Hacking stroke in women: towards aetiology-driven precision prevention

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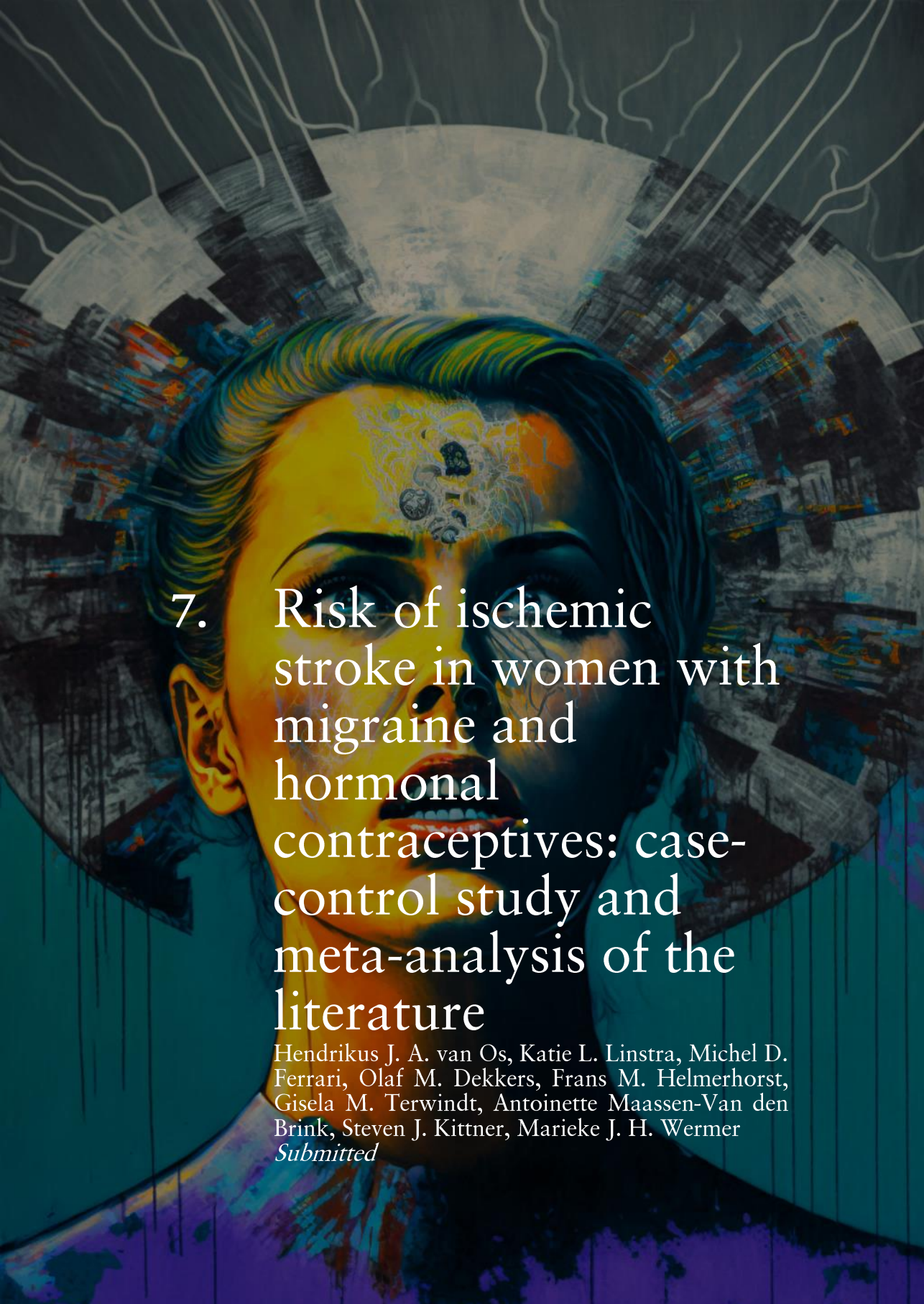

7. Risk of ischemic stroke in women with migraine and hormonal contraceptives: case-control study and meta-analysis of the literature

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Submitted

Abstract

Background and purpose: Migraine and the use of combined oral contraceptives (COCs) are both proven and independent risk factors for ischemic stroke. This study aims to investigate whether migraine and the use of COCs have a supra-additive risk-increasing effect on ischemic stroke.

Methods: We performed an interaction analysis of migraine, COC use and risk of ischemic stroke in a population-based, nested case-control study of women aged 18–49 years with no history of ischemic stroke. In addition we did a systematic review of the extant literature as well as an extended meta-analysis including the present study. We included cohort or case-control studies in premenopausal women with data on migraine and hormonal contraception status and first-ever ischemic stroke as clinical outcome. We extracted adjusted odds ratios (aORs) and performed a subanalysis based on a COC estrogen dose of <50 µg.

