Stroke and myocardial infarction with contemporary hormonal contraception: real-world, nationwide, prospective cohort study

Harman Yonis,[1,2,3] Ellen Løkkegaard,[4,5] Kristian Kragholm,[6] Christopher B Granger,[3] Amalie Lykkemark Møller,[2,7] Lina Steinrud Mørch,[7] Christian Torp-Pedersen,[1,2] Amani Meaidi[1,7]

[1]Department of Cardiology, Nordsjaellands Hospital, Hilleroed, Denmark
[2]Department of Public Health, University of Copenhagen, Copenhagen, Denmark
[3]Duke Clinical Research Institute, Durham, NC, USA
[4]Department of Gynecology, Nordsjaellands Hospital, Hilleroed, Denmark
[5]Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark
[6]Department of Cardiology, Aalborg University Hospital, Aalborg, Denmark
[7]Cancer and Medicine, The Danish Cancer Institute, Copenhagen, Denmark

Correspondence to: H Yonis
harman@live.dk
(@HarmanYonis;
ORCID 0000-0003-1711-7726)

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ABSTRACT

OBJECTIVE

To evaluate the association between contemporary hormonal contraceptive use and the risk of incident ischaemic stroke and myocardial infarction.

DESIGN

Real-world, nationwide, prospective cohort study.

SETTING

Denmark, by use of national registries.

PARTICIPANTS

All women aged 15-49 years residing in Denmark between 1996 and 2021, with no history of arterial or venous thrombosis, antipsychotics use, cancer, thrombophilia, liver disease, kidney disease, polycystic ovary syndrome, endometriosis, infertility treatment, hormone therapy use, oophorectomy, and hysterectomy.

MAIN OUTCOME MEASURES

First time diagnosis of ischaemic stroke or myocardial infarction at discharge.

RESULTS

Among 2 025 691 women followed up for 22 209 697 person years, 4730 ischaemic strokes and 2072 myocardial infarctions occurred. Standardised ischaemic stroke rate per 100 000 person years were 18 (95% confidence interval 18 to 19) for no use, 39 (36 to 42) for combined oral contraception, 33 (25 to 44) for progestin-only pills, and 23 (17 to 29) for intrauterine device. Standardised myocardial infarction rate per 100 000 person years were 8 (8 to 9) for no use, 18 (16 to 20) for combined oral contraception, 13 (8 to 19) for progestin-only pills, and 11 (7 to 16) for intrauterine device. Compared with no use, current use of combined oral contraception was associated with an adjusted rate ratio of 2.0 (1.9 to 2.2) for ischaemic stroke and 2.0 (1.7 to 2.2) for myocardial infarction. These corresponded to standardised rate differences of 21 (18 to 24) extra ischaemic strokes and 10 (7 to 12) extra myocardial infarctions per 100 000 person years. Compared with no use, current use of progestin-only pills was associated with an adjusted rate ratio of 1.6 (95% CI 1.3 to 2.0) for ischaemic stroke and 1.5 (1.1 to 2.1) for myocardial infarction, equating to 15 (6 to 24) extra ischaemic strokes and four (−1 to 9) extra myocardial infarctions per 100 000 person years. Increased arterial thrombotic risk was also observed with use of the combined vaginal ring (adjusted incidence rate ratio of 2.4 (1.5 to 3.7) for ischaemic stroke and 3.8 (2.0 to 7.3) for myocardial infarction), patch (3.4 (1.3 to 9.1) and no myocardial infarctions), and progestin-only implant (2.1 (1.2 to 3.8) and ≤3 myocardial infarctions), whereas no increased risk was observed with progestin-only intrauterine device (1.1 (1.0 to 1.3) for ischaemic stroke and 1.1 (0.9 to 1.3) for myocardial infarction).

CONCLUSIONS

Use of contemporary oestrogen-progestin and progestin-only contraceptives was associated with an increased risk of ischaemic stroke and, in some cases, myocardial infarction except for the levonorgestrel-releasing intrauterine device, which was not associated with either. Although absolute risks were low, clinicians should include the potential risk of arterial thrombosis in their assessment of the benefits and risks when prescribing a hormonal contraceptive method.

WHAT IS ALREADY KNOWN ON THIS TOPIC

While observational studies and meta-analyses suggest an increased risk of arterial thrombotic events with hormonal contraception use, findings have been inconsistent and from outdated studies

Evidence on the effects of mode of administration, oestrogen type, progestin type, and duration of use is lacking

WHAT THIS STUDY ADDS

This nationwide cohort study found that contemporary oestrogen-progestin and progestin-only contraceptives, except for the levonorgestrel-releasing intrauterine device, were associated with an increased risk of arterial thrombotic events

The highest risk estimates were observed with oestrogen-containing products; duration of use did not seem to influence the risk of an arterial thrombotic event

Introduction

At least 248 million women worldwide are estimated to use hormonal contraception according to the World Health Organization.[1] All currently marketed hormonal contraceptives have an acceptable and similar effectiveness in preventing unwanted pregnancies and safety is a key consideration when making clinical recommendations on which type of hormonal contraceptive to use.

