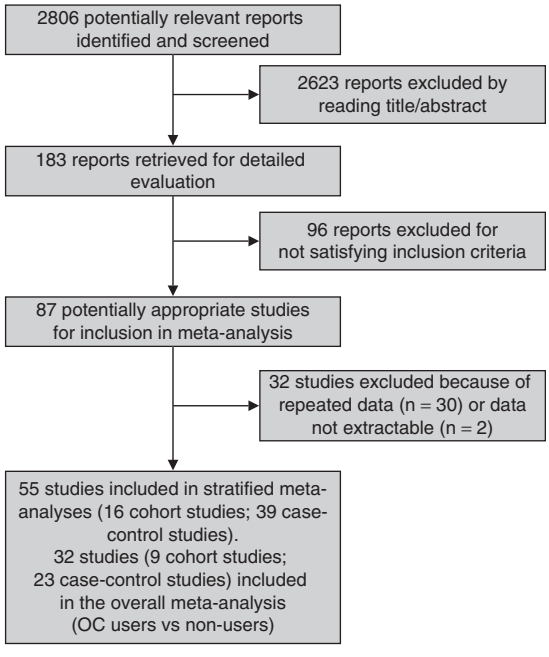

Fig. 1. Flow of the included studies in each stage of the bibliographic search. **OC** = oral contraceptive.

Compared with non-users, women taking OCs of any type were significantly more likely to experience an episode of VTE in 28 of 32 studies than non-users, and the overall OR associated with OC use was 3.41 (95% CI 2.98, 3.92 [table I]). The exclusion of studies published before 1976 (in which only first-generation OCs could be plausibly evaluated) did not change the overall estimate. Overall, the risk of VTE in OC users versus non-users appeared lower in cohort studies (2.91; 95% CI 2.33, 3.62) than in case-control studies (3.60; 95% CI 3.01, 4.31 [see figure S1, SDC]), although CIs overlapped.

3.2 Meta-Analyses Stratified According to Study or Sample Characteristics

As shown in table I, cohort studies showed lower summary estimates of risk compared with case-control studies in most stratified meta-analyses. Besides study design, the risk of VTE for OC users compared with non-users was lower in population-based studies (OR 3.31 vs OR 4.19 in hospital-based studies), in studies evaluating all VTE rather than idiopathic VTE only (OR 3.09 and 4.94, respectively [see figures S2 and S3, SDC]), in studies (co)sponsored by one or more pharmaceutical companies (OR 2.70 vs 4.14 in studies funded by non-profit institutions) and in non-smokers (OR 2.00 vs OR 5.40 among current smokers). Only marginal differences in summary estimates were observed according to the level of statistical adjustment, sample size and age of participants. A significant increase in VTE risk was observed among OC users versus non-users who were also carriers of two genetic mutations: G20210A (OR 1.63; 95% CI 1.01, 2.65), and FVL (OR 1.80; 95% CI 1.20, 2.71), whereas only one study reported data on MTHFR mutation (OR 2.73; 95% CI 0.78, 9.56) and it was non-significant. Notably, the reported ORs for genetic

Table I. Risk of VTE of OC users vs non-users, overall and according to selected study and sample characteristics. All meta-analyses are based on a generic inverse-variance approach