Results: Our nested case-control study included 617 women with first-ever ischemic stroke. Mean age was 37 years (SD ± 6.4). Of all cases, a history of migraine was registered for 18.6% in the primary care electronic patient record and 20.6% were COC users; we could not discern between migraine with or without aura. Comparing women with migraine who used COCs to women with neither of the two risk factors, we found a substantial increase in the risk of ischemic stroke (aOR: 6.83; 95% CI: 3.95–11.7). Women with migraine who used COC and also smoked compared with women without migraine and who did not smoke or use COCs, had an even higher risk of stroke (aOR: 30.2; 95% CI: 4.22–610). The systematic review identified 782 potentially eligible articles, of which six studies met the inclusion criteria. In these studies, including our nested case-control study, the risk of ischemic stroke in women who had migraine and used COCs compared with women who did not have either risk factor were all positively associated and ranged from an aOR of 2.04 to 16.9 (pooled aOR: 4.95; 95%CI: 2.13–11.5, I^2 = 84.7%). In a subanalysis based on estrogen dose, the risk of ischemic stroke in women who had migraine and used COCs containing <50 µg estrogen ranged from an aOR of 1.80 to 13.9 (pooled aOR: 3.14; 95%CI: 1.75–5.62; I^2 = 86.6%).

Conclusion: In women aged 18–49 years, the co-occurrence of migraine and use of COCs, even of low estrogen dose, results in a substantially increased risk of ischemic stroke. The additive effect of smoking appears to be large.

Introduction

Migraine, especially with aura, increases the risk of ischemic stroke approximately two times.[1] This risk increase appears to be strongest in women of reproductive age.[2] In women in this age group the use of hormonal contraceptives, especially combined oral contraceptives (COCs), is another common risk factor for ischemic stroke.[3] COCs are the most commonly prescribed form of hormonal contraceptives, and are used by approximately 20% of women of childbearing age in developed countries.[4] The absolute risk of ischemic stroke remains low because COC-users are usually young and healthy.[3, 5] Moreover, the risk of ischemic stroke associated with COC use depends on the estrogen dose, and has decreased significantly in recent decades as estrogen doses have fallen to <50 µg.[6,7] However, the use of COCs by women with migraine may lead to an increase in the risk of ischemic stroke, which seems supra-additive compared with the effect of the two risk factors alone.[8, 9] Smoking may have a further additive effect on the risk of ischemic stroke.[10] Consequently, the World Health Organization (WHO) and the American Congress of Obstetricians and Gynecologists (ACOG) have advised against the use of COCs in women with migraine, particularly with aura.[11, 12] However, this advice has been questioned due to the limited availability and quality of the evidence.[13, 14] Women with migraine represent up to 33% of the female population, of whom one third has migraine with aura.[15] Defining migraine as a contraindication to the use of COCs may therefore impose a significant burden on society, given the contraceptive and non-contraceptive importance of COCs.[16]

The evidence on the risk of ischemic stroke in women with migraine using COCs, including those with a low (<50 µg) estrogen dose, has been extensively reviewed. The prevailing conclusion is that too little data are available to draw strong conclusions about the safety of prescribing COCs in women with migraine.[17, 18, 19] Therefore, we firstly present data from a nested case-control study based on a prospective population-based cohort, in which we assessed the risk of ischemic stroke in women with migraine using COCs and the potential additive effect of smoking. We then integrated our results with previously published evidence using a systematic review and meta-analysis.

Methods

Nested case-control study

We used data from the STIZON database, which directly retrieves data from electronic patient records of a large number of healthcare providers throughout the Netherlands. From the STIZON general practitioner (GP) database we selected women from general practice centers which, based on their location, were in the catchment area of hospitals participating in the STIZON network. This enabled us to link information on hospital diagnoses with primary care data. The STIZON GP database contains International Classification of Primary Care (ICPC) diagnosis codes for clinical entities and Anatomical Therapeutic Chemical (ATC) medication prescriptions from primary care pharmacies.[20,21] ICD-9 and ICD-10 codes are present for all in-hospital diagnoses during follow-up, and ICPC diagnosis codes are in principle available from birth. The inclusion criteria for both cases and controls were women who were registered in a STIZON general practice between 1st of January 2007 and 31st of December 2020 for at least one year, and were aged between 18–49 years within this time window. We used a nested case-control design in which cases were defined as patients with a first-ever ischemic stroke based on either one ICD-9 or ICD-10 hospital or ICPC diagnosis code registered during follow-up. The date of the first-ever ischemic stroke was used as the index date. For each case we then randomly sampled ten controls who had the exact same age as the case on the index date, without replacement. The index date was used to define the baseline characteristics for cases and age-matched controls. The ascertainment of a history of migraine was clinic-based, and was defined using registrations in the electronic patient record of an ICD-9, ICD-10 or ICPC diagnosis code for migraine, or migraine-specific drugs (ATC-code: N02C* with * indicating all registration subcodes) before the index date. Migraine-specific drugs included ergot alkaloids, flumedroxone, triptans, and monoclonal antibodies against calcitonin gene-related peptide (CGRP) or its receptor. We defined current COC use based on the registration of one or more ATC medication prescription codes: current COC use (ATC: G03AA*, G03AB*), within 180 days before the index date. Further, we examined other risk factors for ischemic stroke including age, smoking, diabetes mellitus, hypertension, a history of hemorrhagic stroke, TIA, subarachnoid hemorrhage, myocardial infarction, angina pectoris, and peripheral artery disease. We could not sufficiently distinguish between past and present smoking status based on our data. The local medical research and ethics committee declared that this study was not within the scope of the Dutch Medical Research Involving Human Subjects Act.