Previous studies have suggested a potential increased risk of ischaemic stroke and myocardial infarction with use of hormonal contraception,[2-4] but the evidence is inconsistent, with studies finding both no association and even a protective effect of hormonal contraception use.[5 6]

Most existing research has investigated the influence of only combined oestrogen-progestin oral contraceptives on arterial thrombosis risk without consideration of other types of contemporary hormonal contraceptives such as the combined vaginal ring, transdermal patch, progestin-only pills, intrauterine devices, subcutaneous implant, and

intramuscular injection.[3 5-12] A single Danish cohort study published in 2012 examined the associated ischaemic stroke and myocardial infarction risk with different types of hormonal contraceptives and found a significantly increased risk with use of combined oral contraceptives and the vaginal ring.[2] Although main estimates for some progestin-only contraceptives were indicative of an increased risk of ischaemic stroke and myocardial infarction, the study was insufficiently powered to conclude the direction of association for systemic progestin-only products.[2]

In this nationwide, prospective cohort study, we assessed the association of using contemporary hormonal contraceptives on the risk of incident ischaemic stroke and myocardial infarction according to oestrogen type, oestrogen dose, progestin type, mode of administration, and duration of use. The types of contraception that we considered were combined oestrogen-progestin pills, vaginal ring, and transdermal patch as well as progestin-only pills, intrauterine devices, subcutaneous implant, and intramuscular injection.

Methods

Study design and population

We conducted a nationwide prospective cohort study of all Danish women aged 15-49 years during 1996-2021 with no medical history of any arterial or venous thrombosis, cancer (except non-melanoma skin cancer), thrombophilia, liver disease, kidney disease, use of antipsychotics, infertility treatment, hormone therapy use, oophorectomy, hysterectomy, polycystic ovary syndrome, and endometriosis.

We followed up women from 1 January 1996, or from their 15th birthday if this occurred after the study began, and until 1 July 2021, emigration, death, or the occurrence of any arterial or venous thrombosis, cancer (except non-melanoma skin cancer), thrombophilia, liver disease, kidney disease, use of antipsychotics, infertility treatment, hormone therapy use, oophorectomy, hysterectomy, polycystic ovary syndrome, or endometriosis, whichever came first. Immigrated women entered the cohort five years after the date of immigration to ensure information on the eligibility criteria. Supplementary table S1 outlines the exact definitions of the exclusion and censoring criteria.

A unique personal identification number given to all Danish citizens at birth or on immigration was used to facilitate reliable data linkage across registries. We used six registries: (1) the Civil Registration System,[13] which contains information about all Danish citizens' sex, date of birth, and vital status since 1968; (2) the National Registry of Medicinal Product Statistics,[14] which includes information on all redeemed prescriptions at Danish pharmacies since 1995; (3) the National Registry of Patients,[15] which comprises information on discharge diagnoses and surgical procedures for all somatic admissions to hospital since 1976; (4) the Danish National Birth Registry,[16] which holds information on all live and death births since 1973; (5) The Registry of Legally Induced Abortions,[17] which includes information on all induced abortions in Denmark since 1973; and (6) Statistics Denmark,[18] which provides a yearly update on the education status for all Danish citizens.

Hormonal contraception

Women were classified as current users of hormonal contraception if they filled a prescription for any hormonal contraceptive. The National Registry of Medicinal Product Statistics provided daily updated, individual level data for all redeemed prescriptions of hormonal contraception throughout the study period, including the date of redemption, type, and quantity of the contraceptive.[14]

Women were considered exposed to hormonal contraception from the date of prescription redemption. For hormonal contraceptives taken orally, via a vaginal ring, patch, or injection, the duration of use was calculated based on the number of daily doses purchased. For long acting reversible contraceptives, such as subcutaneous implants and intrauterine devices, we assumed a duration of use one year shorter than the maximum approved period to account for potential early discontinuation. All prescriptions were extended by 28 days to accommodate possible delays in initiation. Gaps longer than 28 days between prescriptions were considered a time of no use. Exposure time was paused if a woman filled a prescription for a different hormonal contraceptive or became pregnant. In a sensitivity analysis, we excluded the first four weeks after the acquisition of a new hormonal contraceptive to address challenges in determining which product might be responsible for any arterial thrombotic events during product transitions.

A comprehensive list of contemporary hormonal contraceptives available during the study period, along with their anatomical therapeutic chemical codes, is provided in supplementary table S2.

Ischaemic stroke and myocardial infarction

Incident cases of ischaemic stroke and myocardial infarction were identified using the Danish National Patient Registry and the National Danish Registry of Causes of Death. Ischaemic strokes were classified according to the International Classification of Diseases, 10th revision (ICD-10) codes I63 and I64, while myocardial infarction was identified using ICD-10 code I21.[15 19]

Confounding factors

Time updated information about age, calendar time, educational level, pregnancy, surgery, use of oral tranexamic acid, and comorbidities was available for the entire study population (supplementary table S1).

Information about comorbidities, including hypertension, diabetes, hypercholesterolaemia, atrial fibrillation, and atrial flutter, was retrieved for all included women from The Danish National Patient

Registry and The National Registry of Medicinal Product Statistics (supplementary table S1).

To reduce potential bias from the temporary confounding effect of pregnancy, surgery, and the use of tranexamic acid, women were temporarily censored and did not contribute with person time and events to the analysis during these periods.

The Danish Medical Birth Registry provided information on all births undergone by the cohort, and a woman was censored temporarily during pregnancy, for six months after delivery, and for 12 weeks after other types of pregnancy terminations, which were identified through The Danish National Patient Registry and The Registry of Legally Induced Abortions (supplementary table S1).

