Stroke

CLINICAL AND POPULATION SCIENCES

Oral Contraceptives, Hormone Replacement Therapy, and Stroke Risk

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BACKGROUND: Millions of women worldwide use exogenous hormones as oral contraceptives or hormone replacement therapy. Still, time-dependent and long-term consequences of exogenous hormones on stroke risk remains unclear.

METHODS: We examined the association between self-reported oral contraceptive and hormone replacement therapy use and stroke risk in 257 194 women from the UK Biobank, born between 1939 and 1970. Outcomes included any type of stroke, ischemic stroke, intracerebral hemorrhage, and subarachnoid hemorrhage. Exposures were analyzed as time-varying variables in Cox regression models.

RESULTS: During first year of oral contraceptive use, an increased event rate of any stroke was observed (hazard ratio [HR], 2.49 [95% CI, 1.44–4.30]), while the hazards were found to be comparable during remaining years of use (HR, 1.00 [95% CI, 0.86–1.14]), compared with nonusers. Similarly, first year of hormone replacement therapy use was associated with higher hazard rates of any stroke (HR, 2.12 [95% CI, 1.66–2.70]), as well as cause-specific stroke, including ischemic stroke (HR, 1.93 [95% CI, 1.05–3.57]) and subarachnoid hemorrhage (HR, 2.17 [95% CI, 1.25–3.78]), which remained increased for any stroke during remaining years of use (HR, 1.18 [95% CI, 1.05–1.31]), and after discontinuation (HR, 1.16 [95% CI, 1.02–1.32]).

CONCLUSIONS: Oral contraceptive use and hormone replacement therapy were associated with an increased risk of stroke, especially during the first year of use, possibly due to immediate changes in hemostatic balance. This study provides new insights on the effects of hormone exposure on stroke risk and provide evidence of not only an overall risk but also a pronounced effects seen in the beginning of treatment.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Premenopausal women are less likely to suffer a stroke than men of similar ages or postmenopausal women.[1] This difference in epidemiology has been ascribed to the protective effects of estrogen exposure.[2] Endogenous estrogen has potent effects on arterial endothelium that promote vasodilation and blood flow as well as protective effects by promoting cell survival, increasing mitochondrial efficiency, and stimulating angiogenesis.[3] In premenopausal women, estrogens are mainly produced by the ovaries, with circulating levels fluctuating from 40 to 200–400 pg/mL across the menstrual cycle. After menopause, estrogen plasma levels drop to less than 20 pg/mL as the ovaries cease to produce estrogen.[4] Hormone replacement therapy (HRT) is used to recover the loss of endogenous estrogen and has been suggested to improve cardiovascular health. Conversely, oral contraceptive (OC) use suppresses and stabilize the fluctuations of both estrogen and progesterone over time and might exert additional effects on arterial function.[5]

Studies have showed that OC use is associated with an increased risk of venous thrombosis,[6] while

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Nonstandard Abbreviations and Acronyms

OC	oral contraceptive
HR	hazard ratio
HRT	hormone replacement therapy
UKB	UK Biobank
WHI	Women's Health Initiative

fewer studies have examined the relation between OC and stroke, and those available have reported conflicting results.[7–9] Similarly, studies have yielded conflicting results regarding the risk of stroke with HRT,[10–13] and a possible increased risk seems to be mainly attributed to the first years after initiation,[10] while continued use may become protective.[14] This short-term increased risk of exogenous estrogen has been ascribed to its immediate procoagulant effect.[15] Thus, we hypothesize that use of OCs or HRT increase the risk of stroke by increasing the blood concentration of procoagulants in the beginning of treatment. The hemostatic imbalance has been proposed to stabilize with prolonged use and the increased risk of stroke might be outweighed by its beneficial effect on the underlying progression of atherosclerosis.[3] Therefore, we hypothesize that women using OCs or HRT for a longer duration will have a similar risk of stroke events, or possibly even a smaller risk, compared with never users.

It is predicted that some clinical effects of HRT are more likely to be beneficial when initiated and used by younger women closer to menopause.[16] Studies that have addressed this issue, have so far, not included women taking HRT in the stage just before menopause (ie, perimenopause), when its most commonly initiated in clinical settings.[17,18] Thus, the stroke risk among women who initiate HRT before entering menopause remains unclear. Because HRT is the most effective treatment option for relieving perimenopausal symptoms, it is important to resolve whether stroke risk needs to be considered before prescribing HRT to perimenopausal women.

The aim of this study was to fill the knowledge gaps of which effects exogenous hormones have on stroke risk by estimating the time-dependent and long-term consequences of OC and HRT use. In addition, we examined the difference in effect of HRT use depending on initiation before or after menopause.