To assess the interaction effect between COC use and migraine, we performed an analysis of additive interaction in a standard case-control comparison.[22] We used logistic regression analysis to estimate odds ratios (ORs) and associated 95% confidence intervals (CIs) as a measure of the relative risk of ischemic stroke for COC use alone, migraine only, and the presence of both compared with the reference category with neither risk factor. All ORs from the logistic regression models were adjusted for age, hypertension, hypercholesterolemia, diabetes and smoking (aORs). In addition, we performed an analysis of additive interaction for COC use, migraine, and smoking, for which we compared women who had all three risk factors with women without any of the three risk factors.

Systematic review and meta-analysis

The following inclusion criteria were used for the systematic review. First, we only included studies with a cohort or (nested) case-control design. Second, participants were women of reproductive age. Studies focusing on (peri)menopause were excluded. Third, studies had to contain information on both migraine and use of any form of hormonal contraception (i.e. COC as well as progestogen-only preparations in all available types of administration [oral, transdermal, vaginal ring, injection, intra-uterine device]). Hormonal contraceptive use was compared with non-use, defined as either never having been exposed to a hormonal contraceptive or being a former hormonal contraceptive user. To perform a meta-analysis of the combined effect of hormonal contraception and migraine on the risk of ischemic stroke compared with women without migraine who did not use hormonal contraception, we included only studies that reported data on the combined effect. COCs were classified according to the estrogen dose, as this is the likely thrombogenic component. Studies on emergency contraception were excluded. Fourth, we chose first-ever ischemic stroke as the clinical outcome, which was defined in the original publications. The outcome was measured at the end of the follow-up period of the study. Finally, Two authors (HO, KL) independently reviewed titles and abstracts of the records obtained from the electronic searches and excluded irrelevant studies. Of the remaining records, full copies were obtained to identify studies suitable for inclusion. We settled disagreements by discussion with an independent third review author (MW). We searched in the following databases: PubMed, Embase, Web of Science, Cochrane Database of Systematic Reviews, CENTRAL, CINAHL, PsycINFO, Academic Search Premier, ScienceDirect, LWW, and Wiley. The search strategy was amended for each database. We have not set a language restriction on the study search, and searched for meeting abstracts in Embase and Web of Science to find additional studies. Databases were searched on February 5th 2022, from the date of their inception. The complete search strategy can be found in Appendix I.

Statistical analysis

We extracted adjusted odds ratios (aORs) or adjusted risk ratios (aRRs) depending on what was reported in the original publications. To assess the influence of both migraine and hormonal contraceptive use on risk of ischemic stroke, we pooled effect estimates for migraine versus no migraine, contraceptive use versus no contraceptive use, and for both factors combined versus neither of both factors present. For the pooling of effect estimates of the included studies, we used random-effects models and pooled by weighing the log of the odds ratios or hazard ratios by the inverse of their variance. Cochran's Q and Higgin's I^2 statistic were reported to assess heterogeneity across studies. Since differences in estrogen dose of COCs across studies may be an important source of heterogeneity, a subanalysis based on use of COCs with <50 µg estrogen was performed. R version 4.1.0 was used for all analyses.

Risk of bias assessment

We used a version of the Newcastle-Ottawa tool that was customized for risk of bias assessment in case-control studies.[5] The following risk of bias assessment criteria were customized: 1. Selection of participants (low risk of bias: study with controls/ unexposed sampled from source population or same community as cases/ exposed; high risk of bias: controls not representing the study population). 2. Adjustments for confounding (low risk of bias: adjustment for age or adjustments by design such as matching; high risk of bias: no adjustments in analyses). 3. Hormonal contraceptive exposure evaluation (low risk of bias: database record selection or written self-report, type and dosage reported, differentiation made between current and past; high risk of bias: no description). 4. Migraine exposure evaluation (low risk of bias: migraine diagnosis according to International Headache Society-criteria (version I, II or III); high risk of bias: self-report without diagnostic criteria). 5. Outcome (low risk of bias: (pre)defined outcome assessment, objectively confirmed stroke in all cases by MRI or CT, and distinction between ischemic and hemorrhagic stroke; high risk of bias: no (pre)defined outcome assessment, or not objectively confirmed in in all cases or unclear).

Results

Nested case-control study

From the 1st of January 2007 to the 31st of December 2020, 617 of all 258,828 women aged between 18–49 years had a first ischemic stroke. This corresponded to an average annual cumulative incidence of 26 strokes per 100,000 women. We included these 617 cases and 6170 age-matched controls. The mean age was 37 years. Of all cases, 115 (18.6%) women fulfilled our defined criteria for clinic-based migraine, versus 556 (9.0%) women in the control group, resulting in an increased risk of ischemic stroke of aOR: 1.67 (95% CI: 1.31–2.61). Women who currently used COCs also had an increased risk of ischemic stroke compared with those who did not currently use COC (20.6% versus 9.4%; aOR: 2.40; 95% CI: 1.91–2.65).