From the Danish National Patient Registry, we retrieved information about all surgeries. If a woman was admitted to hospital for at least one day due to surgery, she would be temporarily censored from the date of surgery until eight weeks following her discharge date (supplementary table S1).

To further strengthen our analysis of the impact of hormonal contraceptive use on arterial thrombotic risk, we also implemented a temporary censorship of women using the antifibrinolytic tranexamic acid, which is potentially thrombogenic, and prescribed for heavy menstrual bleeding. Women were temporarily censored for eight weeks from the date of tranexamic acid prescription redemption (supplementary table S1).

If a woman had an event, died, emigrated, or met any permanent censoring criterion during a period of temporary censoring, she was permanently censored from the date of the given incident.

Data for family history was available only for women whose parents had resided in Denmark from midlife onward. A woman was classified as having a family history of thrombosis if her mother had a thromboembolic event before age 60 or her father before age 55.

Information about smoking status and body mass index was only available for parous women from the Danish Medical Birth Registry, which collects data for body mass index and smoking status just before pregnancy for women who have given birth from the year 2004 and onwards.

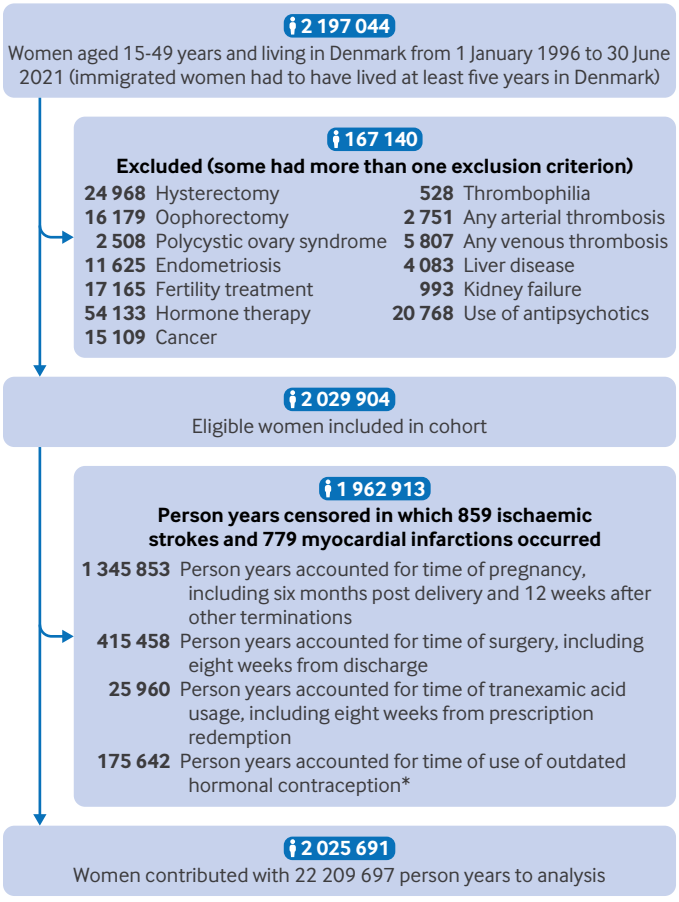


Fig 1 | Flowchart for study inclusion. *Use of hormonal contraceptives withdrawn from the market in Denmark before 2010 was censored, since data on these products already have been published in 2012 without the possibility of this study adding new information about the products.[2] They include combined oral contraceptives containing 50 µg ethinyl oestradiol, 30-40 µg pills containing the progestin norethisterone, and the levonorgestrel-only oral contraceptive

Statistical analysis

We used Poisson regression to estimate the adjusted incidence rate ratio of ischaemic stroke and myocardial infarction with current use of the different types of hormonal contraceptives. All models were adjusted for age in one year intervals and calendar year in five year intervals as well as educational level, hypertension, diabetes, hypercholesterolaemia, and atrial fibrillation or flutter. No use constituted the reference group in all primary analyses.

We conducted a sensitivity analysis to further mitigate the potential for user bias, whereby users of hormonal contraception may have an elevated baseline risk of arterial thrombotic events, independent of the contraceptive itself. We used person time for former hormonal contraception users (defined as those who had discontinued use for at least six months) as the reference group.

To eliminate potential carryover effects from prior hormonal contraceptive use, we conducted an additional sensitivity analysis. In this analysis, women were censored at the time that they discontinued their first hormonal contraceptive, ensuring that only person time related to their initial product was included. The study period for this analysis began in 2000, providing a minimum of five years of exposure history before study entry. Only women with no history of hormonal contraceptive use during this period were included. Women who had not redeemed a prescription for hormonal contraception contributed to the never-use exposure category, which was the reference group.