METHODS

Study Population

UK Biobank (UKB) is a population-based cohort of > 502 000 United Kingdom residents aged between 37 and 73 between 2006 and 2010 when recruited.[19] Participants attended one of the 22 UK assessment centers to collect extensive data from questionnaires, interviews, health records, physical measures, imaging and biological samples. Participants included in our study were women who reported that they were White Irish, White British, or other White participants (N=257 194). Participants with noncomplete information on the variables needed for the statistical analyses were excluded (see Supplemental Material for more information). UKB obtained informed consent from all participants. UKB was approved by the research ethics committee (reference 11/NW/0382) and the analysis performed in this study was approved by UKB (application No. 41143) and the Swedish Ethical Review Authority (dnr: 2020-04415). The data used for this study is available for bona fide researchers from the UK Biobank. Resource (http://www.ukbiobank.ac.uk/about-biobank-uk/) and can be accessed by an application to the UK Biobank.

Assessment of Exposure

Information on OC use and HRT, including age when initiating and discontinuing hormone exposure, were assessed during the initial visit to the assessment center and obtained from the touchscreen questionnaire (see Supplemental Material for more information).

Assessment of Stroke Diagnoses and Covariates

First occurrence of stroke was obtained from the algorithmically defined stroke outcomes provided by UKB[20] (Table S1). Data sources on which the algorithm relies on include medical history, linked hospital admissions, and death register data (see Supplemental Material for more information). We subtyped stroke as ischemic stroke, intracerebral hemorrhage, and subarachnoid hemorrhage. General characteristics (Table) and information on covariates and potential confounders were assessed from data collected during the initial visit to the assessment center. See Table S2 for details of each covariate identified in UKB.

STATISTICAL ANALYSIS

Cox Regression

The association between hormone exposure and stroke was investigated using Cox regression. Follow-up started at birth until the first occurrence of stroke or the end of study follow-up (ie, age at assessment center visit), whichever came first. Hormone exposure was modelled as a time-varying variable by the counting process,[21,22] such that it changed state from unexposed to exposed at the time of initial hormone exposure. A time-varying representation of hormone initiation avoids misclassification of users' survival time before initiation of hormones as the exposed follow-up time.[23] In the first set of analyses, ever-users who initiated hormone exposure remained in the exposed state during rest of follow-up. The reference group consisted of nonusers, defined as those who never used oral contraceptives and nonexposed users (the person-years the women contributed with before oral contraceptive initiation). This method is an observational analogue of the intention-to-treat (ITT) principle that guides the main analysis of randomized clinical trials. We

estimated the hazard (rate) ratio (HR) of first occurrence of stroke in users and nonusers and calculated its 95% CI. All analyses were performed using R version 3.6.0.

To estimate the effects of hormone exposure during and after use, as well as to capture the early effects of hormone exposure on the risk of stroke, the time-varying exposure variable was extended to allow for > 2 states. In the second set of analyses, the exposure variable changed states when (1) participants initiate hormone exposure, (2) after first year of use, and (3) when users reported they discontinued treatment. For further details on the methods, see the Supplemental Material.

We used the directed acyclic graph approach[24] to select suitable covariates for the main model (Figure S1). The following covariates were added in the main model: year of birth, Townsend deprivation index (used as proxy for socioeconomic status), body mass index, smoking status, hysterectomy, bilateral oophorectomy, number of live births, menopausal status, and family history of stroke. An effective control of age is guaranteed since age is used as the primary time scale in the Cox models.[25] Smoking, hysterectomy, bilateral oophorectomy, menopause, and HRT/OC use were modeled as time-varying covariates. Since we primarily are interested in estimating the total effect of hormone exposure on stroke risk, we excluded blood pressure in our main model. However, blood pressure was included as a covariate in a sensitivity analysis (Model 2). For further details on methodology, variables, and adjustment justification,[26–31] see Tables S3 and S4 and the Supplemental Methods.

To investigate whether the HRT associated stroke risk depends on the order of treatment initiation and menopause, we generated a time-varying exposure variable combining both age at HRT initiation and age at menopause (see supplementary data for more information and Figure S2 for illustration).

In the main analysis, only stroke diagnoses occurring before assessment visit were included since no information on starting and discontinuation of hormone exposure was provided after assessment (2006–2010). However, in a secondary analysis, we extended the follow-up until February 2018 and re-estimated the HR between users and nonusers.

RESULTS

A total of 257 194 women were included in this study. Among these, 3007 stroke diagnoses of any type were identified before initial visit to the assessment center (end of follow-up in our study), of which 578 were ischemic stroke, 177 intracerebral hemorrhage, and 478 subarachnoid hemorrhage. Furthermore, 1774 diagnoses were self-reported as stroke of any type and could not be classified and are only included in the any type of stroke analyses (for details see Table S1).