Table 1. Baseline characteristics of ischemic stroke cases and controls of ages 18–49 years

Baseline characteristics	Cases (n = 617)	Controls (n = 6170)
Age (mean ± SD)	37.3 (6.4)	37.3 (6.4)
Cardiovascular risk factors, *n (%)*		
Smoking (ever)	91 (14.7)	382 (6.2)
Hyperlipidemia	80 (13.0)	158 (2.6)
Hypertension	199 (32.3)	723 (11.7)
Diabetes mellitus	27 (4.4)	120 (1.9)
Hemorrhagic stroke	7 (1.1)	0 (0.0)
TIA	13 (2.1)	5 (0.1)
Subarachnoid hemorrhage	4 (0.6)	0 (0.0)
Myocardial infarction	6 (1.0)	11 (0.2)
Angina pectoris	4 (0.6)	8 (0.1)
Peripheral artery disease	9 (1.5)	48 (0.8)
Migraine	115 (18.6)	556 (9.0)
Preeclampsia	23 (3.7)	119 (1.9)
Hormonal contraceptive use, *n (%)*	127.0 (20.6)	583.0 (9.4)

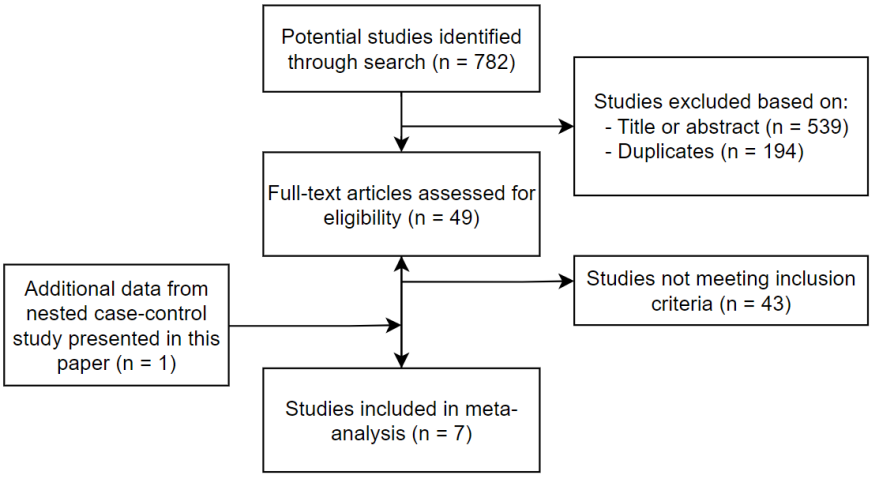
For combined migraine and COC use versus neither factor we found a significant increase in the risk of ischemic stroke (3.1% versus 0.4%; aOR: 6.83; 95% CI: 3.95–11.7), which was supra-additive to what would be expected from the presence of migraine (aOR: 1.52; 95% CI: 1.16–1.97) or COC use alone (aOR: 2.19; 95%

CI: 1.71–2.79, Table 2a). Women with migraine who both smoked and used COCs versus women without migraine who neither smoked nor used COCs, had a clearly increased risk of stroke (aOR: 30.2 95% CI: 4.22–610, Table 2b).

Systematic review

Our systematic review identified 782 potentially eligible articles through an electronic search, of which 194 were duplicates. We excluded 534 articles based on title and abstract assessment. In addition, 49 articles were excluded after a full review. Seven studies, including the case-control study presented in this paper, met the inclusion criteria[9, 10, 23-25] (Figure 1).

Figure 1. PRISMA study flow diagram



Authors of one included study shared additional data on the joint effect of migraine and COC use, the joint effect of migraine, COC use and smoking on risk of ischemic stroke, and on the subanalysis based on low estrogen dose.[24] All seven included studies had a case-control design, with ischemic stroke as the outcome measure.[9, 10, 23-25] Two included studies also performed a subanalysis for hemorrhagic stroke as outcome measure.[10, 25] Hormonal contraception consisted mainly of COC use, and no studies reported isolated effect estimates for other hormonal contraceptives. Two studies distinguished between migraine with and without aura[23, 24], and two studies assessed the joint effect of migraine, hormonal contraceptives and smoking on the risk of ischemic stroke.[9, 24] Characteristics of the seven included studies are listed in Table 3. One study reported only the aOR for migraine with and without aura separately, while all other studies reported the aOR for migraine with and without

aura combined. To include this study in the quantitative analysis, we combined the OR from migraine with and without aura.[23]

Risk of ischemic stroke in women with migraine, use of COCs, or both

In the seven included studies, the aORs for ischemic stroke in women without migraine who used COCs compared with women without migraine who did not use COC ranged from 1.11–4.90 (pooled aOR: 1.85; 95% CI: 1.24–2.74; Q: 30.2, $p < 0.001$; I^2: 87.7%). The risk of ischemic stroke in women with migraine compared with women without migraine, the aORs ranged from 1.03–3.70 (pooled aOR: 1.57; 95% CI: 1.22–2.01; Q: 10.9, $p = 0.03$; I^2: 72.1%). The risk of ischemic stroke in women with migraine and use of COCs compared with women who did not have migraine and did not use COCs, the aORs ranged from 2.04–16.9 (pooled aOR: 4.44; 95% CI: 2.40–8.21; Q: 22.6, $p < 0.001$; I^2: 84.7%, Figure 2).