Variables	No. of studies	VTE risk		
		OR (95% CI)	p-Value	I^2 (%)[a]
All studies	**32**	**3.41 (2.98, 3.92)**	<**0.001**	**74**
Cohort design[8,32-36,38,40,43]	9	2.91 (2.33, 3.62)	<0.001	64
Case-control design[4,6,9,10,47-57,62,64,65,67,70,71,73,75,77]	23	3.60 (3.01, 4.31)	<0.001	73
All studies excluding those published before 1976 (first-generation OC)[4,6,8-10,33-36,38,40-43,52-57,61,62,64,65,67,68,73,75,77]	28	3.28 (2.85, 3.78)	<0.001	75
Population-based studies only	**23**	**3.31 (2.84, 3.85)**	<**0.001**	**76**
Cohort design[8,32,33,35,36,38,43]	7	2.81 (2.17, 3.62)	<0.001	67
Case-control design[4-6,9,10,27,47,52,56,57,65,67,70,71,73,75,77]	16	3.49 (2.86, 4.25)	<0.001	73
Hospital-based studies only				
Case-control design[4,5,10,48-50,53-55,61,62]	11	4.19 (3.19, 5.50)	<0.001	69
Studies on idiopathic VTE only	**15**	**4.94 (4.23, 5.78)**	<**0.001**	**0**
Cohort design[33-36]	4	4.47 (2.84, 7.03)	<0.001	0
Case-control design[6,10,48,49,51-54,56,67,71]	11	5.01 (4.24, 5.92)	<0.001	0
Studies with mixed VTE only	**22**	**3.09 (2.67, 3.58)**	<**0.001**	**78**
Cohort design – population-based[8,32,38,40,43]	5	2.61 (2.07, 3.30)	<0.001	73
Case-control design – all[4,6,9,10,27,47,52,53,55-57,60,61,65,70,73,75,77]	17	3.26 (2.67, 3.98)	<0.001	76
Case-control design – population-based[4,6,9,10,27,47,52,56,57,65,70,73,75,77]	13	3.38 (2.72, 4.20)	<0.001	78
Case-control design – hospital-based[42,55,60,61]	4	2.72 (1.40, 5.30)	0.003	71
Adjusted studies[b]	**17**	**3.54 (2.98, 4.21)**	<**0.001**	**82**
Cohort design[8,32-34,40]	5	2.77 (2.12, 3.62)	<0.001	77
Case-control design[4,9,10,27,48,49,53-55,61,70,75,77]	12	3.99 (3.17, 5.03)	<0.001	78
Unadjusted studies[b]	**15**	**3.22 (2.50, 4.14)**	<**0.001**	**57**
Cohort design[35,36,38,43]	4	3.46 (2.22, 5.38)	<0.001	16
Case-control design[6,47,51-53,56,57,62,67,71,73]	11	3.10 (2.28, 4.20)	<0.001	66
Smaller studies[c]	**16**	**3.87 (3.12, 4.81)**	<**0.001**	**51**
Cohort design[33,34,36,40]	4	3.95 (2.54, 6.14)	<0.001	38
Case-control design[47-49,52,53,56,57,61,65,67,70,71]	12	3.85 (2.96, 5.01)	<0.001	57
Larger studies[c]	**16**	**3.41 (2.98, 3.92)**	<**0.001**	**82**
Cohort design[8,32,35,38,43]	5	2.58 (1.96, 3.39)	<0.001	73
Case-control design[4,6,9,10,27,51,54,55,62,73,75,77]	11	3.40 (2.64, 4.39)	<0.001	82
Age ≥25 years only[d]	**7**	**3.95 (2.37, 6.58)**	<**0.001**	**88**
Cohort design[35]	1	3.33 (1.36, 8.18)	0.009	NA
Case-control design[9,27,48,50,54,55]	6	4.05 (2.32, 7.10)	<0.001	90
Age <25 years only	**7**	**3.32 (2.45, 4.51)**	<**0.001**	**30**
Cohort design[35]	1	1.40 (0.13, 15.3)	0.08	NA
Case-control design[9,27,48,50,54,55]	6	3.37 (2.44, 4.64)	<0.001	38
Funding source				
Funded by non-profit institutions[4,6,9,34-36,43,48,51,53,55-57,61,70,75,77]	16	4.14 (3.43, 4.99)	<0.001	53
Funding source not reported[38,47,49,62,65,67,71,73]	8	3.15 (2.20, 4.52)	<0.001	69
Funded by one or more pharmaceutical companies[8,10,27,32,33,40,52,54]	8	2.70 (2.21, 3.31)	<0.001	78
Current smokers only				
Case-control design[4,61,66,77]	4	5.04 (3.21, 7.92)	<0.001	70