Of the women included in this study, 81% were classified as users as they reported they had initiated OCs, while 19% reported they had never used OCs at any time during the study follow-up. Among participants with information on HRT, 37% reported they had initiated HRT during our study follow-up. For participant characteristics see the Table.

Intention-to-Treat Effects on Stroke Risk

The hazard rate of any stroke or stroke subtypes did not differ between women who had used OCs, compared with nonusers (Table S5; Figure 1A). When extending the follow-up time until February 2018, we observed that women previously exposed to OCs had a lower hazard rate of any stroke and ischemic stroke (HR, 0.90 [95% CI, 0.84–0.97] and HR, 0.84 [95% CI, 0.76–0.94], respectively; Table S6).

The HR of any stroke for HRT users versus nonusers was 1.22 (95% CI, 1.11–1.35), without considering when users discontinued (Table S5; Figure 1B). When analyzing stroke subtypes, the HR of subarachnoid hemorrhage was 1.33 (95% CI, 1.04–1.71) for HRT users compared with nonusers. For ischemic stroke and intracerebral hemorrhage, the hazard rate did not significantly differ between users and nonusers. The results were similar when extending the follow-up time until February 2018 across stroke types, with the exception that women exposed to HRT had a significant higher rate of ischemic stroke (HR, 1.12 [95% CI, 1.01–1.24]; Table S6). Adjusting for blood pressure (Model 2), the effect of HRT on stroke risk remained similar (Table S7).

Time-Varying Effects During and After Use on Stroke Risk

During first year of OC use, we observed an increased hazard of any stroke (HR, 2.49 [95% CI, 1.44–4.30]; Table S8; Figure 2A), while no difference in hazard rates between users and nonusers were found during remaining years of use and after discontinuation (HR, 1.00 [95% CI, 0.86–1.14] and HR, 0.93 [95% CI, 0.84–1.02]), respectively. However, it should be highlighted that the majority of stroke incidences occur late in life; therefore, the number of events during first year of use was small, which limits the possibility to analyze stroke subtypes.

For HRT, we observed an increased hazard of stroke during first year of use (Table S8), for any stroke (HR, 2.12 [95% CI, 1.66–2.70]: Figure 2B), ischemic stroke (1.93; 1.05–3.57: Figure 2C), and for subarachnoid hemorrhage (2.17; 1.25–3.78: Figure 2E). The increased hazard rate remained significant only for any stroke during remaining years of exposure (HR, 1.18 [95% CI, 1.05–1.32]; Table S8; Figure 2B). After discontinuation,

Table. Distribution of General Characteristics in Users and Never Users of Hormone Exposure