We calculated incidence rates of ischaemic stroke and myocardial infarction standardised by age, calendar time, and education, per 100 000 person years using the distribution of these factors in the entire cohort as the standard. Standardised incidence

Table 1 | Characteristics of the study population

Exposure	No. of person years	Age*, years	University education, %	Body mass index*	Smoking, %	Hypertension, %	Diabetes, %	Hypercholesterolaemia,%	Atrial fibrillation or flutter,%
No use of hormonal contraception	14 894 594	34 (23-42)	20.0	23 (20-26)	18.8	0.3	1.0	0.7	0.1
Combined hormonal contraception									
Oral, ethinyl oestradiol, 30 to 40 µg									
Norgestimate	502 577	24 (20-31)	15.1	23 (21-26)	23.5	0.1	0.6	0.3	0.1
Levonorgestrel	1 608 798	23 (19-31)	18.2	23 (21-27)	20.4	0.2	0.7	0.4	0.1
Gestodene	1 241 913	26 (21-33)	15.4	23 (21-26)	24.5	0.2	0.6	0.4	0.1
Desogestrel	297 933	28 (22-35)	15.6	23 (21-27)	27.0	0.3	0.7	0.5	0.1
Drospirenone	319 755	23 (19-30)	17.9	22 (20-26)	22.0	0.1	0.9	0.3	0.1
Cyproterone acetate	227 400	23 (20-30)	18.2	22 (20-25)	23.7	0.2	1.1	0.4	0.1
Dienogest	1,365	22 (19-26)	24.0	23 (20-25)	11.1	0.1	3.2	0.5	0.0
Oral, ethinyl oestradiol, 20 µg									
Levonorgestrel	34 785	19 (17-23)	12.7	23 (20-26)	16.5	0.0	0.7	0.2	0.0
Gestodene	743 838	22 (18-27)	15.1	23 (21-26)	19.8	0.1	0.6	0.3	0.1
Desogestrel	789 890	23 (19-29)	15.9	23 (21-26)	20.5	0.1	0.6	0.3	0.1
Drospirenone	77 361	22 (18-27)	19.9	22 (20-25)	15.2	0.1	1.2	0.3	0.0
Oral, oestradiol	14 472	29 (21-40)	28.4	22 (20-25)	13.0	0.2	1.9	1.1	0.2
Vaginal ring									
Vaginal ring	82 841	25 (22-31)	29.0	23 (21-26)	18.8	0.1	0.7	0.3	0.1
Patch									
Patch	11 721	24 (19-31)	12.6	22 (20-25)	20.3	0.1	0.7	0.3	0.0
Progestin-only contraception									
Oral									
Norethisterone	114 749	33 (25-40)	28.0	22 (20-26)	15.6	0.6	1.3	0.9	0.2
Desogestrel	186 428	29 (22-38)	31.8	23 (21-26)	15.7	0.5	1.5	1.3	0.1
Drospirenone	16	27 (21-32)	45.0	23 (21-30)	7.2	0.0	3.3	0.0	0.4
Intrauterine device	977 191	38 (32-43)	39.2	23 (21-26)	13.1	0.6	1.5	1.4	0.2
Implant	59 327	21 (18-28)	8.5	24 (21-28)	28.4	0.1	1.2	0.5	0.0
Injection	22 741	23 (19-30)	3.6	24 (21-29)	44.7	0.3	2.2	1.2	0.1

Row percentages of are person time.
*Weighted median (first to third quantile); the weight was calculated as the ratio of the person time with a given age/body mass index to the total person time for the specific exposure category. Information about body mass index (from year 2004) and smoking (from year 1991) was available for parous women only; body mass index for 349 208 women for 2 747 548 million person year; smoking for 483 939 women for 4 731 577 million person years.

rate differences were calculated for each type of hormonal contraceptive with no use as the reference.

In a subcohort of women with data for family history of thrombosis, further adjustment for family history was made. In a subpopulation of parous women with the information available, further adjustments of smoking and body mass index were made. Analyses were repeated in the age strata of younger than 35 years and 35 years or older. The effect of duration of hormonal contraception use was also investigated. The durations were categorised based on uninterrupted periods of use, with categories defined as less than a year, one to four years, and more than four years. Women contributed person time and events to the relevant duration category based on the length of their uninterrupted use. Data were managed with SAS software, version 9.4,[20] and analysed using R software version 4.2.1.[21]

Patient and public involvement

Other than the women of reproductive age included in the research group, no patients or members of the public were involved in the design, analysis, or reporting of this study, as the project lacked funding for patient and public involvement initiatives.

Results

A total of 2 025 691 women aged 15 to 49 years contributed with 22 209 697 person years of follow-up time (fig 1). During follow-up, 4730 incident ischaemic strokes and 2072 incident myocardial infarctions occurred. A total of 93 (2.0%) women who developed ischaemic stroke and 185 (8.9%) women who had a myocardial infarction died within 30 days from diagnosis.

Characteristics of the whole study population are shown in table 1.

Table 2 provides the adjusted incidence rate ratios and incidence rate differences of ischaemic stroke and myocardial infarction according to exposure status with no use of hormonal contraception as the reference group.

Combined oral contraceptives

Standardised ischaemic stroke rate per 100 000 person years was 39 (95% confidence interval 36 to 42) with use of combined oral contraception. Myocardial infarction rate was 18 (16 to 20) per 100 000 person years.