Continued next page

Table I. Contd

Variables	No. of studies	VTE risk		
		OR (95% CI)	p-Value	I^2 (%)[a]
Non-smokers only				
Case-control design[4,61,66,77]	4	2.00 (0.74, 5.37)	0.2	95
G20210A only	**4**	**1.63 (1.01, 2.65)**	**0.046**	**36**
Cohort design[44]	1	1.31 (0.47, 3.62)	0.6	NA
Case-control design[65,74,75]	3	1.67 (0.90, 3.09)	0.11	53
FVL only	**7**	**1.80 (1.20, 2.71)**	**0.005**	**50**
Cohort design[44]	1	3.30 (0.67, 16.3)	0.14	NA
Case-control design[17,61,65,71,74,75]	6	1.74 (1.14, 2.67)	0.01	54
MTHFR only				
Case-control design[75]	1	2.73 (0.78, 9.56)	0.11	NA

a Higher I^2 values indicate higher between-study heterogeneity.

b A study was 'adjusted' if the OR was adjusted for age and other factors (i.e. parity, obesity, etc.); 'unadjusted' if the OR was adjusted for age only or unadjusted.

c A study was 'smaller' if the sample size was below the median (n = 700 for case-control studies; 50 000 person-years for cohort studies).

d Except for the studies by van Hylckama et al.[9] and WHO,[55] in which the age cutoff was 30 years instead of 25 years.

FVL = Factor V Leiden; **MTHFR** = methylenetetrahydrofolate reductase; **NA** = not applicable; **OC** = oral contraceptive; **OR** = odds ratio; **VTE** = venous thromboembolism.

mutations are referred to the comparison between OC users and non-users in samples where both users and non-users are carriers of the same mutation, which in turn is associated with a relevant increase in VTE risk.[25]

3.3 Meta-Analyses Stratified According to OC Characteristics

The summary OR of the ten studies that included only OC users who had been taking OCs for ≤1 year was 5.28 compared with non-users (95% CI 4.27, 6.55), while the OR of women treated with OCs for >1 year was 3.52 versus non-users (95% CI 2.83, 4.37) [table II]. Differences in VTE risk were also observed according to oestrogen dose: women taking OCs containing <50 μg oestogren had an overall OR of 3.59 (95% CI 3.01, 4.27), while those taking ≥50 μg had an OR of 5.21 (95% CI 3.63, 7.47) compared with non-users. Such a pattern was confirmed in the meta-analysis of direct comparisons between users of OCs at doses ≥50 μg versus users of OCs at doses <50 μg (OR 1.42; 95% CI 1.15, 1.76).

Differences in VTE risk were also observed according to OC generation. Compared with non-users, use of second-generation OCs was associated with the lowest increase in VTE risk (OR 2.92; 95% CI 2.29, 3.72); the OR of third-generation OCs was 4.73 (95% CI 3.48, 6.43); and the OR of fourth-generation OCs was 3.44 (95% CI 1.89, 6.25). The significant increase in risk associated with third-generation OCs compared with second-generation OCs was confirmed in the meta-analysis directly comparing third- versus second-generation OC users (OR 1.57; 95% CI 1.24, 1.98).

The results of the meta-analyses restricted to individual drugs were in line with the above results; levonorgestrel use showed the lowest VTE risk increase compared with non-OC users (OR 2.88) and desogestrel the highest (OR 4.88). Even the newest preparations (containing drospirenone) were associated with a significantly higher VTE risk compared with levonorgestrel (OR 1.65; $p < 0.001$). By contrast, when drospirenone-containing OCs were compared with all other OCs, the VTE risk did not significantly increase (OR 1.13; 95% CI 0.94, 1.35).

3.4 Meta-Regression

Multiple meta-regression analyses showed that, among the variables related to sample or study characteristics, the only co-variate that significantly

Table II. Risk of VTE of OC users vs non-users, according to selected OC characteristics. All meta-analyses are based upon a generic inverse-variance approach