	Oral contraceptives			Hormone replacement therapy		
	Users	Never users	*P* value	Users	Never users	*P* value
Number (%)	202 964 (81%)	46 218 (19%)		90 338 (37%)	155 838 (63%)	
Year of birth, median (full range)	1952 (1936 to 1970)	1945 (1936 to 1970)	<0.001	1947 (1936 to 1970)	1955 (1936 to 1970)	<0.001
BMI, median (Q1–Q3)	26 (23.4 to 29.5)	26.5 (23.7 to 30.1)	<0.001	26.4 (23.8 to 29.8)	25.8 (23.2 to 29.5)	<0.001
Age, median (Q1–Q3)	56 (49 to 62)	63 (57 to 66)	<0.001	61 (57 to 65)	53 (47 to 61)	<0.001
TDI, median (Q1–Q3)	−2.29 (−3.7 to 0.14)	−2.2 (−3.63 to 0.39)	<0.001	−2.33 (−3.72 to 0.09)	−2.23 (−3.67 to 0.26)	<0.001
Diastolic blood pressure, median (Q1–Q3)	80 (73 to 87)	81 (74 to 88)	<0.001	80 (74 to 88)	80 (73 to 87)	<0.001
Systolic blood pressure, median (Q1–Q3)	134 (122 to 148)	141 (127 to 156)	<0.001	139 (126 to 153)	133 (120 to 147)	<0.001
Age at menarche, median (Q1–Q3)	13 (12 to 14)	13 (12 to 14)	0.25	13 (12 to 14)	13 (12 to 14)	<0.001
Age at menopause, median (Q1–Q3)	50 (48 to 53)	50 (48 to 53)	<0.001	50 (46 to 53)	51 (48 to 53)	<0.001
Post-menopausal, yes, N (%)	118 595 (58.4)	33 838 (73.2)	<0.001	67 159 (74.34)	82 174 (52.73)	<0.001
Post-menopausal, no, N (%)	51 666 (25.5)	5526 (12)	<0.001	2024 (2.24)	56 126 (36.02)	<0.001
Post-menopausal, not sure hysterectomy, N (%)	23 060 (11.4)	5734 (12.4)	<0.001	18 923 (20.95)	8941 (5.74)	<0.001
Post-menopausal-not sure other, N (%)	9543 (4.7)	1009 (2.2)	<0.001	2144 (2.37)	8457 (5.43)	<0.001
Had hysterectomy, N (%)	21 390 (10.54)	6182 (13.39)	<0.001	15 279 (16.93)	11 079 (7.11)	<0.001
Had bilateral oophorectomy, N (%)	15 401 (7.59)	4647 (10.07)	<0.001	15 928 (17.64)	3800 (2.44)	<0.001
Had neither hysterectomy or bilateral oophorectomy, N (%)	166 082 (81.87)	35 323 (76.54)	<0.001	59 066 (65.43)	140 870 (90.45)	<0.001
Smoking-current, N (%)	14 579 (7.2)	2539 (5.5)	<0.001	6611 (7.32)	10 389 (6.67)	<0.001
Smoking-never, N (%)	115 479 (56.9)	30 223 (65.4)	<0.001	47 639 (52.73)	96 458 (61.9)	<0.001
Smoking-occasional, N (%)	4432 (2.2)	726 (1.6)	<0.001	1767 (1.96)	3375 (2.17)	<0.001
Smoking-previous, N (%)	67 854 (33.4)	12 525 (27.1)	<0.001	33 979 (37.61)	45 153 (28.97)	<0.001
Family history of stroke, N (%)	20 241 (10)	5754 (12.44)	<0.001	10 775 (11.93)	14 718 (9.44)	<0.001
No of live birth, median (Q1–Q3)	2 (1 to 2)	2 (0 to 3)	<0.001	2 (1 to 3)	2 (1 to 2)	<0.001
HRT use, N (%)	71 401 (35.2)	16 453 (35.6)	<0.001			
OC use, N (%)				71 401 (79.04)	124 528 (79.91)	<0.001
Age when initiated HRT, median (Q1–Q3)	48 (45 to 50)	49 (45 to 52)	<0.001	48 (45 to 51)	…	
Age when discontinued HRT, median (Q1–Q3)	55 (50 to 58)	57 (52 to 60)	<0.001	55 (51 to 59)	…	
Duration of HRT, median (Q1–Q3)	6 (2 to 10)	7 (3 to 11)	<0.001	6 (2 to 10)	…	
Age when initiated OCs, median (Q1–Q3)	21 (18 to 24)	…		22 (19 to 25)	20 (18 to 23)	<0.001
Age when discontinued OCs median (Q1–Q3)	32 (27 to 40)	…		32 (27 to 40)	31 (26 to 39)	<0.001
Duration of OC use, median (Q1–Q3)	9 (4 to 15)	…		9 (4 to 14)	10 (5 to 16)	<0.001
Stroke, N (%)	3630 (1.8)	1313 (2.8)	<0.001	2284 (2.5)	2506 (1.6)	<0.001
Ischemic stroke, N (%)	1406 (0.7)	578 (1.3)	<0.001	953 (1.1)	976 (0.6)	<0.001
Intracerebral hemorrhage, N (%)	390 (0.2)	135 (0.3)	<0.001	233 (0.3)	278 (0.2)	<0.001
Subarachnoid hemorrhage, N (%)	647 (0.3)	164 (0.4)	0.24	351 (0.4)	447 (0.3)	<0.001
Preassessment any stroke N (%)*	2135 (1.1)	720 (1.6)	<0.001	1271 (1.41)	1492 (0.96)	<0.001
Preassessment ischemic stroke N (%)*	397 (0.2)	148 (0.3)	<0.001	232 (0.26)	296 (0.19)	<0.001
Preassessment intracerebral hemorrhage N (%)*	126 (0.1)	42 (0.1)	0.04	56 (0.06)	105 (0.07)	0.68
Preassessment subarachnoid hemorrhage N (%)*	368 (0.2)	88 (0.2)	0.72	185 (0.2)	264 (0.17)	0.05

Note that percentages do not add up to 100% exactly due to some missing data in each specific variable. Q1=First quartile, Q3=third quartile. BMI indicates body mass index; HRT, hormone replacement therapy; OC, oral contraceptive; and TDI, Townsend deprivation index.