Risk of ischemic stroke in women with migraine with aura versus those without aura

Two studies distinguished between migraine with and without aura. One study found an aOR of 6.08 (95% CI: 3.07–12.1) for the risk of ischemic stroke in women with migraine with aura and using COCs compared with women without migraine and using COCs. In women with migraine without aura and using COCs compared with women without migraine and using COCs, the aOR was 1.77 (95% CI: 1.09 – 1.88).[23] The second study found an aOR of 2.34 (95% CI: 1.09–5.00) for risk of ischemic stroke in women with migraine with probable visual aura who used COC compared with women without migraine and using COCs. In the same study, the risk of ischemic stroke in women with migraine with and without aura combined who used COC versus women with no migraine who did not use COCs resulted in an aOR of 2.21 (95% CI: 1.16–4.21).[24]

Table 2a. Risk of ischemic stroke: interaction analysis of migraine and combined oral contraceptive use

	COC* use	Cases	Controls	OR (95% CI)	aOR** (95% CI)
Migraine	Yes	19 (3.1)	23 (0.4)	9.78 (5.86–16.2)	6.83 (3.95–11.7)
	No	52 (8.4)	311 (5.0)	2.1 (1.63–2.69)	1.52 (1.16–1.97)
No migraine	Yes	108 (17.5)	560 (9.1)	2.28 (1.79–2.87)	2.19 (1.71–2.79)
	No	438 (71.0)	5276 (85.5)	Ref.	Ref.

**COC = combined oral contraceptive; aOR = adjusted odds ratio*

***Odds ratio adjusted for age, smoking, diabetes, hypertension, hyperlipidemia*

Table 2b. Risk of ischemic stroke: interaction analysis of migraine, combined oral contraceptive use, and smoking

	COC* use + smoking	Cases	Controls	OR (95% CI)	aOR** (95% CI)
Migraine	Yes	5 (0.8)	1 (0.0)	68.2 (11.0–1308)	30.2 (4.22–610)
No migraine	Neither	68 (11.0)	473 (7.7)	Ref.	Ref.

**COC = combined oral contraceptive; aOR = adjusted odds ratio*

***Odds ratio adjusted for age, smoking, diabetes, hypertension, hyperlipidemia*

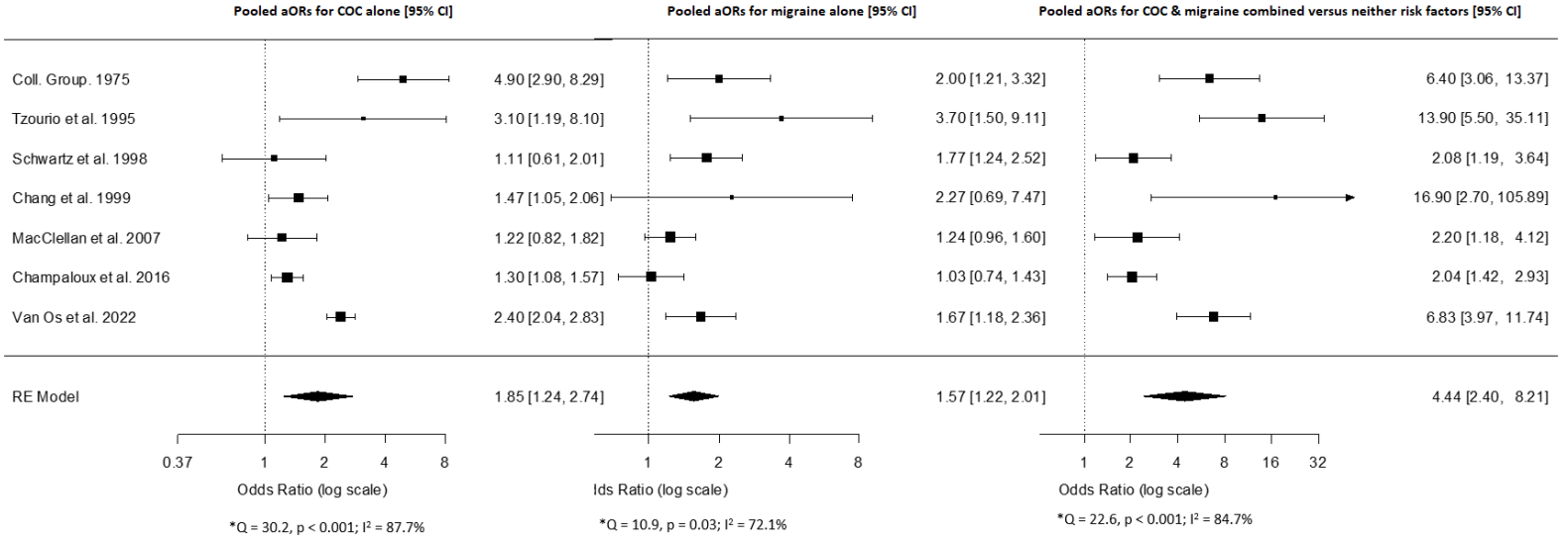
Table 3. Characteristics of studies included in the systematic review