Variables	No. of studies	VTE risk		
		OR (95% CI)	p-Value	I^2(%)[a]
Duration of use <1 year only	**10**	**5.28 (4.27, 6.55)**	**<0.001**	**64**
Cohort design[8]	1	4.17 (3.73, 4.66)	<0.001	NA
Case-control design[4,9,27,48,49,54,68,72,75]	9	5.62 (4.46, 7.07)	<0.001	46
Duration of use ≥1 year only	**10**	**3.52 (2.83, 4.37)**	**<0.001**	**87**
Cohort design[8]	1	2.87 (2.70, 3.06)	<0.001	NA
Case-control design[4,9,48,49,54,64,68,72,75]	9	3.64 (2.86, 4.64)	<0.001	78
Oestrogen dose <50 μg only	**9**	**3.59 (3.01, 4.27)**	**<0.001**	**75**
Cohort design[8,36]	2	3.23 (3.04, 3.45)	<0.001	0
Case-control design[4-6,27,48,54,57]	7	3.75 (2.90, 4.85)	<0.001	69
Oestrogen dose ≥50 μg only	**5**	**5.21 (3.63, 7.47)**	**<0.001**	**35**
Cohort design[36]	1	10.3 (1.74, 60.9)	0.01	NA
Case-control design[4-6,54]	4	5.11 (3.50, 7.46)	<0.001	43
Oestrogen dose ≥50 μg vs <50 μg	**5**	**1.42 (1.15, 1.76)**	**0.001**	**0**
Cohort design[33,36,37,45]	4	1.35 (1.07, 1.71)	0.01	0
Case-control design[9]	1	1.90 (1.08, 3.34)	0.03	NA
Only second-generation OCs	**11**	**2.92 (2.29, 3.72)**	**<0.001**	**82**
Cohort design[8,32,40,43]	4	2.10 (1.72, 2.57)	<0.001	30
Case-control design[4,6,9,10,27,57,70]	7	3.44 (2.72, 4.33)	<0.001	64
Only third-generation OCs	**10**	**4.73 (3.48, 6.43)**	**<0.001**	**84**
Cohort design[8,40,43]	3	3.24 (2.13, 4.93)	<0.001	63
Case-control design[4,6,9,10,27,57,70]	7	5.65 (3.65, 8.75)	<0.001	82
Only fourth-generation OCs (drospirenone only)	**3**	**3.44 (1.89, 6.25)**	**<0.001**	**86**
Cohort design[8,32]	2	2.83 (1.39, 5.74)	0.004	NA
Case-control design[9]	1	6.30 (2.90, 13.7)	<0.001	92
Third- vs second-generation OCs	**18**	**1.57 (1.24, 1.98)**	**<0.001**	**79**
Cohort design[8,39-42,45]	6	1.88 (1.09, 3.26)	0.02	88
Case-control design[4,6,7,9,10,57,63,64,66,69,70,76]	12	1.39 (1.14, 1.71)	0.002	53
Levonorgestrel vs non-OC use	**11**	**2.88 (2.26, 3.66)**	**<0.001**	**74**
Cohort design[8,32,40,43]	4	2.04 (1.79, 2.31)	<0.001	0
Case-control design[6,9,57,58,64,70,75]	7	3.47 (2.86, 4.22)	<0.001	23
Desogestrel vs non-OC use	**7**	**4.88 (3.02, 7.88)**	**<0.001**	**82**
Cohort design[40]	1	2.09 (1.44, 3.04)	<0.001	NA
Case-control design[6,9,57,58,62,64]	6	5.87 (4.19, 8.20)	<0.001	48
Gestodene vs non-OC use	**5**	**4.41 (2.59, 7.51)**	**<0.001**	**79**
Cohort design[40]	1	2.25 (1.40, 3.61)	<0.001	NA
Case-control design[6,9,58,64]	4	5.36 (3.04, 9.42)	<0.001	74
Desogestrel vs levonorgestrel	**12**	**1.71 (1.46, 2.01)**	**<0.001**	**27**
Cohort design[8,39,40,42]	4	1.71 (1.02, 2.86)	0.04	70
Case-control design[7,9,57,58,64,66,69,76]	8	1.74 (1.47, 2.05)	<0.001	0
Gestodene vs levonorgestrel	**9**	**1.36 (1.04, 1.77)**	**0.02**	**63**
Cohort design[8,39,40,42]	4	1.41 (0.66, 3.00)	0.04	82
Case-control design[7,9,58,64,66]	5	1.34 (1.10, 1.64)	0.004	0