*First occurrence of stroke diagnoses that occurred before the initial assessment visit and were included in the main analysis.

women who had been exposed to HRT continued to have a higher hazard rate of any stroke (HR, 1.16 [95% CI, 1.02–1.32]). These results were similar when including blood pressure in the model (Table S9).

Timing of HRT Initiation in Relation to Menopause

Initiation of HRT was associated with an increased hazard rate of any stroke in both pre- and postmenopausal

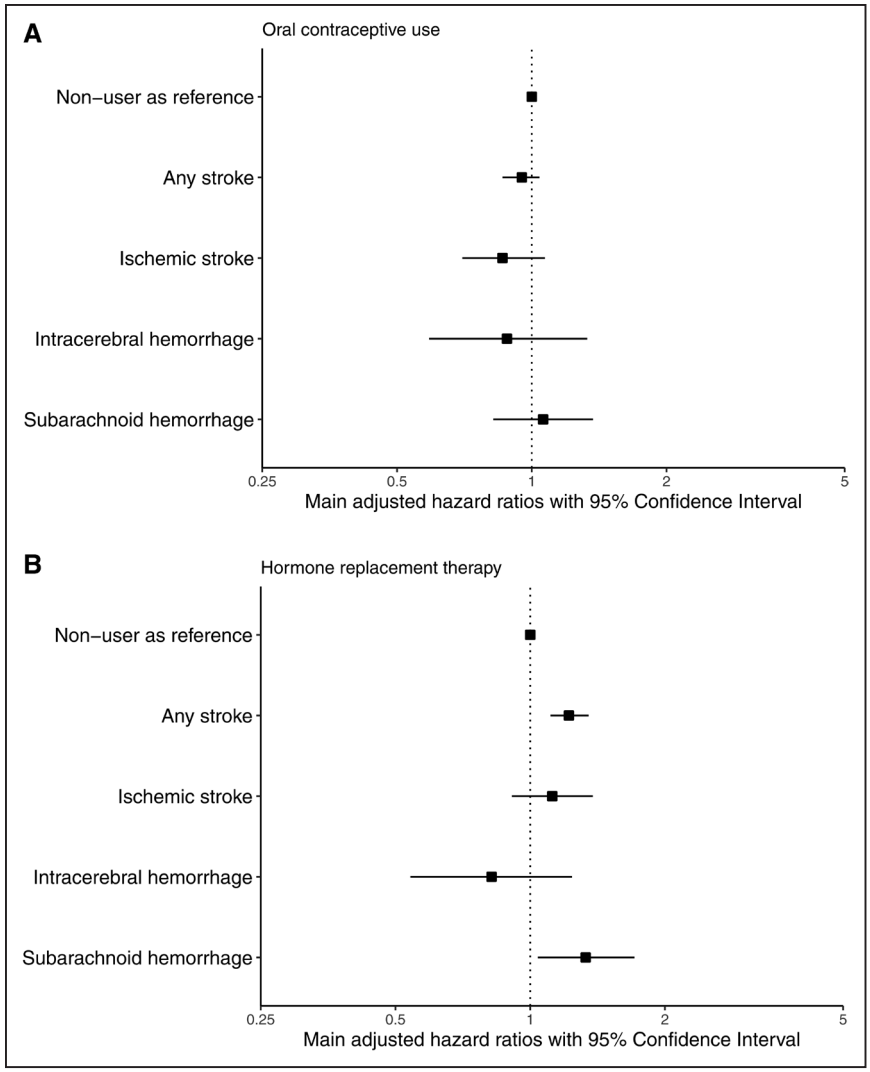

Figure 1. Intention-to-treat effects on stroke risk.
Hazard rates (squares) for oral contraceptive use (**A**) and hormone replacement therapy (**B**) are shown, relative to nonusers. Error bars denote 95% CI.

women, but the HR was higher (Table S10) in premenopausal women (HR, 1.96 [95% CI, 1.58–2.45], and HR, 1.23 [95% CI, 1.08–1.40]), respectively. Conversely, nonexposed women had a higher HR of any stroke associated with entering menopause (HR=1.77 [95% CI, 1.53–2.05]), compared with women who had initiated HRT before entering menopause (HR, 1.09 [95% CI, 0.88–1.39]). However, among women that ever started to use HRT and that reached menopause before end of follow-up, it appeared to be no difference between initiation of HRT before or after entering menopause (HR, 2.14 [95% CI, 1.84–2.49] and HR, 2.17 [95% CI, 1.84–2.57], respectively, compared with nonexposed premenopausal women). Similar results were observed after we excluded those women that had performed a hysterectomy or bilateral oophorectomy (Table S10).