Author, Year, Setting	Design	Population	Age	Migraine	Contraceptive use	Outcome	Adjustments
Collaborative Group 1975, hospitals in 12 cities, US	Case-control, inclusion 1969-1971	598 cases, 429 hospital controls matched for age, race and geographical area, 451 neighbourhood controls matched for race and age	15-44	Self-reported during structured interview not based on IHS-criteria. No subspecification with/without aura	Data from participant questionnaire. Dose: 100 µg and 50 µg, distribution of dose not further specified*	Ischemic and hemorrhagic stroke based on discharge diagnosis, confirmed by neurologist	None
Tzourio et al. 1995, five hospitals in France	Case-control, inclusion 1990-1993	72 cases, 173 hospital controls with rheumatologic of orthopedic diagnoses	18-44	Neurologist interview based on IHS criteria. No subspecification with/without aura	Data from participant questionnaire. Distribution estrogen dose: 30-40 µg (73%), 50 µg (15%), 20 µg (7%), progestin only (5%)	Ischemic stroke, defined clinically using WHO criteria, confirmed by imaging	None
Schwartz et al. 1998, from Kaiser Permanente (KP) Medical Care Plans and University of Washington Study	Case-control, inclusion 1991-1995	175 cases, 1191 population controls, for Kaiser Permanente study matched on exact year of birth and facility of usual care	18-44	Self-reported: migraine diagnosis from clinician or having visited clinical for migraine	Self-reported. Distribution estrogen dose: <50 µg for all patients	Ischemic stroke, 2 physicians reviewed medical records or single board-certified neurologist reviewed the records	Treated hypertension, treated diabetes, smoking ethnicity, BMI, and menopausal status
Chang et al. 1999, hospitals in eight cities in Europe	Case-control, inclusion 1990-1993	291 cases, 736 hospital controls from same hospital as matched cases, matched for age and time of admission	20-44	Neurologist interview based on IHS criteria, stratified for migraine with and without aura	Data from patient questionnaire, distribution estrogen dose: ≥50 µg (31%), <50 µg (69%)	Ischemic and hemorrhagic stroke based on clinical diagnosis, confirmed by review medical records	High blood pressure, education, smoking categories, family history of migraine, alcohol, and social class;
MacClellan et al. 2007, 59 hospitals in Baltimore, US	Case-control, inclusion 1992-2003	386 cases, 614 population controls matched for geographic area, race and age	15-49	Standardized questionnaire using IHS-criteria, differentiated between migraine with probable visual aura and migraine without	Data from patient questionnaire, estrogen dose specified in 75% of participants, in whom: ≥50 µg (3%), <50 µg (97%)	Ischemic stroke discharge diagnosis, confirmed by review medical records and imaging (CT/MRI)	Age, race, geographic region, study period
Champaloux et al. 2016, National Healthcare claims database, US	Case-control, inclusion 2006-2012	1884 cases, 7536 age-matched controls from database	15-49	ICD-9 codes in database, recorded prior to stroke	Data from pharmaceutical claims database, estrogen dose not specified	Ischemic stroke, ICD-9 codes in database	Hypertension, diabetes, obesity, smoking, ischemic heart disease, and valvular heart disease;
Van Os et al. 2022, population-based open cohort in The Netherlands	Nested case-control, inclusion 2007-2020	617 cases, 6170 age-matched controls	18-49	ICPC-, ICD-9 and ICD-10 codes including migraine specific drugs (ATC N09C)	Data from pharmaceutical database (ATC codes), estrogen dose not specified	Ischemic stroke, ICD-9 and ICD-10 codes in database	Ischemic stroke, ICD-9 and ICD-10 codes in database

Table 4. Risk of bias assessment of included studies

Author, year	Selection of participants	Adjustments for confounding	OC exposure evaluation	Migraine exposure evaluation	Outcome
Collaborative Group 1975	Low	Low	High	High	High
Tzourio et al. 1995	High	Possible	Low	Low	Low
Schwartz et al. 1998	High	Low	Low	High	Low
Chang et al. 1999	High	Low	Low	Low	Low
MacClellan et al. 2007	Low	Low	Low	Low	Low
Champaloux et al. 2016	Low	Low	High	High	High
Van Os et al. 2023	Low	Low	High	High	High