Compared with no use of hormonal contraception, current use of oral contraceptives containing oestrogen and progestin was associated with adjusted incidence

Table 2 | Adjusted incidence rate ratios and rate differences of ischaemic stroke and myocardial infarction according to type of hormonal contraception, mode of administration, oestrogen dose, oestrogen type, and progestin type

		Ischaemic stroke				Acute myocardial infarction			
Exposure	No. of person years	No. of events	Standardised incidence rate*	Adjusted incidence rate ratio† (95% CI)	Standardised incidence rate difference*	No. of events	Standardised incidence rate*	Adjusted Incidence rate ratio† (95% CI)	Standardised incidence rate difference*
No use of hormonal contraception	14 894 594	3120	18 (18 to 19)	Ref	Ref	1491	8 (8 to 9)	Ref	Ref
Combined hormonal contraception									
Oral, ethinyl oestradiol, 30 to 40 µg									
Norgestimate	502 577	101	37 (27 to 50)	1.9 (1.6 to 2.3)	19 (8 to 30)	40	18 (12 to 26)	2.2 (1.6 to 3.0)	9 (3 to 16)
Levonorgestrel	1 608 798	311	37 (32 to 43)	2.0 (1.8 to 2.2)	19 (14 to 24)	123	18 (15 to 22)	2.1 (1.7 to 2.5)	10 (6 to 14)
Gestodene	1 241 913	316	40 (34 to 47)	2.0 (1.8 to 2.3)	21 (15 to 28)	114	17 (13 to 21)	1.9 (1.6 to 2.4)	8 (4 to 13)
Desogestrel	297 933	107	40 (31 to 50)	2.5 (2.0 to 3.0)	22 (13 to 31)	40	22 (15 to 31)	2.3 (1.7 to 3.2)	13 (6 to 21)
Drospirenone	319 755	69	52 (32 to 80)	2.2 (1.7 to 2.8)	34 (11 to 57)	17	14 (7 to 26)	1.8 (1.1 to 3.0)	6 (−3 to 14)
Cyproterone acetate	227 400	37	39 (23 to 62)	1.8 (1.3 to 2.4)	21 (3 to 39)	15	25 (7 to 60)	2.2 (1.3 to 3.6)	16 (−7 to 39)
Dienogest	1365	0	-	-	-	0	-	-	-
Oral, ethinyl oestradiol, 20 µg									
Levonorgestrel	34 785	≤3	—	—	—	0	—	—	—
Gestodene	743 838	115	32 (24 to 42)	1.8 (1.5 to 2.2)	13 (5 to 22)	33	23 (12 to 38)	1.8 (1.3 to 2.6)	14 (2 to 26)
Desogestrel	789 890	151	45 (35 to 57)	2.0 (1.7 to 2.4)	27 (16 to 38)	34	14 (7 to 24)	1.4 (1.0 to 1.9)	6 (−2 to 14)
Drospirenone	77 361	9	11 (4 to 24)	1.6 (0.8 to 3.1)	−8 (−16 to 1)	≤3	—	—	—
Oral, oestradiol	14 472	≤3	—	—	—	≤3	—	—	—
Vaginal ring	82 841	20	46 (25 to 78)	2.4 (1.5 to 3.7)	28 (4 to 52)	9	49 (11 to 141)	3.8 (2.0 to 7.3)	41 (−14 to 96)
Patch	11 721	4	17 (5 to 45)	3.4 (1.3 to 9.1)	−1 (−19 to 16)	0	—	—	—
Progestin-only contraception									
Oral									
Norethisterone	114 749	36	35 (24 to 50)	1.6 (1.2 to 2.2)	17 (4 to 30)	15	11 (6 to 19)	1.5 (0.9 to 2.4)	3 (−3 to 9)
Desogestrel	186 428	46	35 (19 to 60)	1.6 (1.2 to 2.2)	17 (−2 to 36)	18	24 (8 to 57)	1.6 (1.0 to 2.5)	16 (−5 to 37)
Drospirenone	16	0	—	—	—	0	—	—	—
Intrauterine device	977 191	268	23 (17 to 29)	1.1 (1.0 to 1.3)	4 (−2 to 10)	116	11 (7 to 16)	1.1 (0.9 to 1.3)	2 (−2 to 6)
Implant	59 327	11	28 (11 to 57)	2.1 (1.2 to 3.8)	4 (−2 to 10)	≤3	—	—	—
Injection	22 741	5	24 (8 to 57)	1.8 (0.8 to 4.4)	6 (−16 to 27)	0	—	—	—

CI=confidence interval; Ref=reference.
*Standardised incidence rate was No. of events/100 000 person years (95% CI) and standardised by age, calendar-time, and education according to the distribution of these factors in the entire cohort.
†Adjusted for age, calendar-time, education, hypertension, diabetes, hypercholesterolaemia, and atrial fibrillation and flutter.

rate ratio of 2.0 (95% confidence interval (CI) 1.9 to 2.2) for ischaemic stroke and 2.0 (1.7 to 2.2) for myocardial infarction.

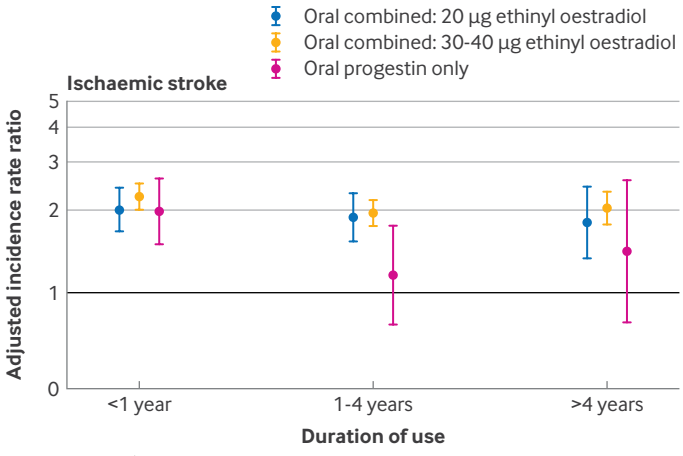
The corresponding numbers of extra ischaemic strokes per 100 000 person years (standardised incidence rate difference) was 21 (18 to 24) and of myocardial infarctions was 10 (7 to 12). These values equate to approximately one extra ischaemic stroke for every 4760 women using combined oral contraceptives for one year and one extra myocardial infarction for every 10 000 women per year of use compared with no users.