DISCUSSION

We have shown that both OC use and oral HRT is associated with an increased risk of any stroke, as well as that HRT is associated with an increased risk of ischemic stroke and subarachnoid hemorrhage during the first year after initiation. This risk remains increased during, as well as after discontinuation of HRT, while limited to first year of OC use.

We found an ≈20% increased event rate of any stroke among women who had ever initiated HRT. This estimate is slightly lower than those reported from the WHI (Women's Health Initiative) trials,[17,32,33] and observational studies[18] (30%–40%). However, the WHI trial only covered a selected population of postmenopausal women within a specific age range (50–79 years),[34] as compared with our participants' age range at recruitment (37–73 years). Our study included a longer follow-up time and a longer duration of average use, and our estimates are therefore weighted toward a long-term effect as compared with the WHI. When we analyzed stroke subtypes, an increased risk of stroke was observed also for subarachnoid hemorrhage. This adds to previous knowledge, where the risk of subarachnoid hemorrhage in previous studies has not been possible to evaluate due to limited power.[17,18] This has not only clinical significance but also gives new insights on a possible additional mechanism of

exogenous hormones, given the important differences in the pathogenesis of stroke subtypes, especially ischemic and hemorrhage.

We observed a dramatic increased rate of any stroke as well as cause specific stroke, including ischemic stroke and subarachnoid hemorrhage during the first year of HRT use. There are limited data on the impact of hormone therapy on stroke risk during the first year of use, since the number of cases during first year of use have been small in clinical trials, while time-averaged risk estimates in observational studies are heavily weighted toward long-term effects. However, research on cardiovascular disease has shown that HRT increases the risk of coronary heart disease, with the most apparent elevation in risk at 1 year after treatment initiation.[35] In our study, with continued use of HRT, the increased risk of any stroke declined and the positive association with ischemic stroke and subarachnoid hemorrhage were no longer significant. The increased rate of ischemic stroke during the first year of use could be a result of