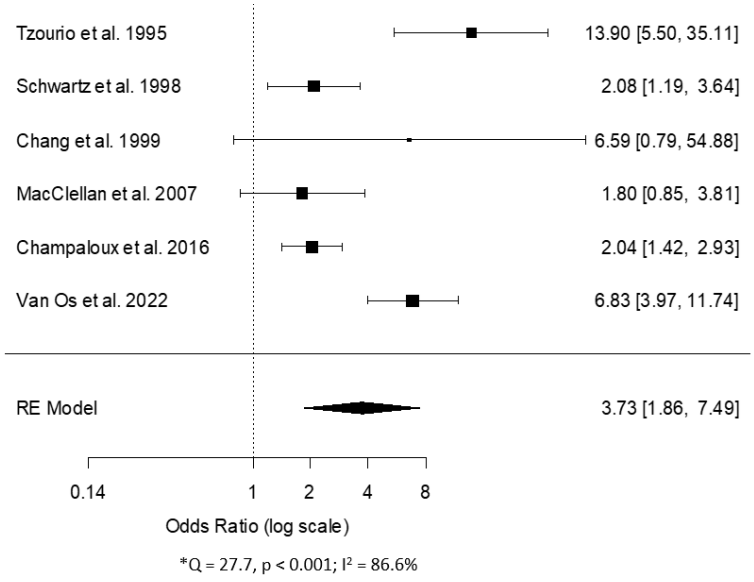
Figure 2. Association of hormonal contraceptives and migraine alone, and both combined with risk for stroke



Three-way interaction between migraine, use of COCs, and smoking

One study found an aOR of 34.4 (95% CI: 3.27–361) for the risk of ischemic stroke in women with migraine who used COCs and were current smokers (nine in the cases and two in the controls) versus women without any of these three risk factors.[10] In another study, a similar comparison resulted in an aOR of 5.33 (95% CI: 1.81–15.7) (unpublished data, see supplement).[24] In our nested case-control study, we found an aOR of 30.2 (95% CI: 4.22–610), which was also based on a very small number of exposed cases and controls (five cases and one control with migraine who used COC and smoked).

Figure 3. Association of hormonal contraceptives with estrogen dose of <50µg and migraine combined with risk for stroke



Risk of ischemic stroke in women with migraine and use of low dose estrogen COCs

One study reported the subanalysis based on use of COC with <50 µg estrogen in the original publication,[10] and authors of another study shared data on this subanalysis with us.[24] For one case control study from 2017 and our nested case-control study no information on COC estrogen dose was available. However, it can be assumed that during this follow-up period more than 75% of all women used low estrogen dose.[23] In the six studies included in the subanalysis of low dose

estrogen, aORs for ischemic stroke in women with migraine with aura and use of COCs ranged from 1.80–13.9 (aOR: 3.14; 95%CI: 1.75–5.62; Q = 27.7, $p < 0.001$; $I^2 = 86.6\%$, Figure 3).

Risk of bias in included studies

Four studies sampled controls from the general population, two studies used hospital-based controls and in one study controls came from the US National Health Claims database, and the exact origin of controls was unknown. All studies adjusted for confounding either with matching or through multivariate analysis, or both. Three studies reported distribution of estrogen dose of COCs across the study population. Three studies collected migraine data with International Headache Society-criteria, and two studies explicitly reported ascertainment of stroke diagnosis with imaging (Table 4).

Discussion

We first conducted a nested case-control study in women aged 18–49 years and found that migraine, use of COCs, and smoking were independent and supra-additive risk factors for first-ever ischemic stroke. The additive relative effect of smoking was substantial, but remained small in absolute terms. We then conducted a systematic review of the literature and identified six studies that reported on the joint effect of migraine and use of COCs on the risk of ischemic stroke. A pooled analysis of these six previous studies together with our novel nested case-control study showed that migraine and the use of COCs have an supra-additive increasing effect on the risk of first-ever ischemic stroke in women. Pooled estimates for migraine and COCs use together resulted in high heterogeneity ($I^2 = 84.7\%$), indicating that there was a large discrepancy between reported odds ratios. Importantly, all studies showed that the risk of ischemic stroke for migraine and COC use was positively associated, meaning that the studies are in agreement that the combination of migraine and COC increases the risk of ischemic stroke. In a subanalysis in women with migraine who used COCs containing <50 µg of estrogen, the pooled effect estimate for the risk of ischemic stroke remained supra-additive, although the aOR was lower (pooled aOR: 3.14; 95%CI: 1.75–5.62) compared with total COCs use and migraine (pooled aOR: 4.44; 95% CI: 2.40–8.21). This analysis also suffered from a high heterogeneity ($I^2 = 86.6\%$).

Compared with the extant literature[17, 18], the present study adds unpublished data from a previously published case-control study[24], our nested case-control study, as well as a meta-analysis of all six “old” studies plus our “seventh new” study,

meeting the critical inclusion criteria. The findings of our nested case-control study provide an additional argument that migraine and the use of COCs – even those with low-dose estrogen – have a supra-additive increasing effect on the risk of ischemic stroke, consistent with the findings of other studies.[9, 10] Our nested case-control study and meta-analysis, however, could not distinguish between migraine with and without aura. This distinction is important, because based on the literature it seems to be specifically migraine with aura that is associated with an increased risk of ischemic stroke.[26] Further, one previous study found a clearly supra-additive effect of migraine with aura and concomitant COC use on the risk of ischemic stroke[23], while this could not be confirmed in another study.[24]