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Table II. Contd

Variables	No. of studies	VTE risk		
		OR (95% CI)	p-Value	I^2(%)[a]
Cyproterone vs levonorgestrel	**3**	**1.90 (1.55, 2.33)**	**<0.001**	**0**
Cohort design[8]	1	1.88 (1.47, 2.41)	<0.001	NA
Case-control design[7,9]	2	1.94 (1.37, 2.75)	<0.001	0
Drospirenone vs levonorgestrel	**2**	**1.65 (1.29, 2.10)**	**<0.001**	**0**
Cohort design[8]	1	1.64 (1.27, 2.10)	<0.001	NA
Case-control design[9]	1	1.70 (0.70, 3.90)	0.2	NA
Drospirenone vs other OCs	**4**	**1.13 (0.94, 1.35)**	**0.20**	**0**
Cohort design[8,32,46]	3	1.10 (0.90, 1.33)	0.3	3
Case-control design[9]	1	1.70 (0.72, 4.01)	0.2	NA

a Higher I^2 values indicate higher between-study heterogeneity.

OC = oral contraceptive; **NA** = not applicable; **OR** = odds ratio; **VTE** = venous thromboembolism.

affected the estimates of risk was the type of outcome, confirming that the choice of 'all VTE' as the outcome, rather than 'idiopathic VTE only', reduced the excess risk associated with OC use (table III). This finding was even more significant when the level of statistical adjustment was included in the model. Despite some relevant differences in stratified analyses, once the type of outcome was included in the model neither the setting (population- or hospital-based) nor the design of the study, sample size (larger or smaller, as well as sample size as a continuous variable), study continent (US, Europe or others) or publication year were associated with significant variations in the summary estimate of VTE risk.

3.5 Heterogeneity and Publication Bias

The Egger test was significant (p = 0.031) and the funnel plot displaying ORs of the individual comparisons versus the logarithm of their SE (precision) appeared slightly skewed to the right, suggesting the presence of some publication bias (figure 2). The direction of such bias suggests that the actual risk associated with VTE might be lower than the current estimates in this study. However, as noted above, the meta-analyses stratified for sample size (either 'larger' or 'smaller' studies) did not show a relevant difference in the excess risk associated with OC use either among case-control studies (OR 3.40 in larger studies; OR 3.85 in smaller studies) or among cohort studies (OR 2.58 and OR 3.95, respectively, with overlapping 95% CIs [see figure S4, SDC]).

4. Discussion

The only meta-analysis comparing the risk of VTE in OC users versus non-users was published in 1995.[14] Forty studies have been published thereafter and have been included in the present meta-analysis, which also updates and expands on the results of two other meta-analyses, published in 2001, which compared the risk of VTE

Table III. Multiple meta-regression predicting the summary estimate of thromboembolism risk of oral contraceptive users vs non-users

Variables included in the model[a]	Regression coefficient	p-Value
Design (case-control = 0; cohort = 1)	−0.258	0.19
Outcome (idiopathic VTE = 0; mixed VTE = 1)	−0.415	0.034
Setting (population-based = 0; hospital-based = 1)	+0.051	0.77

a See text for details on meta-regression modelling and definitions. Other co-variates (sample size, publication year, country, funding source and level of statistical adjustment) were tested for inclusion and were not significant at the p = 0.10 level.

VTE = venous thromboembolism.