Stratified by oestrogen dose, the adjusted incidence rate ratio of ischaemic stroke was 1.9 (1.7 to 2.2) for current use of combined oral contraceptives containing 20 µg of ethinyl oestradiol and 2.0 (1.9 to 2.2) for current use of tablets including 30-40 µg, when compared with no use of hormonal contraception and with further adjustment for progestin type. For myocardial infarction, the corresponding adjusted incidence rate ratios were 1.6 (1.2 to 2.0) for the 20 µg tablets and 2.1 (1.8 to 2.3) for the 30-40 µg tablets. As shown in table 2, no consistent pattern was shown between progestin type in combined oral contraceptives and risk of ischaemic stroke and acute myocardial infarction.

In a sensitivity analysis, where previous use of hormonal contraception constituted the reference group, the adjusted rate ratios of ischaemic stroke and myocardial infarction with current use of combined hormonal contraception remained significantly increased (1.6 (1.5 to 1.8) for ischaemic stroke and 1.5 (1.3 to 1.7) for myocardial infarction).

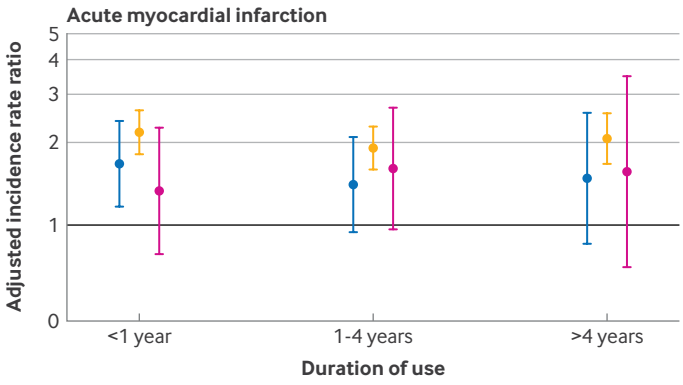
Combined non-oral contraceptives

Compared with no use of hormonal contraception, current use of the combined vaginal ring was associated with an adjusted incidence rate ratio of 2.4 (95% CI 1.5 to 3.7) for ischaemic stroke and 3.8 (2.0 to 7.3) for myocardial infarction, corresponding to standardised incidence rate differences of 28 (4 to 52) ischaemic strokes per 100 000 person years and 41 (−14 to 96) myocardial infarctions per 100 000 person years. The corresponding adjusted ischaemic stroke rate ratio with current use of the combined hormonal patch was 3.4 (1.3 to 9.1), while no myocardial infarctions were observed in women during patch use. The positive associations persisted with statistical significance, with a small reduction in estimates, when previous use of hormonal contraception constituted the reference group (vaginal ring: 2.0 (1.3 to 3.2) for ischaemic



No of events/No of person years

	<1 year	1-4 years	>4 years
Oral combined: 20 µg ethinyl oestradiol	128/796 018	105/663 616	44/186 240
Oral combined: 30-40 µg ethinyl oestradiol	396/1 964 128	365/1 734 494	180/501 119
Oral progestin only	49/182 852	23/97 924	10/20 417



No of events/No of person years

	<1 year	1-4 years	>4 years
Oral combined: 20 µg ethinyl oestradiol	31/796 018	26/663 616	12/186 240
Oral combined: 30-40 µg ethinyl oestradiol	131/1 964 129	132/1 734 495	86/501 119
Oral progestin only	14/182 853	14/97 924	5/20 417

Fig 2 | Adjusted incidence rate ratio of ischaemic stroke and myocardial infarction with use of oral contraceptives according to type and duration of use with non-use as the reference. Adjusted for age, calendar-time, education, hypertension, diabetes, hypercholesterolaemia, and atrial fibrillation and flutter

stroke and 3.1 (1.6 to 6.1) for myocardial infarction; patch; 2.8 (1.1 to 7.6) for ischaemic stroke).

Progestin-only oral contraceptives

Standardised ischaemic stroke rate per 100 000 person years was 33 (95% CI 25 to 44) with use of progestin-only pills, while the myocardial infarction rate was 13 (8 to 19) per 100 000 person years.

Compared with no use of hormonal contraception, current use of progestin-only oral contraceptives was associated with adjusted incidence rate ratios of 1.6 (95% CI 1.3 to 2.0) for ischaemic stroke and 1.5 (1.1 to 2.1) for myocardial infarction with corresponding standardised incidence rate differences per 100 000 person years of 15 (6 to 24) ischaemic strokes and four (−1 to 9) myocardial infarctions.