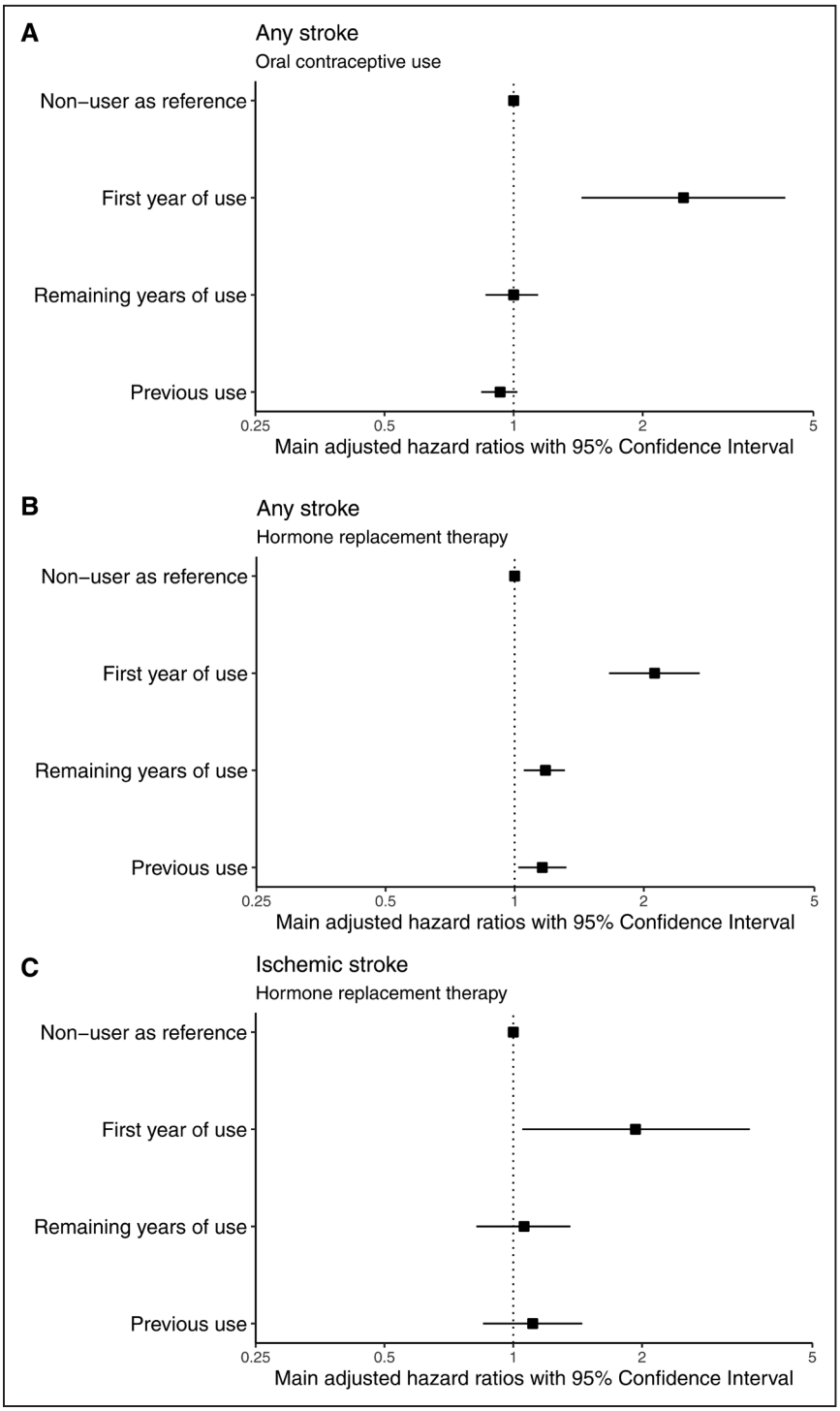

Figure 2. Time varying effects on stroke risk.
Hazard rates (squares) for oral contraceptive use (**A**) and hormone replacement therapy (**B**–**E**) are shown, relative to nonusers. Error bars denote 95% CI. **A**, Time-varying effects of OC use on any stroke risk. **B**, Depicts time-varying effects of HRT on any stroke risk. **C**–**E**, The time-varying effects of HRT on stroke subtype risk. **C**, Ischemic stroke; (**D**) intracerebral hemorrhage; and (**E**) subarachnoid hemorrhage. Squares represent hazard ratio (HR) and error bars 95% CI. Note: due to the small number of intracerebral hemorrhages, we were not able to investigate the association of HRT during first year of use. (*Continued*)

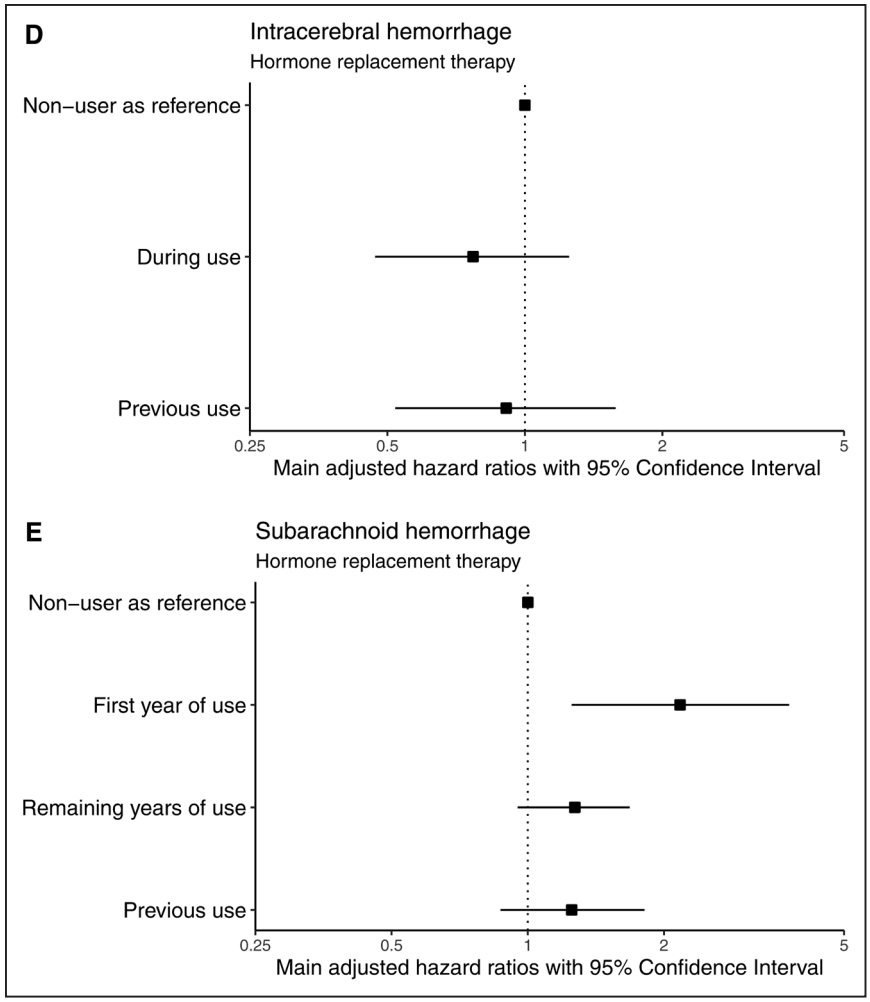

Figure 2 Continued.

an immediate prothrombotic effect[15] of the treatment that gradually declines due to adaptation of the hemostatic imbalance during remaining years of use. However, the underlying mechanism through which HRT confers an immediate increased risk of subarachnoid hemorrhage is less clear. The short-term increased risk could be explained by cerebral vasodilation[36] together with a transient elevation in systemic blood pressure[37] following HRT initiation, causing rupture of preexisting aneurysm.