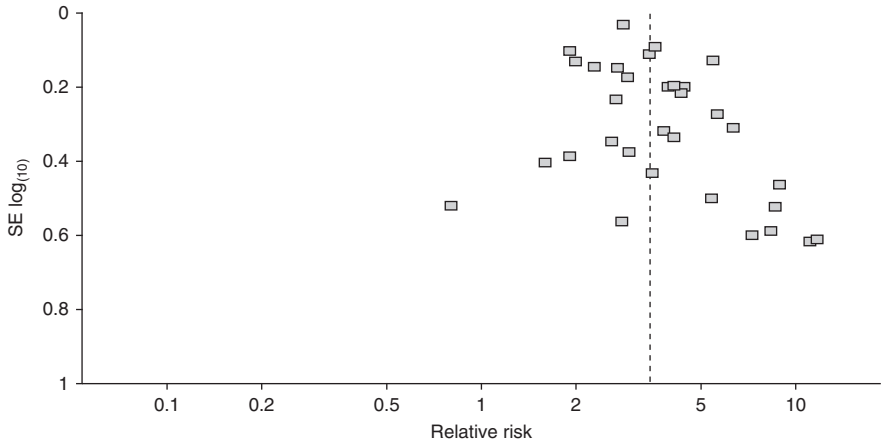

Fig. 2. Funnel plot of the relative risks vs the logarithm of their SE (in studies evaluating the risk of thromboembolism of oral contraceptives users vs non-users). The dashed vertical line shows the summary relative risk (3.41). **SE** = standard errors.

with use of third- versus second-generation OCs.[78,79] Despite the additional evidence, our findings are concordant with those of previous meta-analyses; compared with non-users, the use of OCs is associated with a 3- to 4-fold increase in VTE risk;[14] higher doses of oestrogens (>50 μg) are associated with increased VTE risk,[14,64] and this increased risk is highest in the first year of OC use.[79] Furthermore, third-generation OCs increase VTE risk more than second-generation preparations.[78,79]

In addition to the above, we had the opportunity to evaluate other important issues. First, when the analysis was restricted to the carriers of the genetic mutations FVL and G20210A, which have a higher baseline VTE risk,[25] OC users were still significantly more likely to experience VTE than non-users. Two meta-analyses have compared the VTE risk of OC users who were also carriers of a mutation versus non-users and non-carriers.[11,13] However, no estimates are available to date on the risk of VTE associated with OC use among the carriers; a measure that is more informative about the contribution of OCs in also determining the risk of VTE among the carriers of genetic mutations. The practical implications of these findings are later discussed in detail.

Second, the meta-analyses comparing the most recently available OCs – cyproterone and drospirenone (a fourth-generation OC that is currently the most commonly used OC in the US[15]) – with levonorgestrel showed a significant increase in VTE risk associated with cyproterone or drospirenone use. Notably, this finding was confirmed in two recent case-control studies (published during the submission process[80,81]), and when these new studies were added to the meta-analysis the summary OR rose from 1.65 to 2.01 (95% CI 1.51, 2.68 [data not shown]). Conversely, the direct comparison between OCs containing drospirenone and all other OCs failed to show a significant increase in VTE risk, and the overall VTE risk associated with drospirenone use (vs non-use) was in line with that of other contraceptives (OR 3.44 vs the summary OR 3.41). Unfortunately, both findings are based upon a limited number of studies and require confirmation.

Third, given that previous analyses were based on observational data and were therefore susceptible to several biases (which have been detailed elsewhere[69,78,79]), we tried to explore the potential impact of confounders in two ways: (i) performing meta-analyses stratified for several study and sample characteristics; and (ii) using multiple meta-regression analyses to formally test the independent association of each characteristic with the overall estimates of risk. Some of the findings are noteworthy and are summarized below.

Cohort studies are known to be less susceptible to bias than case-control studies because

characteristics of the cases and controls do not influence inclusion into the study.[82] Indeed, the study design seemed to be a relevant issue in the meta-analysis by Koster et al.[14] (where the overall OR was 2.1 in cohort studies and 4.2 in case-controls). Conversely, we found the summary estimate depended little on study design. Although the summary ORs from case-control studies were larger than those from cohort studies in almost all meta-analyses, the magnitude of such differences was frequently small, 95% CIs were overlapping and meta-regression analysis was not significant.

The study setting also did not seem to substantially affect VTE risk. Although the overall OR from hospital-based case-control studies was larger than that from population-based studies (OR 4.19 vs OR 3.49), such a difference was not statistically significant either with univariate analysis or meta-regression. Moreover, this finding was consistent in all individual studies that simultaneously and separately analysed both control types.[4,5,10]

We also had the chance to explore, for the first time in the field, the potential impact of the source of funding on the overall estimate of VTE risk. Although the influence of commercial interests seemed substantial in stratified meta-analyses, because the ORs of VTE risk were significantly smaller in studies (co)funded by pharmaceutical companies versus those funded by non-profit organizations (OR 2.70; upper confidence limit 3.31 vs OR 4.14; lower confidence limit 3.43), the funding source was not statistically significant in the meta-regression model ($p > 0.2$) when the analysis was adjusted for study design, study setting or outcome type. In any case, the validity of such analysis was limited by the relatively high number of studies (8 of 32, or 25%) that did not report the funding source.