When compared with previous use of hormonal contraception, the rate ratio of ischaemic stroke with use of oral progestin-only products was estimated at 1.3 (1.1 to 1.7) for ischaemic stroke and 1.2 (0.9 to 1.7) for myocardial infarction.

Progestin-only non-oral contraceptives

Current use of the progestin-only intrauterine device was not associated with increased risk of ischaemic stroke and acute myocardial infarction (table 2). The intrauterine device releasing high doses of 52 mg levonorgestrel accounted for 88.8% of the exposure time of hormonal intrauterine device use in the study.

The adjusted incidence rate ratio of ischaemic stroke was 2.1 (95% CI 1.2 to 3.8) with current use of the subcutaneous progestin-only implant and 1.8 (0.8 to 4.4) with current use of the progestin-only injection compared with no use of hormonal contraception (table 2). The adjusted rate ratios for myocardial infarction with use of the implant and injection could not be calculated due to the very low number of events.

The rate ratio of stroke was 1.7 (1.0 to 3.2) with current implant use and 1.5 (0.6 to 3.5) with current injection use when compared with previous hormonal contraception use.

All associations persisted when the first four weeks after a product switch was excluded from either contraceptive category in cases where the new product was purchased before the previous product prescription ran out (supplementary table S3).

An increase in size of the estimated positive associations was observed in a sensitivity analysis, in which a woman only contributed with exposed time during her first use and in which never-use comprised the reference group (supplementary table S3).

Duration of use

Figure 2 provides the adjusted incidence rate ratios of ischaemic stroke and myocardial infarction with current use of oral contraceptives according to type and duration of use. The increased risk of ischaemic stroke and myocardial infarction with use of combined oral contraceptives remained stable with increasing duration of use (fig 2). Less power was available to study the effect of duration of use of progestin-only pills on arterial thrombotic risk. However, no consistent change in risk was observed over time (fig 2).

The adjusted rate ratios of stroke in the first, second, and third year of use of the levonorgestrel-releasing intrauterine device were 1.1 (95% CI 0.9 to 1.4), 1.2 (0.9 to 1.5), and 1.1 (0.9 to 1.4), respectively. For myocardial infarction, they were 1.0 (0.7 to 1.4), 1.2 (0.9 to 1.7), and 0.8 (0.5 to 1.3).

Further adjustment of family history in a subcohort of women with this information available provided

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incidence rate ratios consistent with primary findings (supplementary table S3).

Supplementary table S3 shows the adjusted incidence rate ratios of ischaemic stroke and myocardial infarction according to type of hormonal contraception with further adjustment of body mass index (BMI) and smoking in a subpopulation of parous women with this information available. The positive associations persisted with statistical significance for combined oral contraceptives. Compared with no use, the further adjusted incidence rate ratio of ischaemic stroke for smoking and BMI with use of combined oral contraceptives was 1.7 (95% CI 1.4 to 2.0) and for myocardial infarction, it was 1.5 (1.1 to 2.2). The ischaemic stroke risk also remained increased with significance after the adjustment of BMI and smoking with use of the vaginal ring (rate ratio of 2.6 (1.2 to 5.4)) and progestin-only pills (1.6 (1.1 to 2.3)).

The associations observed for combined oral contraceptives were similar between women younger than 35 years and women aged 35-49 years (supplementary table S4). With progestin-only pills, the main rate ratio of showed a 50% increase for ischaemic stroke and a 35% increase for myocardial infarction among young women compared with women aged 35 years and above, however with overlapping 95% confidence intervals (supplementary table S4).

Discussion

Principal findings

In this nationwide, prospective cohort study, current use of contemporary hormonal contraception, including combined oral contraceptive pills, vaginal ring, patch, progestin-only pills, and subcutaneous implant, was associated with an increased risk of ischaemic stroke and for some also myocardial infarction compared with no use. Use of the levonorgestrel-releasing intrauterine device was found not to be associated with increased arterial thrombotic risk.

Considering the low baseline risks of ischaemic stroke and myocardial infarction among women of reproductive age, the increased relative arterial thrombotic risk observed with hormonal contraception use translated to low absolute excess risks. The highest statistically significant number per 100 000 person years were 34 additional ischaemic strokes and 14 additional myocardial infarctions, with the use of combined pills containing third or fourth generation progestins.

The increased risk with progestin-only pill, implant, and injection was accompanied by uncertainty due to limited data.

Strength and limitations of this study

The strengths of our study include its nationwide design, minimising selection bias, and the use of high quality national registries. These factors allowed for individual level, day-to-day updated information about use of hormonal contraception, development of arterial thrombotic events, and the occurrence of multiple potential confounders, including cancer, thrombophilia, hypertension, diabetes, atrial fibrillation or flutter, hypercholesterolaemia, pregnancy, and surgery.

Given the observational nature of the study, the exposure was not randomised, leaving the possibility of residual confounding. Considering the clinical awareness of the venous thrombotic risk with combined hormonal contraceptive products, women with higher cardiovascular risk are potentially more likely to be prescribed a progestin-only product. As such, confounding by indication is an unlikely explanation for the increased arterial thrombotic risks observed with combined oral contraceptives, vaginal rings, and patches. Yet, potential for bias remains when estimating the risks associated with progestin-only products. We addressed this concern by controlling for multiple potential confounding factors through study design and statistical analyses, including the adjustment for BMI and smoking in a subcohort with this information available. The increased arterial thrombotic risk with progestin-only pills persisted, which reduces the likelihood of confounding by indication. If this bias was present, we would expect a similar increase in risk with the progestin-only intrauterine device, especially because this option is often recommended for women at high cardiovascular risk. However, we did not observe such an association, further supporting our findings. Moreover, if differences in cardiovascular profiles between the treatment group and the control were driving the results, we would expect no increased risk when comparing with prior users; however, this was also not the case.