In our study, we observed an increased risk among previous HRT users compared with nonusers. This could be a result of sudden estrogen withdrawal, which may cause vasoconstriction and potentially trigger stroke events in women at high risk of stroke, as the vasodilatory effects of estrogen abruptly drop.[38,39] However, it is also possible that atherosclerotic lesions are built up during treatment as a result of various processes, including elevated C-reactive protein levels during HRT use,[40] and that these lesions remain and result in higher stroke risk persisting also after discontinuation.

We observed no difference in stroke risk between nonusers and women who had ever initiated OC use. One of the largest studies to date on OC use and stroke risk was performed in a Danish cohort including >1.6 million women.[8] They found a small but increased risk of stroke among current users, as well as short-term users (<1 year of use), but not among previous users. We obtained an HR of 2.49 during first year of OC use, while the risk with prolonged use was similar to the risk among nonusers. The majority of current users in the Danish study had used OCs for a short time interval suggesting that their results are potentially driven by short-term effects. A recent mendelian randomization study[41] has shown that endogenous estrogen protects against thromboembolism and ischemic stroke among males. Although we did observe a decreased hazard of stroke among OC users as compared with nonusers when following participants until 2018, these results should be interpreted with care since no information on initiating and discontinuation of OC use was provided after assessment (2006–2010). Taken together, our results agree with an immediate increased risk of stroke, while the lifetime risk might not be that different between women who have been exposed to OCs and those who have not.

The potential existence of a window of opportunity to reduce cardiovascular disease risk by use of hormonal therapy is mainly supported by laboratory studies[42] and studies on heart disease.[35,43,44] In contrast, our results

together with similar findings[18] propose that the stroke risk is similar regardless of the timing of HRT initiation in relation to menopause onset. One suggestion for this distinction between heart disease and stroke is that thrombotic mechanisms play a larger role in causing stroke than heart disease in younger postmenopausal women.[45] Nonetheless, our results are consistent with that entering menopause increases the risk of stroke among nonusers but women who are exposed to HRT have no additional increase in stroke risk when they enter menopause.

Our findings must be interpreted in the light of several limitations. First, UKB is subject to sample selection bias as it consists of a healthier population compared with the general population of United Kingdom.[46] Furthermore, we only included White women in our study, and our findings might therefore not be generalizable to the general UK population or other ethnicities. Second, we did not have the possibility to investigate different formulations or administration routes of exogenous hormones which might influence the risk of stroke differently.[8,47] It is especially important to highlight that the estrogen dose in later generation of OCs is lower compared with the first pills introduced in the 1960s. Since we did not have information on estrogen dose or progestin component in our study, our results might not be generalizable to all types of OCs used today. However, one would suspect, given the birthyear distribution of our study population, that our results are based mainly on the first and second generation of OCs containing a combination of both estrogen and progesterone, which are still used today. Similarly, we would expect that the majority of HRT users have been prescribed oral medication containing estrogen combined with either first or second generation progestins. Third, we did not further distinguish between subtypes of ischemic stroke due to the low number of participants receiving a subspecific ischemic stroke diagnosis. Future studies should investigate whether exogenous hormones show distinct effects on the risk of etiological subtypes, to further understand the underlying mechanisms of stroke. Fourth, as the self-reported data has not been validated, there is a potential for recall bias. Last, some of the stroke risk factors were measured only once, which might have an effect on the risk estimates. However, when possible, we included time-varying covariates to capture behavioral and lifestyle changes within the follow-up time.

CONCLUSIONS

Our findings indicate that HRT is associated with an increased risk of stroke, regardless of the timing of initiation or duration. We also provide additional support to the hypothesis that HRT and OC use increase the short-term stroke risk dramatically, and our data imply that this risk might gradually decline with longer duration of OC use. While some of our results support earlier findings, parts of our results add to previous knowledge. Notably, we were able to identify an increased risk for specific causes of stroke, including an increase in the risk of ischemic stroke which seemed to be limited to the initial year of hormone use. We have also shown that HRT is not only limited to the increased risk of thrombotic or embolic occlusion but also subarachnoid hemorrhage.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Supplemental Material and Methods
STROBE Checklist
Tables S1–S10
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