In contrast, our results suggest that the type of outcome might be a key factor in determining the magnitude of VTE risk associated with OC use, confirming the findings by Heinemann and colleagues[10] (and, partially, by Bloemenkamp et al.[6]) When the analysis was restricted to 'idiopathic VTE only' (excluding the large proportion of VTE cases that occurred in women with potential risk factors for VTE[7]), the summary OR was significantly larger than that from studies including 'all VTE cases' (OR 4.94 vs OR 3.09, respectively). Such a difference was maintained after stratification for study setting (data not shown) and confirmed in multiple meta-regression, even when the analysis was controlled for all of the other study characteristics. including the level of statistical adjustment. This is critical as it may be supposed that the inclusion of women with risk factors in the absence of a statistical control might have relevantly biased the estimates of risk.

None of the other study or sample characteristics investigated (publication year, country and sample size) significantly affected the overall estimates of VTE risk. Unfortunately, we could not use meta-regression to further investigate the observed large difference in VTE risk according to smoking status (summary ORs were 5.04 and 2.00, respectively, among smokers and non-smokers), because data were available from four studies only.[4,60,66,77] Although the results of single studies were consistent, such difference was not significant with univariate analysis. Clearly, if confirmed, this finding would provide further support to the current practice to avoid OC prescription in current smokers, a practice that was not entirely supported by the results of the four meta-analyses evaluating the risk of cardiovascular disease among OC users according to smoking status (all of which found small and non-significant differences between smoking and non-smoking OC users).[23,82-84]

Similar to smoking, data on the VTE risk for OC users at different ages were available from seven studies only[9,27,35,48,50,54,55] and meta-regression could not be performed. However, given that the 95% CIs of the ORs of women aged ≥25 years and <25 years were largely overlapping, it seems unlikely that such a difference may have been significant even after adjustments. Because the risk of VTE in younger OC users was greater than older users in six of seven studies, we repeated the meta-analyses excluding the 'outlier' study,[48] with no substantial change (data not shown). Therefore, age did not seem to be a determinant of VTE risk among OC users.

Most meta-analyses showed a high level of between-study heterogeneity, which represents a limitation of meta-analyses of observational studies. However, recent empirical data suggested that the

pooled estimates from observational studies are, on average, quite similar to those from randomized trials.[85] Also, a high degree of heterogeneity may not be surprising given the large variation among studies in terms of design, setting, analysis method and OC preparation (interestingly, the only comparison where no heterogeneity was observed was the one restricted to idiopathic VTE cases only, again suggesting that such a choice may be critical in determining study results). Finally, when the fixed-effect method of analysis was used instead of the random-effect method, none of the results was substantially different (except for CIs, which were typically tighter).

We found a suggestion of publication bias, but when smaller studies were excluded in stratified analyses the overall estimates of risk were not substantially altered. If such bias does exist, it would shift the estimates towards a lower VTE risk for OC users, given that smaller studies were less represented in the left section of the funnel plot and, on average, higher VTE risks were reported.

4.1 Practical Implications and Absolute Risks

Since the public health implications of relatively rare conditions (such as VTE) might be less of a priority even in the presence of relatively high relative risks, it is extremely important to also consider the absolute risks associated with a particular risk factor.[82] In computing the absolute VTE risk associated with OC use, however, we should consider that substantially different summary ORs resulted from studies using idiopathic cases rather than all VTE cases. Both approaches have advantages and disadvantages; considering idiopathic VTE only permits more reliable estimates of the 'real' contribution of OC use in determining VTE risk, but a very high proportion of VTE cases (up to 50%[86]) are excluded, thus disregarding clinical reality.[10] In addition to which should be considered the 'best' outcome to use, it would clearly be incorrect to apply the ORs of only idiopathic cases to incidence rates that include all VTE cases, and vice versa. Therefore, two computations of the absolute risk have been performed – one for only idiopathic cases and one for all VTE cases. For both approaches, the annual VTE incidence for non-OC users was extracted from the most recent and largest population-based studies. Lidegaard and colleagues[8] excluded pregnant women and those with cancer or cardiovascular diseases from their cohort study on Danish women (a total of 10 447 373 women-years); Dinger and colleagues[32] considered all VTE cases in the EURAS study (142 475 women-years collected from seven European countries).