Exposure time was defined by purchase records, which may have led to misclassification, particularly for long acting contraceptives such as the levonorgestrel releasing intrauterine device. Early, undetected removal could result in non-exposure being misclassified as exposure. Nevertheless, the null association between intrauterine device use and arterial thrombosis was consistent in the first year following prescription redemption, in which women are most likely to be exposed, suggesting that misclassification is an unlikely explanation for the null association observed.

Finally, external generalisability may be limited by the study population's homogeneity and health profile.

Comparison with other studies

A Cochrane meta-analysis including data from 24 studies found an increased arterial thrombotic risk with use of combined oral contraceptives.[22] The largest and most recent study contributing to this meta-analysis is a Danish observational cohort study published in 2012, which found a positive association between combined oral contraception use and the development of ischaemic stroke and myocardial infarction.[2] The study was not sufficiently powered to detect the association with progestin-only pills and non-oral hormonal contraceptives.[2] Considering the increase in use of progestin-only pills in Denmark since then and the additional 12 years of data in our analysis,[23] we

were able to study the effect of progestin-only products and non-oral contraceptives on arterial thrombotic risk. We observed a significantly increased arterial thrombotic risk with combined non-oral products as well as with progestin-only pills.

A study from the UK Biobank similarly reported an increased stroke risk among hormonal contraception users, with the highest risk occurring during the first year of use.[24] However, our findings did not suggest a time dependent variation in risk. Unlike the UK Biobank study, which relied on self-reported survey data, thereby susceptible to recall bias, our study used prescription records, offering a more precise measure of exposure timing.[24] Notably, the median age of women in the UK Biobank study at the time of exposure assessment was 56 years, despite the median age of initiation of hormonal contraception being 21 years.[24] This significant gap in time increases the likelihood of recall bias, particularly when recalling details about the timing and duration of contraceptive use.

Possible explanations for study findings

Exogenous oestrogens are recognised to have a prothrombotic effect.[25] We found the highest estimates of thrombotic risk during use of oestrogen containing hormonal contraceptives. Among the oestrogen containing products, the vaginal ring and patch seemed to increase the thrombotic risk the most. Contrary to oral products, these products are continuously releasing oestrogen, bypassing the first-pass metabolism. Studies have shown a 60% higher plasma level of oestrogen in women using the combined contraceptive patch compared with those using the corresponding combined oral contraceptive.[26] Thus, our findings may reflect this increased oestrogen dose with use of non-oral combined products compared with oral products.

Furthermore, previous studies have also found an increased venous thromboembolic risk with the patch and ring compared with combined oral contraceptives.[27] Although the main pathophysiology of venous thromboembolism differ from that of arterial thrombosis, coagulation, which is important for venous thromboembolism, interplays with platelet aggregation, a key factor in the formation of arterial thrombosis.[28]

The effects of progestin alone on thrombosis risk are less understood. The type of progestin in combined products is known to influence venous thrombosis risk.[29] While previous studies have not found an increased risk of venous thrombosis with progestin-only oral products and the intrauterine device, these studies have indicated an increased risk of venous thrombosis with the progestin-only implant and injection.[30 31] Similar to the combined non-oral products, these non-oral progestin-only products continuously release progestin, bypassing first-pass metabolism. Our findings may suggest a dose-related association between progestin-only products and arterial thrombotic risk with the highest risk associated with implant use, then pills. Intrauterine devices, which cause the smallest increase in serum progestin level, were not associated with increased risk.

Conclusion and implications

While we observed a statistically significant increase in the risk of ischaemic stroke and, in some cases, myocardial infarction with contemporary hormonal contraceptive use, except for the levonorgestrel-releasing intrauterine device, the absolute risks remained low. However, given the widespread use of these products and the severity of arterial thrombotic events, the findings have important public health implications. Healthcare providers should consider these risks when assessing the benefit-risk profile of hormonal contraceptives.

Contributors: The study was initiated by AM. The study was designed by HY and AM with contributions from all co-authors. HY and AM conducted the data collection. HY and AM conducted the analyses. Interpretation and writing of the manuscript were done by all authors, led by HY and AM. All authors approved the final version and made the decision to submit for publication. All authors had access to the statistically analysed data. HY, CT-P, and AM had access to and verified the raw data. HY and AM are the guarantors.

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Ethical approval: Granted by the Danish Health Data Board (approval ID: FSEID-00005931) and the Danish Data Protection Agency (approval ID: P-2019-280). Written informed consent was waived as this is not required for registry studies in Denmark.

Data sharing: Raw data used to conduct this study is only accessible through approval from the Danish Data Protection Agency and the Danish Health Data Board. Although anonymised, the data was available on an individual level, making data sharing restricted by the General Data Protection Regulation of EU law.

Transparency: The lead author (the manuscript's guarantor) and the last author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Dissemination to participants and related patient and public communities: The study's findings will be shared with the public and healthcare professionals through press releases and presentations at scientific conferences.

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