Strengths of our nested case-control study include the linkage of multiple data sources (primary care data, hospital diagnosis codes, and pharmacy registrations) and the prospective collection of data. A strong point of our systematic review and meta-analysis is that we were able to retrieve previously unpublished data from one study.[24] Our study has several potential limitations. First, the migraine definition in our nested case-control study was derived from electronic patient record registrations, and may have suffered from underreporting.[27] The cumulative lifetime incidence of migraine in our nested case-control study was 18.6% in cases and 9% in controls, which is substantially higher compared with a previous report on Dutch primary care electronic patient record registrations of migraine (2.5%).[28] This was potentially because we used multiple sources of electronic patient record registrations for our migraine definition (primary care, hospital, and medication registrations) and we included women of reproductive age in whom active migraine prevalence is highest.[29] However, the lifetime incidence of migraine in our nested case-control study was still lower than the estimated cumulative lifetime incidence of migraine according to population based studies, in which the migraine diagnosis was verified using the International Headache Society criteria (up to 33%).[15, 29] The underreporting of migraine may be due to the fact that a substantial proportion of migraine patients do not visit the general practitioner for their migraine[29] and when they do, migraine may not be accurately reported by the GP in the electronic patient record.[27] However, differential misclassification of migraine by case-control status was unlikely, as all data were routinely and prospectively recorded and problems such as recall bias were absent. Therefore, the underreporting of migraine may have led to an underestimation of the association between migraine and the risk of ischemic stroke which we found in this study.[30] Because we used a clinic-based definition of migraine in our nested case-control study, our migraine group likely consists of women who have searched for help in primary or hospital care or are treated for migraine. In this subgroup of migraine patients, the risk of ischemic stroke may be relatively more increased compared with the overall migraine population.[31] Second, in Dutch electronic patient records, often overall stroke

classification codes are used instead of codes specific to ischemic or hemorrhagic stroke. Therefore, we included the codes for overall stroke in our definition of ischemic stroke. Of all events in our nested case-control study, only 23% were based on codes for overall stroke. Since about 80% of strokes are ischemic, it is likely that less 5% of all stroke registrations in our nested case-control study represents hemorrhagic stroke. Misclassification of hemorrhagic as ischemic strokes may have caused a small dilution of the observed effects. Third, we found significant heterogeneities in the random-effect analyses, which complicates interpretation of the pooled aORs. Multiple potential sources of bias for the included studies could be identified in our risk of bias assessment, which made it difficult to identify a primary cause for the heterogeneities and to perform meta-regression or sensitivity analyses.

Implications for clinical practice

Recently, the European Headache Federation (EHF) and the European Society of Contraception and Reproductive Health (ESC) published a consensus statement in which authors suggested against prescription of COCs in women with migraine with aura. The supra-additive increase in the risk of stroke in the migraine patients who use COCs, which was found in our nested case-control study, likely constitutes a lower limit of the risk increase in migraine patients with aura because of the following. Although we could not distinguish between migraine with or without aura based on our data, we do know that migraine with aura constitutes only 30% of all migraine cases. Moreover, since more than a decade the Dutch national primary care guideline for hormonal contraceptive use mentions migraine with aura as a risk factor for ischemic stroke, and states migraine with aura in combination with smoking as a contraindication for the prescription of COC.[32] It is, therefore, likely that a substantial number of GPs have refrained from prescribing COC to women with migraine with aura, which would result in a relatively smaller fraction of women with migraine with aura in our overall migraine group. Because the effect of migraine with aura on the risk of ischemic stroke appears to be much stronger than that of migraine without aura, the effect we found in our nested case-control study could have been diluted compared with the true effect of migraine with aura. However, if the supra-additive increase in the risk of ischemic stroke would have only been caused by the smaller migraine with aura subgroup, this implies that the effect of migraine with aura would be many times higher than the effect that we found in our study. Compared with findings from previous studies this is unlikely[23, 24], and, therefore, we cannot exclude the possibility of a supra-additive effect on the risk of ischemic stroke in migraine patients who use COCs. Regarding women without aura who have additional cardiovascular risk factors, authors of the EHF and ESC consensus statement suggest non-hormonal contraception or progestogen-

only contraceptives as the preferential option.[33] Given the supra-additive effect of smoking in addition to migraine and the use of COCs in our case-control study (aOR: 30.2), our study supports this suggestion. Although the absolute risk of ischemic stroke in young women is low (11–25 per 100.000[23]), migraine, COCs use and smoking can still significantly increase the risks and stroke at young age will often result in many years of disability.[34] Based on our results, we advise healthcare professionals – and in particular general practitioners – to (i) be careful in prescribing COCs to women with migraine without aura who also smoke, (ii) to actively ask about migraine including aura status in this context, and (iii) to invest in the quality of routine care registrations of migraine diagnoses.

Future research should focus on more personalized advice on the use of COCs in women with migraine. This includes explaining relative and absolute risks of ischemic stroke for different doses of estrogen and taking into account migraine attack frequency and aura status[2, 31] and the presence of traditional cardiovascular female-specific and psychosocial risk factors.[35, 36] For many women with migraine, the contraceptive and non-contraceptive benefits of COCs (e.g. reduction in the risk of ovarian and endometrial cancer[37]may outweigh the relatively small increase in absolute risk of ischemic stroke.

Conclusion

In young women, migraine with aura and possibly also without aura, COC use and smoking have supra-additive effects on the risk of ischemic stroke. This effect may be slightly lower but still significant for COCs containing low doses of estrogen.

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