With regard to idiopathic VTE cases, with a summary OR of 4.94 due to OC use, a woman's annual VTE risk would be expected to increase from 30.1 to 149 VTE events per 100 000 based on background incidence rates.[8] Therefore, treatment of 845 women would be expected to lead to a single additional VTE event each year.[87] Concerning all VTE cases, the summary OR of 3.09 leads to an expected increase in women's annual VTE risk from 47 to 145 events per 100 000.[32] Thus, treating 1019 women would lead to an additional VTE event each year. Notably, the absolute VTE risk for OC users was very similar using both approaches – around 150 cases per 100 000 women treated yearly (with an absolute risk difference ranging from 98 to 119). Given that death occurs in no more than 1% of VTE cases in women aged 20–44 years,[88] OC use may cause approximately one additional death per 100 000 women yearly (which is in agreement with previous specific estimates[89]). Given this, it has been estimated that unwanted pregnancies, which may occur with less effective forms of birth control, can result in a maternal mortality rate of 12 per 100 000 live births.[90] Therefore, when absolute risks are considered in addition to relative risks, the excess VTE risk associated with OC use does not seem to overcome the health benefits, at least in women who do not have other baseline risk factors for VTE.

In fact, the computation of absolute risks becomes even more important for the carriers of genetic mutations such as FVL and G20210A, which are associated with increased VTE risk.[25] We observed an 80% and 63% increase in VTE risk associated with OC use (versus non-use) among the carriers of FVL and G20120A mutations, respectively. Both summary ORs are smaller than the

summary OR of the general population of women, but they are superimposed on a 'background' relative risk as large as 9.45 for FVL and 3.17 for G20210A mutation carriers.[25] Multiplying the ORs related to OC use with those deriving from the mutation, we obtain a relative risk of 17.0 and 5.2 for FVL and G20210A women using OCs, respectively, compared with women who are non-carriers and non-users (values that are very close to those reported by two previous meta-analyses on the topic[11,13]). Using such values, and considering that most genetic studies adopted all VTE cases as the main outcome, yearly absolute risks would be expected to rise from 47 to 799 events per 100 000 for OC users who are also carriers of FVL mutation to 244 per 100 000 for carriers of the G20210A mutation. Therefore, the treatment of 134 and 508 women with the FVL or G2021A mutation, respectively, would lead to one additional VTE event each year.

The only cost-effectiveness analysis based upon a systematic review that was performed to date recommended a selective screening of women with a family history of thrombosis or thrombophilia.[13] Our values of absolute risks and numbers needed-to-treat may be supportive of such a view. However, routine screening for all women before using OCs has been classified as 'not appropriate' by the WHO Expert Working Group for medical eligibility criteria for OC use,[91] and several criticisms were also expressed by other experts in the field.[12] Certainly, this issue deserves further investigation, and future economic evaluations are strongly needed to determine the cost and relative value of a thrombophilia screening programme with respect to other healthcare programmes. Currently, in the absence of universal screening, physicians must consider the safer type of OC when prescribing OCs to first-time users.

5. Conclusions

Based on the results of 55 observational datasets, this meta-analysis confirms that OC use significantly increases VTE risk. The strength of this association, however, varies according to the generation of OC, type of outcome, presence of a genetic mutation and, eventually, smoking status, with ORs ranging from 3 to 5. When the newest OCs containing drospirenone were compared with non-drospirenone-containing OCs (except those containing levonorgestrel only), VTE risk did not significantly increase. As regards the type of outcome, the development of methodological standards for studies on VTE is strongly warranted to reduce the variation in the estimates of single studies, or at least to prevent misinterpretation of the strength of the association between OC use and VTE.

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